Title

Explorations of Postural Orthostatic Tachycardia Syndrome with Electrodermal Measures of Sympathetic Function

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Explorations of Postural Orthostatic Tachycardia Syndrome with Electrodermal Measures of Sympathetic Function

A dissertation submitted in partial satisfaction of the requirements

for the degree Doctor of Philosophy in Nursing

by

John Oyigoga Akuma Odeh

2024

ABSTRACT OF THE DISSERTATION

Explorations of Postural Orthostatic Tachycardia Syndrome With Electrodermal Measures of Sympathetic Function

by

John Oyigoga Akuma Odeh

Doctor of Philosophy in Nursing

University of California, Los Angeles, 2024

Professor Wendie A Robbins, Chair

Background: Autonomic reflex screening (ARS) is central to the diagnosis of dysautonomia. Postural orthostatic tachycardia syndrome (POTS) is a heterogenous disorder involving the autonomic nervous system (ANS) with varying etiology. Electrodermal activity (EDA) is an indicator of sympathetic nervous system activity, however its utility in mechanistic characterization of POTS is unexplored.

Aim: To explore characteristics of postural orthostatic tachycardia syndrome (POTS) through analyses of associations, trends, and values among measures of gold standard (or reference) indices of autonomic function tests (AFTs), as well as those of electrodermal activity (EDA) traces, measured concurrently during autonomic reflex screening (ARS) appointments at the University of California, Los Angeles' (UCLA's) Cardiac Arrhythmia Center (CAC).

Methods: Of 595 patients referred for autonomic testing, 100 patients with head up tilt-table testing (HUTT), and palmar-EDA were included and classified as POTS-cases (n=75) or control subjects (n=25). Beat-to-beat noninvasive blood pressure, heart rate, and symptoms were concurrently assessed at

baseline, HUTT, Valsalva maneuver, and deep breathing. Quantitative sudomotor data were collected.

Results: Average sample age was 32 ± 16; 28, and 76.0% were female (n=76). Heart rate changes to HUTT in POTS-patients were greater than in controls (54.8 ± 10.4; 52.7 vs. 26.6 ± 7.4; 26.1 bpm, p<0.01). Four tonic-EDA patterns (Transient, Absent, Delayed, and Persistent) reflecting differing sympathetic responses were identified during tilt. The distribution of EDA patterns differed between POTS-cases and controls (p<0.01). Specifically, the EDA pattern most common in control patients (Transient) was seen in a minority of POTS patients, while the EDA pattern indicating persistent sympathetic drive for the duration of upright-tilt was seen in 42.7% of POTS-patients but 0% of controls (p<0.01). The EDA pattern reflecting delayed sympathoexcitation to HUTT, was associated with high heart rates and clinical symptoms (100%) (p<0.01) in POTS-patients. Skin conductance responses (SCRs), during deep breathing, Valsalva and upright tilt, exhibited shorter SCR rise in the cases with POTS versus the controls. Similarly, the half-recovery times were shorter in the POTS-cases versus the controls. The raw amplitudes of the event-based SCRs were higher in the POTS-patients than in control-patients. The medians of the Z-score transformed raw amplitudes were lower in the control-patients than in the patients with POTS. In contrast, during deep breathing, the medians of the T-score transformed raw amplitudes, were higher in the control-patients than in patients with POTS. The strength of associations ranged from weak to very strong, with strong associations between certain EDA indices and the AFTs of HR difference during deep breathing, indices of vagal response during Valsalva, and the difference between the HR at the minimum SBP during upright tilt, and its pre-tilt baseline value.

Conclusion: Phasic and Tonic-EDA patterns during upright-tilt, indicate differing mechanisms of POTS and identify highly-symptomatic-patients. Further studies are needed to validate these findings, and to explore the utility of understanding EDA differences in patients with POTS.

Supplemental Materials: Excel workbooks containing datasets constructed from the patient records appraised in the course of this study, will be uploaded to electronic archives for the interested reader.

This dissertation of John Oyigoga Akuma Odeh is approved.

Mary-Lynn Brecht

Jeffrey Laurence Ardell

Olujimi A Ajijola

Wendie A Robbins, Committee Chair

University of California, Los Angeles

2024

DEDICATION

To God, my parents, family, teachers, patients, and those who inspire others to seek knowledge.

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ACKNOWLEDGEMENTS

Let me start by expressing my heartfelt gratitude to both the UCLA School of Nursing and the UCLA Division of Graduate Education for an award of the Graduate Dean's Scholar Award, without which I would not have been able to start my studies in the PhD program. This award provided the funding I used to cover my educational and living expenses during the first two years of my doctoral formation and was an indispensable launchpad for my academic career here at UCLA.

Next, I wish to express my gratitude to the UCLA School of Nursing, Regents of the University of California, UCLA Division of Graduate Education, California Black Nurses Association (CBN), U.S. Federal Government Administrator of Care Grants, as well as Kaiser Permanente's Deloras Jones' Scholarship Committee, for various other forms of financial support over the course of my years in the PhD program.

Let me also seize this opportunity to give a special mention of my appreciation to my teacher, mentor, faculty adviser, former Associate Dean of Academic and Student Affairs, first Chair of my dissertation Committee, and then later a Co-Chair of the committee, Professor Emerita Lynn Veronica Doering, DNSc, RN, FAAN, for her invaluable counsel, encouragement, mentorship, recommendations for various scholarships and grants, as well as other forms of support, right from the very beginning of my journey here at UCLA (when she co-taught my first two courses in the PhD program), almost to the very end of my journey. Without your support, I would not have come this far.

To my distinguished dissertation committee Chair, Professor Wendie Anne Robbins, PhD, MSN, RN, FAAN, FAAOCN, who after interacting with me in various highly beneficial ways within the environs of the School of Nursing, got to formally teach me for the first time during the 2018 Summer Term, as the instructor for a course in occupational health which had a strong research component and was a truly eye-opening course. Let me also seize this opportunity to say that you have been an amazing teacher, mentor, source of counsel and encouragement, nominator and recommender for awards and grants, as well as a provider of other forms of support, such as the loan of a brand new laptop from your

research lab to support my education, and your offer to cover (as well as coverage of) the costs of my attendance at the 42nd Biennial Sigma Theta Tau International (STTI) Convention in Indianapolis, Indiana, USA, in 2021 (inclusive of the costs of the air tickets for my trip to from the convention, board, lodging and other travel expenses). Additionally, I wish to express my heartfelt gratitude for having made yourself available to meet with me several times to put together my UCLA webIRB application, as well as several other matters of critical importance to the smooth advancement of my formation as a PhD student and candidate. You have been a masterful Chair and advocate, as well as an adviser who has given me great advice and encouragement at critical points in my journey toward a PhD, and I must say that I would not have made it this far without your support.

Next I would like to express my deep gratitude to each of the other members of my dissertation committee, starting with Dr. Olujimi Adeoluwa Ajijola, II, MD, PhD, who has been my primary research mentor at the UCLA Division of Cardiology, my immediate Supervisor and Principal Investigator at the UCLA Cardiac Arrhythmia Center and Ajijola Lab, as well as Manager at the UCLA Electrophysiology and Neurocardiology Research Group. You have been a powerful formative influence in my research journey and growth as a neuroscientist and physiologist, a thought-provoking teacher, a provider of opportunities to explore new avenues of research, and a key source of funding over the past three years and eight months of my stay in the PhD program. Without the opportunities I gained from your tutelage since July 2020, I would not have arrived at this point in my research career.

To Dr. Mary-Lynn Brecht, PhD, the sole statistician on the committee; a teacher who taught me during two statistics courses, as well as a quantitative methods of research course, not to mention all of those one-on-one tutoring sessions in your office to clarify difficult points of statistics I did not grasp at the outset, plus stopping by in the hallways of the Factor Building, or sometimes even when walking on Charles E. Young Drive enroute to the parking lot, to clarify some point of research methodology and/or statistics, and the directed individual research course you supervised in 2020, I must say that you have

been an excellent teacher, mentor, counsellor, and pillar of support throughout my journey at UCLA.

To Dr. Jeffrey Laurence Ardell, PhD, who as a superb neuroscientist and one of the three founders of the field of neurocardiology, is an inspiration to me to grow into the best neuroscientist I can be, let me express my deep appreciation for kindly meeting with me for an interview when I was just embarking on this by now almost four-year voyage with the UCLA Electrophysiology and Neurocardiology Research Group. I still remember our first conversation in your office, and all those research articles (four in number) that you so generously printed out yourself and handed over to me, as well as those times when I sent you a quick email inquiry about some point of research interest or discussed a similar point during one of our annual staff dinners or research team meetings. Your support over the years has been invaluable and is a substantial part of what has led me to this milestone.

To Professor Sarah Choi, PhD, RN, FNP-BC, FAAN, who was the first member of the School of Nursing Faculty that I matched with during my application for admission into the PhD program I say thanks a lot! You attended my PhD admission interview and thereafter you were appointed to serve in the role of my very first faculty adviser. You inspired me to shift my initial broader research interest in diabetic neuropathy (with a focus on diabetic peripheral neuropathy), to a focus on cardiovascular autonomic neuropathy (CAN), which subsequently led me unto my current research focus on postural orthostatic tachycardia syndrome (POTS).

To Professor Paul Michael Macey, PhD, who is the Principal Investigator of the first research lab I volunteered (and then later served) in as a graduate student researcher, as an electrical engineer and a neuroscientist, you exposed me to acquisition of electrophysiologic data from study participants, got me certified in the collection of MRI data, recruitment of study participants, and other sundry research lab duties, notably the design of a research project and concretization of study variables. You also co-taught a core course in quantitative research, and I built on this foundation in my next lab appointment, where I settled on my current PhD project. You were the second faculty of the School of Nursing I matched

with during the admission process, and I am grateful for your offer to serve as the technology expert on my dissertation committee. Thank you so much, for without the two years I spent first as a volunteer, then later as a paid graduate student researcher in your OSA/Brain Studies Lab, I would not be where I am today.

To Professor Felicia Schanche Hodge, DPH, thanks so much, first for being the third School of Nursing faculty I matched with, secondly for teaching me all those core PhD course with such aplomb, and then thirdly for your advice, encouragement and support over the years, as well as for selecting me to serve as your teaching assistant in the health policy and advocacy course. It was an eye-opening experience.

To all my professors at the School of Nursing who have either taught me, chosen me to serve with them as a TA, given me freely and generously of their time, counsel and encouragement, as well as written letters of recommendation in support of my applications to this grant or that scholarship. Also to my wonderful teachers at California State University Northridge, who during my second baccalaureate formation in nursing, enkindled in me a desire for a career in academia and research; I am speaking here of Chair of the CSUN nursing department Dr. Mariane Hattar, PhD, as well as Dr. Samira Moughrabi, PhD, Dr. Martha Highfield, PhD, (who taught me research), and Dr. Martha Harmon, PhD, all of whom wrote excellent letters of recommendation in support of my application for admission to the UCLA School of Nursing's PhD program, and all my teachers in all the schools I have ever attended, who may have in one way or the other, fanned the embers of curiosity and a hunger for knowledge in me, I say a most hearty Thank You!

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VITA

Education

University of California Los Angeles (2019) MSN, nursing education in research science.
California State University Northridge (2016) BSN, post-licensure baccalaureate level nursing.
American Intercontinental University Los Angeles (2003) MBA, global technology management.
University of Lagos (1999) B.Sc. (Honors), electrical engineering.

Honors & Awards

2023. Recipient of the UCLA Graduate Division Doctoral Travel Grant to Support Attendance and Presentation of a Research Poster at the July 17-19, 2023, 4T-Phys BIOPAC Human Physiology Research and Training Conference at UC Santa Barbara, Santa Barbara, California, USA.
2022. Recipient of the 2022 Spring Quarter School of Nursing Audriene Moseley Stipend
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2019. Recipient of the School of Nursing Audriene Moseley Stipend
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2018. Recipient of the Dr. Birthale Archie's Jerry Allen Moore Scholarship
2017. Recipient of the University of California Los Angeles Graduate Dean's Scholar Award.
2016. Induction into Sigma Theta Tau International (STTI) Honor Society of Nursing, Gamma Tau At-large Chapter.
2008. Recipient of the High Desert Auxiliary Health System's Scholarship
2008. Recipient of the Richard C. Mallyon Memorial Scholarship
2007. Recipient of the Richard C. Mallyon Memorial Scholarship
2006. Recipient of the Governor Arnold Schwarzenegger and Roman Catholic Archdiocese of Los Angeles Job Training Grant and Stipend
2005. Recipient of the Dean's List Award. Los Angeles Pierce College, Woodland Hills, California.
1997. Recipient of the First Prize in the 1st Chief Mrs. Kuburat Olayinka Okoya's Nigerian Universities Short Story Competition
1994. Participant in the Junior Category of the 20-29 August 1994, 18th Lloyds' Bank Masters, International Chess Tournament, in Cumberland Hotel, Marble Arch, London.
1992. Recipient of the Bronze Medal. University of Lagos Inter-hall Sports Competition. Chess Event.

Licenses

06/25/2012 to present. RN License with California Board of Registered Nursing. License # 822143.

09/12/2016 to present. PHN Certificate with California Board of Registered Nursing. License # 551129.

Professional experience

1/2023 to 6/2024. University of California Los Angeles School of Nursing. Teaching Fellow. Served as the teaching assistant for four baccalaureate pre-licensure nursing courses, N162A - Foundational Concepts for Tertiary Prevention and Care of Medical-Surgical Patients and Families, N162B - Tertiary Prevention and Care of Medical-Surgical Patients and Families, N162C - Tertiary Prevention and Care of Complex Medical-Surgical Patients and Families and N3 - Human Physiology, a graduate post-licensure advanced practice registered nursing courses, N264 - Professional Role Issues in Advanced Practice Registered Nursing, as well as a graduate pre-licensure nursing course, N204 – Research Design and Critique.

7/2020 to 3/2024. University of California Los Angeles Division of Cardiology/David Geffen School of Medicine (UCLA Cardiac Arrhythmia Center, Electrophysiology and Neurocardiology Research Team, Neurobiology Research Group, and Ajijola Research Laboratory). Graduate Student Researcher. Worked in a research team that recruited study participants with epilepsy, vagal nerve stimulator implants, and dysautonomia such as orthostatic hypotension, orthostatic intolerance, neurogenic syncope, postural orthostatic tachycardia syndrome, as well as disorder and syndromes such as baroreflex dysfunction and inappropriate sinus tachycardia, for electrophysiologic and neurocardiology studies. Reviewed patients' electronic medical records (EMRs), took physiologic measurements, extracted electrophysiologic signal data, performed data analyses. Vagal Nerve Stimulator Study Coordinator. Conducted electrophysiologic studies on individuals with epilepsy and vagal nerve stimulator implants in a conscious ambulatory and clinical setting, as well as sedated operating room intraoperative-surgical settings. Assisted in obtaining informed consent for these studies, prepped patients for these studies during preop, took physiologic measurements, extracted the data from related electrophysiologic traces, analyzed such data, and made presentations of such data to primary research mentor and other members of the research team.

10/2022 to 12/2022. University of California Los Angeles School of Nursing. Teaching Associate. Served as teaching assistant for a baccalaureate level pre-licensure nursing course, N54B - Pathophysiology II.

10/2019 to 6/2020. Macey Brain Studies and Obstructive Sleep Apnea Laboratory. University of California Los Angeles School of Nursing. Graduate Student Researcher. Works as a graduate student researcher in a research team that recruits study participants with obstructive sleep apnea, conducts brain studies, takes physiological measurements & performs analyses on collected data.

10/2019 to 06/2020. UCLA School of Nursing. Graduate Teaching Associate. Served as the teaching assistant in three graduate level pre-licensure nursing courses, N230A - Advanced Pathophysiology, N225A - Advanced Pharmacology I and N225B - Advanced Pharmacology II.

10/2018 to 06/2019. UCLA School of Nursing. Graduate Teaching Assistant. Served as the teaching assistant in two baccalaureate level pre-licensure nursing courses N152W - Health Promotion: Growth & Development in Culturally Diverse Populations (Lead Discussion Section C), and N162A - Foundational Concepts for Tertiary Prevention and Care of Medical-Surgical Patients and Families, and one graduate level pre-licensure nursing (i.e., a masters entry level clinical nurse, MECN) course, N267 - Health Policy.

Academic papers & presentations

01/2024. Subtype Differentiation in Postural Orthostatic Tachycardia Syndrome Using Electrodermal Measures of Sympathetic Function. Manuscript in Review by the Journal of the American Medical Association Cardiology (JAMA Cardiology). Received on January 18, 2024.

Odeh, J. Subtype Differentiation of Postural Orthostatic Tachycardia Syndrome Using Electrodermal Measures of Sympathetic function. Poster and Conference Presentations at Ackerman Building, UCLA, Los Angeles, California. 2023 Annual Department of Medicine Research Day. First Annual Breakout Discussion Sessions (PowerPoint Presentation with Questions and Answers Session).

CHAPTER 1

INTRODUCTION

Chapter 1: Introduction

Background

Postural orthostatic tachycardia syndrome (POTS) is a term used to refer to a syndrome of ailments affecting the autonomic nervous system, leading to cardiovascular dysautonomia. It is the emergence without orthostatic hypotension (OH), of orthostatic symptoms associated with an incremental change in heart rate (ΔHR) ≥ 30 beats per minute (bpm), and tachycardic heart rates that are usually 120 bpm or more (Grubb, 2008; Grubb et al., 2006; Kavi et al., 2012; Low et al., 2009; Novak, 2011; Raj et al., 2020; Raj & Levine, 2013; Sheldon et al., 2015). Symptoms of orthostatic intolerance are generally classified based on their association with brain hypoperfusion, or sympathetic hyperactivity (Aboseif et al., 2023; Low et al., 2009; Raj et al., 2020; Raj & Levine, 2013; Sheldon et al., 2015).

Hyperadrenergic postural orthostatic tachycardia syndrome (HA-POTS), is a subtype of POTS that is associated with high levels of norepinephrine (Feigofsky & Fedorowski 2020; Freeman et al., 2011; Kanjwal et al., 2011; Low et al., 2009; Taub et al., 2021). Treatment of persons with HA-POTS is challenging, partly because they are not readily identifiable from a population of patients with a mixture of POTS subtypes, or distinguishable from persons with neuropathic POTS (Kanjwal et al., 2011). The ongoing challenge of differentiating persons with HA-POTS, from persons with neuropathic POTS, hinders the development of standardized protocols for the treatment of HA-POTS (Kanjwal et al., 2011).

Significance to Healthcare Delivery Systems

Misdiagnosis of POTS, leads to cardiac dysrhythmias, impaired gait/mobility, recurrent syncope, inadequate treatment, disability, lost school and/or work hours, poor quality of life (QoL), cognitive deficits, and increased healthcare costs (Grubb et al., 2006; Grubb, 2008; Kavi et al., 2012; Low et al., 2009; Raj et al., 2020; Revlock, 2018; Seeley, 2021; Sheldon et al., 2015). Currently assessment, detection, and diagnosis of this complex and multifaceted dysautonomia requires use of data obtained from measures such as autonomic reflex screening (ARS) (inclusive of tilt table testing), measures of

orthostatic blood pressure (BP) and HR, and/or tests of plasma norepinephrine levels (Eftekhari et al., 2021; Freeman et al., 2011; Raj, 2006; Sheldon et al., 2015; Taub et al., 2021; Thijs et al., 2021).

However, in the diagnosis of POTS, there is a dearth of information on the utility of measures of electrodermal activity taken during head up tilt-table testing (HUTT), particularly regarding identification of HA-POTS (Braithwaite et al., 2015; Boucsein, 2012; Boucsein et al., 2012; Critchley, 2010; Dawson et al., 2001; Grubb et al., 2006; Grubb, 2008; Kanjwal et al., 2011; Low et al., 2009). Thus, the study for this dissertation examined the use of measures of electrodermal activity (EDA) in the assessment, detection, and diagnosis of POTS, as well as its utility in the determination of HA-POTS. It also examined the utility of measures of electrodermal activity recorded during head up tilt-table testing (HUTT) in mapping out prognostic factors, identifying medication effects on HUTT results, and explored its utility in teasing out mechanisms and pathophysiological characteristics of POTS. The findings of this PhD study, may furnish physicians, physician assistants, nurse practitioners, other advanced practice registered nurses (inclusive of occupational health nurses, nurse anesthetists and midwives), and registered nurses responsible for the provision of care at the bedside, with a greater understanding of the underlying pathophysiological characteristics POTS (Cheshire et al., 2021; Eftekhari et al., 2021; Freeman et al., 2011; Gleason et al., 2017; Raj, 2006; Sheldon et al., 2015; Taub et al., 2021; Thanavaro & Thanavaro, 2011; Thijs et al., 2021).

Significance for Nursing Practice

Because misdiagnosis of POTS may be associated with a delay in treatment and poor patient outcomes (Bhatia, 2018; Cheshire et al., 2021; Eftekhari et al., 2021; Grubb, 2006; Grubb, 2008; Seeley & Lau, 2021; Revlock, 2018; Sheldon et al., 2015), such as a deterioration of quality of life (QoL), disability, lost school and/or work hours, anxiety, depression, cognitive deficits, cardiac dysrhythmias (Kanjwal et al., 2011; Kavi et al., 2012), nursing research to address gaps in this area is important. Such nursing research lies within the scope of at least three of the four metaparadigms of nursing, namely the metaparadigms of patient, health and nursing (Nifkarid et al., 2018). Also, untreated POTS is associated

with the development of onerous symptoms, such as light-headedness (occasionally associated with recurrent syncope), palpitations, anxiety, blurry vision, brain fog, disorientation, exercise-intolerance, fatigue, headaches, dizziness, nausea, and tremors (Gunning III et al., 2019; Grubb, 2008; Kanjwal et al., 2011; Low et al., 2009; Raj et al., 2020; Sheldon et al., 2015), all of which are appropriate for nursing assessment, diagnosis and treatment. Furthermore, the identification, prevention and elimination of diagnostic error is of interest to all nursing professionals (Gleason et al., 2017). Nursing professionals may employ findings from this study to development of nurse-driven patient-teaching interventions, as well as other nursing interventions (Gleason et al., 2017).

Of additional significance, are any identifiable correlations between variables of interest, such as patient reported symptoms and electrodermal activity (EDA) waveform types (or EDA response subtypes), composite autonomic severity score, and EDA waveform types (or EDA response subtypes). Findings of a correlation across variables such as a person's cardiovascular-health related medical history, EDA response subtypes, and other EDA variables such as tilt-up EDA, tilt-down EDA, and peak-to-peak EDA, could increase knowledge of the pathophysiology of POTS (Braithwaite et al., Boucsein, et al., 2012; Boucsein, 2012; Cheshire et al., 2021; Critchley, 2010; Dawson, et al 2001). An examination of correlations across these indices is pertinent because measures of electrodermal activity (or skin conductance) are yet to be validated as reliable tests of autonomic function (Cheshire et al., 2021).

We aimed to improve the reliability of EDA measures of autonomic function, by running correlational statistical tests such as Pearson's Correlations, or Spearman's Correlations for non-parametric sample distributions, as well as to examine the coefficient of variation, and/or the intraclass correlation. An examination of EDA measures across repeated autonomic function tests performed on the same individual (e.g., measures of EDA skin conductance levels or the amplitudes of skin conductance responses recorded during repeated heart rate deep breathing (HRDB) tests and Valsalva maneuver (VM) tests), could improve the reliability of such measures (Matheson, 2019). Records of

healthy study participants are often used to assess reliability in validation studies (Matheson, 2019). However, each record examined for the purposes of this study, involved a patient referred for autonomic function screening because of pertinent signs and/or symptoms indicative of potential dysautonomia. As such our comparison group was comprised of only relatively healthy (as opposed to completely healthy) patients, and therefore use of the above-mentioned criterion is not applicable to this exploratory clinical study. Nonetheless, validity of EDA measures in appraisal of autonomic functions and/or dysautonomia, may have been improved, by our inclusion in our samples of controls and POTS cases, the broadest category of patients possible, despite our use of convenience sampling in identifying and selecting patient records for inclusion in this study. In addition to the feature of test-retest reliability inherent in recording EDA measures during repeated tests of deep breathing and Valsalva, this study improved the reliability of EDA measures via appraisal of internal consistency and inter-rater reliability; wherein the PI and co-investigator examined pertinent focus areas of the various EDA signal traces recorded concurrently with the administration of respective autonomic function tests (Matheson, 2019).

Because POTS is a cluster of conditions/disorders with varying pathophysiology, development of therapeutic regimens tailored to each specific underlying disorder (or POTS subtype), are needed. (Abed, et al., 2012; Raj & Levine, 2013). Such findings could open up avenues for future research in the area of POTS related therapeutics (Abed, et al., 2012). A high correlation between medication holding adherence (which is a patient's adherence to the requirement to hold certain medications 48 hours before ARS), and specific EDA signal types, may indicate a need to provide nurse-centered patient teaching prior to the administration of autonomic reflex screening tests, to improve diagnostic accuracy (Raj & Levine, 2013).

Since many of the symptoms reported by persons with POTS such as blurred vision (or tunneled vision), brain fog (or mental clouding), chest discomfort (or pressure), disorientation, dizziness, dyspnea, headaches, lightheadedness, nausea, palpitations, and tremulousness, are akin to the adverse (or side)

effects occasioned by drinking alcohol, coffee (or any other caffeinated drinks), and/or taking anticholinergic medications (for example Ativan, Benadryl, Carisoprodol, Depakote, Elavil, Fentanyl, Phenobarbital, Seroquel and Xanax), their ingestion within 48-hours of screening for cardiovascular dysautonomia is proscribed. This is because they might have a confounding effect on the interpretation of the electrophysiologic data obtained during screening, and consequently exert an adverse impact on diagnostic accuracy (Raj, 2006). Provision of a nurse-centered teaching intervention, to improve patients' medication-holding adherence before administration of autonomic screening tests, may increase their compliance with the medication-holding requirement, and thereby improve the degree of diagnostic accuracy (Novak, 2011; Raj, 2006). Findings of a high correlation between the subset of those individuals who did not hold proscribed medications for 48-hours before screening and any specific EDA response types, may also identify persons in need of a nurse-driven teaching intervention, individually tailored to improve compliance with any post autonomic reflex screening (ARS) therapeutic regimen, that is prescribed by a care-provider (Cheshire et al., 2021; Novak, 2011; Raj, 2006; Raj & Levine, 2013).

Research Question, Aims and Exploratory Hypotheses

Review of the literature on the utility of EDA in diagnosis of POTS, and determination of hyperadrenergic POTS, reveals a dearth of knowledge of the etiology of POTS. While adrenergic state, deconditioning, and neuropathic pathways have been proposed as mechanisms underlying POTS, evidence to validate the existence of these mechanisms is currently limited. As such, the research question and hypotheses of this study have been designed to examine whether there are any associative relationships among variables of interest such as, tonic EDA, change in HR, systolic blood pressure (SBP) change from the baseline before tilt-up, minimum SBP during HUT, HR at minimum SBP, maximum HR during HUT, minimum HR during HUT, pressure recovery time (PRT), and composite autonomic severity score (CASS). The research question, as well as its related specific aims, and their associated exploratory hypotheses are as follows.

Research Question

Are there associations among EDA indices derived from the EDA traces recorded during the tilt table testing period of autonomic reflex screening (ARS), and variables measured with gold standard autonomic function tests (AFTs) over the same tilt table testing period, via use of validated autonomic reflex screening (ARS) protocols. Furthermore, can such EDA indices be used as markers of sympathetic nervous system activity for development of diagnostic, or prognostic measures, mechanistic characterization, subtype differentiation of POTS, and identification of any medication effects and symptoms experienced during the tilt table testing in persons with POTS?

Specific Aims

There are six specific aims of this PhD project, each of which has at least one associated hypothesis. These are as follows:

Aim One

Determine whether there are there any notable differences (determined by a $p<0.05$) in the distribution of EDA Response Subtypes in the group of patients diagnosed with POTS, as well as in the group of controls, selected from the population of patients screened for evidence of dysautonomia at the UCLA CAC from 2017 to 2021.

Exploratory Hypothesis One. There are notable differences (determined by a $p<0.05$) in the distribution of EDA Response Subtypes in the group of persons with POTS versus controls.

Aim Two

Determine whether BP trends during head up tilt (HUT) testing, are associated with any of the other variables or indices obtained from autonomic function test results (determined by the ranking of results from running correlations tests, as either very weak, weak, moderate, strong, or very strong), or if they can be distinguished by groups (controls or cases) and/or by EDA response subtypes (determined by comparison between groups and/or subgroups, and a $p<0.05$).

Exploratory Hypothesis One. BP trends during HUT are associated (determined by the ranking of results from running correlations tests, as either very weak, weak, moderate, strong, or very strong), and/or they can be distinguished by comparison of groups (controls or cases) and/or EDA response subtypes (determined by comparison between groups and/or subgroups, and a $p<0.05$).

Aim Three

Determine whether HR trends during head up tilt (HUT) testing, are associated with other variables or indices obtained from autonomic function test results (determined by the ranking of results from running correlations tests, as either very weak, weak, moderate, strong, or very strong), or if they can be distinguished by groups (controls or cases) and/or by EDA response subtypes (determined by comparison between groups and/or subgroups, and a $p<0.05$).

Exploratory Hypothesis One. HR trends during HUT are associated (determined by the ranking of results from running correlations tests, as either very weak, weak, moderate, strong, or very strong), and/or they can be distinguished by comparison of groups (controls or cases) and/or EDA response subtypes (determined by comparison between groups and/or subgroups, and a $p<0.05$).

Aim Four

Determine whether EDA variables derivable from EDA signal traces recorded during HUT, are associated with other variables or indices obtained from autonomic function test results (determined by the ranking of results from running correlations tests, as either very weak, weak, moderate, strong, or very strong), or if they can be distinguished by groups (controls or cases) and/or by EDA response subtypes (determined by comparison between groups and/or subgroups, and a $p<0.05$).

Exploratory Hypothesis One. EDA variables derived from EDA signal traces recorded during HUT, are associated (determined by the ranking of results from running correlations tests, as either very weak, weak, moderate, strong, or very strong), and/or they can be distinguished by comparison of groups (controls or cases) and/or EDA response subtypes (determined by comparison between groups

and/or subgroups, and a $p<0.05$).

Aim Five

Determine whether any of the measures obtained during a patient's autonomic reflex screen (ARS), including (but not limited to) symptoms or symptom clusters, each component of the composite autonomic symptom score (CASS), the CASS (i.e., the Total CASS or the degree of General Autonomic Impairment {GAI} if any), each of the latency variables, the pressure recovery time (PRT), any of the QSWEAT variables, and/or the pre-ARS medication-holding adherence, are associated (determined by the ranking of results from running tests for correlations, as being either very weak, weak, moderate, strong, or very strong), with any of the continuous EDA indices, or any of the standard ARS measures.

Exploratory Hypothesis One. There are associations (determined by the ranking of results from running tests for correlations, as being either very weak, weak, moderate, strong, or very strong), among ARS derived measures such as symptoms or symptom clusters, components of the composite autonomic symptom score (CASS), the CASS (i.e., the Total CASS or the degree of General Autonomic Impairment {GAI} if any), latency variables, the pressure recovery time (PRT), QSWEAT variables, the pre-ARS medication-holding adherence, continuous EDA indices, and any of the standard ARS measures (i.e., variables or indices).

Aim Six

Explore the potential utility of EDA Response Subtypes and other EDA variables (determined by comparison between and within groups as well as a $p<0.05$, sensitivity and specificity tests, receiver operating characteristic curves {ROCs} with their associated area under the curve {AUC} values, as well as correlation coefficients), in the diagnosis of POTS, and in the determination of hyperadrenergic POTS.

Exploratory Hypothesis One. EDA Response Subtypes are associated (determined by comparison between and within groups as well as a $p<0.05$, sensitivity and specificity tests, receiver operating characteristic curves {ROCs} with their associated area under the curve {AUC} values, as well

as correlation coefficients), with one or more of the ARS derived gold standard variables used to diagnose POTS.

Exploratory Hypothesis Two. One or more of the other continuous EDA variables or indices, are associated (determined by comparison between groups {controls or cases} and within groups {i.e., when stratifying by ERS} and a $p<0.05$, sensitivity and specificity tests, receiver operating characteristic curves {ROCs} and their related area under the curve {AUC} values, as well as correlation coefficients), with one or more of the ARS derived gold standard variables used to identify the likely presence of hyperadrenergic POTS.

Outcomes and Conclusion

Outcomes

Intended outcomes of this study included an identification of indicia of POTS in general, and hyperadrenergic POTS in particular, from analyses of the EDA traces that were recorded during ARS sessions with patients referred to the UCLA Cardiac Arrhythmia Center, over the period from April 2017 to December 2021. This exploratory study sought to investigate the existence and characteristics of any tonic EDA signal waveform patterns (or tonic EDA response subtypes), which may be used by healthcare professionals, e.g., nurse practitioners, nurse anesthetists, other advanced practice nurses, physicians, physician assistants, or any other healthcare providers, to assess, detect and diagnose cases of POTS and hyperadrenergic POTS in persons referred for ARS. Its findings may also yield valuable insights into the underlying mechanisms of POTS, which would be an addition to the current state of the science on the etiology of POTS.

Conclusion

This PhD project explored the utility of EDA as a marker of sympathetic nervous system activity underlying POTS, and for distinguishing subtypes of POTS. Because this was a cross-sectional study, which did not follow a cohort of patients over a period of time, it could not fully explore the prognosis of

POTS. However, it may help in the identification of factors that are of interest in the diagnosis, prognosis, management and treatment of POTS (Kent et al., 2020). Furthermore, the findings of this study may help tease out underlying pathophysiologic mechanism of POTS, which would be an improvement upon the currently limited understanding of the etiology of POTS (Aboseif et al., 2023).

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CHAPTER 2

REVIEW OF THE LITERATURE

Chapter 2: Review of the Literature

This chapter is a review of the literature on applications of electrodermal activity (EDA) to the diagnosis of diseases or health disorders, investigation of pathophysiologic mechanisms, and its use in studies of variables pertinent in mapping out the prognosis of postural orthostatic tachycardia syndrome (POTS). It looked for any publications, on the employment of EDA measures in diagnostic, mechanistic and prognostic investigations of postural orthostatic tachycardia syndrome (POTS), and identification of POTS subtypes. To this end, this review of the literature (RoL), examined the state of the science in these areas of inquiry, via searches of databases such as CINAHL, EMBASE, PubMed and Web of Science. Also reviewed, were literature on existing methods for POTS diagnosis, to determine whether measures of EDA are already employed in diagnostic testing for POTS, or in the determination of subtypes of POTS. It aimed to identify any gaps in the body of science, as well as uncover any avenues for research that such gaps might offer for the development of nursing and pathophysiologic science.

Therefore the overarching theme of this review of the literature, is an investigation of the utility of measures of electrodermal activity (EDA), also known as galvanic skin response (GSR) (Zamzow et al., 2016), and skin conductance (SC) (Nagai et al., 2004; Zamzow et al., 2016), in diagnosis of POTS (Grubb 2008; Grubb et al., 2006; Raj et al., 2020; Raj & Levine, 2013; Raj, 2006; Raj et al., 2005; Rocha et al., 2021; Thanavaro & Thanavaro, 2011; Thijs, 2021), identification of mechanisms of POTS, and mapping out factors pertinent to the prognosis of POTS. The secondary theme is an examination of EDA's utility as an electrophysiologic measure for distinguishing subtypes of POTS, such as hyperadrenergic postural orthostatic tachycardia syndrome (HA-POTS). To this end, review papers on a variety of subjects such as diagnosis and differentiation of hyperadrenergic postural orthostatic tachycardia syndrome (HA-POTS) from other POTS subtypes, the autonomic function tests (AFTs) comprising an autonomic reflex screen (ARS), and diagnosis of cardiovascular dysautonomia and cardiovascular autonomic neuropathy (CAN), were appraised, because of their pertinence to the overarching and secondary themes.

Objective

In their guide to writing literature reviews, Galvan and Galvan (2017), stated that reviews of the literature, should be built upon, centered around, driven with, and informed by a guiding principle, such as a research question (or a set of research questions). This view is shared by Mellor (n.d.), who holds the view that a systematic review begins with asking a research question, crafting a research plan (or a research protocol), and thereafter, proceeding to answer the research question by synthesizing all of the abstracted evidence that meets a set of previously established criteria. As such, the overarching objective of this review of the literature, is to survey the existing body of literature (especially vis-à-vis the corpus of peer-reviewed primary source publications), as well as the state of the art (or science) on, applications of measures (i.e., recordings of signal traces) of electrodermal activity, to investigations of various health conditions, non-health related phenomena (e.g., lie detection tests, and stress response during combat simulations and cheating during exams), and various psychophysiological responses of etiological interest (Boyce et al., 2016; Kozel et al., 2009; Taylor et al., 2022).

To this end, this review was founded on, and will be guided by the question of whether there are "…any associations among EDA indices derived from the EDA traces recorded during the tilt table testing period of an ARS, and any variables measured with gold standard AFTs over the same tilt table testing period via use of validated ARS protocols." Furthermore, this review was shaped by the question, of whether these EDA indices, may be used for the diagnostic, prognostic, mechanistic characterization, and subtype differentiation of POTS, as well as identification of symptoms experienced during head up tilt-table testing in persons with POTS, and impact on ARS results of any medications not held for at least 48-hours before autonomic screening.

Review Type Selection

Several review types were considered with an eye toward selecting the most appropriate type of review for the purposes of this PhD dissertation project. Following an appraisal of many review types,

we narrowed our choices to two review methods. Specifically, these included systematic reviews; which are the strongest level of evidence, and scoping reviews; which are rigorous too (Mak & Thomas, 2022).

According to Mellor (n.d.), a systematic review requires the involvement of at least two (if not more) investigators, who must work independently to conduct searches of the literature for purposes of identifying all pertinent sources. Thereafter they screen such identified sources in strict accordance with a set of previously established inclusion and exclusion criteria, go on to select appropriate documents for inclusion in the proposed systematic review, abstract information from such sources, and synthesize findings from the body of literature so reviewed (Mellor, n.d.). This is often quite a personnel intensive as well as time-consuming process, which might require a period of six to eighteen months (Treadwell Virtual Library, 2022). It also requires at a minimum, participation by at least two investigators (Galvan & Galvan, 2017; Mellor, n.d.).

Scoping reviews are an approach to synthesizing knowledge, which employs an iterative as well as a systematic method, toward the identification and synthesis, of either an emerging or existing body of literature on a given subject. Although there are various reasons for carrying out a scoping review, the main reasons are to map the extent, range, and nature of the literature, as well as to determine possible gaps in the literature on a topic (Mak & Thomas, 2022). They are also conducted to assess the feasibility of conducting a systematic review. Scoping reviews are not limited to peer-reviewed literature (Mak & Thomas, 2022). Because of the aforementioned features of a scoping review, and the exploratory nature of this PhD project, it is quite suitable for reviewing the state of the science in an emerging field. So, the PI decided to conduct a scoping review of the literature pertinent to this study (Galvan & Galvan, 2017; Mellor, n.d.).

Definition of Some Key Terms

Adrenergic

This is a word that is often used in reference to a possible etiological pathway or mechanism for

POTS, as well as in the description of the characteristics of a certain subtype of POTS (Abed et al., 2012; Hieble, 2009). Since the word adrenergic is also used to denote certain receptor nerve cells (i.e., adrenoreceptors or adrenergic receptors), within which adrenaline or epinephrine, norepinephrine or noradrenaline, or similar substances perform a neurotransmitter function (Hieble, 2009), persons with the subtype of adrenergic POTS, have the type of postural orthostatic tachycardia syndrome that affects the sympathetic nervous system, and is mediated at essentially all sites throughout the body by the neurotransmitters epinephrine and norepinephrine (Abed et al., 2012; Hieble, 2009).

Adrenergic POTS

Is the name of a POTS subtype that affects the sympathetic nervous system and the action of adrenaline, norepinephrine and similar substances (Abed et al., 2012; Hieble, 2009). It is often delineated from other POTS subtypes, by the use of catecholamine tests (Abed et al., 2012).

Cardioprotection

This is a term that encompasses all of the measures and mechanisms taken to preserve (or involved in the preservation of) the heart, by decreasing or preventing injury to myocardial tissue (Intachai, 2018; Kubler & Haass, 1996; Nuntaphum et al., 2018).

Cardiovascular Autonomic Neuropathy (CAN)

Is the term for a neuropathy of the cardiovascular autonomic system, which often exists alongside diabetes mellitus (DM) in the absence of other neuropathic etiologies (AlOlaiwi, et al, 2018), such as chemotherapy (or other types of drug) induced neuropathy.

Cardiovascular Dysautonomia

This is a term related to the phrase cardiac dysautonomia, in that it refers to cardiovascular disorders arising from a malfunctioning of the autonomic nervous system (ANS) (Feigofsky & Fedorowski, 2020). Among such disorders are arterial hypertension, inappropriate sinus tachycardia, orthostatic hypotension, postural orthostatic tachycardia syndrome and reflex syncope. When the

processes by which the ANS regulates cardiovascular hemostasis become impaired, cardiovascular dysautonomia occurs. Such processes may either be chronic in nature or paroxysmal (Feigofsky & Fedorowski, 2020).

Classic Papers (or Seminal Papers)

Is a phrase used to describe manuscripts with research findings that have remained relevant and are frequently cited by researchers in in their respective fields of study, despite having been published (sometimes well) over five years ago (Henderson, 2017; Orduna-Malea et al., 2018). Such papers are typically manuscripts that present new research findings. Therefore peer-reviewed publications such as introductory articles, review articles, commentaries, editorials and guidelines have not been deemed classic or seminal papers for the purpose of this review of the literature. Also excluded are articles with less than 20 citations. (Henderson, 2017; Orduna-Malea et al., 2018).

Deconditioning

This is a phrase that refers to a possible etiological and mechanistic pathway for the development of POTS (Joyner & Masuki, 2008; Zhao & Tran, 2022). However, this view has been rejected by researchers such as Blitshteyn and Fries (2016), who argue that while it may be valid to state that many persons with POTS could be said to be deconditioned vis-à-vis their state of physical fitness, this is more a case where correlation is not indicative of causation, than it is of a situation in which persons develop POTS because they have a poor degree of fitness (Blitshteyn & Fries, 2016). As such these scholars, hold the view that deconditioned persons with Ehlers Danlos Syndrome or POTS, become deconditioned as a result of POTS, instead of a situation in which they develop POTS, because they have become deconditioned (Blitshteyn & Fries, 2016; TEDS, 2016; Tirraoro, 2016).

Electrodermal Activity (EDA)

Which is also known as galvanic skin response, refers to autonomic variations in the skin's electrical properties, which are frequently caused by minute amounts of secreted sweat, and which also

give rise to a skin conductance response (SCR) and a skin conductance level (SCL) (Braithwaite, 2015;). It should be noted that EDA is an umbrella term, which encompasses phenomena such as skin resistance level (SRL), as well as short-term reactions, which develop over the course of a few seconds such as, sympathetic skin response (SSR) and skin resistance response (SRR) (Critchley & Nagai, 2013). However, SSRs and electrochemical skin conductance are often used to study sudomotor function, rather than psychophysiological phenomena like emotional arousal (Porubcin & Novak, 2020).

Finger pulse volume (FPV)

This is also referred to as blood volume pulse (BVP), and is a photoplethysmography (PPG) based electrophysiologic measure of the amount of the change in the volume of the blood that flows through a fingertip, during each heart beat (Bloom et al., 1976; Bloom & Trautt. 1977; Elgendi, 2012; Fredrikson, & Öhman, 1979; Furedy, 1968; Mathews & Lader, 1971; Smith et al., 1984). Although the utility of PPG in exploratory investigation of POTS is not the focus of the paper, it should be noted that measures of FPV were recorded concurrently with the EDA measures recorded on each study participant during their ARS appointments at the UCLA CAC. So, a brief description of photoplethysmography is given below.

Hyperadrenergic POTS

Is a phrase derived from the word hyperadrenergic (which refers to a high level of adrenalin), and the acronym for the dysautonomia postural orthostatic tachycardia syndrome (POTS). As such hyperadrenergic POTS is a term used for that subtype of postural orthostatic tachycardia syndrome, wherein the plasma norepinephrine level is ≥ 600pg (Abed et al., 2012).

Neuropathic POTS

This is the most common subtype of POTS, and refers to that variant of POTS, in which small nerve fibers in the lower peripheral appendages that are responsible for contraction of blood vessels in the lower limbs, are impaired to such a degree that the process of venous blood return upon standing is defective, and consequently individuals with neuropathic POTS, experience symptoms of orthostasis,

e.g., dizziness (Grubb et al., 2006; Grubb, 2008; Kavi et al., 2012; Low et al., 2009; Novak, 2011; Porubcin & Novak, 2020; Raj et al., 2020; Raj & Levine, 2013; Sheldon et al., 2015).

Photoplethysmography

Is a term that refers to a measure used for estimating the volume of blood flowing through skin tissue via means of infrared light (Elgendi, 2012). Researchers from a broad spectrum of scientific disciplines have taken a growing interest in PPG usages in both clinical practice and research, because of its benefits as a convenient, inexpensive, and non-invasive diagnostic tool. A photoplethysmogram measures the oxygen saturation, cardiac output, and BP, and therefore it is used to assess autonomic functions (Elgendi, 2012).

Postural Orthostatic Tachycardia Syndrome (POTS)

This is not a single disease. Rather it is a term used in reference to a group of diseases. (Grubb et al., 2006; Grubb, 2008; Kavi et al., 2012; Low et al., 2009; Novak, 2011; Raj et al., 2020; Raj & Levine, 2013; Sheldon et al., 2015). Excessive and persistent tachycardia after postural change, either from a lying or siting position to a standing position, without a significant drop in systolic and/or diastolic blood pressure, the presence of medical conditions (e.g., inappropriate sinus tachycardia; which is a confounder of POTS), or anticholinergic medications (which can skew the results of autonomic function tests), or chronic symptoms of orthostatic intolerance, is clinically characteristic of POTS, and one of its diagnostic criteria (Arnold et al., 2018).

Secondary POTS

Is a term used to refer to a form of POTS that is associated with other ailments which are known to possibly result in autonomic neuropathy (AN), such as connective tissue disorders, DM, and sarcoidosis (Abdulla & Rajeevan, 2015; Grubb et al., 2006). These associated ailments include mast cell activation syndrome, Hypermobile Ehlers–Danlos Syndrome and Hypermobility Spectrum Disorder, Small Fiber Neuropathy and Complex Regional Pain Syndrome, Chronic Fatigue Syndrome, (Steinberg et

al., 2023).

Literature Search Methods

Literature searches were conducted from January 2022 to March 2023, to identify any peer reviewed research articles related to the phenomena of research interest. One of the inclusion criteria for this review is that articles selected for review, had to have been published within the past five years, except for seminal articles. Because of a paucity of peer-reviewed articles on the subjects of interest, the inclusion criteria were broadened to include other sources such as books, guides, and product-manuals. A review was done on carefully screened articles yielded by searches of the databases CINAHL, EMBASE, PubMed and Web of Science. After this review of the literature, other sources were consulted through August 2024 for any updates to the state of the science, for reflection in the discussion chapter.

These databases were searched for suitable peer reviewed articles related to the utility of EDA measures in assessments of POTS and hyperadrenergic POTS (HA-POTS). Articles were deemed suitable if they met the inclusion and exclusion criteria. Please, refer to Table 1 and Figure 1 (in this chapter), as well as to the Supplemental Tables 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, and 13 (in Appendix A), for details of how the various literature searches were conducted, as well as the specific search strings (and each of the combinations thereof) that were used in these searches, and details of the articles returned by the various literature searches. Figure 1 is an adaptation for this project of the “PRISMA Flowchart diagram for new systematic reviews which included searches of databases, registers and other sources”(Page et al., 2021). It shows the processes of article identification, article screening, determination of article eligibility, and selection of the articles for inclusion in the review. Supplemental Table 13 is a table of evidence (ToE), constructed from abstractions of content in the primary source manuscripts included.

Exclusion and Inclusion Criteria

Exclusion Criteria

Identifying, screening and then selecting out of the articles screened peer reviewed paper

related to the main concepts in the research question, was the imperative throughout the course of this review of the literature. As such, except for guides and manuals of relevance to this study, most non-peer-reviewed sources were excluded from further consideration. Documents published more than five years ago were excluded, unless they were either classic, classical, historical, landmark, pertinent, pivotal, or seminal publications of relevance to this proposed project. Determination of the relevance and/or seminal status of such papers, was based on a combination of factors, among which are, how many times it may have been cited or referenced by other scholars, impact on the field of research, and relation (or connection) to the constructs in this study.

Three constructs of interest shaped this literature review. One, the utility of EDA in the diagnosis of POTS. Two, the utility of EDA in the prognosis of POTS, and three, the utility of EDA in identifying any pathophysiological mechanisms of POTS. Thus, documents were excluded after careful consideration of their titles and abstracts (if any), for absence of a match with either of the aforementioned constructs. Articles written in a non-English Language that did not have an accessible English Language translation were also excluded. There was a preference for studies with human subjects because of the population of subjects in this study. However, because of a paucity of papers specific to the subject of this project, relevant animal studies were identified and screened for potential inclusion. Despite being identified and screened, whenever an identified EDA and/or POTS study, had no relationship to applications of EDA to the comparative or concurrent assessment, detection, evaluation, measurement, or screening of either asymptomatic and also symptomatic individuals for the diagnosis, mechanistic characterization, and prognosis of POTS, dysautonomia, cardiovascular disease, or at least to some health disorder or human experience that is akin to POTS (e.g., motion sickness), it was excluded from final inclusion in the literature review.

Inclusion Criteria

All documents returned by database, citation, or web searches, which had a name/title match, a

match with any or more of the three study constructs, or a match with such study constructs that was only observed after a careful examination of the full text of the document, were included. Five years of publishing recency was preferred. However, this was not a hard inclusion cut-off, because allowances were made for document pertinency and/or seminality, even for documents that were published more than ten years ago. Publications were identified, screened and ultimately included, despite the lack of a peer-review publication process, whenever they were directly germane to the subject under study, if in addition they were published by organizations involved in the manufacture, sale, and/or distribution of hardware equipment and software packages used in the assessment, detection, diagnosis, evaluation, measurement, and screening of patients suspected of dysautonomia (e.g., BIOPAC Incorporated, Goleta, California, and WR Medical Electronics Company, Maplewood, Minnesota).

Articles (or other types of sources) that pertain to the recording of measures of electrodermal activity during (or alongside) the administration of any component of an autonomic reflex screen (ARS) such as the heart rate deep breathing (HRDB) test, Valsalva Maneuver (VM) test, the head up tilt table (HUTT) test, or the quantitative sudomotor axon reflex test (QSART) or any of its variants such as the QSWEAT test, which is also known as the Q-Sweat test or the Quantitative Sweat Measurement System and is a commercial offspring of the QSART test from WR Medical Electronics Co., Stillwater, MN (Sletten et al., 2010), or related sudomotor function tests, such as the electrochemical conductance (EC) test, electrochemical skin conductance (ESC) test (Goel et al., 2017), or any sympathetic skin response (SSR) tests (be they a palmar or plantar or any other type of SSR test), have been deemed eligible for screening and possible inclusion in this review of the literature. Studies with recordings of EDA measures for evaluating post-op cardiovascular status were included because of the use of EDA in such projects.

Literature Review Synthesis

Articles on adrenergic, neuropathic and secondary POTS were reviewed, to identify any related diagnostic tests, and also appraise the various diagnostic criteria used in the determination of subtypes

of POTS. In furtherance of exploration of the utility of EDA measures as a potential diagnostic marker for POTS, literature on the accuracy of diagnostic tests were screened, to establish a gauge for the value of EDA measures in the diagnosis of POTS and other types of dysautonomia (Habbema et al., 2002; Kaye et al., 2005; Knottnerus & Muris, 2003). Also screened were articles on any studies undertaken to validate the use of EDA measures as an electrophysiologic index of health disorders or indeed, any other type of phenomena. Information pertaining to such validation studies was sought in review articles, database searches, and also via citation searches. Despite, the widespread study and utilization of EDA since the later end of the first half of the 19th Century (Dawson et al., 2001; Sequeira et al., 2021), there is still a scarcity of research for validation of the measuring function (i.e., measurement accuracy) of EDA as a physiologic measure (Geršak & Drnovšek 2020). The types and numbers of the documents included in this review of the literature, are presented in the results section of this chapter.

Results

Fifty three peer-reviewed primary source manuscripts have been included in the table of evidence (ToE) of this review of the literature (please see Supplemental Table 13). Also included in this review of the literature (albeit not in Supplemental Table 13), are the findings from two meta-analyses that are partially systematic reviews, two solely systematic review papers, two non-systematic review papers (one narrative review), two consensus statements, one book, one book chapter, nine guides, and six manuals. The contents of Supplemental Table 13 are an abstraction of data pertaining to the most study-relevant characteristics of the primary source articles included. Characteristics of each of the other documents included in this review of the literature (specifically, the secondary source articles such as the meta-analyses, systematic reviews, narrative reviews, scoping reviews, consensus statements, book, book chapter, guides, and/or recommended-guidelines, and manuals), are described in the following subsections of the results.

Each of the primary source articles that were selected for data abstracted into the table of

evidence in (see Supplemental Table 13), were chosen based upon how closely matched they are to any of the three main constructs in the research question, as well as how much they address (or are matched with) any of the subthemes in the research question. These constructs are one, the utility of EDA in the diagnosis of POTS, two the utility of EDA in the prognosis of POTS, and three, the utility of EDA in the mechanistic characterizations (or elucidation) of POTS. Some of the primary source articles abstracted into Supplemental Table 13, were also included, because of their relation to subthemes in the research question such as, the effect of certain medications on autonomic reflex screening (ARS) related tilt table test (TTT) results, any associations of EDA variations with patient reported symptoms during HUTT, pharmacological and/or non-pharmacological treatment of POTS, or applications of EDA to the management and/or treatment of various disorders and phenomena (e.g., the use of EDA Biofeedback in the management of health related disorders or other phenomena).

Synthesis One: A Synthesis of the Documents Reviewed and Included in Supplemental Table 13

Geographical Characteristics of the Studies Presented in the Table of Evidence

There is geographical breadth to the sources included, with the breakdown as follows; Canada (n = 3) (Balegh et al., 2019; Edwards et al., 2004; Schondorf et al., 1997;), China (n =3) (Tao et al., 2019; Wang et al., 2022; Yang et al., 2019), Germany (n = 4) (Boettger et al., 2010; Mönnig et al., 2004; Schach et al., 2022; Siepmann et al., 2003), India (n = 1) (Akbar et al., 2017), Iraq (n = 3) (Bari, 2020; Bari et al., 2020; Bari et al., 2018), Israel (n = 1) (Peleg et al., 2018), Italy (n = 1) (Ghiasi et al., 2020), Japan (n = 1) (Morishima et al., 2004), Jordan (n = 1) (Al abdi et al., 2018), Spain (n = 2) (Nandi et al., 2018; Zangróniz et al., 2017), Sweden (n = 2) (Kharraziha et al., 2019; Melander et al., 2018), Switzerland (n = 1) (Rodriguez et al., 2020), South Korea (n = 3) (Jang & Kim, 2018; Kim et al., 2022; Moon et al., 2018), United Kingdom (n = 3) (Kaye et al., 2005; Smyth et al., 2021; Wass et al., 2015), United States (n = 24) (Blitshteyn & Whitelaw, 2021; Boyce et al., 2016; Del Pozzi et al., 2019; Dusi et al., 2020; Enechukwu, M & Blitshteyn, 2018; Goldstein et al., 2002; Gunning III et al., 2019; Heyer et al., 2016; Kesserwani, 2020;

Kong et al., 2023; Kozel et al., 2009; Plash et al., 2013; Poh et al., 2010; Raikes et al., 2016; Posada-Quintero & Chon, 2019; Posada-Quintero & Chon, 2016; Posada-Quintero, et al., 2016; Raj et al., 2005; Taub et al., 2021; Teng et al., 2021; Taylor et al., 2022; Wickramasuriya & Faghih, 2020; Zamzow et al., 2016; Zhang et al., 2022). (see Supplemental Table 13).

Characteristics of Participants in Studies Reviewed in the Table of Evidence

All of the study participants in the studies included in the table of evidence, are human study subjects. The participants of one study had only Caucasian participants (Bari et al., 2020). Healthy volunteers only comprised the study population in five projects (Bari, 2020; Bari et al., 2020; Bari et al., 2018; Ghiasi et al., 2020; Kozel et al., 2009; Posada-Quintero & Chon, 2019). Eight of the primary source studies were case reports; four of them with just one patient (Del Pozzi et al., 2019; Kesserwani, 2020; Mönnig et al., 2004; Morishima et al., 2004), and of these four, two of them had a female study participant each (Kesserwani, 2020; Mönnig et al., 2004), and of the other two, each had a male study participant (Del Pozzi et al., 2019; Morishima et al., 2004). Eight of the non-case-report studies, have reported a female majority in their respective populations of study participants (Blitshteyn & Whitelaw, 2021; Heyer et al., 2016; Gunning III et al., 2019; Kharraziha et al., 2019; Kim et al., 2022; Posada-Quintero & Chon, 2019; Wang et al., 2022; Zhang et al., 2022), while five of the non-case-report studies have a male majority among the study participants (Bari et al., 2018; Boettger et al., 2010; Boyce et al., 2016; Dusi et al., 2020; Wickramasuriya, 2020). The population of two non-case-report study is comprised only of males (Kaye et al., 2005; Taylor et al., 2022). (see Supplemental Table 13).

Populations in seventeen of the studies had diagnoses of POTS (Blitshteyn & Whitelaw, 2021; Del Pozzi et al., 2019; Enechukwu & Blitshteyn, 2018; Goldstein et al., 2002; Gunning III, 2019; Kesserwani, 2020; Kharraziha et al., 2019; Kim et al., 2022; Moon et al., 2018; Morishima et al., 2004; Plash et al., 2013; Raj et al., 2005; Rodriguez et al., 2020; Taub et al., 2021; Tao et al., 2019; Wang et al., 2022; Zhang et al., 2022). The population of one study had COVID-19 infections as well (Blitshteyn &

Whitelaw, 2021). One study population had cardiomyopathy (Dusi et al., 2020). The population of another study had signs and symptoms of motion sickness (Smyth et al.,). In one of the case reports with just one patient, the study subject was diagnosed with POTS as well as Asymptomatic Brugada Syndrome (Morishima et al., 2004). One female participant had inappropriate sinus tachycardia (Mönnig et al., 2004), while one male patient had Asymptomatic Brugada Syndrome (Morishima et al., 2004). One of the study populations with POTS also concurrently suffered for neurocardiogenic syncope (Goldstein et al., 2002). In one study, 202 study participants had a diagnosis of cardiovascular autonomic neuropathy (CAN) (Akbar et al., 2017). Furthermore in the Teng et al. (2021) study, the six study subjects suffered from chemotherapy and radiation linked cardiovascular autonomic dysfunction (CAD). (see Supplemental Table 13).

An Overview of the Study Types of the Manuscripts Listed in the Table of Evidence

All of the primary source studies included in this literature review are quantitative studies. They range in design from four single patient case reports (Del Pozzi et al., 2019; Kesserwani, 2020; Mönnig et al., 2004; Morishima et al., 2004), to four case reports that were also case series (Blitshteyn & Whitelaw, 2021; Enechukwu & Blitshteyn,2018; Rodriguez et al., 2020; Teng et al., 2021), and four experimental studies (Moon et al., 2018; Siepmann et al., 2003; Taub et al., 2021; Zamzow et al., 2016). One study had a descriptive, cross-sectional and observational design (Bari et al., 2020), while three of the studies had multiple data collection points and were also prospective studies (Dusi et al, 2020; Siepmann et al., 2003; Smyth et al., 2021). One of the studies was a conference report (and oddly enough the number of study participants is not stated in this report) (Peleg et al., 2018). Three of the experimental studies had a randomized, double-blinded, and cross-over design (Siepmann et al., 2003; Taub et al., 2021; Zamzow et al., 2016). While one of the experimental studies had a randomized design, as well as a 2 X 2 factorial design, and furthermore it was a three month long clinical trial of a novel medical therapeutical regimen in individuals with POTS (Moon et al., 2018). In total, 11 out of the 45 non-case report type studies, had

a prospective study design (Dusi et al, 2020; Heyer et al., 2016; Melander et al., 2018; Moon et al., 2018; Poh et al., 2010; Schach et al., 2022; Siepmann et al., 2003; Smyth et al., 2021; Tao et al., 2019; Taub et al., 2021; Zamzow et al., 2016). (see Supplemental Table 13).

Synthesis Two: A Synthesis of the Other Documents Examined and Included in this Literature Review

Review Papers

One meta-analysis (Casanovas-Ortega et al., 2022), which is also a systematic review paper states that in a synthesis of the results of 19 studies, which included 550 participants and 1115 seizures, all of these papers revealed an increase in EDA in the ictal as well as post-ictal periods, whereas just three revealed pre-ictal EDA responses. This meta-analysis revealed a collective EDA response incidence of 82 out of 100 seizures (95% CI 70-91). The tonic-clonic seizures (both generalized the tonic-clonic seizures (GTCS) and focal to bilateral tonic-clonic seizures (FBTCS)), engendered EDA responses of longer duration and greater amplitude, in comparison with those evoked by focal seizures (excluding FBTCS) (Casanovas-Ortega et al., 2022). Which shows that measures of EDA may be used to distinguish between types of seizures (Casanovas-Ortega et al., 2022).

Another meta-analysis cum systematic review manuscript, comprising of a synthesis of findings from 21 studies, states that this topical assessment showcases the potential utility of GSR biofeedback therapy, and would inspire (or lead to), as well as guide (or shape), formulation of ideal study designs, for the larger scale studies that are now required to establish the utility of this non-invasive, and non-pharmacological interventional approach, much more definitively for use in the management of drug-resistant epilepsy (Nagai et al., 2019). Four of the studies appraised in this particular meta-analysis were interventional trials, which enrolled 99 individuals with drug resistant epilepsy between them. Three of the studies in this appraisal had a cohort of controls and reported a therapeutic benefit from the use of EDA biofeedback (Nagai et al., 2019). The difference in biofeedback control (i.e., in the seizure frequency percentage), ranged between −54.4 and −74.0%, "…with an overall weighted mean difference of −64.3%

(95% CI: −85.4 to −43.2%). The response rates (proportion of patients manifesting >50% reduction in seizure frequency) varied from 45 to 66% across studies" (Nagai et al., 2019, p. 1). This indicates that the EDA Biofeedback, is an effective therapeutic intervention for the reduction of the number of seizures in persons suffering from drug-resistant epilepsy, and demonstrates another potential application of EDA to patient care (Nagai et al., 2019; Nagai et al., 2004).

One of the four systematic review manuscripts, synthesized findings from 36 studies, with the authors stating that only three of these studies (one of them being a Class II, while the other two were Class IV) did not reveal among populations of individuals with a history of concussions, abnormalities in autonomic nervous system function (Pertab et al., 2018). This systematic review concludes that there are observable negative impacts upon ANS functioning, occasioned as sequelae to a concussion (Pertab et al., 2018). It states with respect to EDA (in terms of skin conductance) that the sympathetic nervous system may be stimulated via an application of environmental stressors (e.g., cold or loud noise), or the application of physical stressors (e.g., exercise or pain). The authors state that ANS-mediated changes in heart rate and the sweat response (measured via skin conductance), are either directly measurable, or may be assessed via contrasting skin conductance levels in pathological cases with controls to identify anomalous autonomic responses (Pertab et al., 2018).

Another systematic review paper and narrative synthesis, screened 1,287 papers, included 77 of them, and states that these papers on the average, consistently found that a muted EDA response was a typical characteristic of EDA measures recorded from individuals afflicted by depression (Sarchiapone et al., 2018). Furthermore this review states that data from studies reviewed showed preliminary evidence that EDA surveillance may facilitate identification of different phases of mood disorders (Sarchiapone et al., 2018). It states additionally that some of the studies reviewed offered evidence of the utility of EDA in distinguishing acutely suicidal individuals from depressed individuals, who despite their depression, were not highly suicidal. Authors of the review assert that even though the utility of EDA as a sensitive

and valid marker of suicidal ideation, attempted suicide, and violent suicidal behavior has been well established, the antidepressant treatment received by the individuals with depression, also appears to exert a certain degree of confounding influence (Sarchiapone et al., 2018).

One review paper notes that there is a difference in EDA responses between persons who present with spontaneous and habitual reflexes (also known as labiles), versus those with few and non-habitual EDA reflexes (Grapperon et al., 2012). Such blunting of the EDA reflex has also been observed in antisocial persons, although for such individuals a steep decline in primeval behavioral reticence has been posited as an underlying mechanism (Grapperon et al., 2012). Another review (a narrative review) of the utility of EDA in acupunctural remedies, highlighted the heterogeneity of some approaches to EDA assessments and the differences between standard clinical practices and the scientific evidence behind such practices (Colbert et al., 2011). It also presents pilot data that indicates that testing for EDA at auricular acupuncture points may differentiate pathology-related acupuncture points from non-pathology-related points, reported correlations between reduced skin conductance and fatigue (or low energy), and stated that EDA testing at the Jing-Well acupuncture points, as well as on the tips of the fingers and toes, could facilitate the monitoring of the effectiveness of acupuncture treatment (Colbert et al., 2011). However, the evidence presented in this review does not support the use of VEGA testing for allergic status (Colbert et al., 2011).

Consensus Statements

One of two consensus statements selected for inclusion in this review of the literature (Sheldon et al., 2015), provides a detailed overview of the various approaches to the diagnosis and treatment of POTS, inappropriate sinus tachycardia (IST), and vasovagal syncope (VVS), in the “2015 Heart Rhythm Society (HRS)’ Expert Consensus Statement on the Diagnosis and Treatment of Postural Orthostatic Tachycardia Syndrome, Inappropriate Sinus Tachycardia, and Vasovagal Syncope”. It defines subtypes of POTS, and remains one of the reference standards vis-à-vis the establishment of consensus diagnostic

criteria for POTS (Sheldon et al., 2015). This consensus statement describes some of the most widely proposed pathophysiologic mechanisms of POTS, and also proffers certain therapeutic regimens for the management of patients with POTS. Notably absent however, was any mention of the use of EDA in the diagnosis, prognosis, or mechanistic characterization of POTS (Sheldon et al., 2015). This suggests there is a gap in the science here, one that this PI proposes to attempt to bridge, via means of the findings of this proposed PhD project.

In the second consensus statement, which is endorsed by the American Autonomic Society, AAS, the American Academy of Neurology, AAN, and the International Federation of Clinical Neurophysiology, IFoCN (Cheshire et al., 2021), recommendations for the guidance of clinical electrodiagnostic testing are presented. In contrast with the Sheldon et al. (2015) consensus statement, in addition to giving clinicians and researchers an overview of the various methods for autonomic function testing, it also detailed the use of autonomic function deficit scoring scales such as the composite autonomic severity score (CASS), which is used for the grading and localization of autonomic deficits (Cheshire et al., 2021). This review makes mention of the catalytic role the novel technology of photoplethysmography played in changing autonomic testing from a mere research tool to a widely used clinical tool (Cheshire et al., 2021). Yet, it barely makes mention of the utility of EDA as a tool for either the diagnostic, prognostic, or mechanistic investigation of POTS, which suggests yet again that herein lies another gap in the science. When this consensus statement mentioned EDA, it only did so in reference to it being allegedly one of a number of "…tests of unproven validity" (Cheshire et al, 2021, p. 673) for the detection of autonomic function impairment (Cheshire et al., 2021). The authors stated that even though use of non-invasive measures of skin conductance to appraise autonomic dysfunction is tempting because of its simplicity, administration of this test is confined to assessments of sweat gland function in areas that have large sweating output, such as the palms of a test-subject's hand and/or the soles of their feet, which are highly responsive to emotional activation. Because they do not directly appraise the integrity of sudomotor axons, they are

in the view of Cheshire et al., not true tests of an individual's autonomic function (Cheshire et al., 2021).

This lack of confidence in the utility of skin conductance in diagnosis of autonomic dysfunction, may however, be deemed an inadvertent invitation to pursue the sort of research that might someday turn EDA into a major catalyst, for a transition in the current clinical modalities in place for the diagnosis, study and treatment of POTS (Cheshire et al., 2021). However, this consensus statement did mention a use of measures of sympathetic skin response (SSR) in determination of autonomic function. Yet it states that because SSRs are activated by an emotional mechanism instead of a thermoregulatory mechanism, they are quite variable, and only have a modest degree of sensitivity and specificity, they have limited utility in the diagnosis of sudomotor nerve (or small nerve fiber) impairment (Cheshire et al., 2021).

Guides and Guidelines

One of the nine guides evaluated, is a guide from BIOPAC Inc., and pertains to instructions on how to set up and use the MP System; an expandable data acquisition device designed to serve multiple purposes, among which are playing the roles of an onscreen recorder, an X/Y plotter and an oscilloscope (BIOPAC Systems Inc., 2012). The MP System Hardware Guide contains detailed instructions, regarding how to add modules for the acquisition of data measures pertinent to autonomic function testing, such as blood pressure, electrodermal activity, finger pulse volume (which is measured by plethysmography), heart rate, respiration, skin temperature, and compression-grip strength (BIOPAC Systems Inc., 2012).

Another guide contains instructions on medications (especially anticholinergic) that should be held at least 48 hours before participation in an ARS (UCLA CAC, n.d.). It also briefly presents a rationale for holding anticholinergic medications before undergoing an ARS (UCLA CAC, n.d.). One clinical handout issued by the UCLA Cardiac Arrhythmia Center (CAC), which is titled "UCLA Autonomic Nervous System (ANS) Testing Instructions 2018", presents CAC patients scheduled for ARS appointments, with a list of instructions about what to do before their ARS appointments, as well as what to expect during their ARS visit. It provides patients with some of the pathophysiologic underpinnings of what occurs during an ARS

in a concise and succinct manner (albeit laid out in simple layman terms), which is quite instructive, even to a researcher such as the PI (UCLA CAC, 2018).

Six more guides were included in this literature review, because their content is pertinent to at least one of the constructs imbedded in the research question. Two of them are peer-reviewed journal manuscripts that contain clinical and/or laboratory guidelines for the administration of autonomic reflex screens; including the orthostatic (or postural) challenge of a head up tilt-table test (Novak, 2011; Thijs, 2021). In Thijs (2021), guidelines for conducting HUT tests as well as other "…provocative cardiovascular autonomic tests in conditions that may cause transient loss of consciousness" (Thijs, 2021, p. 1) in some tested individuals are presented. Novak (2011) gives an overview of various approaches to quantitative investigations of autonomic dysfunction in a manuscript titled "Quantitative Autonomic Testing" (Novak, 2011, p. 1). Therein he described various testing protocols and normative scales that are used to detect, assess, and measure indicia of dysautonomia. The composite autonomic severity score (CASS) as well as all its components are described, together with various autonomic function tests. Among these are, the HRDB test, HUTT test, VM test, and quantitative sudomotor axon reflex test (QSART), which are the tests administered to the patients scheduled for ARS testing at the UCLA CAC (Novak, 2011; UCLA CAC, 2018).

Another guide titled "A Fancruft Guide to the Autonomic Reflex Screening", provides detailed instructions for the administration of the four above-listed ARS tests via use of equipment manufactured by BIOPAC Inc., Goleta, California, United States of America, CNSystems Medizintechnik AG, Graz, Austria, and WR Medical Electronics Co., Maplewood, Minnesota, United States of America (BIOPAC Systems Inc., 2012; CNSystems, 2012; Hale, 2018; WR Medical Electronics Co., 2018a; WR Medical Electronics Co., 2018b; WR Medical Electronics Co., 2017; WR Medical Electronics Co., 2016). In it Hale (2018), states that physiologic variables such as blood pressure, electrodermal activity, heart rate, skin temperature and respiratory rate, are known to be highly impacted by an individual's emotional state. Therefore, he recommends that an administrator of tests during an ARS, should minimize all controllable

parameters that have a potential to skew the accuracy and/or precision of test results. This guide to ARS testing contains information that is pertinent to the analyses of the data acquired, while administering the various tests it describes. Furthermore, interwoven into these testing protocols, are nuggets of valuable mechanistic insights and rationales for some of the testing steps (Hale, 2018).

According to Grubb et al. (2006), while many individuals with POTS may present with a similar degree of functional impairment as that which is experienced by persons with either congestive heart failure (CHF), or chronic obstructive pulmonary disease (COPD), oftentimes they are misdiagnosed as cases of individuals that are suffering from anxiety or panic disorder (Grubb et al., 2006). This guide has developed and presented in its Table 1, a grading system for assessing severity of orthostatic intolerance that is alleged by Grubb et al., to be akin to a grading system that is used for an evaluation of the extent of heart failure (Grubb et al., 2006). Noting that the then current diagnostic criteria for POTS was based in part upon an increase in heart rate of at least 30 bpm within 10 minutes of a HUTT test, Grubb et al., 2006 hold the view that such a focus upon heart rate variation during HUTT testing, may fail to consider other factors, such as gastrointestinal function, thermoregulatory function, and/or an individual's sweat response or sweating function (Grubb et al., 2006).

Two of these guides or guideline documents present information pertaining to the use of EDA in various circumstances. Notably among these applications of EDA in clinical care settings, and in research settings, are a description of the most infrequently used method of recording EDA data (i.e., the method of) "exosomatic recording with alternating current…" (Boucsein et al., 2012, p. 1), which back in the year 2012, was a rarely used, yet quite promising method for acquisition of EDA data (Boucsein et al., 2012).

In their often cited 2015 guide for the analysis of EDA data, which is titled "A Guide for Analysing Electrodermal Activity (EDA) & Skin Conductance Responses (SCRs) for Psychological Experiments (Revised version: 2.0)", Braithwaite et al. (2015), lay out various not just a concise (yet quite substantial) history of the study and applications of EDA measures to research and clinical care, but they also point

out avenues for future applications and research (Braithwaite et al., 2015). One notable feature of the EDA information that is presented in this guide, is that it describes the use of equipment and software manufactured and developed by the company BIOPAC Inc. This was quite useful, because a substantial number of the hardware equipment employed in the acquisition of the data used in this PhD project, as well as the software app (AcqKnowledge) used in extracting and thereafter analyzing the EDA data, were either developed or manufactured, and/or vended by BIOPAC (Braithwaite et al., 2015).

Keenly interesting and also quite intriguing to this researcher, amidst the vast treasure trove of information within this guide, is a revelation by Braithwaite et al. (2015) that despite the focus upon and interest generated by the high frequency phasic EDA components such as skin conductance responses (SCRs), these constitute only a small part of the entire EDA complex, such that there remains a plethora of EDA components to be examined, with an eye to mining such frequently overlooked EDA components for valuable raw data, statistical results, and research findings that may eventually prove to be of clinical significance (Braithwaite et al., 2015).

Manuals

Six manuals were reviewed and included in this literature review, because of the information they provide that is pertinent to the performance of diagnostic tests. One of these manuals, is an operator's manual from the makers of the continuous non-invasive arterial pressure system, which is used to measure blood pressure continuous via application of photoplethysmography through use of a finger-cuff blood pressure device. This device also uses a regular noninvasive blood pressure (NBP) cuff for calibration of the CNAP finger-cuff system. The CNAP system measures the pulse rate in tandem, and contains information on the monitoring of patient hemodynamics, which are an important feature of autonomic function testing (CNSystems, 2012).

Another manual is an instruction manual for a set of experiments that examine galvanic skin response to cheating during examinations (Wagner & Wagner, n.d.). Four manuals from WR Medical

Inc., contain information on the use of equipment manufactured by WR Medical Inc., for conducting autonomic function tests. The first of these titled “TestWorks catalog 6-16 Brochure”, deals with instructions for the use of the TestWorks software application for recording data from patients during the course of administering autonomic reflex screening (ARS) tests, how to extract such data from data files, signal traces and other graphical images. The detailed instructions and testing protocols yield valuable insights into autonomic dysfunction, as well as forms of dysautonomia, e.g., POTS (WR Medical Electronics Co., 2016).

Yet another manual, this one titled “TestWorks user manual: Neurological testing management software, version 3.2 user guide”, contains information pertaining to how to use the TestWorks app for the acquisition, extraction and analyses of autonomic function data with a neurological character and/or focus (WR Medical Electronics Co., 2017). In the manual, which is titled “Q-SWEAT: Quantitative sweat measurement system, 01/17/18 instructions for use”, detailed instructions are given for administering tests with the QSWEAT device. This is a test for sudomotor function, and this manual contains useful information on the assessment of dysfunction in the small nerve fibers via tests of an individual’s sweat response (WR Medical Electronics Co., 2018b). Finally, the laboratory manual titled “HRV Acquire: Heart Rate Variability Acquisition, 01/26/18 instructions for use”, contains information about the acquisition, extraction and analysis of data that is quite pertinent to determinations of heart rate variability (HRV). Because HRV is an important feature in the diagnostic criteria for cardiovascular autonomic neuropathy (CAN), which is related to a dysautonomia such as POTS, the PI found the information in this manual quite instructive (WR Medical Electronics Co., 2018a). Furthermore, the HRV Acquisition module is used during ARS appointments, for data acquisition during the course of administering the heart rate deep breathing (HRDB) test and the Valsalva Maneuver (VM) test (WR Medical Electronics Co., 2018a).

Book and Book Chapter

In a chapter titled “The Electrodermal System”, which was published as Chapter 8 of the 2nd

Edition of “The Handbook of Psychophysiology” (and which was edited by John T. Cacioppo, Louis G. Tassinary and Gary G. Berntson) in the year 2001, Dawson et al. (2001), provide a detailed overview of EDA, which covers the history of its discovery and use, in a manner that makes the subject accessible to students, researchers, and/or practitioners, who might not be specialists in the use of this particular electrophysiologic measure (Dawson et al., 2001). The primary takeaway from this book chapter that is pertinent to this PhD project, is that it focuses upon uses of the exosomatic method of EDA use, wherein recordings of skin resistance (or of its reciprocal, which is known as skin conductance) are made, via the placement of electrodes (usually at two points) on an individual’s skin to read the ohmic effect caused passage of an electric current across the surface of the individual’s skin (Dawson et al., 2001). Also, a description of the exosomatic method for acquiring an EDA signal trace is relevant to this dissertation study, because it is the most widely used method for EDA data collection, was the means used to obtain the data the PI for this dissertation project.

Similarly Boucsein, who has been dubbed the father of modern EDA research in some scholarly circles (Boucsein et al., 2012), presents a thorough overview of various applications of EDA to the study of diseases, health disorders and other kinds of non-health related phenomena in the second edition of his 1992 book, which is titled “Electrodermal Activity” (Boucsein, 2012). Therein, in Chapter 2 and also in Chapter 3, methods for recording EDA and applications of EDA are addressed. In keeping with advances that have occurred since publication of the first edition in 1992, the 2012 edition includes new material on the use of brain imaging techniques such as functional magnetic resonance imaging (fMRI) as well as positron emission tomography (PET) in tandem with EDA, which offers new insights into the underlying brain mechanisms of EDA. These parts of the second edition are quite pertinent to the PhD dissertation project, vis-à-vis the construct of “the utility of EDA in explorations of the mechanistic characteristics of POTS” (Boucsein, 2012). Also relevant to the above-stated construct, are the parts of Nagai et al., 2004, and Braithwaite et al., 2015, which pertain to the association of various EDA complexes (e.g., the tonic

electrodermal responses or SCLs, and the phasic electrodermal responses or SCRs), with different neural mechanisms or systems (Braithwaite et al., 2025; Nagai et al., 2004).

Discussion: Gaps and Conclusion

This review of the literature has been driven by the goal of appraising the state of the science on the utility of EDA as a marker of the sympathetic nervous system in investigations of the diagnosis, prognosis and mechanistic underpinnings of POTS. As such, it has involved literature searches guided by three main constructs. The first of these is *the utility of EDA in studies of the diagnosis of POTS*. Second among these constructs is the utility of EDA in studies of the prognosis of POTS. Finally, the third construct is *the utility of EDA in explorations of underlying pathophysiological mechanisms of POTS*.

Gaps

This review reveals gaps in the literature in the area of applications of EDA to investigations of POTS, whether such investigations pertain to the diagnosis, prognosis, or underlying pathophysiological mechanisms of POTS. Only two documents were found that report the findings of studies, wherein EDA measures were used to investigate characteristics of health disorders during head up tilt table (HUTT) testing. One of these studies is a manuscript by Edwards et al., which was published in 2004 (and which among other variables, examined the utility of EDA measures in hypothesis testing). The other study was part of a dissertation (i.e., the third manuscript in a dissertation) submitted by a PhD candidate at McGill University, in Montreal, Quebec, Canada. It reveals findings from a study of the utility of EDA responses, in mapping out the effects of HUTT testing upon the EDA levels, of persons with a history of vasovagal syncope (VVS). These EDA values were measured over the course of a HUTT test (Balegh, 2019). Due to a dearth of science on the use of EDA measures in studies of POTS and its subtypes, the PI proposed a PhD dissertation study that was designed to investigate the utility of electrodermal measures of sympathetic function, in explorations of the diagnosis, prognosis and mechanisms of POTS. These measures of EDA, were recorded during various autonomic function tests, performed during autonomic reflex screening.

Conclusion

Electrodermal activity is an electrophysiologic phenomenon that has been widely studied from as far back in time as 1849, and it has been applied to investigations of various diseases, disorders, and phenomena. Some of these applications include the use of EDA as a measure of the effects of emotions and/or feelings, such as aggression, anger, anxiety, calm, disgust, fear, happiness, horror, joy, nausea, revulsion, or tranquility on the sympathetic nervous system (Balegh, 2019; Boucsein et al., 2012; Boucsein, 2012; Dawson et al., 2001; Smyth et al., 2021). It has been used to study compulsive gambling and other addictive behaviors (Agren et al., 2019; Rocco et al., 2020).

Similarly, it has been employed in investigations of age-related differences in diseases (or health disorders), attention-span (or attentiveness), autism spectrum disorder, behavioral inhibition systems, biofeedback control of seizure-frequency, cheating, dementia, epilepsy, falsehood, gender-related differences in diseases (or health disorders), motion-sickness, pain, schizophrenia, sleep apnea, stress, threat-response, to mention but a few of the various uses of EDA (Baeuchl et al., 2019; Balegh, 2019; Bari, 2020; Bari et al., 2020; Bari et al., 2018; Boucsein, 2012, Boucsein et al., 2012; Boyce et al., 2016; Braithwaite et al., 2015; Critchley, 2002; Dawson et al., 2001; Edwards et al., 2004; Ghiasi et al., 2020; Kozel et al., 2009; Melander et al., 2018; Peleg et al., 2017; Smyth et al., 2021; Taylor et al., 2022; Nagai et al., 2019; Nagai et al., 2004; Venables & Christie, 1980; Zamzow et al., 2016). However, searches of the literature revealed only two studies, wherein EDA measures had been taken concurrently with the administration of a head-up tilt table test, and then assessed for pertinent associations (Edwards et al., 2004; Balegh, 2019).

Findings from one of these publications, were reported in a PhD dissertation submitted in 2019 by a doctoral student at McGill University in Montreal, Quebec, Canada, which is titled “Vasovagal Syncope: A Psychophysiological Evaluation”. Therein, the author stated that Edwards et al. (2004) had suggested that EDA in HUTT testing, could be reflecting “…centrally mediated processes of…” vasovagal

syncope (VVS) (Balegh, 2019, p. 129). In the third of the Balegh (2019) dissertation manuscripts, the EDA related finding was that mean EDA responses measured at baseline and during HUTT testing, revealed a significant difference between individuals with a purely emotive history of/trigger for VVS, those with a purely orthostatic VVS response, and those with a mixture of an emotive and orthostatic VVS response during HUTT testing (Balegh, 2019).

Persons with an exclusively emotions-based history of VVS displayed notable EDA during the initial stages of HUT. However, the results also indicate that clinical history is not related to the absence or presence of EDA during the occurrence of presyncopal events (Balegh, 2019). The results also indicate that individuals with a total peripheral resistance (TPR) reactor mediated drop in their blood pressure, were more likely to display EDA prior to the onset of presyncope (Balegh, 2019). Those with exaggerated cardiovascular responses upon initial HUT such as marked heart rate and blood pressure changes, were shown to be more likely to display EDA at the same time (Balegh, 2019).

As such, one of major findings of this study, is that there is a strong association between the probability of a presyncopal episode, and the occurrence of notable EDA changes toward the conclusion of a HUTT test (Balegh, 2019). The author therefore holds the view that the measures of EDA recorded during the early and late stages of HUTT testing, appear to exhibit variable processes, such as the occurrence of emotional distress early on during HUT, versus an occurrence of central nervous system (CNS) activity associated with presyncope toward the end the HUTT testing period (Balegh, 2019). These findings from the Balegh (2019) study opens up the possibility of using EDA as an investigative measure for elucidating underlying pathophysiological mechanisms of VVS.

Similarly, Edwards et al. (2004), found the sweat response (which when assessed by EDA is an index of sympathetic nervous system (SNS) activity), tends to occur before the emergence of HUT induced VVS, even though the levels of the blood pressure, cerebral blood velocity and expired carbon dioxide of the patient undergoing HUT at that time, has not yet changed (Edwards et al., 2004). As such,

Edwards et al. (2004) concluded that on account of the timing, the sweat response (and its associated EDA), is unlikely to be a consequence of stress felt by such patients, either prior to, or after experiencing an episode of vasovagal syncope (Balegh, 2019; Edwards et al., 2004). However, the pathophysiological mechanism underlying this phenomena of heightened EDA together with increased sweating before and following a VVS, remains unknown. As such further research is required to tease out the etiology. According to Atack (n.d.), the psychoanalyst Carl Jung observed via means of an old-fashioned galvanometer, while asking some emotionally penetrating questions of his patients during interviews conducted in 1904 that EDA rather dramatically and specifically varied, such that he was moved to make exclamation, “Aha, a looking glass into the unconscious!” (E-Meter section, para. 2). It was hoped that the data collected, results generated by statistical analyses of such data, as well as the findings gleaned via an interpretation of such results in the course of conducting this proposed study, would yield such insights into the diagnosis, prognosis and/or still mysterious pathophysiological mechanisms of POTS that the PI might similarly be moved to exclaim in a paraphrased version of Carl Jung’s often quoted exclamation, “Aha, (here at last is an EDA based) looking glass into the (diagnosis, prognosis, and etiological mysteries of the underlying mechanisms of POTS)!”

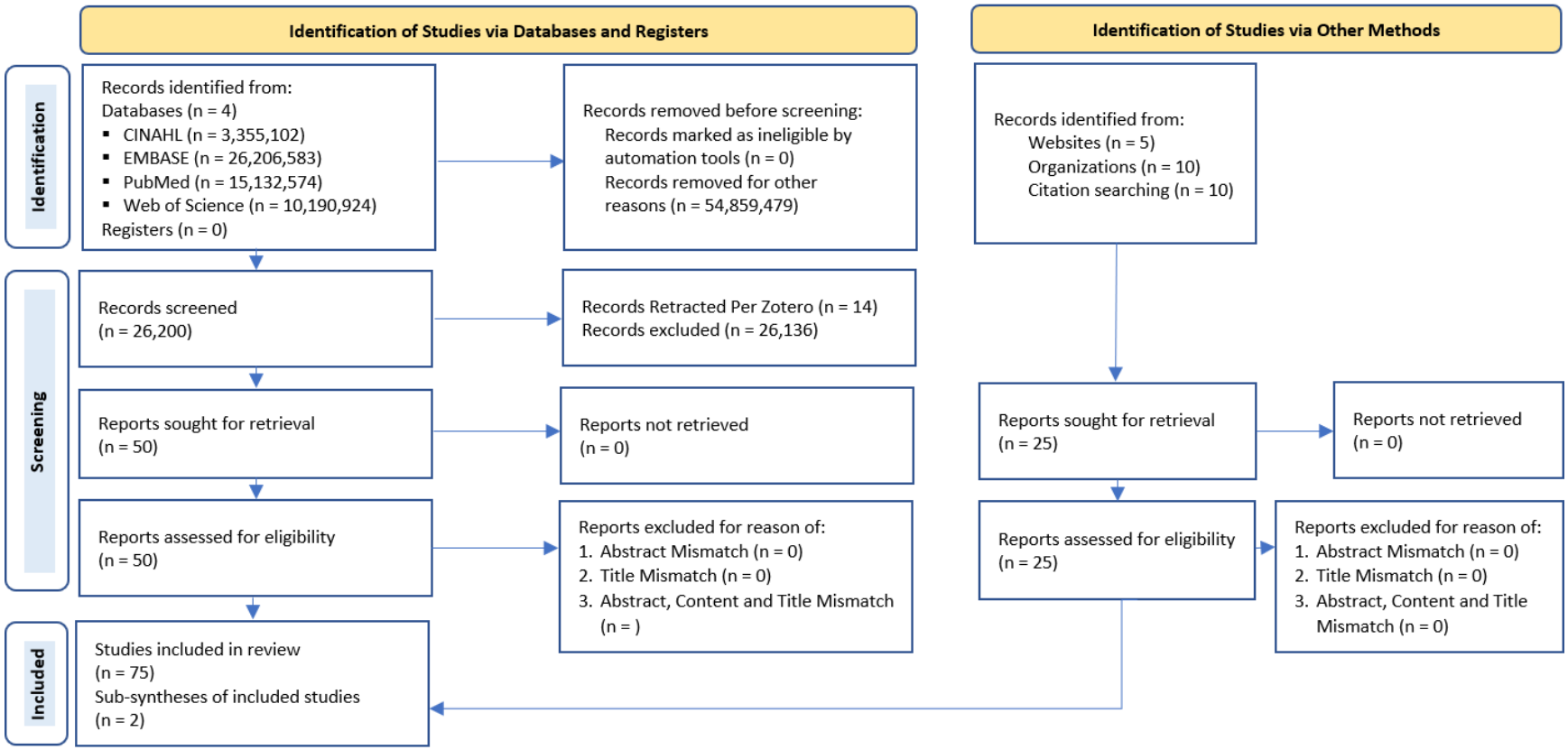
Table 1

Table of Reviewed Sources: Tally of Primary Articles, Secondary Articles, Books, Guides and Manuals Reviewed

Type of Source	**Numbers of Sources Included in Review of the Literature**
Primary Articles on the Diagnosis, Prognosis and/or Mechanisms of POTS (with or without EDA use)	53
Secondary Articles on the Diagnosis, Prognosis and/or Mechanisms of POTS (with or without EDA use)	3
Books on the Uses of EDA	1
Book Chapters on the Uses of EDA	1
Consensus Statements	2
Guides for Administering AFTs for the Diagnosis, Prognosis and/or Mechanisms of POTS	9
Manuals for Administering AFTs for the Diagnosis, Prognosis and/or Mechanisms of POTS	6
Total Number of Sources Included	75

Figure 1

Search Methods Flowchart Based on the "PRISMA 2020 flow diagram for new systematic reviews which included searches of databases, registers and other sources"



Note: The search methods flowchart used in the review of the literature. Adapted from "The PRISMA 2020 statement: an updated guideline for reporting systematic reviews," by M. J. Page, J. E. McKenzie, P. M. Bossuyt, I. Boutron, T. C. Hoffmann, C. D. Mulrow, L. Shamseer, J. M. Tetzlaff,

E. A. Akl, S. E. Brennan, R. Chou, J. Glanville, J. M. Grimshaw, A. Hróbjartsson, M. M. Lalu, T. Li, E. W. Loder, E. Mayo-Wilson, S. McDonald, . . . D. Moher, 2021, *BMJ (Clinical research ed.), 372*(1), p. 71 (https://doi.org/10.1371/journal.pmed.1003583). Copyright 2021 by the PRISMA Group. Adapted with permission.

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CHAPTER 3

CONCEPTUAL FRAMEWORK

Chapter 3: Conceptual Framework

This investigation was focused on the exploration of measures of electrodermal activity (EDA) (which is also known as galvanic skin response (GSR) and skin conductance (SC)), as a marker of sympathetic nervous system activity in the diagnosis and prognosis of postural orthostatic tachycardia syndrome (POTS), exploration of the mechanisms underlying POTS, and determination of the POTS-subtype hyperadrenergic postural orthostatic tachycardia syndrome (HA-POTS). In the course of performing one of his duties as a graduate student researcher (GSR) and registered nurse assigned to the University of California Los Angeles (UCLA)'s Cardiac Arrhythmia Center (CAC), the principal investigator (PI) was assigned the tasks of finding and studying the medical records of cardiovascular dysautonomia patients referred to the UCLA CAC for autonomic reflex screening (ARS), inclusive of head-up tilt-table testing (HUTT) or a tilt table test (TTT), which is performed with a motorized tilt table. While performing these tasks, the PI administered and observed full sequences of autonomic reflex screening tests, stand-alone tilt table tests (which are partial autonomic reflex screens), as well as complete and partial sequences of cardiometabolic testing, which included the administration of pulmonary function tests (PFTs).

Informed by these experiences, the PI decided to investigate the utility of electrodermal activity (EDA) signal traces, as an additional non-invasive measure for the diagnosis and prognosis of postural orthostatic tachycardia syndrome (POTS), and also to explore any insights an analyses of EDA measures may yield on the pathophysiological mechanisms of POTS. This exploratory project lies within the scope of diagnostic, prognostic and mechanistic research (Sackett et al., 1991; Knottnerus & Buntinx, 2009). As such the conceptual models and theoretical frameworks underpinning this study, are Dr. David L. Sackett's, Dr. Brian R. Haynes' and Dr. John J. You's "Architecture of Diagnostic Research" (Sackett & Haynes, 2002; Haynes & You, 2008), as well as Dr. Peter Kent's, Dr. Carol Cancilliere's, Dr. Eleanor Boyle's, Dr. John David Cassidy's and Dr. Alice Kongsted's ideas on prognostic research, which were

published in a manuscript titled “A Conceptual Framework for Prognostic Research” (Kent et al., 2020). It should be noted that the “Architecture of Diagnostic Research” is the main conceptual/theoretical foundation for this study. However, this proposed inquiry, intersects all of the four metaparadigms of nursing, in that it touches upon the person (as the recipient of care and self-reporter of symptoms), such a person’s environment (e.g., whether the care settings are primary, secondary or tertiary), their health, and nursing, i.e., with respect to the nurse’s role as clinician, diagnostician, prognostic researcher, as well as a mechanistic and/or pathophysiologic researcher (Branch et al., n.d.; Treseler, 1994; Gleason et al., 2017; Nikfarid et al., 2018).

Architecture of Diagnostic Research

In diagnostic testing, the main goal is to distinguish between what is considered to be clinically normal, and what is considered abnormal (Murphy, 1972; Sackett & Haynes, 2002; Haynes & You, 2008). As such defining what is normal and what lies within the normal range is the fundamental matter for consideration in diagnostic research (Murphy, 1972; Sackett et al., 1991; Sackett & Haynes, 2002; Haynes & You, 2008). In their 2009 edition of the Architecture of Diagnostic Research, Haynes and You note the importance of realizing that differing definitions of normality are widely utilized in clinical medicine. Six such definitions are known to the writers, who credited five of these definitions to Tony Murphy (Murphy, 1972; Sackett et al., 1991; Sackett & Haynes, 2002; Knottnerus & Buntinx, 2009). Even though use of the gaussian definition of normality has been the traditional practice in such research, a therapeutic definition of normality is held to be of more clinical relevance (Murphy, 1972; Sackett & Haynes, 2002; Haynes & You, 2008).

It is therefore of crucial importance that the diagnostic research question to be answered is formulated carefully (Sackett & Haynes, 2002; Haynes & You, 2008), in such a manner that it forms the basis for selecting the most suitable research path (Sackett & Haynes, 2002). Furthermore, because a significant amount of related work has been done at the juncture between clinical healthcare and

research science, to achieve key related goals: 1) attainment of optimal validity and utility of diagnostic tests (Sackett & Haynes, 2002), and 2) examination of study architectures and the distinct questions derived from the diagnostic research that have been used to answer them, the architecture of diagnostic research is focused upon conversion of clinical questions into suitable research designs (Sackett & Haynes, 2002). To illustrate these concepts, Sackett and Haynes (2002) used as an example, a case wherein an assessment was made of the utility of the plasma concentration of B-type natriuretic peptide (BNP), in the diagnosis of left ventricular dysfunction (Hobbs, 2000; Sackett & Haynes, 2002).

As a prelude to this example, it was posited by the scientists that while there are different ways to investigate the actual or probable diagnostic value of a laboratory test or a physical sign (e.g., a biomarker such as B-type natriuretic peptide), each approach is suitable to addressing one type of question, but may be unsuitable for addressing another kind (Sackett & Haynes, 2002). They considered four questions most pertinent, out of all conceivable questions for addressing the link between a presumptive diagnostic test such as BNP, and a target disorder such as left ventricular dysfunction (LVD), and classified these as Phase I, Phase II, Phase III, and Phase IV questions (Sackett & Haynes, 2002).

Phase I Questions

During this phase, researchers ask "…do test results in patients with the target disorder differ from those in normal people?" (Sackett & Haynes, 2002, p. 1). The format of this question is depicted in Table 1 of the Architecture of Diagnostic Research. For instance, a convenience (or non-systematic) sample of a cohort of normal controls, and a cohort of individuals with various combinations of hypertension, ventricular hypertrophy, and left ventricular dysfunction, had their BNP concentrations measured by some scientists at a university hospital in Britain (Talwar, 2000; Sackett & Haynes, 2002).

They found substantial disparities in the median concentrations of BNP precursors between both cohorts, without overlap in the ranges (Sheldon et al., 2000; Talwar, 2000; Sackett & Haynes, 2002). Therefore, they concluded that measurements of BNP concentration is a useful diagnostic tool

for assessing left ventricular dysfunction (Sheldon et al., 2000; Talwar, 2000; Sackett & Haynes, 2002; Sackett et al., 2003; Knottnerus & Buntinx, 2009). Usually Phase I studies are done on a set of patients who have an established diagnosis of a target disease (or disorder), as well as another set of individuals who certainly do not have the disease, instead of being conducted on persons with a probability of having the condition (Sackett & Haynes, 2002; Knottnerus & Buntinx, 2009).

Because of this, Phase I of a diagnostic study cannot be employed as an intervention. However, it can yield insights into the pathophysiological mechanisms of a disease or disorder, as well as facilitate future studies that are designed for the development of novel diagnostic approaches and/or therapeutic interventions. One of the other benefits of Phase I studies is that they are quickly conducted and are also affordable. Furthermore, negative findings in Phase I trials can save researchers from conducting studies to answer the more difficult, time intensive expensive questions posed by Phases II, III and IV studies (Sackett & Haynes, 2002).

Phase II Questions

Herein, researchers address matters such as whether individuals with specific test results have a higher chance of having the ailment of interest, than other individuals with different test results. In response to positive findings from a Phase I Study, it makes sense to move on to pose a Phase II question. However, interpretation of answers to such questions is different from the interpretation of answers to Phase I questions, in that the course of interpretation moves from the point of the diagnostic test result to the point of diagnosis (Sackett & Haynes, 2002).

Despite the possibility of using the same dataset used in answering a Phase I question to answer Phase II questions, the manner in which Phase II questions are asked and answered are different (Sackett & Haynes, 2002). To illustrate this, another set of researchers (this time around based in a university hospital in Belgium), gauged the BNP concentration levels of the members of a cohort of normal controls, as well as those of members of three cohorts comprised of individuals with various

degrees of left ventricular dysfunction and coronary artery disease (CAD) (Selvais et al., 1998; Sackett & Haynes, 2002). One of the analyses performed was a simple plot of each BNP result, which produced the results in Table 2, by choosing the cut-off point, most suited to delineating controls without the disorder, from patients with severe left ventricular dysfunction (Sackett & Haynes, 2002).

Sackett and his colleagues hold that the Table 2 results are promising. Regardless of whether the test is used to rule out left ventricular dysfunction (LVD) via means of its high sensitivity (SnNout), or to "rule it in" with its high specificity (SpPin), there appears to be high utility of measurements of BNP concentration (Sackett et al., 1991). As such, it is hardly surprising that Sackett and Haynes (2002) concluded "BNP concentrations are good indicators of the severity and prognosis of congestive heart failure" (Sackett & Haynes, 2002, p. 2).

The next question becomes one of whether the results in Table 2 of Sackett and Haynes (2002) might be too promising. After all, this table displays a comparison of test results from sets of patients with established diagnoses, instead of patients who are just considered likely to have the target disorder. As such it compares an ideal cohort of normal controls, with an ideal cohort of patients with a severe case of the target disorder (Sackett & Haynes, 2002).

As such the results in Table 2, can only be said to indicate whether the measures of BNP concentration show promise of diagnostic utility in ideal settings (Sackett & Haynes, 2002). Were the authors and/or readers of a report on the findings of a Phase II explanatory study to make sweeping generalizations regarding the effectiveness of a certain diagnostic test (for e.g., BNP) in regular clinical settings without cognizance of this limitation, they could be asserting a fallacy (Sackett & Haynes, 2002; Knottnerus & Muris, 2003; Knottnerus & Buntinx, 2009). To avoid an assertion of such a fallacy, authors and readers of reports on the findings of Phase II explanatory studies, should not use them as a basis for making assertions of practical importance about the effectiveness and/or applicability of such findings in

regular clinical practice. If assertion of this fallacy is avoided, then potential damage from misconstrued results would be averted (Sackett & Haynes, 2002).

Phase III Questions

In this phase, researchers ask if test results distinguish patients with the target disorder from patients without the target disorder, within populations of patients, in whom it is clinically credible to think the disease would be present. Due to the encouraging results shown by BNP concentration in Phase I and II studies, it was tested in a Phase III study to gauge its utility in that context for patients with LVD. A group of clinical researchers in the United Kingdom, did so by inviting local general practitioners to send patients with suspected cases of heart failure to their clinic for testing (Landray & Lehman, 2000; Sackett & Haynes, 2002).

Independent blind BNP measurements and echocardiography tests were administered to those patients (n = 126), and their results were as shown in Table 3 of the Architecture of Diagnostic Research (Sackett & Haynes, 2002). Left ventricular dysfunction (LVD) signs were observed via echocardiography in about one third of the patients (Sackett & Hayes, 2002). Consequently, the researchers reported that measurements of BNP concentration were not quite as heartening when tested in the real-life setting of a phase III study involving everyday clinical practice. So, they decided that standardization of BNP measurements was probably not going to improve symptomatic LVD diagnosis in their community (Sackett & Haynes, 2002).

Threats to the Validity of Phase III Studies

Estimates of diagnostic test accuracy may be warped by various threats to the validity of Phase III studies. The first threat is a breach of the venerable rule of critical appraisal, which asks us if there has "…been an independent, blind comparison with a gold standard of diagnosis?" (Sackett et al., 1991; Knottnerus & Buntinx, 2009, p. 32). What is meant by "independent", is that each of the study participants underwent the diagnostic test under consideration, as well as the reference (i.e., the gold)

standard evaluation (Sackett & Haynes, 2002; Knottnerus & Buntinx, 2009). More specifically, it means that the gold standard test, has been employed/used, notwithstanding the result of the diagnostic test (Sackett & Haynes, 2002; Knottnerus & Buntinx, 2009). The term “Blind” is used to indicate the reference standard has been administered and any results therefrom has been interpreted completely without knowledge of what the diagnostic test results were, with the converse being true (Sackett et al., 1991; Sackett & Haynes, 2002; Knottnerus & Buntinx, 2009).

It is possible to minimize such threats to validity of Phase III studies, if they are expected at the onset, i.e., during the preliminary question building period of a study (Sackett & Haynes, 2002; Knottnerus & Buntinx, 2009). Whenever researchers control selection of the higher limit of what is considered normal, one more threat to the validity of approximations of accuracy produced by Phase III studies emerges. If researchers can select whichever cut-off point they want, they understandably would choose to set it at a value designed to maximize sensitivity, specificity, or the total number of participants that have been categorized accurately within the specific training cohort of study participants (Sackett & Haynes, 2002), However, if the study were repeated with the very same cut-off point, within a second, independent test cohort of study participants, the investigators may observe that the diagnostic test under evaluation functions less effectively (Sackett & Haynes, 2002).

As such, until a diagnostic test has been assessed through use in at least one independent study, its real accuracy cannot be established (Sackett & Haynes, 2002). Such threats to validity exist, regardless of whether the diagnostic test is made up of just one quantification of a phenomenon, or if it is a multivariate mix of various phenomena (Sackett & Haynes, 2002). The authors state as an example of this, a previous study by Wells et al, which established the diagnostic accuracy of a mixture of various variables, from the medical history, non-invasive testing and physical examination, in diagnosis of deep vein thrombosis (Sackett & Haynes, 2002). They allege that even though this study by Phillip Wells and fellow investigators yielded comparable results in a center in Italy and two more centers in Canada,

Wells et al., recommended further prospective testing be done, before implementation of a general use of such a mix of items (Wells et al., 1998; Sackett & Haynes, 2002; Knottnerus & Buntinx, 2009).

Limits to the Applicability of Phase III Studies

According to Sackett and Haynes (2002), beginner courses in epidemiology introduce the idea that predictive values tend to vary as we oscillate from screening interventions and/or from primary care environments, which have a small pervasiveness or pretest probability of presence of the ailment of interest, to settings such as secondary and tertiary care, which have a larger prevalence or greater probability of presence of the ailment of interest (Sackett & Haynes, 2002). This statement assumes that sensitivity and specificity do not vary despite the setting (Sackett & Haynes, 2002). Nonetheless, there is a variation in the types of patients across these settings. For example, screening (also a form of primary care) is conducted during the early stages of a disease in asymptomatic individuals, while individuals with florid diseases (or whom are at advanced stages of disease) are cared for in tertiary settings (Sackett & Haynes, 2002).

Since persons in primary care with positive diagnostic test results (which include false positives and true positives) get referred thereafter to secondary and tertiary care, specificity is expected to drop as they travel the referral track (Sackett & Haynes, 2002). The authors state that Wagner demonstrated this effect in more than 2000 patients in a study of clinically suspected appendicitis observed in primary care and also in inpatient surgical settings (Sackett & Haynes, 2002). In their view, these diagnostic test results were the clinical indicia sought when clinicians suspect a patient may have a case of appendicitis, and the reference standard was a composite of pathology reports on appendices whenever operations were performed, as well as a favorable clinical course whenever they were not performed (Sackett & Haynes, 2002).

When results of such tests in both primary and tertiary care were compared, researchers found a 63% increase in the proportion of patients with appendicitis in tertiary care settings, from an initial

14% proportion of patients in primary care settings. However, this surge in prevalence transpired in part, due to the tendency to refer patients with findings of right lower quadrant pain to a higher level of care, without regard to whether the findings were true or false positives (Sackett & Haynes, 2002). Conversely, there was a tendency not to refer-out patients with no findings of right lower quadrant tenderness, to a higher level of care, which was validated by an increase in a 21% proportion of the patients presenting with this sign in primary care settings, to an 82% slice of the patients presenting with this sign in tertiary care settings (Sackett & Haynes, 2002).

Despite widespread knowledge of such increases in the proportion of positive diagnostic test results, awareness of their impact upon test-accuracy is not as highly appreciated (Sackett & Haynes, 2002). There was a spectacular drop of 89% to 16%, in the specificity in this study (Sackett & Haynes, 2002). However, drops in specificity are a common consequence of onward referrals of patients with false positive test results (Sackett & Haynes, 2002). Thus, a diagnostic indicator of concrete value in a primary care setting, such as a positive likelihood ratio of 8, plus a negative likelihood ratio of 0.2, becomes useless in a tertiary care setting, if the positive and negative likelihood ratios are 1 each (Sackett & Haynes, 2002).

It could be said that the diagnostic utility of the indicator has been depleted in the journey from test through referral (Sackett & Haynes, 2002). This diagnostic trait may significantly limit generalization of findings from Phase III studies carried out in one environment to another, if the combination of test results varies in the next setting (Sackett & Haynes, 2002). However, Sackett and Haynes claim this issue can avoided, by repeating encouraging Phase III studies in different test environments, with the types of patients the test is alleged to help (Sackett & Haynes, 2002).

Because there is not always a drop in specificity across primary and tertiary care settings, it is not possible to use this trait to balance out such variations among both settings (Sackett & Haynes, 2002). Exact approximations of the pretest likelihood of the occurrence of a disorder of interest in a

certain care setting and locale, is needed by clinicians who wish to employ Bayesian characteristics of diagnostic tests in their practice (Sackett et al., 2000; Sackett & Haynes, 2002). Such estimates may draw upon multiple sources including, practice databases, data on population prevalence data, a primary study of pretest probability in a different care environment, personal experience, and the published manuscript that describes the diagnostic test of interest (Sackett et al., 2000; Sackett & Haynes, 2002).

Phase IV Questions

These generally ask whether "…patients who undergo this diagnostic test fare better (in their ultimate health outcomes) than similar patients who are not tested?" (Sackett & Haynes, 2002, p. 3; Wright et al., 2003). The authors held that the true value of any diagnostic test, lay in the health outcomes that result from additional diagnostic and therapeutic interventions that the results obtained from using such a test yields (Sackett & Haynes, 2002; Wright et al., 2003). They allege that at times this boon is obvious, such as the apparent benefit of furnishing an accurate diagnosis of individuals with life-threatening ailments, who thereby receive the lifesaving treatments they need (Sackett & Haynes, 2002; Wright et al., 2003).

Phase III studies may indicate beneficial outcomes when the reference standard for an absence of the target ailment is a clement clinical course with no need for active treatment. However, whenever tests administered for early detection of asymptomatic disorders are employed, it is more often the case that it is only possible to answer Phase IV questions by a longitudinal investigation of patients, whom have been randomly selected to receive/undergo the diagnostic test under study, another test, or no test (Knottnerus & Buntinx, 2009). An example of the findings from a study that was designed to address Phase IV questions, is given in Table 4 of the Architecture of Diagnostic Research (Sackett & Haynes, 2002). This study was conducted by investigators in New Zealand, who administered BNP tests to 307 patients, who had been enrolled in the study (a randomized trial), after each of them had presented to their general practitioner (GP) with signs of dyspnea and/or edema (Knottnerus & Buntinx, 2009). The

highlights of the results of this study are given in Table 4. Subsequent analyses of the data underlying these results, led investigators to conclude that the improvement in the diagnostic accuracy of the test displayed in tests of the BNP group, was largely a result of the improvement in GPs' ability to accurately rule-out heart failure (Knottnerus & Buntinx, 2009). Therefore, valuable insights may be gleaned from the results of similar studies of comparative accuracy, even though such studies are conducted only in rare instances (Knottnerus & Buntinx, 2009). Without evidence that a novel diagnostic test yields more accurate results than the gold (or reference) standard) diagnostic tests (approaches or modalities), it will be difficult to attract funding for additional Phase IV Questions related research designed for exploration of concrete clinical outcomes, because it would be hard to visualize how the novel test could yield better health outcomes, and thus prove to be an investment worth making (Knottnerus & Buntinx, 2009).

Phase V Questions

Researchers ask in Phase V if "…use of the diagnostic test lead to better health outcomes at an acceptable cost?" (Knottnerus & Buntinx, 2009, p. 38). The costs incurred from diagnostic tests is rapidly climbing, such that it is increasingly pertinent to evaluate the cost-effectiveness of using such tools. Even though the structure of cost-effectiveness studies may vary, the "cost-effectiveness ratio" (Iglehart, 2006; Mueller et al., 2006; Knottnerus & Buntinx, 2009, p. 38), is a common metric used for reporting findings of such studies. It is the extra expense (or savings in cost) run-up by each extra unit of the health benefit accrued from (or dissipated by) use of the novel diagnostic test, in comparison with use of a more traditional diagnostic approach (Mueller et al., 2006; Knottnerus & Buntinx, 2009). For example, out of 425 patients that were seen at an Emergency Department, Swiss researchers selected subsets via randomization, in which one cohort underwent a conventional diagnostic test, whereas the other cohort underwent a diagnostic test that involved administration of rapid BNP measurements (Mueller et al., 2006; Knottnerus & Buntinx, 2009).

A Brief Description of the Figures in this Conceptual Framework

Potential outcomes of a Phase V Study are depicted in Figure 1, which is derived from Figure 2.2 of the Architecture of Diagnostic Research (Sackett & Haynes, 2002). Figure 2 is the conceptual model of the Architecture of Diagnostic Research (Sackett & Haynes, 2002). It will be adapted in Figure 3, to depict the application of relevant phases of Sackett and Haynes's Architecture of Diagnostic Research to this specific study, together with pertinent aspects of the model of prognostic research by Dr. Peter Kent and his colleagues, which is titled "A Conceptual Framework for Prognostic Research" (Kent et al., 2020).

A Conceptual Framework for Prognostic Research

For prognostic research, Kent et al. (2020) state that the best design is a cohort study. So, the cross-sectional design of this study is not ideal for conducting prognostic research, since we cannot follow each of the study participants prospectively over a period of time, from a baseline, through interventions (if any), to an endpoint (Kent et al., 2020). According to Kent et al. (2020), important aims of prognostic research include making descriptions of a health disorder's clinical course and natural history, examining variables related to pertinent health outcomes, assessing the chance that a person would develop alternative outcomes, exploring clinical applications of prediction models, and examining factors of recovery that may guide the design of interventions for the betterment of patient outcomes (Kent et al., 2020). Frequently though, prognostic studies have been done and interpreted shoddily, which indicates a misunderstanding of a number of its conceptual precepts (Kent et al., 2020).

To raise understanding of the concepts behind prognostic research, remedies such as the Prognosis Research Strategy (PROGRESS) and the "Transparent Reporting of a multivariable prediction model for Individual Prognosis or Diagnosis (TRIPOD) Statement" (Hemingway et al., 2013; Kent et al., 2020, p. 1) have been promoted. The main thrust of this PhD project is an investigation of the utility of electrodermal activity (EDA) in the diagnosis of postural orthostatic tachycardia syndrome (POTS). The

utility of EDA in eliciting information regarding mechanisms and prognosis of POTS will also be explored, as a secondary goal (Knottnerus & Muris, 2003; Hemingway et al., 2013).

Examining whatever EDA patterns and/or variables might reveal regarding symptoms reported during autonomic reflex screens (ARSs), the severity of such symptoms, and the impact of adherence or non-adherence to the requirement to hold certain pre-ARS medications on the results obtained during head up tilt table (HUTT) testing is pertinent. This goal is in alignment with those aims of prognostic research, which seek to describe a disease's (or disorder's) clinical course and natural history, investigate variables linked to health outcomes (e.g., potential associations of EDA with BP, HR, and/or variations in BP or HR, etc.), or to map out characteristics of those predictors of recovery that may shape therapy development for better patient outcomes (Kent et al., 2020).

The authors of the Conceptual Framework for Prognosis Research, sought to demonstrate links among the various types of prognostic research, distinguish exploratory prognostic research from confirmatory prognostic studies, review mediators and moderators, and furthermore demonstrate the importance of comprehending concepts underlying prognostic study designs, and distinctions between causality and prediction (Kent et al., 2020). However, application of their framework to this study will be limited to its utility in guiding the design of exploratory prognostic research (Kent et al., 2020), because of the exploratory nature of this project.

Authors of this conceptual framework allege there are four main goals of prognostic research, namely "description, association, prediction and causation" (Kent et al., 2020, p. 1). The first three of these goals constitute the core aims of exploratory prognostic research (Kent et al., 2020). Somewhat coincidentally, these three objectives also happen to be the overarching aims of this PhD project, which sought to describe both the utility of EDA in the study of the diagnosis of the POTS syndrome, as well as any underlying characteristics of the ailment (i.e., the health disorder POTS) that an analysis of measures EDA might elucidate. Furthermore, this PhD dissertation study included an examination of associations

between variables of interest, such as reference standard variables like BP, HR, change in BP, variations of HR, time to peak of BP and HR and other latency variables. This is in alignment, with one of the five goals of prognostic research, which were outlined at the beginning of their discourse, by the authors of this conceptual framework (Kent et al., 2020).

Finally, identification of associations between diagnostic test variables of interest (such as the various EDA variables), and reference standard variables such as the various BP, HR and latency variables (Novak, 2011; Kanjwal, 2015), could facilitate design of a prediction model for POTS prognosis (Kent et al., 2020). To this end, Figure 3 depicts the role of description, association and prediction in prognostic studies. It is the first figure given in the Conceptual Framework for Prognostic Research, published by Kent et al., in their 2020 manuscript (Kent et al., 2020).

As shown in this visualization of the conceptual framework for prognostic research, a description study characterizes the course and effects of a disease or disorder on individuals (Kent et al., 2020). Given this PhD project's proposed retrospective, observational and cross-sectional study design, study results cannot fully describe the progression of POTS in the target study population. Nonetheless, study findings may be able to describe effects of certain predictor variables on cases versus controls (Kent et al., 2020). The investigation of the associations component of the model, when applied to this proposed project, could yield data needed to identify potential prognostic factors (Kent et al., 2020).

If such factors improve predictive reliability in a prediction model, they are non-causal prognostic markers of POTS (Kent et al., 2020). This could lead to the development of clinical decision and prediction rules, were such prediction models, to receive external validation from further studies (Kent et al., 2020). With clinical decision rules shaping patient care pathways, following external validation via a randomized control trial (RCT), for example, may be a future endeavor (Kent et al., 2020). However, such potential studies are beyond the scope of this PhD project, because of time and financial constraints.

As such, the third objective of exploratory prognostic research, namely the prediction phase depicted in Figure 3, which envisages the development of prediction models via use of prognostic determinants or markers and internal validation, will neither be pursued nor implemented during this study (Kent et al., 2020). Figure 4 is a merged model derived from both the Architecture of Diagnostic Research and the Conceptual Framework of Prognostic Research. Therefore, it will be the conceptual model guiding this proposed study of the utility of electrodermal activity in the diagnosis, prognosis and illumination of identifiable pathophysiologic mechanisms of postural orthostatic tachycardia syndrome (Sackett & Haynes, 2002; Knottnerus & Buntinx, 2009; Kent et al., 2020).

Rationale for Study Design

Careful specification of the diagnostic problem under investigation is an indispensable step in diagnostic accuracy studies because the contrast of interest could be a single test contrast, a comparison two or more single tests, additional testing on top of preceding diagnostic tests, and a juxtaposition of different diagnostic approaches (Knottnerus & Muris, 2003). Collection of data for a diagnostic study is usually done prospectively (Knottnerus & Muris, 2003). However, it can also be done via adoption of an ambispective or retrospective approach, whenever such methods are either the only avenues possible and/or suitable (Knottnerus & Muris, 2003; Knottnerus & Buntinx, 2009).

Furthermore, potential modifiers of test accuracy and any confounders, need to be clearly defined (Knottnerus & Muris, 2003), as well as the determinants of main interest. In the case of diagnostic research projects, this is (or these are) the diagnostic test (or diagnostic tests) under investigation, (Knottnerus & Muris, 2003; Knottnerus & Buntinx, 2009). Administration of the reference standard process should be independent from implementing the process that yields test results (Knottnerus & Muris, 2003). It can be quite a challenge to apply a reference standard, if, there are classification errors, an absence of a distinct pathophysiologic hypothesis and/or theory, an existence of

incorporation bias, or when complex inquiries and/or invasive investigations are involved (Wells, 1998; Knottnerus & Muris, 2003; Knottnerus & Buntinx, 2009).

Some of the feasible remedies to this difficulty are employment of an independent expert panel, and use of a delayed-type cross-sectional study design (i.e., one with a clinical follow-up) (Knottnerus & Muris, 2003; Knottnerus & Buntinx, 2009). Another possible approach is to select a prognostic criterion to overcome the difficulty of applying a reference standard (Knottnerus & Muris, 2003; Knottnerus & Haynes, 2009). To make these studies relevant for practice with real-life patients, the inclusion criteria applied to the recruitment of study participants for such studies "…must be selected based on an "intention to diagnose" or (an) "intention to screen" (Knottnerus & Muris, 2009, p. 1). According to Knottnerus and Muris (2003), a successive series of presenting patients, or screening individuals selected from a target population, respectively, is the preferred recruitment procedure (Knottnerus & Buntinx, 2009).

Routine sample size estimation should be done, and data analysis should be centered on (or around) the contrast of interest (Knottnerus & Muris, 2003). Predicting outcomes and making useful test accuracy approximations requires an employment of distinct strategies (Knottnerus & Muris, 2003). For clinical or external validation, duplication of these studies in similar or in other populations, is required (Knottnerus & Muris, 2003). Also, systematic reviews and meta-analysis have a role to play in such studies (Knottnerus & Muris, 2003). Observance and implementation of the STARD guidelines, by writers of diagnostic research reports, is recommended to facilitate an assessment by readers, regarding whether the crucial methodology-based issues, have been adequately tackled in the reports (Knottnerus & Muris, 2003; Knottnerus & Buntinx, 2009).

Conclusion

In conclusion, it is important to note that the data intended for use in this PhD project were acquired on the basis of a previous prospective study design. However, it has and will be applied to this

study from the perspective of a researcher that uses a retrospective record review design to address the research question and aims (Elstein, & Schwarz, 2002; Hemingway et al., 2013). The principal investigator, in his role as a GSR assigned to the UCLA CAC, participated in collection of some of the data proposed for use. This involvement in the primary data acquisition occurred between the beginning of July 2020, and the end of December 2021. Regarding this project, the doctoral student serves as Principal Investigator (PI), and retains full/sole responsibility, for the identification, retrieval, extraction, analyses, interpretation, and presentation of all of the secondary data hereby proposed for use, in this PhD dissertation project. Despite the limitations of the Architecture of Diagnostic Research and the Conceptual Framework for Prognostic Research, for example the limitations of applying Phase III questions to diagnostic research (Sackett et al., 1991; Sackett & Haynes, 2002; Knottnerus & Muris, 2003; Knottnerus & Buntinx, 2009; Kent et al., 2020), as well as any extra limitations that may accrue from only a partial use of Kent et al.'s Conceptual Framework for Prognostic Research, the PI holds the view that the merged model given in Figure 4, is an adequate conceptual foundation for this proposed project.

Table 2

Example of Results from a Diagnostic Test to Answer a Phase I Question

Table 1.
Answering a phase I question: do patients with left ventricular dysfunction have higher concentrations of B-type natriuretic peptide (BNP) precursor than normal individuals?

	Patients known to have disorder	Normal controls
Median (range) concentration of BNP precursor (pg/ml)	493.5(248.9-909.0)	129.4(53.6-159.7)

Note. From Table 1 of "The Architecture of Diagnostic Research," by D. L. Sackett, and R. B. Haynes, 2002. *BMJ (Clinical research ed.)*, *324*(7336), p539 (https://doi.org/10.1136/bmj.324.7336.539).

Table 3

Example of Results from a Diagnostic Test to Answer a Phase II Question

Table 2.
Answering a phase II question: are patients with higher concentrations of B-type natriuretic peptide (BNP) more likely to have left ventricular dysfunction than patients with lower concentrations?

	Patients known to have target disorder	Normal controls
High BNP concentration	39	2
Normal BNP concentration	1	25

Test characteristics (95% CI): Sensitivity=98% (87% to 100%) Specificity=92% (77% to 98%) Positive predictive value=95% (84% to 99%) Negative predictive value=96% (81% to 100%) Likelihood ratio for an abnormal test result=13 (3.5 to 50.0) Likelihood ratio for a normal test result=0.03 (0.0003 to 0.19)

Note. From "The Architecture of Diagnostic Research," by D. L. Sackett, and R. B. Haynes, 2002. *BMJ (Clinical research ed.)*, *324*(7336), p540 (https://doi.org/10.1136/bmj.324.7336.539). Copyright 2002 by the authors Sackett and Haynes. Reprinted with permission.

Table 4

Example of Results from a Diagnostic Test to Answer a Phase III Question

Table 3.
Answering a phase III question: among patients in whom it is clinically sensible to suspect left ventricular dysfunction (LVD), does the concentration of B-type natriuretic peptide (BNP) distinguish patients with and without left ventricular dysfunction?

	Patients with LVD on echocardiography	Patients with normal results on echocardiography
Concentration of BNP:		
High (>17.9 pg/ml)	35	57
Normal (<18 pg/ml)	5	29
Prevalence (pretest probability) of LVD	40/126=32%	

Test characteristics (95% CI): Sensitivity=88% (74% to 94%) Specificity=34% (25% to 44%) Positive predictive value=38% (29% to 48%) Negative predictive value=85% (70% to 94%) Likelihood ratio for an abnormal test result=1.3 (1.1 to 1.6) Likelihood ratio for a normal test result=0.4 (0.2 to 0.9)

Note. From "The Architecture of Diagnostic Research," by D. L. Sackett, and R. B. Haynes, 2002. *BMJ (Clinical research ed.)*, *324*(7336), p540 (https://doi.org/10.1136/bmj.324.7336.539). Copyright 2002 by the authors Sackett and Haynes. Reprinted with permission.

Table 5

Example of Results from a Diagnostic Test to Answer a Phase IV Question

Table 2.9 Answering a Phase IV question: Do patients undergoing BNP testing fare better than those who do not? (using improvement in the percentage of correct diagnoses as a surrogate for improved health outcomes)

	GP diagnosis at Initial visit	GP diagnosis at next visit
BNP group, % correct diagnoses	49%	70%
Control group, % correct diagnoses	52%	60%

BNP, B-type natriuretic peptide; GP, general practitioners.

Note. Adapted from "The Architecture of Diagnostic Research," by R. B. Haynes, and J. J. You, in J. A. Knottnerus & F. Buntinx (Eds.), *The Evidence Base of Clinical Diagnosis: Theory and Methods of Diagnostic Research. 2nd edition* (p. 37), 2009. Blackwell Publishing Ltd. Copyright 2009 by Blackwell Publishing Ltd. Adapted with permission.

Figure 2

Potential Outcomes of a Phase V Study

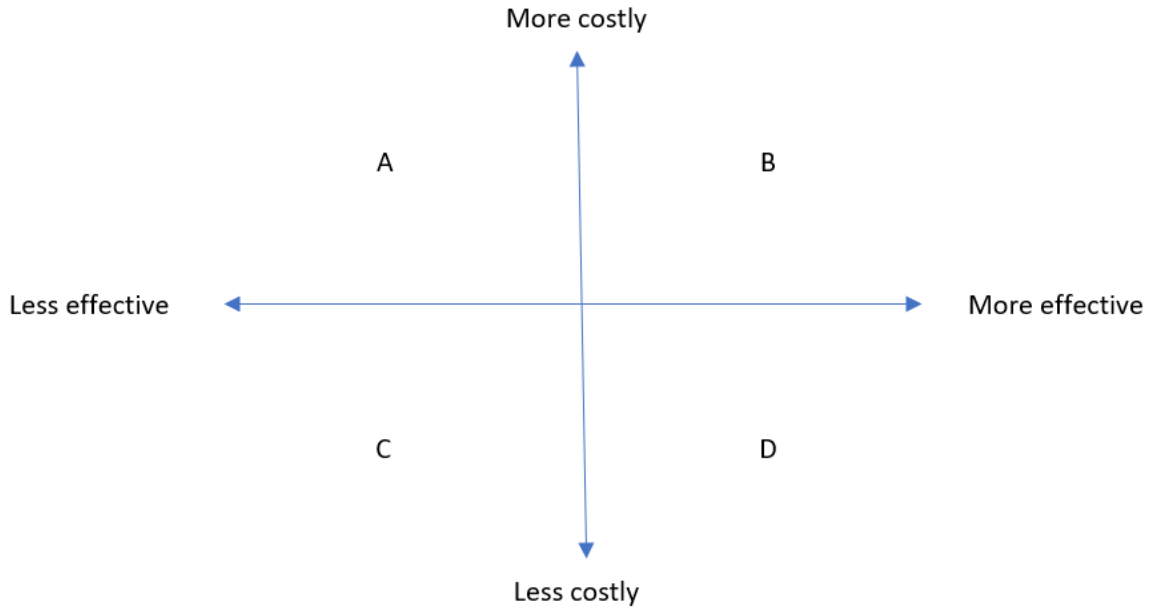
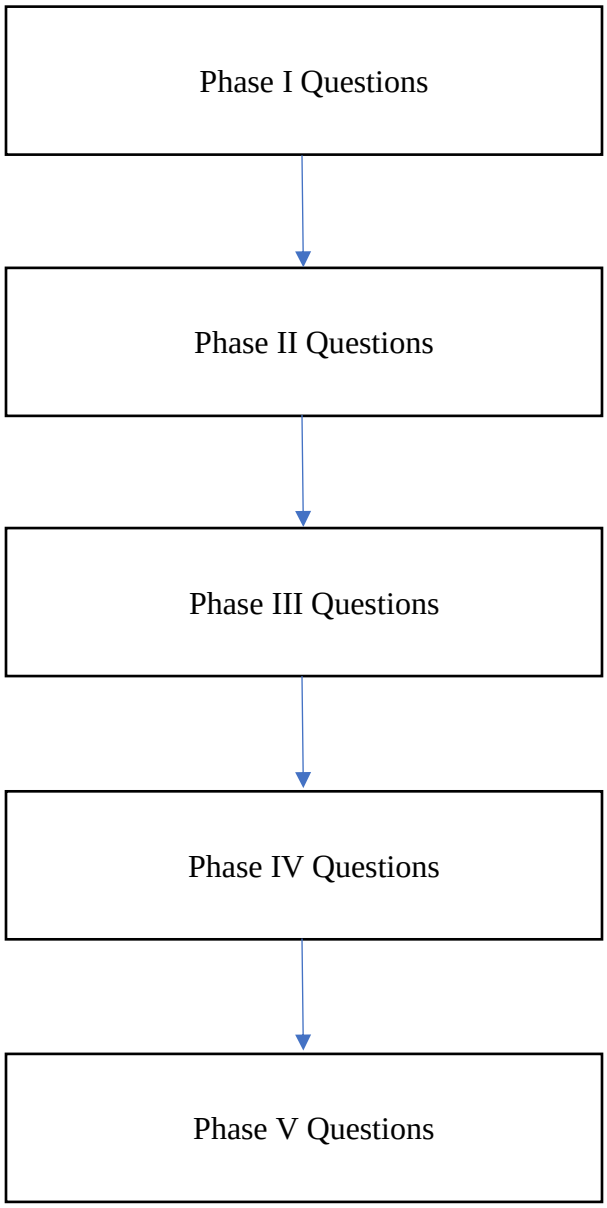


Figure 2.2 Four possible outcomes of a Phase V study: A, the test is more costly and less effective (undesirable); B, the test is more costly, but more effective; C, the test is less costly, but less effective; D, the test is less costly and more effective (most desirable).

Note. Adapted from "The Architecture of Diagnostic Research," by R. B. Haynes, and J. J. You, in J. A. Knottnerus & F. Buntinx (Eds.), *The Evidence Base of Clinical Diagnosis: Theory and Methods of Diagnostic Research. 2nd edition* (p. 39), 2009. Blackwell Publishing Ltd. Copyright 2009 by Blackwell Publishing Ltd. Adapted with permission.

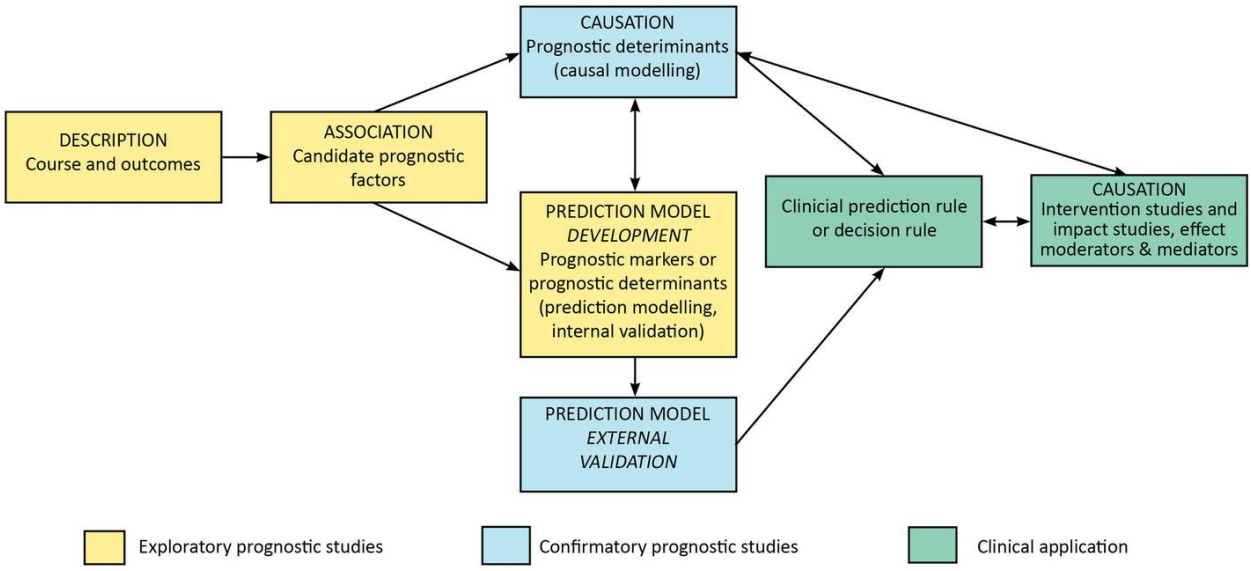
Figure 3

Phases I through V of the Architecture of Diagnostic Research



Note: Phases I through V of the Architecture of Diagnostic Research.

Figure 4
Prognostic Research Conceptual Framework

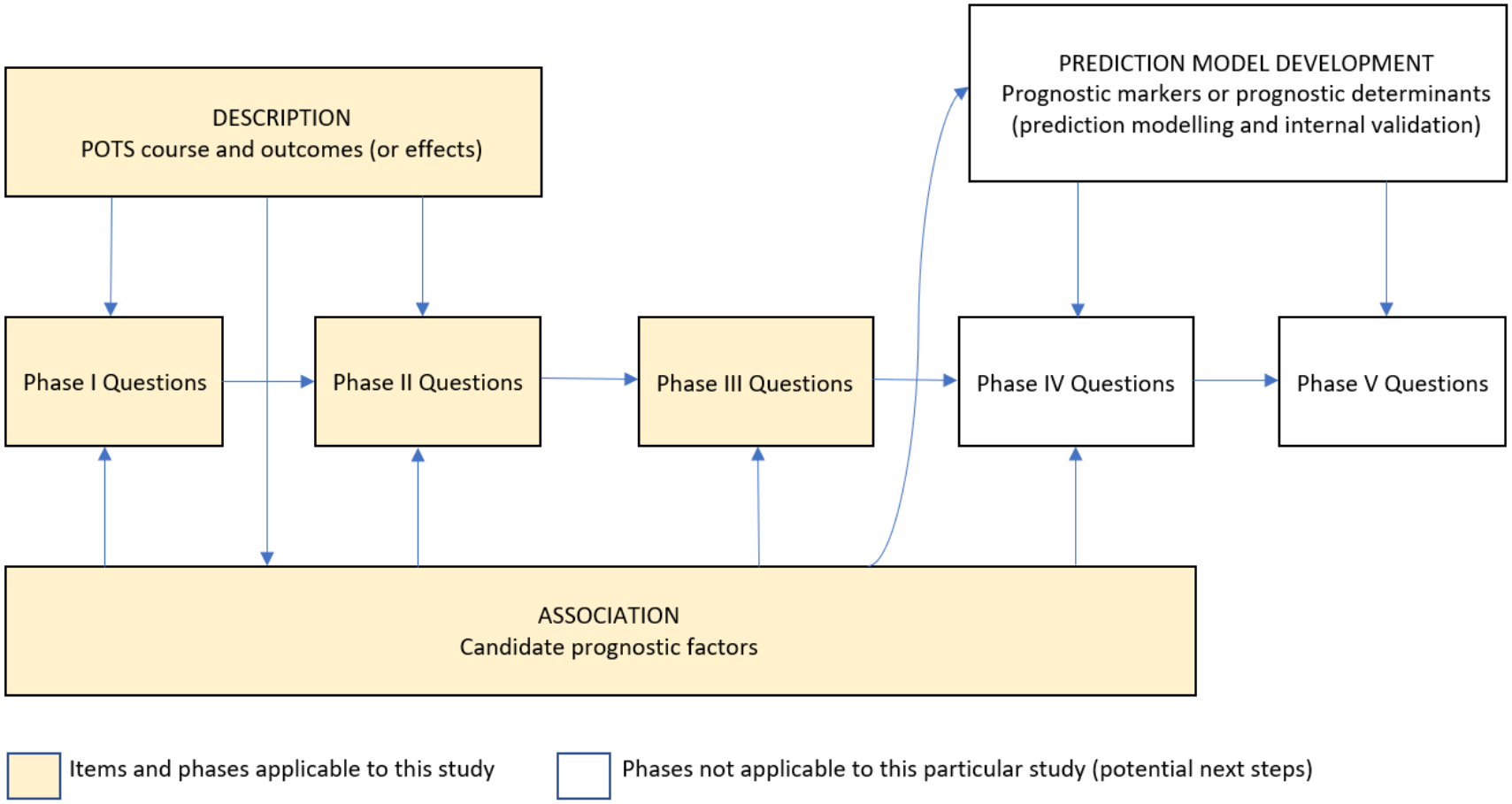


Description studies describe the course and outcomes of people with a health condition and may indicate which variables should be tested for association with a target outcome. ***Candidate prognostic factors*** are identified in association studies. ***Prognostic factors*** that increase the accuracy of a prediction in a prediction model are ***prognostic markers*** (non-causal) and prognostic factors with a causal relationship to outcome are ***prognostic determinants*** (causal). Prognostic factors are the building blocks of **prediction models** that estimate an individual's probability of a target outcome. **Externally validated prediction models** can be translated into simple **clinical prediction rules** and **clinical decision rules** (inform care pathways) for clinical use. Clinical prediction and decision rules, as well as prognostic determinants can be tested in **intervention studies** (e.g., randomized trials) to determine their impact on patient outcomes or cost-effectiveness of care.

Note: A conceptualization of the components of the "Conceptual Framework for Prognostic Research" and their inter-relationships, as envisioned by its authors. Adapted from "A Conceptual Framework for Prognostic Research," by P. Kent, C. Cancelliere, E. Boyle, J. D. Cassidy, A. Kongsted, 2020, *BMC Medical Research Methodology*, *20*(1), p. 172 (https://doi.org/10.1186/s12874-020-01050-7). Copyright by the authors P. Kent, C. Cancelliere, E. Boyle, J. D. Cassidy, A. Kongsted, 2020. Adapted with permission.

Figure 5

Merged Model for Investigating the Utility of EDA in a Study of the Diagnosis, Prognosis and Mechanisms of POTS



Note. A merged model derived from the five phases of Sackett & Haynes (2002)'s Architecture of Diagnostic Research and Figure 1 of Kent et al. (2020)'s A Conceptual Framework for Prognostic Research.

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CHAPTER 4:

METHODS

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Background

Postural orthostatic tachycardia syndrome (POTS) is a syndrome of disorders affecting the neuro-cardiovascular systems of persons who present with a variety of symptoms, among which are abdominal pain, anxiety, brain fog, chest pain, cold, disorientation, dizziness, feelings of falling, flight or floating, generalized pain, heat, heart palpitations, lightheadedness, malaise, mental clouding, migraines, numbness, perception of an aura, sweatiness, tingling, and tremor in the extremities, to name but a few (Arnold et al., 2018; The Dysautonomia Project, 2022). It is the most common form of dysautonomia, and because it often affects multiple organs and/or systems, its clinical presentation among patients is heterogenous (Arnold et al., 2018; The Dysautonomia Project, 2022). Because of its increasing prevalence and the preponderance of a chronic presentation on persons with POTS, this syndrome of disorders predisposes its patients to functional and/or occupational disability, deterioration in individuals' activities of daily living, and an impairment of their heath related quality of life (Arnold et al., 2018).

While the etiology of POTS is still poorly understood, there is an increase in the numbers of patients who present with its signs/symptoms, in various clinical settings such as cardiology and neurology clinics, or in the emergency rooms of various emergency departments (Arnold et al., 2018). Dr. Amy Arnold and her colleagues, stated in their 2018 review that between 0.1% and 1% of the U.S. population suffered from POTS, with the caveat that this estimate may not be correct because of the lack of accurate epidemiologic data on the population (Arnold et al., 2018). Yet, despite rising health costs related to the deleterious personal and occupational impact of POTS, with a concomitant increase in clinical interest in the syndrome, not much is known about the underlying mechanisms of POTS, and diagnostic/treatment modalities remain limited (Arnold et al., 2018; Raj & Levine, 2013; Raj 2006; Rodriguez et al., 2020; Seeley & Lau, 2021; Sheldon et al., 2015; Taub et al., 2021). So, it is pertinent to

investigate the potential utility of an alternative electrophysiologic measure of sympathetic nervous system (SNS) activity such as electrodermal activity (EDA), galvanic skin response (GSR), or skin conductance (SC), in the investigation of the diagnosis of POTS, as well as its applicability to explorations of prognostic factors and mechanisms of this heterogenous syndrome of disorders (Posada-Quintero & Chon, 2020; Raj 2013; Raj 2006; Revlock, 2018; Thijs, 2021).

Study Population

Patients presenting with symptoms of dysautonomia, who were referred to the university of California Los Angeles (UCLA) Cardiac Arrhythmia Center (CAC) between January 1, 2017, and December 31, 2021, to undergo autonomic reflex screen (ARS) tests, to determine whether they display evidence of general autonomic impairment (GAI), were assessed for enrollment in this proposed study. This chapter describes both the methods used to test patients undergoing such ARS tests, as well as the methods used by the PI in his partially retrospective review of records of such ARS visits from January 1, 2017, through December 31, 2020. The PI was present at some of the ARS appointments, subsequent to his appointment to serve as a graduate student researcher (GSR) at the UCLA CAC. Initially his role was only to shadow the lab technician who was responsible for administering the ARS tests. However later on, he began to assist the lab technician with administration of various ARS tests.

Regardless of whether the PI was present at the testing of certain ARS patients seen at the UCLA CAC or not, he was responsible for identifying, obtaining, and reviewing all of the ARS related test records, for each patient seen at the UCLA Cardiac Arrhythmia Center from January 1, 2017, to December 31, 2021. A segment of such ARS patients, specifically, those who met the criteria set out for the diagnosis of POTS, and those who could be ruled out because they were persons who neither had POTS, orthostatic intolerance (OI), orthostatic hypotension (OH), sinus tachycardia (which is a confounder of POTS), nor any other form of dysautonomia, were enrolled in this study, either as POTS cases or controls (Arnold et al., 2018; Raj & Levine, 2016; Raj, 2006; Sheldon et al., 2015). Note however

that the controls may not have been perfectly healthy, because they were referred to the UCLA CAC by other health care providers, after presenting with symptoms that were deemed potentially indicative of the presence of some form of dysautonomia.

Such diagnostic criteria were established based upon findings from various previous studies. The diagnostic criteria chosen to guide enrollment of persons into this proposed study have been published in clinical practice guidelines, and peer-reviewed manuscripts on the subject. They are also widely employed in clinics, hospitals, and other clinical settings, for the diagnosis of patients with POTS and other kinds of dysautonomia. These manuscripts and clinical practice guidelines include the 2015 Hearth Rhythm Society's Consensus Statement on the Diagnosis of Postural Orthostatic Tachycardia Syndrome, a review on the diagnosis, pathophysiology and prognosis of POTS by Arnold et al. (2018) titled "Postural tachycardia syndrome – Diagnosis, physiology, and prognosis", a manuscript by Feigofsky and Fedorowski (2020) titled "Defining Cardiac Dysautonomia - Different Types, Overlap Syndromes; Case-based Presentations" and an article by Thanavaro and Thanavaro (2011) titled "Postural orthostatic tachycardia syndrome: Diagnosis and treatment" among others (Arnold et al., 2018; Feigofsky & Fedorowski, 2020; Sheldon et al., 2015; Thanavaro & Thanavaro, 2011).

Additional Exclusion Criteria for the Selection of Subjects into the Cohort of POTS Cases

Transient POTS occurs in minor and adult patients, albeit more frequently in minors in comparison with adults (Raj, 2006; Park et al., 2022). Inclusion of such patients may skew study findings. As such, a stricter (or more stringent) diagnostic criteria was employed in the selection of subjects into the cohort of patients with POTS, to exclude patients with merely fleeting indicia of POTS, from those with sustained evidence of POTS.

Standard age-based criteria for diagnosis of POTS, require a HRΔ of ≥ 30 bpm for persons aged 20 years or older, or a HRΔ of 40 bpm in persons aged 19 years old or younger during HUT (Arnold et al., 2018; Novak, 2011; Park et al., 2022; Raj & Levine, 2016; Raj, 2006; Sheldon et al., 2015). Evidence of

such changes in HR, where HRΔ is the difference between the maximum and minimum HRs during HUT, together with a HR rise of ≥ 120 bpm (which is sustained for 3 or more minutes of HUT), in the absence of diagnostic indicia of orthostatic hypotension, and/or a 20 mmHg or more drop in SBP, or a 10 mmHg or more drop in DBP, are a basis for a diagnosis of POTS (Arnold et al., 2018; Novak, 2011; Park et al., 2022; Raj & Levine, 2016; Raj, 2006; Sheldon et al., 2015). However, for subject enrollment in this study, the HRΔ cut-offs were raised to 40 bpm and 50 bpm, for patients in the ≥ 20-years-old and ≤ 19-years-old ranges, respectively.

Additional Exclusion Criteria for the Selection of Subjects into the Cohort of Controls

Another exclusionary set of criteria adopted for this project, were an exclusion of anyone with a CASS in any of the CASS related domains (i.e., adrenergic, cardiovagal and sudomotor), or even those patients with merely an undetermined and/or indeterminable CASS from the cohort of controls. The rationale for excluding such patients from the group of controls, is that so long as a potential for general autonomic impairment (GAI) cannot be definitively ruled out (e.g., in a patient with an unknown or indeterminable CASS), then such a patient cannot be deemed to be without some form of dysautonomia (Arnold et al., 2018; Novak, 2011; Park et al., 2022; Raj & Levine, 2016; Raj, 2006; Sheldon et al., 2015; Sletten et al., 2010). Patients with partial ARSs (i.e., those that only underwent HUT testing related screening for dysautonomia), could not be assessed for presence of general autonomic impairment in either the adrenergic domain (since they did not undergo a Valsalva Maneuver [VM] test and adrenergic sensitivity analysis could not be performed), or in the cardiovagal domain (as neither a heart rate deep breathing [HRDB] test nor a VM test were performed), or in the sudomotor domain (as a quantitative sudomotor axon reflex test (QSART) based quantitative sweat (QSWEAT) test was not performed) (Illigens & Gibbons, 2009; Novak, 2011; Sletten et al., 2010), have an indeterminable and unknown CASS, and as such they were excluded from enrollment in the cohort of controls. Furthermore, the results of a QSART/QSWEAT test may indicate small nerve fiber dysfunction. So the presence of neuropathic POTS

cannot be ruled out, and ARS patients with an unknown might have some degree of dysautonomia (Illigens & Gibbons, 2009; Novak, 2011; Sletten et al., 2010). A full list of the various autonomic function tests (AFTs) that were administered during the patients full or partial autonomic reflex screens (ARSs), is given in Table 19, with the variables being assessed, and their respective unit of measure (Table 19).

Study Sample

We included participants referred to the UCLA Cardiac Arrhythmia Center (CAC), between April 2017 and December 2021 for autonomic assessment. A total of 595 patient records were reviewed, from which we included 100 consecutive patients (POTS n=75 and controls n=25). Ninety percent of patients underwent a full autonomic reflex screening test (ARS), which consists of a head up tilt table test (HUTT), a Valsalva maneuver test, assessment of heart rate during deep breathing (HRDB), and quantitative sudomotor testing (QSWEAT). The rest of the patients screened only underwent HUTT. EDA was sampled in all patients during the course of administering such testing. For clinical characteristics and outcomes, we reviewed patient medical records until June 2023. Data were extracted on age, sex, body mass index (BMI), medications, and medical history including symptoms. Extracted data were de-identified per guidelines in the Health Insurance Portability and Accountability Act (HIPAA).

Synthesis of the Inclusion and Exclusion Criteria

The approach to patient selection and classification (case vs. control) is illustrated in the study flowchart (Figure 7). Controls were included if they had no clinical signs or diagnosis dysautonomia, e.g., POTS, orthostatic hypotension (OH), initial OH, orthostatic intolerance (OI), inappropriate sinus tachycardia (IST), and any other forms of dysautonomia in other organs) (Arnold et al., 2006; Raj, 2006; Raj et al., 2020; Sheldon et al., 2015). Standard age-based criteria for the diagnosis of POTS (Sheldon et al., 2015), require an increase in heart rate (HRΔ) of ≥30bpm for persons aged ≥20 years, or a HRΔ of ≥40bpm in persons aged ≤19 years, during upright tilt (Sheldon et al., 2015).

Other criteria for POTS diagnosis include a sustained HR increment of ≥120bpm (which lasts for

≥3 minutes of tilt) in the absence of OH (Arnold et al., 2006; Novak, 2011; Park et al., 2022; Raj, 2006; Raj et al., 2020; Sheldon et al., 2015), i.e., an SBP drop of ≥20mmHg, or a DBP drop of ≥10mmHg. We adopted more stringent diagnostic criteria for POTS, by raising the HRΔ cut-offs by 10bpm for each POTS age-group, i.e., ≥40bpm for patients ≥20-years-old, and ≥50bpm for those ≤19-years-old to avoid including transient POTS (Park et al., 2022; Raj, 2006), which may skew the results (Abi-Samra et al., 1998; Eftekhari et al., 2021; Feigofsky & Fedorowski, 2020; Freeman et al., 2011; Frey & Hoffler, 1998; Grubb et al., 2006; Grubb, 2008; Kanjwal et al., 2011; Kavi et al., 2012; Low et al., 2009; Novak 2011; Park et al., 2022; Raj, 2006; Raj et al., 2020; Seeley & Lau, 2021; Sheldon et al., 2015; Swai et al., 2019; Taub et al., 2021; Thijs et al., 2011).

We excluded the records of patients with known psychiatric, cardiovascular, respiratory, and/or neurological diseases (Giada et al., 2005; Isen et al., 2010; Revlock, 2018; Rodriguez et al., 2021). Any of the patients with the potential of inclusion as a control that however exhibited evidence of adrenergic, cardiovagal, or sudomotor impairment, or an abnormal composite autonomic symptom score (CASS), were excluded (Raj et al., 2020; Sheldon et al., 2015; Arnold et al., 2011; Novak, 2011; Park et al., 2022; Sletten et al., 2010).

Ethical Approval

Both of the study protocols used in this project were approved by the University of California Los Angeles (UCLA) Institutional Review Board. This approval was granted, after an expedited review process was conducted by the Medical Institutional Review Board 1 (MIRB1) of UCLA (see Supplemental Material B1 in Appendix B).

Study Design

This study was hypothesis generating in nature rather than hypothesis driven, due to the paucity of evidence related to the utility of EDA as a marker of sympathetic nervous system activity in POTS. The study was quantitative in nature (or type), and it employed a partially prospective as well as partially

retrospective, observational, descriptive, and cross-sectional design. Two groups were studied for the effects of undergoing autonomic reflex screening (ARS), with an eye to identifying any data of potential diagnostic, prognostic, or mechanistic utility, which may be gleaned from analysis of measures of electrodermal activity (EDA). One of the groups studied comprised of a disease group made up of patients diagnosed with POTS, while the other group was a comparison (or control) group.

The group of patients diagnosed with POTS (nPOTS=75) were comprised of patients who either underwent a full set of autonomic reflex screening (ARS) tests, or those who only underwent a partial ARS such as a tilt table test (TTT). Whereas, because of an application of the most stringent of diagnostic criteria, only those patients who underwent a full set of all four standard ARS tests were enrolled in the group of controls (ncontrols=25) (Novak, 2011). Other inclusion criteria for the controls, were that ARS test results must indicate an absence of any cardiovascular dysautonomia such as postural orthostatic tachycardia syndrome (POTS), orthostatic intolerance (OI), and orthostatic hypotension (OH), as well as an absence of a history of any other major cardiovascular diseases (Arnold et al., 2018; Raj & Levine, 2016; Raj, 2006; Sheldon et al., 2015).

Data Acquisition Approaches

Data Collection Approach for Obtaining Physiologic Measures During ARS or HUT Tests

Over the course of a period, which spans January 1, 2017, and December 31, 2021, ARS tests were administered to persons referred by various healthcare providers to the UCLA Cardiac Arrythmia Center (CAC) for autonomic function related tests. Measures taken at such screening visits, included the sweat response and related electrophysiologic measures of sympathetic nervous system activity including electrodermal activity (EDA); which is also known as galvanic skin response (GSR), or skin conductance (SC). To measure EDA, electrodes manufactured by BIOPAC Systems Inc., Goleta, California, were placed on the palms of the right-hands of ARS patients, while they lay supine upon a motorized tilt table (Table 6).

Such electrodes were attached to sensors made by BIOPAC Systems Inc. in one of two ways: 1) by cables using an EDA100C Electrodermal Activity Amplifier Module (Dusi et al., 2020), or wirelessly, as is the ongoing protocol, which uses a wrist worn device (the BioNomadix Transmitter from BIOPAC Systems Inc.) that communicates data wirelessly to the newer and currently installed wireless receiver (the PPGED-R Module from BIOPAC Systems Inc.). Data acquired by such hardware equipment was recorded and stored for later analysis, via means of various versions of a BIOPAC Systems Inc. designed data processing software application called AcqKnowledge. The versions of AcqKnowledge used to record and store the data obtained during these ARS appointments, range from the AcqKnowledge 4.0.0 version of the software application to the AcqKnowledge 5.0.0 version of the software application.

During autonomic reflex screen appointments, non-invasive electrophysiologic measures such as finger cuff beat-to-beat blood pressure (BP) and upper forearm cuff variably timed blood pressure (BP), beat-to-beat electrocardiography (ECG), palmar electrodermal activity (EDA), as well as measures of photoplethysmography based finger pulse volume (FPV), were obtained over the entire period of each autonomic function related test (Dusi et al., 2020). As such these measures were obtained during rest periods prior to as well as after the application various stressors (Dusi et al., 2020), and also during the application of each autonomic stressor (amongst which were a heart rate deep breathing; HRDB test routine, a Valsalva Maneuver routine, a posture change; specifically, a head up tilt [HUT] routine or test, and a QSWEAT or quantitative sudomotor axon reflex test [QSART] routine). Administration of all four of these autonomic function tests (AFTs) or autonomic nerves testing routines, constitute the full testing protocol of an ARS. However, a significant percentage of the patients tested at the UCLA CAC only underwent a partial ARS, because they only underwent HUT testing during their ARS appointments. The variables measured for an appraisal of a patient's autonomic function, as well as the specific autonomic responses tested during autonomic disorder screening, are outlined in Table 6.

The protocol followed for administering each of these AFTs, is outlined in the steps of "A

Fancruft Guide to the Autonomic Reflex Screening," which was updated by Jeff Hale on November 1, 2018. Some of the content in the Fancruft Guide was derived from BIOPAC System Inc.'s manuals for taking EDA and FPV measures, the pre-procedure patient education instructions for autonomic reflex screen related testing outlined in the UCLA CAC's patient instruction handouts titled "UCLA Autonomic Nervous System (ANS) Testing Instructions 2018" and "Autonomic Lab Medication to Hold", as well as testing manuals from WR Medical Electronics Co. (BIOPAC System Inc., 2012; CNSystems, 2012; Hale 2018; UCLA Cardiac Autonomic Labs, 2018; WR Medical Electronics Co., 2018a; WR Medical Electronics Co., 2018b; WR Medical Electronics Co., 2017; WR Medical Electronics Co., 2016).

Summary

Additional details regarding data acquisition are provided in the appendix for supplementary materials (Appendix A). Briefly, full ARSs were performed via employment of the TestWorks System (WR Medical, Minneapolis, MN). Cardiovagal, adrenergic, and sudomotor function, as well as the CASS, were assessed per clinical standards (Novak, 2011). Also, right-palmar EDA, was sampled continuously using the EDA100C module via MP160 Data Acquisition System (BIOPAC Systems, Goleta, CA). Data from both of these systems, were simultaneously acquired during autonomic testing, with a synchronized trigger to mark each of the pertinent events (i.e., each of the successive autonomic function tests).

Data Collection Approach for Building Both of the EDA-POTS Study Datasets

Individual case reports for all patients referred to the UCLA CAC from January 1, 2017, through December 31, 2021, for an autonomic reflex screen (ARS), were examined for the extraction of pertinent electrophysiologic data collected during either the full quartet of ARS tests, or from the partial ARS test (comprised of just the head-up tilt table test). As such, part of the data for this study was extracted from the results of the Quantitative Sweat Measurement System (or the Q-Sweat Measurement System), which is the commercial version of the Quantitative Sudomotor Axon Reflex Test (QSART) (Sletten et al., 2010). Other components of the requisite data were obtained from the HRDB test, the VM test, and the

head-up Tilt Table Test (TTT) (Low et al., 2009; Raj et al., 2020; Sheldon et al., 2015; Sletten et al., 2010; Thijs et al., 2021).

Extraction of skin conductance response (SCR) related data, which are the fast-moving high frequency components of the overall electrodermal signal trace, was done after first smoothing the signal via means of "median value smoothing" at 250 samples per second, because some researchers hold that EDA signals should be sampled at a rate between 200-400 samples per second at a minimum, to be able accurately distinguish phasic from tonic components of the trace (Figner & Murphy, 2011). Thereafter, the "Connect Endpoints" feature in AcqKnowledge was utilized for removing artifacts, before a highly selective low pass FIR filter, with a frequency cutoff fixed at 1 Hz over a Blackman -61dB Window, was applied to each EDA signal trace, for the removal of noise from the signal. The unspecified SCRs were located via use of the "Locate SCRs" feature of AcqKnowledge, to be found in the drop-down menu of the Electrodermal Activity item, under the Analysis tab. Then similarly, event-related SCRs (e.g., specific phasic EDA waveforms associated with specific events such as each of the deep breathing tests, Valsalva maneuvers, tilt-up, and tilt-down), were identified by applying the "Event-related EDA Analysis" feature of AcqKnowledge, which can be found within the drop-down menu of the Electrodermal Activity item, under the Analysis tab (Braithwaite et al., 2015).

For such data extractions, a minimum separation of 1 second in-between the stimulus event and the SCR was selected, while a maximum separation of 10 second in-between the stimulus event and the SCR was also selected. The location of each of the non-specific SCRs, was done with the "Threshold" set at 0.01 micro Siemens, because after application of a highly selective low pass FIR digital filter of 1 Hz, it was deemed necessary for the purposes of this particular study, to identify every single SCR that passed through such filtration. In line with this rationale the "EDA Preferences" were set to "Reject SCRs under" 0% of maximum, and phasic EDA signals were set to be constructed using "0.05 Hz High Pass Filter". For both the specific SCR (SSCR) and non-specific SCR (NSSCR) summary count options, "Fixed Width Time

Epochs" of 10-seconds were selected, to ensure identification of all SCRs located within the minimum and maximum separation time (latency) windows in-between each of the stimulus events as well as their respective event-related SCRs (Braithwaite et al., 2015).

All of the ARS cases selected for this project were reviewed and curated, as one of the tasks performed by the PI over the past two years as a GSR assigned to the UCLA CAC. These are cases of patients referred to the UCLA CAC for autonomic reflex screen related tests, from April 17, 2017, to December 23, 2021. Patient electronic medical records held in lab computers, as well as others accessed via CareConnect, were reviewed for the extraction of pertinent data. Then the PI built two main datasets from such data for use with this PhD dissertation project, and stored them in a secure 16-digit password protected padlock drive. Approval to extract and compile this data was initially covered by a pre-existing institutional review board (IRB) approval to which the PI had been added as a key personnel. This is IRB# 11-002516. However, following approval of IRB# 22-000769, which covers research for the PI's PhD dissertation project, as well as consultation with the UCLA Clinical and Translational Sciences Institute (CTSI), the CTSI identified and extracted a total of 736 records of patients who underwent ARSs at the UCLA CAC during the period from January 1, 2017, to December 31, 2021. This represents an additional 141 ARS cases.

Thereafter, the PI built another dataset, this time comprising phasic EDA components focused data, extracted from an age, sex, and ARS type matched sample of just 28 study participants, who are a subset of the 100 study participants that were included in the first dataset (or database). Specific study variables, listed by column in each respective Excel worksheet, are given (or listed) in associated tables and Excel worksheets (Table 6, Supplemental Tables 14, 15, 16, 17, 18, 19). These tables have been placed in pertinent chapters within the main body of this dissertation, or else they have been included as supplementary materials in the appendices.

After reviewing the aforementioned additional ARS reports, such data was sorted into various

categories, placed in different columns in the worksheets of respective Excel files with suitable headings (equivalent to each variable of interest), and stored in the previously created databases. During this data extraction processes, the datasets were de-identified to conform with the (HIPAA) guidelines, and also to guaranty the safety and confidentiality of protected patient information (USDHHS, 2020). Some of the supplementary material will be uploaded to ProQuest data storage folders, and published in established university electronic archives, when this dissertation is released for public access via ProQuest.

Research Question, Specific Aims and Hypotheses

Research Question

Are there associations among EDA indices derived from the EDA traces recorded during the tilt table testing period of autonomic reflex screening (ARS), and variables measured with gold standard autonomic function tests (AFTs) over the same tilt table testing period, via use of validated autonomic reflex screening (ARS) protocols. Furthermore, can such EDA indices be used as markers of sympathetic nervous system activity for development of diagnostic, or prognostic measures, mechanistic characterization, subtype differentiation of POTS, and identification of any medication effects and symptoms experienced during the tilt table testing in persons with POTS?

Specific Aims

There are six specific aims of this PhD project, each of which has at least one associated hypothesis. These are as follows:

Aim One

Determine whether there are there any notable differences (determined by a $p<0.05$) in the distribution of EDA Response Subtypes in the group of patients diagnosed with POTS, as well as in the group of controls, selected from the population of patients screened for evidence of dysautonomia at the UCLA CAC from 2017 to 2021.

Exploratory Hypothesis One. There are notable differences (determined by a $p<0.05$) in the

distribution of EDA Response Subtypes in the group of persons with POTS versus controls.

Aim Two

Determine whether BP trends during head up tilt (HUT) testing, are associated with any of the other variables or indices obtained from autonomic function test results (determined by the ranking of results from running correlations tests, as either very weak, weak, moderate, strong, or very strong), or if they can be distinguished by groups (controls or cases) and/or by EDA response subtypes (determined by comparison between groups and/or subgroups, and a $p<0.05$).

Exploratory Hypothesis One. BP trends during HUT are associated (determined by the ranking of results from running correlations tests, as either very weak, weak, moderate, strong, or very strong), and/or they can be distinguished by comparison of groups (controls or cases) and/or EDA response subtypes (determined by comparison between groups and/or subgroups, and a $p<0.05$).

Aim Three

Determine whether HR trends during head up tilt (HUT) testing, are associated with any of the other variables or indices obtained from autonomic function test results (determined by the ranking of results from running correlations tests, as either very weak, weak, moderate, strong, or very strong), or if they can be distinguished by groups (controls or cases) and/or by EDA response subtypes (determined by comparison between groups and/or subgroups, and a $p<0.05$).

Exploratory Hypothesis One. HR trends during HUT are associated (determined by the ranking of results from running correlations tests, as either very weak, weak, moderate, strong, or very strong), and/or they can be distinguished by comparison of groups (controls or cases) and/or EDA response subtypes (determined by comparison between groups and/or subgroups, and a $p<0.05$).

Aim Four

Determine whether any EDA variables derivable from EDA signal traces recorded during HUT, are associated with any of the other variables or indices obtained from autonomic function test results

(determined by the ranking of results from running correlations tests, as either very weak, weak, moderate, strong, or very strong), or if they can be distinguished by groups (controls or cases) and/or by EDA response subtypes (determined by comparison between groups and/or subgroups, and a $p<0.05$).

Exploratory Hypothesis One. EDA variables derived from EDA signal traces recorded during HUT, are associated (determined by the ranking of results from running correlations tests, as either very weak, weak, moderate, strong, or very strong), and/or they can be distinguished by comparison of groups (controls or cases) and/or EDA response subtypes (determined by comparison between groups and/or subgroups, and a $p<0.05$).

Aim Five

Determine whether any of the measures obtained during a patient's autonomic reflex screen (ARS), including (but not limited to) symptoms or symptom clusters, each component of the composite autonomic symptom score (CASS), the CASS (i.e., the Total CASS or the degree of General Autonomic Impairment {GAI} if any), each of the latency variables, the pressure recovery time (PRT), any of the QSWEAT variables, and/or the pre-ARS medication-holding adherence, are associated (determined by the ranking of results from running tests for correlations, as being either very weak, weak, moderate, strong, or very strong), with any of the continuous EDA indices, or any of the standard ARS measures.

Exploratory Hypothesis One. There are associations (determined by the ranking of results from running tests for correlations, as being either very weak, weak, moderate, strong, or very strong), among ARS derived measures such as symptoms or symptom clusters, components of the composite autonomic symptom score (CASS), the CASS (i.e., the Total CASS or the degree of General Autonomic Impairment {GAI} if any), latency variables, the pressure recovery time (PRT), QSWEAT variables, the pre-ARS medication-holding adherence, continuous EDA indices, and any of the standard ARS measures (i.e., variables or indices).

Aim Six

Explore the potential utility of EDA Response Subtypes and other EDA variables (determined by comparison between and within groups as well as a $p<0.05$, sensitivity and specificity tests, receiver operating characteristic curves {ROCs} with their associated area under the curve {AUC} values, as well as correlation coefficients), in the diagnosis of POTS, and in the determination of hyperadrenergic POTS.

Exploratory Hypothesis One. EDA Response Subtypes are associated (determined by comparison between and within groups as well as a $p<0.05$, sensitivity and specificity tests, receiver operating characteristic curves {ROCs} with their associated area under the curve {AUC} values, as well as correlation coefficients), with one or more of the ARS derived gold standard variables used to diagnose POTS.

Exploratory Hypothesis Two. One or more of the other continuous EDA variables or indices, are associated (determined by comparison between groups {controls or cases} and within groups {i.e., when stratifying by ERS} and a $p<0.05$, sensitivity and specificity tests, receiver operating characteristic curves {ROCs} and their related area under the curve {AUC} values, as well as correlation coefficients), with one or more of the ARS derived gold standard variables used to identify the likely presence of hyperadrenergic POTS.

Participant Data (Covariates)

It was proposed that the core covariates collected for this EDA-POTS study, should include, age, sex, height, weight, BMI, blood pressures (BPs), heart rates (HRs), ECG signal traces, electrodermal activity (EDA) signal traces, list of medications taken 48 hours before ARS appointments, symptoms reported during head up tilt, QSWEAT measures, heart rate deep breathing test derived measures, Valsalva Maneuver derived measures, HUT derived measures, and Composite Autonomic Severity Score (CASS) (Feigofsky & Fedorowski, 2020; Novak 2011). (also see a list of core autonomic function tests and key variables to measure specific autonomic responses outlined in Table 6). These measures are needed

for diagnosis of autonomic dysautonomia (Feigofsky & Fedorowski, 2020; Novak 2011) in each of the patients screened (including the diagnosis of postural orthostatic tachycardia syndrome [POTS]), and a determination of subtypes of POTS, the identification of any potential confounders, determination of the Composite Autonomic Severity Score (CASS) (Feigofsky & Fedorowski, 2020; Novak 2011), and also for the stratification of the group of persons diagnosed with POTS based upon their ARS results, into pertinent diagnostic age groups; specifically into subgroups of those aged 19 years old or younger, and those aged 20 years old or older (Arnold et al., 2018; Feigofsky & Fedorowski, 2020; Novak 2011; Posada-Quintero & Chon, 2020; Raj & Levine, 2016; Raj, 2006; Thijs et al., 2021; Sheldon et al., 2015).

Data Protection Measures

All PHI were protected by strict adherence to UCLA's data safety guidelines and the data safety plan outlined in the already approved IRB (IRB #22-000769). A coding process was used to ensure that any data extracted from the data set provided UCLA CTSI, was de-identified before their removal from the original CTSI data set used for the PI's PhD dissertation project. Toward this end, each case selected for the cohort of pathologic cases, was identified only by a unique Case Number (but with the patient's MRN, name, initials, and other PHI removed, except for the age, city, and zip code, which were retained for data demographics, to describe disease incidence and prevalence in future studies). If any data from the database were shared with a collaborator or statistician who was not a member of the study team, patient health information (PHI) such as city and zip code were removed, and only the study subjects' age were included (because age is an important diagnostic criterion). The designated coder was the PI, who was responsible for the data coding process. Furthermore the PI, was also responsible for keeping a set of backup folders in the UCLA Health Sciences Box of such data.

Data were stored and transmitted via means of a 16-digit password protected padlock drive, as well as by uploading data to the UCLA Health Sciences Box, and thereafter sharing such data with key study personnel. A firewall was already installed on the UCLA Cardiac Autonomic Lab's Dell computer,

which is also password protected. This computer is kept in a room with restricted access to authorized personnel. Likewise, all laptops used to store and otherwise work on any data related to this project, have firewalls installed, and have been checked out and approved by personnel from the UCLA's digital technology (DGIT) team. Such computers are also password protected to afford an added layer of data safety, and controlled access privileges are only afforded to key study personnel authorized to use any hardware designated for data storage. Any PHI data provided by CTSI from patients' EMRs stored in CareConnect, were locked down in ULead. Whenever data was shared with a non-UCLA collaborator, such data were first de-identified before they were shared. Similarly, for any data that were shared with a statistician, such data were first de-identified before sharing them with the statistician.

Data Analyses

Data extracted from patients' electronic medical records, and then placed in the newly created database in the form of an Excel workbook, were analyzed for pertinent associative relationships, using various statistical analyses (which are listed in the subsequent subsection about the statistical analyses). Since this project was partially a retrospective record review of the data collected with EDA sensors, FPV focused PPG sensors, and AcqKnowledge software (which is developed by BIOPAC Systems Inc.) during autonomic reflex screening, such data were compared with the sets of other data collected concurrently on the same patients using BP, HR, RR and sweat response sensors, as well as TestWorks software (from WR Medical Electronics Co.) (see Supplemental Tables 14, 15, 16, 17 and 18). Both of these data groups were compared, to examine the utility of EDA in investigating the diagnosis and prognosis of POTS, as well as its utility in exploration of pathophysiologic mechanisms of POTS, identification of any indicia of hyperadrenergic POTS, and its potential usefulness in mapping out symptoms and medication effects during autonomic reflex screen related testing.

Raw skin conductance levels (SCLs), abstracted into the second relational database (which is also designated Dataset #2), and which is focused on datums pertinent to phasic (rather tonic) components

of the broad EDA signal trace (see Supplemental Table 19), were whenever appropriate, normalized for parametric analyses through logarithmic transformation, followed by range standardization for comparison across study participants (Braithwaite et al., 2015). Standardizations of some of the other phasic EDA datums; i.e., specifically those parameters that are based upon the faster moving high frequency skin conductance responses (SCRs), in contrast with the SCL indices we extracted, were effected via means of well-established, and also novel, ratio standardization processes, as well as the use of well-known Z-score and T-score data standardization modalities (Ben-Shakhar, 1987; Ben-Shakhar, 1985; Bhaktar et al., 2022; Braithwaite et al., 2015; Boucsein, et al., 2012; Boucsein, 2012; Bush et al., 1993; Dawson et al., 2007; Dawson et al., 2001; Eimontaite, et al., 2013; Lavezzo, et al., 2024; Romine et al., 2022; Stemmler, 1987; Tajadura-Jiménez, & Tsakiris, 2013). The raw amplitudes of the SCR with the maximum SCL during pertinent pre-ARS or other testing periods, as well as the raw amplitudes of each event-related SCR during any of the deep breathing (DB), Valsalva maneuver (VM), and head-up tilt-table test (HUTT) periods, were standardized via means of the aforementioned Z-score and T-score transformation methods, and methods of EDA data standardization for comparison of data across study participants.

For range standardization of certain variables, the procedure outline in Braithwaite et al., 2015, wherein SCLs are corrected via use of the mathematical formula (please see below) was followed.

$$\text{Range Corrected Score } (SCL_{RCS}) = (SCL - SCL_{min}) / (SCL_{max} - SCL_{min})$$

This formula was used with each of the study participant's data, to arrive at each of the three range standardized variables reported in the phasic EDA focused dataset. Note that these are the patients included in the 28-study-participants based Dataset #2 (Braithwaite et al., 2015). When applying this formula, one is computing the minimum SCL during a baseline or rest period (in this instance the focus area encompassing the 2-minutes pre-ARS testing period was used), as well as a maximum SCL during the most arousing period (for this the maximum SCL throughout the entire ARS period was used). Thus

the participants' SCL at any other time period during the ARS study, may then be delineated thereafter, as a percentage of their individual range of psychophysiological response via application of the formula stated above. If stimuli, such as a loud clap, other startle reflex, or graphic image is deemed the maximal type of arousal, the maximum SCL in that period is used (Braithwaite et al., 2015; Dawson et al., 2001).

Data were abstracted into a secure database after review of UCLA medical records. Only data that was within patients' clinical medical records, and also a part of their routine medical care were collected. Patients diagnosed with POTS based upon their ARS reports, were listed within the group of pathologic cases. Whereas those patients that could not be diagnosed with either POTS, orthostatic hypotension OH), orthostatic intolerance (OI), any other form of dysautonomia, and/or a related cardiovascular disease (based upon their ARS reports and past medical history as revealed by searches of their electronic medical records in CareConnect), were selected as controls. No other established study tests, nor patient survey questionnaires were employed for this purpose.

Statistical Analyses

Continuous variables are shown as means ± standard deviation, whereas frequencies are used to describe categorical data. Medians have been reported, for the results obtained from the analyses of samples with non-parametric distributions. For analysis of correlations, we used Pearson's correlations whenever the samples were normally distributed and if they also met the assumptions of the Pearson's Correlations test. If the distribution of the samples were non-Gaussian, then we performed correlational analysis via means of the Spearman's Correlations test. For comparison of non-parametric continuous and ordinal variables between two groups, the Wilcoxon rank sum test was used to compute p-values. However, whenever a couple of samples were normally distributed, we employed the T-Test (or Student T-Test). For comparisons of the means of two independent groups which met the assumption of equality of standard deviations, we employed the unpaired T-Test if other assumptions were met. However, for any of those instances when the standard deviations were not equal, we used the unpaired T-Test with

Welch's correction (see Supplemental Table 16 for common and statistical variable names).

For detecting differences in three or more independent, yet also normally distributed samples, or groups (i.e., categorical variables representing the study groups such as controls vs POTS cases, or the EDA response subtypes, transient, absent, delayed and persistent), we employed the one-way ANOVA or one factor ANOVA test. To make comparisons of either continuous and/or ordinal variables across three or more groups with non-Gaussian samples, we employed the Kruskal-Wallis test for computation of the p values. The p values for group versus EDA response subtype, were computed using Fisher's Exact Test, and the Chi Square test was used to compare differences between independent samples in respect of one variable, when their distribution was non-parametric. Also, the Mann-Whitney U Test, was used to evaluate differences in the rank sum, between two independent samples (or unpaired groups) with a non-parametric distribution.

Mood's Median Test was used to assess differences in the medians of at least two groups, wherein at least one group had a non-Gaussian distribution. Following the use of the Kruskal-Wallis Test, post hoc multiple pairwise comparisons were done. Furthermore, q-values were determined to verify the validity of p-values generated by uses of Spearman's Correlations Test. To appraise the probability of the accuracy of certain novel EDA variables in delineating patients with POTS from our relatively healthy controls, a logistic regression with the RStudio statistical package was performed.

These analyses were performed using statistical software packages such as Excel app's Statistical Analyses Toolkit package, GraphPad Prism version 10.2.0, R 4.03 with RStudio, the SAS app version 9.4.7 (SAS Institute, Cary, NC, USA), and SPSS Statistics 27 (IBM Corporation, Armonk, NY, USA). SPSS Statistics 27 (IBM Corporation, Armonk, NY, USA), was used to generate the boxplots and ROCs with AUCs.

Exploratory Hypotheses Tested by the Statistical Tests

Exploratory Hypothesis One of Aim One. This was tested with a use of Fisher's Exact Test, because the distribution of the samples of controls and POTS cases are nonparametric, and also because

it required the comparison of categorical EDA response subtype variables (i.e., each of the four ERSs), with the binary group variables of controls versus POTS cases.

Exploratory Hypothesis One of Aim Two. This was tested by a use of the Kruskal-Wallis Test, because the distribution of the samples of controls and POTS cases are nonparametric, the distributions of BP trends across the respective ERSs were also non-Gaussian, and also because it required the comparison of a continuous variable (specifically BP), with categorical EDA response subtype variables (i.e., each of the four ERSs), or with the binary group variables of controls versus POTS cases. Whenever the samples were distributed normally, the T-Test was used for comparison of samples that met the assumption of equality of means, otherwise the T-Test with Welch's Correction was used to compare HR across two groups with a parametric distribution. For a comparison of the distribution of HR across three or more subgroups (i.e., three or four subgroups of the ERSs), the Mann-Whitney U Test.

Exploratory Hypothesis One of Aim Three. This was tested by a use of the Kruskal-Wallis Test, because the distribution of the samples of controls and POTS cases are nonparametric, the distributions of HR trends across the respective ERSs were also non-Gaussian, and also because it required the comparison of a continuous variable (specifically BP), with categorical EDA response subtype variables (i.e., each of the four ERSs), or with the binary group variables of controls versus POTS cases. Whenever the samples were distributed normally, the T-Test was used for comparison of samples that met the assumption of equality of means, otherwise the T-Test with Welch's Correction was used to compare HR across two groups with a parametric distribution. For a comparison of the distribution of HR across three or more subgroups (i.e., three or four subgroups of the ERSs), the Mann-Whitney U Test.

Exploratory Hypothesis One of Aim Four. This was tested by a use of the Kruskal-Wallis Test, because the distribution of the samples of controls and POTS cases are nonparametric, the distributions of each of the tonic EDA variable across the respective ERSs were also non-Gaussian, and also because it required the comparison of a continuous variable (specifically each of the phasic and tonic EDA

variables), with categorical EDA response subtype variables (i.e., each of the four ERSs), or with the binary group variables of controls versus POTS cases. Whenever the samples were distributed normally, the T-Test was used for comparison of samples that met the assumption of equality of means, otherwise the T-Test with Welch's Correction was used to compare HR across two groups with a parametric distribution. For a comparison of the distribution of HR across three or more subgroups (i.e., three or four subgroups of the ERSs), the Mann-Whitney U Test.

Exploratory Hypothesis One of Aim Five. This was tested by a use of either Fisher's Exact Test, the T-Test, the T-Test with Welch's Correction, the Mann-Whitney U Test, or the Kruskal-Wallis Test. This is because each of the other measures obtained during a patient's autonomic reflex screen (ARS), including the symptoms or symptom clusters, components of the composite autonomic symptom score (CASS) and the CASS (i.e., the Total CASS or the degree of General Autonomic Impairment {GAI} if any), each latency variable, the pressure recovery time (PRT), QSWEAT variables, and pre-ARS medication-holding adherence, are either categorical variables (for example, Symptoms Were Present During HUTT, or Symptoms Were Not Present During HUTT, or the Patient Held their Medications 48-hours Before their ARS, or the Patient Did Not Hold their Medications 48-hours Before their ARS), or else they were continuous (e.g., QSWEAT variables, components of the composite autonomic symptom score (CASS), the CASS (i.e., the Total CASS or the degree of General Autonomic Impairment {GAI} if any), the Pressure Recovery Time (PRT), and each of the ARS latency variables). This hypothesis was tested by a use of the Kruskal-Wallis Test (or Wilcoxon Rank Sum Test), whenever the distribution of the other ARS variable between the controls and POTS cases was nonparametric, and it involved comparison of a continuous variable (e.g., Sweat Volume), with categorical EDA response subtype variables (i.e., each of the four ERSs), or with the binary group variables of controls versus POTS cases. Whenever the samples were distributed normally, the T-Test was used to compare groups of samples that met the assumption of an equality of means, otherwise the T-Test with Welch's Correction was used to compare HR across two

groups with a parametric distribution. For comparison of the distribution of any of the other continuous ARS variables across three or more subgroups (such as either three or four subgroups of the ERSs), the Mann-Whitney U Test was used.

Exploratory Hypothesis One of Aim Six. This was tested by examining the sensitivity and specificity of each of the core gold-standard ARS diagnostic variables (specifically, HR Delta, the Maximum HR in HUTT, the Minimum SBP in HUTT, the Change in the Minimum SBP in HUTT from its Pre HUTT Value, the individual components of the CASS, the CASS (i.e., the Total CASS or the degree of General Autonomic Impairment {GAI} if any), the PRT, HRDB Delta HR, HRDB E:I Ratio, Valsalva Greatest HR Ratio, and the QSWEAT Total Volume), as well as by generating some associated ROC curves with AUCs. Also, whenever the samples had a parametric distribution, comparisons were made between groups and subgroups, by using either the T-Test for comparison of samples that met the assumption of equality of means, or by use of the T-Test with Welch's Correction. For a comparison of three or more subgroups (i.e., three or four subgroups of the ERSs), the Mann-Whitney U Test was used.

Exploratory Hypothesis Two of Aim Six. This was tested by use of Spearman's Correlations Test when the samples had a non-Gaussian distribution, and with Pearson's Correlations, whenever the distribution of the samples were parametric. This is because some of the gold-standard ARS variables, which were used for the determination of the likelihood of the presence of the hyperadrenergic POTS subtype in a patient with POTS, are continuous numeric variables (e.g., PRT, and the adrenergic component of the CASS). It should be noted however that there are other indicia of the hyperadrenergic POTS subtype, inclusive of symptoms during HUTT such as clamminess, pain in the lower extremities, a hypertensive (rather than a hypotensive) response to upright tilt, together with sustained tachycardia, and/or an exaggerated Phase 1V overshoot during Valsalva, which are categorical variables. However, these indicia are not a certainty that the patient has hyperadrenergic POTS, because further diagnostic testing is required; specifically a catecholamine test, along with an orthostatic challenge using the

plasma norepinephrine levels of blood drawn when the patient is sitting, and when they are standing. A plasma norepinephrine level of ≥ 600 pg/ml with postural change, is indicative of presence of the hyperadrenergic POTS subtype (Feigofsky & Fedorowski 2020; Freeman et al., 2011; Kanjwal et al., 2011; Low et al., 2009;Taub et al., 2021).

Summary

Data abstracted from patients' UCLA records were exported to two relational databases after removal of all patient identifiers. Then the deidentified data underwent statistical analyses with tests such as the Chi Square Test, Fisher's Exact Test, Kruskal-Wallis' Test, Mann-Whitney U Test, Normality and Lognormality Test, Unpaired T Test, Unpaired T Test with Welch's Correction, Linear Regression, Logistic Regression, Sensitivity and Specificity Test, Z test, Mood's Test for Medians, as well as Pearson's Correlations Test, and Spearman's Correlation Test. The statistical tools earmarked for the statistical data analyses were GraphPad Prism version 10.2.0, R 4.03, RStudio, Mood's Median Online Calculator from AtoZmath.com, SAS version 9.4.7 (SAS Institute, Cary, NC, USA), and the SPSS Statistics 27 (IBM Corporation, Armonk, NY, USA), statistical analysis software apps. These packages were used for the various requisite analyses performed during the course of this study. The strength of correlations was determined according to the ranking and interpretation of correlation coefficients depicted in Table 7.

Limitations

Amongst some of the health system factors that impacted the retrospective portion of the data collection process outlined above, are the usual bugs of a retrospective chart review, such as existence of missing patient records, presence of corrupted electronic files (which sometimes were irretrievable), as well as the presence of incomplete physician reports, lab reports, patient medication lists, etc. (Talari & Goyal, 2020). Such actual and/or potential obstacles to the processes of data collection, extraction, analyses, and interpretation, fell broadly into the following four categories. One, the non-availability of accurate/comprehensive autonomic reflex screening reports. Two, the non-availability of accurate,

comprehensive, labelled and time-stamped EDA signal tracings. Three, the non-availability of complete and comprehensive sets of each patient's medical and/or medications history. Fourth and finally, the existence of incomplete and/or inaccurate reporting by patients, of the symptoms they had experienced during head up tilt testing.

Conclusion

It was proposed that the methodology applied to this PhD project, should be an amalgam of several approaches, some of which involved a retrospective record review of existing electronic patient medical records, and others, which involved implementation of a partially prospective data acquisition process from the perspective of the student investigator and PI. It is important to note however that from the perspective of the coinvestigator Dr. Ajijola, all data acquisition related to this project, inclusive of the data collected by the PI, and the new database created by the PI, were from the outset a part of a long-range prospective research endeavor, because he was involved in the data collection at the UCLA Cardiac Arrhythmia Center (a lab he directs), since the very beginning of the research endeavor in 2017.

The steps implemented for the realization of the objectives of this PhD project are outlined in Figure 1. The plan for this study is given in Figure 2. Finally, it should be noted that because knowledge of the etiology of POTS remains limited, yet adrenergic, deconditioning, and neuropathic pathways have been proposed as mechanisms underlying POTS, it was envisaged that the investigation and explorations conducted during the course of this research project, might yield evidence to validate one or more, of the aforementioned proposed pathways (Feigofsky & Fedorowski, 2020; Novak 2011; Posada-Quintero & Chon, 2020; Thijs et al., 2021). Furthermore, any insights gained from analyses of the study findings, may yield novel avenues for the pharmacological, as well as the non-pharmacological treatment of POTS (Arnold et al., 2018; Raj & Levine, 2016; Raj, 2006; Revlock, 2018; Rodriguez et al., 2020; Sheldon et al., 2015; Thanavaro & Thanavaro, 2011; Taub et al, 2021).

Table 6

Appraisal of Autonomic Function and Specific Autonomic Responses Tested

	HRDB Test	Valsalva Test	Postural Test	Sweat Test
SBP (mmHg) DBP (mmHg) MBP (mmHg)	Difference between the means of values at baseline and test values.	Difference between the means of values at baseline and test values.	Difference between the means of values at baseline and test values.	Difference between the means of values at baseline and test values.
HR (bpm)	Difference between the mean test HR and the mean baseline HR.	Difference between the mean test HR and the mean baseline HR.	Difference between the mean test HR and the mean baseline HR.	Difference between the mean test HR and the mean baseline HR.
Total Volume (AU) Response Latency (mins) End Offset (AU) Baselines (AU)				Difference between the means of the test values and the baselines.
EDA (µS)				Difference between the mean value in the 30 seconds before applying the Stressor (i.e., head up tilting from an angle of 0 degree to an angle of 70 degrees) during HUTT testing, or prior to the application of any other autonomic stressor, e.g., HRDB, VM, or QSART, and the mean value over the course of the test.
FPV (Volts)				

Note. Abbreviations: DBP= diastolic blood pressure; EDA=electrodermal activity; HR= heart rate; FPV=finger pulse volume; MBP= mean blood pressure; SBP=systolic blood pressure; AU= arbitrary unit.

Table 7

Strength of Association for Absolute Values of the Correlational Coefficient (r)

Range Number	Range of Correlational Coefficient (r)		Absolute Values of the Correlational Coefficient (r)	Classification or Interpretation
1	0.000 to 0.199		0.000 to 0.199	Very Weak
2		0.000 to -0.199		
3	0.200 to 0.399		0.200 to 0.399	Weak
4		-0.200 to -0.399		
5	0.400 to 0.599		0.400 to 0.599	Moderate
6		-0.400 to -0.599		
7	0.600 to 0.799		0.600 to 0.799	Strong
8		-0.600 to -0.799		
9	0.800 to 1.000		0.800 to 1.000	Very Strong
10		-0.800 to -1.000		

Note. From an interpretation of the ranges of the strength of association of the correlational coefficient (r) between variables given in a BMJ article on correlation and regression. Copyright 2023. 1.1. Correlation and regression. *BMJ*. Calculation of the Correlation Coefficient. Retrieved from the URL https://www.bmj.com/about-bmj/resources-readers/publications/statistics-square-one/11-correlation-and-regression. Note that these ranges for the strength of association between correlated variables are arbitrary (BMJ, 2023). Adapted with permission.

Figure 6

A Flowchart of Steps for Investigating the Utility of EDA in the Diagnosis and Exploration of Mechanisms of POTS

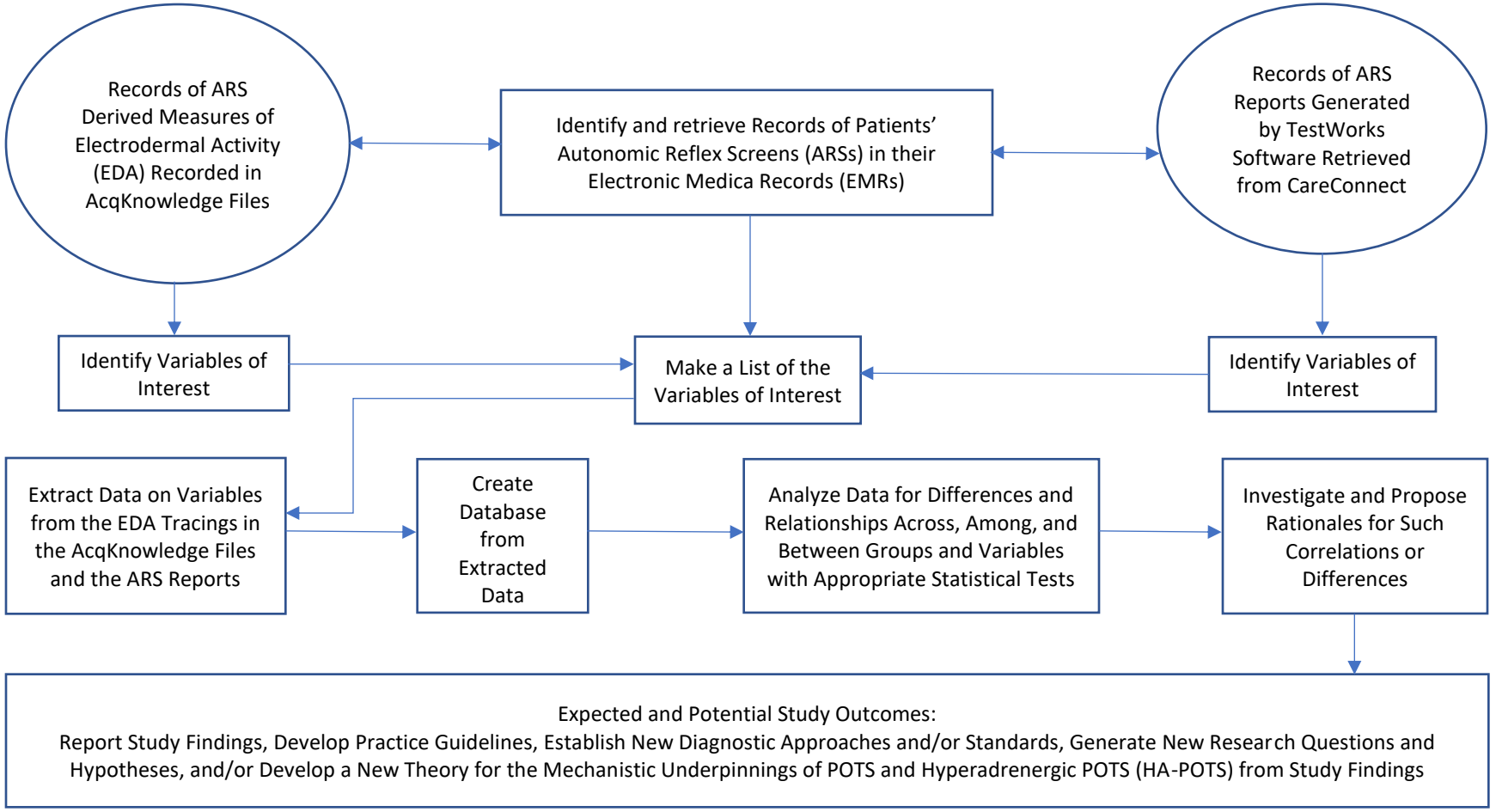
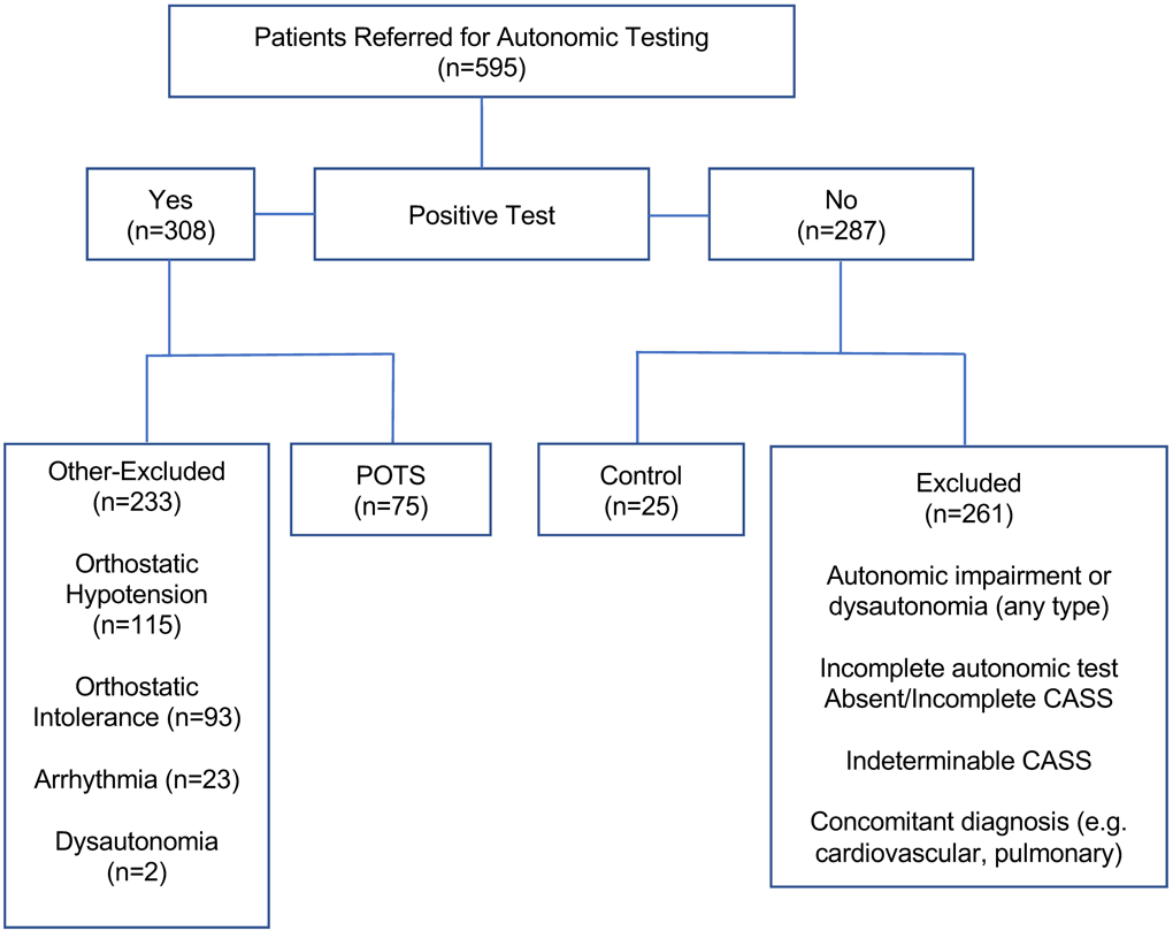


Figure 7

Study Flowchart



Note. Study Flowchart. Adapted from the Consort flow diagram of the cross-sectional study (Surono et al., 2021; Surono et al., 2021). Abbreviations: ARS, autonomic reflex screen; CASS, composite autonomic severity score; HUTT, head up tilt table; OH, orthostatic hypotension; OI, orthostatic intolerance; POTS, postural orthostatic tachycardia syndrome; UCLA, University of California Los Angeles.

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CHAPTER 5

RESULTS

Chapter 5: Results

Background

Postural orthostatic tachycardia syndrome (POTS) is a heterogenous syndrome that may involve the autonomic nervous system. It is the occurrence without orthostatic hypotension (OH), of orthostatic symptoms related to an increase in heart rate (HR) of ≥30 beats per minute (bpm) in persons aged 20 years or older (or a heart rate increase of ΔHR ≥40 bpm in persons aged 19 years or younger), and non-transient, tachycardic heart rates (HRs), of at least 120 bpm or more (Grubb 2008; Sheldon et al., 2015).

There is limited understanding of the etiology of POTS. One subtype, hyperadrenergic POTS (HA-POTS), is characterized by a change in plasma norepinephrine level from sitting to standing of ≥600 pg/dl (Feigofsky & Fedorowski, 2020; Freeman et al., 2011; Kanjwal et al., 2011; Low et al., 2009; Taub et al., 2021). Although HA-POTS has been characterized, its diagnosis and subsequent treatment remains a challenge due to the requirement for venipuncture. Other forms, for example neuropathic POTS (Kanjwal et al., 2011), remain difficult to identify. The challenge of easily differentiating POTS subtypes limits our understanding of the condition and identifying optimal treatment strategies which are often limited in efficacy (Kanjwal et al., 2011).

Electrodermal activity (EDA) is a measure of variations in electrical skin conductance, a validated index of sympathetic nervous system (SNS) activity, and has recently been used as an alternative means for the appraisal of sympathetic nervous system (SNS) activity (Benedek & Kaernbach, 2010; Boucsein, 2012; Boucsein et al., 2012; Braithwaite et al., 2015; Cheshire et al., 2021; Critchley 2002; Dawson et al., 2001; Ellaway et al., 2010; Posada-Quintero et al., 2018a; Posada-Quintero et al., 2018b; Raikes & Schaefer, 2016). Findings from past studies indicate EDA is a quantitative functional measure of sudomotor activity (Benedek & Kaernbach, 2010), which is under sympathetic control. Current applications of EDA include assessment of characteristics of concussion, emotional-responsiveness, stress-associated body-function effects, and treatment of psycho-physiological conditions such as

anxiety, stress-sensitive states and tension headaches, among others (Balegh, 2019; Boucsein, 2012; Boucsein et al., 2012; Braithwaite et al., 2015; Critchley 2002; Critchley, 2013; Dawson et al., 2001; Edward et al., 2004; Grubb, 2008; Grubb et al., 2006; Low et al., 2009; Kanjwal et al., 2011; Raikes & Schaefer, 2016). There is a paucity of research on the utility of EDA in investigations of the diagnosis, mechanisms, and prognosis of POTS (Boucsein, 2012; Critchley, 2002; Dawson et al., 2001; Grubb, 2008; Grubb et al., 2006; Kanjwal et al., 2011; Low et al., 2009).

We aimed to explore the utility of EDA in assessing the sympathetic nervous system's responses in POTS, as well as to explore its potential use in mapping out prognostic factors, medication effects, and symptoms. We hypothesized that EDA measures of sympathetic responses may provide clues into the etiology and subtypes of POTS, and reveal associations among standard and novel test measures. Such findings may yield new insights into the treatment and prognosis of POTS.

Organization of Results

Results are presented in parts, which address various aspects of the aims and hypotheses of this PhD dissertation project. Part One, includes study population descriptives (including their demographic and other characteristics at baseline), a description of the tonic EDA response patterns observed during this study, as well as results, which address aims #s 1 through 5 that pertain to physiologic trends (e.g., BP and HR trends), in the patients that displayed each of the electrodermal response patterns during head up tilt-table testing. This part also examines the differential distribution of the various patterns of tonic EDA response to upright tilt, among the control-patients and the patients diagnosed with POTS.

Part Two, includes results on the strength of association between various variables (Tables 16, 17 and 18), based upon their respective correlation coefficients. A guide to interpreting such correlation coefficients, is given in Table 7. The strength of association between the variables of interest ranged from weak to very strong. Only results deemed most pertinent to the subject of this dissertation project have been reported. However, Excel files with full results are available as supplemental material. The

results on the strength of association between various variables of interest to this PhD dissertation study, address the correlational part of the concept of association included in aims #s 2 through 6, which pertain to the physiologic trends (e.g., BP and HR trends) that are evident in the results of patients that displayed each of the electrodermal response patterns during head up tilt-table testing. Part Two, is also an examination of whether the strengths of associations noted between the various variables of phasic and tonic EDA responses to the deep breathing, Valsalva maneuver, and head up tilt-table based tests of autonomic function, may have some utility in distinguishing hyperadrenergic POTS, from other subtypes of this heterogenous disorder, such as physical deconditioning POTS, neuropathic POTS (i.e., sudomotor or small nerve fiber impairment related POTS), hypovolemic POTS, autoimmune POTS (a subtype that is variably associated with elevated levels of antinuclear antibodies, ganglionic, adrenergic, and muscarinic acetylcholine receptor antibodies, or else is associated with a higher frequency of occurrence of certain autoimmune disorders, such as celiac disease and Sjögren syndrome), chemotherapy induced POTS, and COVID-19 associated POTS.

Part Three, presents the results of a detailed analyses of the skin conductance responses (SCRs), located/identified after extracting the faster-moving and higher frequency components of the overall EDA complex, from the more slowly moving and changing lower frequency components of the entire EDA signal trace. It includes data on well-known phasic features of the overall EDA complex, such as the rise time of an SCR and its half recovery time, as well as the amplitudes (specifically, the raw amplitudes, Z-score transformed amplitudes, and T-score transformed amplitudes) of each of the most pertinent of the SCRs located via use of the “Locate SCRs” feature of the AcqKnowledge software app. The results presented in this part, address Specific Aims #s 1 through 5, which pertain to physiological trends (e.g., BP and HR trends), in the patients that displayed each of the electrodermal response patterns during head up tilt-table testing. This part also examines the differential distribution of the various patterns of tonic EDA response to upright tilt, among the control-patients and the patients diagnosed with POTS.

Chapter Six includes a discussion on the physiologic import of the various results reported in the three parts briefly described above. However, the matter of whether each set of the results reported in any of these three sections (i.e., Parts 1, 2 and 3), either support or refute this PhD dissertation study's aims and hypotheses, will be addressed in the concluding summaries at the end of each of these parts.

Part One: Subtype Differentiation of Postural Orthostatic Tachycardia Syndrome Using Electrodermal Measures of Sympathetic Function

Baseline Characteristics and Demographics

Baseline characteristics of study subjects are displayed in Table 8. Compared with controls, the patients diagnosed with POTS were younger (mean age 27.5 ± 12.2 [standard deviation] years vs. 44.4 ± 18.9 years; $p<0.001$), with a little lower baseline supine systolic pressure (109.5 ± 19.3 mmHg vs. 119.7 ± 18.8 mmHg; $p=0.025$), as well as a slightly lower diastolic blood pressure (BP) (67.4 ± 11.2 mmHg vs. 73.3 ± 10.3 mmHg; $p<0.016$). Female participants were preponderant in both groups (76.0% each).

As expected, when compared to controls, the patients with POTS, had a higher HR response during HUTT (HRΔ 54.8 ± 10.4 bpm vs. HRΔ 26.6 ± 7.4 bpm; $p<0.001$), as well as a faster average HR at the minimum SBP during HUTT (100.2 ± 19.1 bpm vs. 86.8 ± 13.9 bpm; $p<0.001$). Furthermore, more of the study participants from the group of POTS patients, reported symptoms during HUTT (92% vs 64%; $p<0.001$) (Table 8), in comparison with those from the group of controls.

Electrodermal Response Patterns Observed During Upright Tilt

Across the entire study population (N=100), we observed four visually identifiable patterns of tonic EDA during HUTT (Figure 8). We hereafter designate these broad patterns in respective EDA signal traces, as the EDA response subtypes Transient, Absent, Delayed, and Persistent.

In EDA trace pattern 1 (Transient), the EDA response during upright tilt consisted of an initial spike in the EDA amplitude upon tilt, which shortly after peaking dropped down to the baseline, and remained at the baseline for the duration of upright tilt. This pattern reflects the sympathetic surge

initially required to maintain blood pressure and heart rate following the orthostatic challenge. However, a component of this may relate to an anxious response to upright tilt in some patients. Importantly, the initial surge was rapidly extinguished.

In EDA pattern 2 (Absent), the EDA trace showed no significant response to upright tilt, and appeared as a flat-trace for the duration of upright tilt. This might indicate patients that mount no significant sympathetic surge (as measured by EDA) to the orthostatic challenge. For patients displaying pattern 3 (Delayed), the EDA trace stayed at baseline initially during HUTT, however, at about the mid to late portion of upright tilt, the EDA trace increased, peaking toward the end of HUTT and then returned to baseline shortly after tilt down to the supine position. This reflects initial tolerance of the orthostatic challenge, which gives way and requires a sympathetic surge to compensate, driving the tachycardia.

Pattern 4 (Persistent) comprises of an increase in the EDA amplitude shortly after upright tilt, which thereafter was sustained throughout tilt, and returned to the baseline, shortly after tilt down to a supine position (between three-to-four minutes after tilt-down (Figures 2A)). This pattern is reflective of the sympathetic drive required to maintain hemodynamic homeostasis for the duration of upright tilt, which only abates, upon cessation of the orthostatic challenge.

Distribution of Electrodermal Response Subtypes in POTS Versus Control Subjects.

Although four EDA subtypes were identified across the cohort, the subtypes were differentially distributed between the controls as well as the POTS cases, thus supporting Aim One, Exploratory Hypothesis One. Specifically, while the transient pattern was most common amongst controls (72%), only 21% of POTS cases exhibited this pattern. Instead, the most common subtype observed in POTS cases was Persistent (43%), which was not seen in any control cases (0%, $p<0.001$) (Table 9).

Because of the younger age distribution in POTS cases vs controls, we next sought to exclude an association between ERS pattern and age. To accomplish this, we compared a sub-sample of the POTS cases and the controls, which were matched for age, sex, and body mass index (n=18 in each group). In

this matched sample, the observations made in the larger parent sample (N=100), remained unchanged (Table 9). While 78% of control patients exhibited the Transient subtype, only 17% of the patients with POTS, exhibited this response pattern. Instead, the most common response subtype seen among POTS patients was Persistent (44%), which was seen in 0% of patients selected as controls. The distribution of the Absent and Delayed subtypes between control and POTS cases differed as follows. For the Absent pattern: 11% vs 33%; and for the Delayed pattern: 11% vs 6% for control and POTS cases, respectively.

Symptom, Electrodermal, and Hemodynamic Features of the HUTT Response Subtypes in POTS Patients.

Next, we examined the demographic, electrodermal, and hemodynamic characteristics of the four ERS subtypes in controls and POTS patients. As shown in Table 10, for the controls, the subtypes did not differ significantly by age, height, or weight, prior to autonomic function testing. With respect to the patients diagnosed with POTS, the EDA subtypes did not differ significantly by age, sex, height, weight, or medication use, prior to autonomic function testing. Additionally, baseline blood pressure and heart rate did not differ across the subtypes.

In POTS patients the heart rate change to upright tilt was different amongst the subtypes (p=0.021), with the EDA subtype 3 subjects (i.e., Delayed), showing higher heart rate responses (64.7±9.5bpm; 64.1) compared to the Transient, Absent, and Persistent subtypes (56.7±14.2; 51.4, 56.7 ± 14.2; 53.5, and 52.0±8.8; 50.6). This partially supports Aim Three, Exploratory Hypothesis One. No such differences were seen in control patients. This refutes Aim Three, Exploratory Hypothesis One. Also, the Delayed EDA response subtype was further differentiated by a greater likelihood of reporting disorientation during upright tilt (50% compared with 3.1%, 7.1%, and 9.5%, in the other subtypes, p<0.006). Symptoms in the controls differed significantly (p<0.001) by subtype, with each of controls exhibiting the Delayed EDA subtype reporting symptoms during upright tilt (100% compared to 61% [Transient] and 60% [Absent]).

With respect to tonic EDA indices, the magnitude of electrodermal activity (specifically the skin conductance level or SCL), also differentiated the EDA subtypes (Table 10). The Persistent pattern, which exhibits elevated sympathetic response for the duration of upright tilt, was associated with greater peak (maximum) electrodermal activity (13.4 ± 9.9; 10.1 μsiemens, compared to 3.1 ± 5.1; 0.9, to 11.9 ± 11.3; 0.2 μsiemens in other EDA response subtypes or subgroups, p<0.001), and also greater electrodermal response (i.e., maximum – minimum electrodermal activity 8.8 ± 7.0; 7.0 μsiemens, compared with 2.2 ± 3.7; 0.4, and 6.8 ± 5.7; 4.8 μsiemens, respectively, p<0.001). In the controls, the Transient pattern, which reflects the sympathetic surge initially required to maintain blood pressure and heart rate following an orthostatic challenge, was associated with a markedly higher peak (i.e., maximum) tonic electrodermal response (10.3 ± 11.3; 5.9 μsiemens, compared with 0.3 ± 0.3; 0.2, and 4.3 ± 1.5; 4.3, μsiemens, respectively, p=0.001). The Transient pattern observed in the controls, was also associated with a greater tonic electrodermal peak-to-peak (i.e., maximum – minimum electrodermal activity of 6.8 ± 7.6; 4.5 μsiemens, compared with 0.1 ± 0.2; 0.1, and 4.2 ± 1.6; 4.2 μsiemens, respectively, p<0.004). Each of these results support Aim Four, Exploratory Hypothesis One.

Patients exhibiting the Persistent pattern, were also more likely to have higher electrodermal activity (displayed by their higher skin conductance levels) at the end of upright tilt (9.0±7.1 μsiemens compared with 1.5±3.6 to 6.7±7.5 μsiemens, p<0.01). These findings suggest that EDA pattern 4 patients (which is the most prevalent subtype in POTS patients), exhibit higher peak sympathetic responses upon upright tilt, which do not abate during tilt, unlike the trend we observed in patients with electrodermal response pattern 1, which is the predominant subtype in control patients.

Additional Symptomatic Differentiation in the Electrodermal Response Subtypes

We examined other variations in the symptoms reported by the various electrodermal response subtypes, with the following results. In the group of controls, 61.1% of the patients who displayed the transient electrodermal response to head-up tilt, reported symptoms during upward tilt table testing,

60.0% of those displaying the absent tonic EDA pattern reported symptoms during HUTT, and 100.0% 0f those with the delayed response reported symptoms (p<0.001) (Table 12). Appraisal of such symptoms variation in the group of patients with POTS, revealed that 90.5% of those patients that displayed the transient electrodermal in HUTT, also reported symptoms during the period of upright tilt, while 85.7% the patients with the absent electrodermal response pattern reported HUTT symptoms. These results are in support of Aim Five, Exploratory Hypothesis One.

Of the patients showing a delayed electrodermal response to upright tilt, 100.0% also reported symptoms, and 93.8% of those displaying the pattern of a persistent electrodermal response in HUTT, also reported symptoms (p<0.001) (Table 12). While the proportion of symptoms reported by the controls at the time of tilt-up, varied significantly (p<0.001) (Table 12) between the EDA response subtypes, among the controls, it was unremarkable in the cases with POTS (p=0.200) (Table 12). However, when symptomatic differentiation across the ERSs was assessed in both groups, the variation in the presence of symptoms at the time of tilt-down, was equally significant in both controls and POTS cases (p<0.001) (Table 12). These results are in support of Aim Five, Exploratory Hypothesis One.

An examination of the trend in HUTT symptoms revealed significant variation across the ERSs, with respect to those without symptoms (p<0.001) in both the controls and the POTS cases. Similarly, we noted a significant variation across the electrodermal subtypes, vis-à-vis those patients that reported a decrease in their symptoms during HUTT, versus those patients that stated that their symptoms stayed the same during HUTT, as well as those that reported an increase in their symptoms during upright tilt (p<0.001) (Table 12). These results are in support of Aim Five, Exploratory Hypothesis One.

Assessment of symptoms quality and ranking via means of a newly developed symptoms scoring modality developed specifically for this investigation, revealed notable differences across the ERSs in controls as well as POTS, with respect to the numbers of asymptomatic patients during HUTT (p<0.001) respectively (Table 12). The distribution of transient symptoms across the subtypes was unremarkable in

both controls and POTS cases. However, there was marked differentiation across the tonic patterns of electrodermal response to upright tilt, with respect to patient reports of moderate symptoms (p<0.001) in both groups, and severe symptoms during HUTT in controls (p<0.001), and in POTS cases (p=0.002) respectively (Table 12). Differentiation in reports of disorientation during HUTT across each of the four electrodermal response subtypes, was notable in the cases with POTS (p<0.001), but not in the controls. Whereas there was a marked difference in the distribution of patient reports of shortness of breath in both groups (p<0.001) (Table 12). However, reports of lightheaded symptoms during upright tilt, was only statistically significant among the controls (p<0.001), because in the patients with POTS, reports of lightheadedness did not differ notably by EDA response subtype (Table 12). In summary, these results are in support of Aim Five, Exploratory Hypothesis One.

Adrenergic and Cardiovagal Response Patterns Amongst Electrodermal Response Subtypes in POTS

Next, we examined autonomic reflex function across the electrodermal response subtypes. To do so, we compared the patients' heart rate responses to deep breathing (ΔHRDB) and Valsalva ratio (VR), both of which are measures of cardiovagal function, as well as the variable, pressure recovery time (PRT), which is an adrenergic marker following Valsalva maneuver, in controls as well as in the POTS patients. HRDB responses were greater in POTS patients vs. controls (22.8 ± 8.2 bpm vs. 17.1 ± 8.3 bpm, p=0.002), while the Greatest HR Ratio in Valsalva was also significantly different (2.4 ± 0.5 vs 1.8 ± 0.2, p<0.001) (Table 10 and Supplemental Table 21). These data suggest that cardiovagal impairment is not a predominant feature of POTS. The adrenergic marker pressure recovery time (PRT) did not differ in any statistically significant manner, between the controls and POTS cases (2.4 ± 3.0; 1.4 seconds, vs 5.9 ± 12.4; 1.4 seconds, p=0.934) (Supplemental Table 21). These results are partially in support of Aims Three and Five, with their associated Exploratory Hypotheses One, respectively.

We also examined the distribution of ΔHRDB, VR, and PRT in POTS group only, since two electrodermal response subtypes were absent (ERS 4) or nearly so (ERS 3, n=2) in controls. As shown in

Supplemental Table 22, ΔHRDB ranged from 22.0 ± 7.3bpm to 25.9 ± 7.0 bpm and did not differ significantly across the subtypes. Similarly, the Valsalva Ratio (VR), did not differ significantly across the subtypes in POTS patients, ranging from 2.3 ± 0.6 to 2.7 ± 0.6. However, the average PRT was greatest in ERS 3, the electrodermal response subtype with delayed electrodermal responses during upright tilt (5.2 ± 6.4; 2.2 seconds, compared with 1.5 ± 0.9; 1.4, 1.9 ± 2.7; 1.0, and 2.7 ± 3.1; 1.5 seconds, in the other subtypes, *p*=0.015) (Table 10). These results are partially in support of Aims Two, Three and Five, with their associated Exploratory Hypotheses One, respectively.

Predictive value of Electrodermal Activity in POTS During Head Up Tilt Tests

The predictive value of each ERS subtype was assessed in relation to pulse rate area per second obtained during a head up tilt test (HUTT). A moderately strong predictive value in identifying the pulse rate area per second in patients with POTS (AUC = 0.72), was revealed in patients diagnosed with POTS, who were ≥ 20-years-old, and who also displayed the Delayed and Persistent electrodermal response subtypes (Supplemental Figure 1). Furthermore, the Absent electrodermal response subtype, was shown to have a strong predictive value in identifying the pulse rate area per second (AUC = 0.13), Because an AUC = 0.13, is interpretatively equivalent to an AUC = -0.87, which is strong (Supplemental Figure 1). The pulse rate area per second, is physiologically equivalent to an aggregate (or cumulative) of the values of the individual pulse rates measured over the period of upright tilt (or HUTT). This is because, where . . .

Pulse Rate Area = Pulse Rate x Seconds (bpm.second)

$$\text{Pulse Rate Area per Second} = \frac{\text{X units of Pulse Rate (bpm) multiplied by Y units of } \sout{\text{Time}}\ (\sout{\text{second}})}{\text{1 unit of } \sout{\text{Time}}\ (\sout{\text{second}})}$$

∴ Pulse Rate Area per Second = XY units of Pulse Rate ≡ Integral of the Pulse Rate over HUTT

Because, where an area is represented by a surface integral of a function over a 2-dimensional surface, which yields the area of that specific surface when we integrate across it, a curve, such as the arc length of the function of the individual pulse rates measured over the entire period of upright tilt (or

HUTT), is represented by a line integral, which computes the function of the said pulse rate curve, and presents the length of the arc of the pulse rate when we integrate over this curve. Alternatively . . .

$$[\iint_{PR\ Area} f(pr_{area},t)\ dA]/[1\ sec] \equiv [\int_{a,b} \sqrt{\{1+(f'(PR,t))^2 dt\}}] \equiv \text{Arc Length of the Pulse Rate Area Function}$$

Where PR Area is the index of pulse rate area, which was extracted by the AcqKnowledge software application from the PR signal trace derived from the PPG signal trace, as well as a region in the x and y plane of the PR signal trace, $f(pr_{area},t)$ is a function of each point in the PR Area or pulse rate surface area, or pulse rate planar region, and dA is a sliver of the pulse rate area. This tiny piece of the pulse rate area dA, is equivalent to . . .

$$(|[\{\partial \dot{f}\}/\{\partial pr_{area}\}] \times [\{\partial \dot{f}\}/\{\partial t\}]|\, dpr_{area} dt)$$

. . . and it is, the differential of the pulse rate area (Ely & Jones, 2023; Jones, 2020; Khan Academy, 2024; Whitman.edu, 2024). This result supports Aim Six, Exploratory Hypothesis One.

We observed a higher median HRΔ among patients with Transient, Delayed and Absent ERS, vs. the Persistent EDA response subtype, among patients in the group of patients ≤19 years during upright tilt (Supplemental Figure 2). Among those ≥20 years of age, the highest median HRΔ was in the Delayed response category, followed by the Absent, Transient and Persistent ERSs (Supplemental Figure 3). The sensitivity of the Delayed ERS pattern in identifying POTS patients within this diagnostic age range group was quite strong, with an AUC of 0.92 (Supplemental Figure 3). Both of these set of results support Aim Six, Exploratory Hypothesis One.

Comparison of ERSs vs Change in Minimum SBP from Baseline in patients ≥20 years, shows the highest median change in patients displaying the Persistent ERS pattern, followed by those displaying the Transient ERS pattern, the Absent ERS pattern, and lastly the Delayed ERS pattern (Supplemental Figure 4). Sensitivity and Specificity Analysis shows moderate utility of the Transient ERS pattern in the identification of a Change in SBP Minimum from Baseline (AUC = 0.63) (Supplemental Figure 4). These results, partially support (or validate) Aim Six, Exploratory Hypothesis One. A comparison of the

difference between post tilt DBP and baseline DBP reveals the highest median change in patients displaying the Transient ERS pattern, closely followed by those displaying the Persistent, Delayed, and Absent ERS patterns respectively (Supplemental Figure 5). These results, support (or validate) Aim Six, Exploratory Hypothesis One.

There may be some mild clinical utility in the results from an exploratory comparison of AUCs of the ROCs by ERS (Supplemental Figure 6), as these differed with respect to the Minimum Post Tilt DBP from Baseline ΔDBP_{min}) observed during upright tilt, respectively. The sensitivity of the Transient pattern (AUC of 0.59) in identifying patients with the Minimum Post Tilt DBP from the Baseline was the highest, followed by that of Persistent pattern (AUC of 0.51), the Delayed pattern (with an AUC of 0.43), and lastly the Absent pattern (with an AUC of 0.40) (Supplemental Figure 6). So, the sensitivity of either the Delayed or Absent ERSs, offer little more than a chance, of distinguishing patients with the Minimum Post Tilt DBP from the Baseline from other patients. These results, partially support (or validate) Aim Six, Exploratory Hypothesis One.

Furthermore, there were notable differences in the maximum HR during upright tilt across the ERSs, with the highest median *HR Maximum*, being observed in the patients exhibiting the Delayed ERS pattern, followed by those displaying the Transient ERS pattern, next by the patients with the Persistent ERS pattern, and finally by the patients that displayed the Absent ERS pattern (Figure 10). These results support Aim 3, Exploratory Hypothesis One. The ROC curves show a high sensitivity to selection of patients with a sustained HR ≥120 bpm, in POTS cases with the Delayed ERS pattern (Supplemental Figure 7). For this specific ROC curve, the AUC generated from the data for the patients displaying the Delayed ERS pattern was 0.82 (Supplemental Figure 7). These results are in support of Aim 3, Exploratory Hypothesis One., as well as Aim Six, Exploratory Hypothesis One.

Alternative Autonomic Function Assessment Stratified by Electrodermal Activity Response Subtypes

There was no notable difference in pressure recovery time (PRT) between the cases and controls

in the entire study population (2.4 ± 3.0 sec vs. 5.9 ± 12.4 sec; p=0.934) (please see Supplemental Table 21). However, when it was stratified by ERS, PRT differed significantly within the group of POTS patients (ERS 1: 1.9 ± 2.8 sec vs. ERS 2: 1.5 ± 0.9 sec vs. ERS 3: 5.2 ± 6.4 sec, vs. ERS 4: 2.7 ± 3.1 sec; p=0.015) (Table 10), thus supporting Aim Five, Exploratory Hypothesis One. We noted significant differences stratified by the ERSs, in some of the continuous EDA values obtained during HUTTs, namely EDA at tilt-up and tilt-down, maximum EDA during HUT, minimum EDA during HUT, and the EDA difference during EDA during HUT, or the peak-to-peak EDA (Table 10). Additionally there was a significant difference by in prolonged PRT, between the four ERSs in the patients with POTS (Supplemental Table 22). These results support Aim 6, Hypothesis Two, Aim Five, Exploratory Hypothesis One, and Aim Four, Exploratory Hypothesis One, respectively.

Results from the deep breathing, Valsalva and sweat tests, show a significant difference in ΔHR between the POTS patients and controls. Statistically significant differences were observed between the groups from the Valsalva maneuver results, in the maximum HR (p<0.001) and minimum HR (p=0.002), and the greatest HR ratio (p<0.001)) (Supplemental Table 21). The HR ratio was higher (2.4 ± 0.5; 2.4 vs 1.8 ± 0.2; 1.7) in the POTS patients vs. controls (Supplemental Table 21). These results are in support of Aim Three, Exploratory Hypothesis One.

Assessment of deep breathing during ARS, revealed a greater average HR difference (22.8 ± 8.2 bpm vs. 17.1 ± 8.3 bpm; p<0.001) in POTS patients vs. controls (Supplemental Table 21). When stratified by ERS, the average HR difference during deep breathing in POTS patients was higher in ERS 3 and ERS 2 (25.9 ± 7.0 bpm and 24.4 ± 8.2 bpm, respectively) compared with ERS 4 and ERS 1 (22.2 ± 9.2 bpm and 22.0 ± 7.3 bpm, respectively) (Supplemental Table 22). However, while the controls with ERS 2 had the highest average HR difference during deep breathing (22.4 ± 0.0 bpm), those with ERS 1 and ERS 3 had a lower average HR difference during deep breathing (11.7 ± 2.4 bpm and 18.6 ± 9.0 bpm, respectively) (Supplemental Table 22). These results are in support of Aim Three, Exploratory Hypothesis One.

Patients with shortened (p=0.072) or prolonged (p=0.014) PRTs, differed between the patients with POTS and the controls. Of 62 POTS cases that underwent a full ARS, 27.0% had a shortened PRT vs. 40.0% of controls (Supplemental table 23). The corresponding number for the fully-autonomic-reflex-screened POTS patients with a prolonged PRT, was 9.7% vs. 24.0% of controls (Supplemental Table 23). These results are in support of Aim Five, Exploratory Hypothesis One.

Some autonomic abnormalities only noted among the patients with POTS include the following. Patients with a below normal ΔHR were 6.5% of the 62 fully screened POTS patients. Those with above normal ΔHR were 3.2% of such patients. While POTS patients with a below normal Greatest VM HR Ratio were 1.6%, and those with an above normal Greatest VM HR Ratio were 17.7% of such POT patients. These results are in support of Aim Three, Exploratory Hypothesis One. An absence of a Phase 1 response (based on the adrenergic sensitivity analysis of ARS reports) was observed in 1.6% of the patients with POTS. Those without a Phase 2 Recovery constituted 12.9% of fully screened POTS patients. An absence of a Phase 4 Overshoot was observed in 1.6% of the patients with POTS, and a blunted Phase 4 Overshoot in 11.3% of such patients, as well as an exaggerated Phase 4 Overshoot in 21.0% of them (Supplemental Table 23). These results are in support of Aim Two, Exploratory Hypothesis One, as well as Aim Six, Exploratory Hypotheses One and Two, respectively.

Assessment of the severity of autonomic impairment via means of the CASS, revealed presence of abnormal adrenergic function in 46.8% of fully screened POTS patients, whereas 8.1% displayed some indicia of cardiovagal abnormality, and 51.6% had sudomotor function abnormality (Supplemental Table 23). Overall, 80.6% of POTS patients had general autonomic impairment (GAI), ranging from potentially present GAI, mild GAI, moderate GAI to severe GAI (Supplemental Tables 23). Also, 85.7%, 90.9%, 75.0%, and 73.1% (with p=0.002), of the patients with POTS that exhibited the Transient, Absent, Delayed, and Persistent ERSs, respectively, displayed signs of GAI (Supplemental Table 22). These results support Aim Five, Exploratory Hypothesis One. However, the full extent of GAI could not be assessed in 13 (17.3%) of

the overall sample of 75 patients with POTS, i.e., those patients diagnosed with POTS from tilt table tests only (or TTTs-Only), who did not undergo full autonomic tests (Supplemental Table 23). Such missing results may limit the validity of Aim Five, Exploratory Hypothesis One. In the entire study population (with N=100 ARS Reports), GAI differed among the 75 patients with POTS when stratified by ERSs, and the percentages of those with an unknown (or indeterminable) CASS, as Transient (0.0%), Absent (21.4%), Delayed (50.0%) and Persistent (18.8%), with *p*=0.008 (Supplemental Table 26). These results for the patients with unknown GAI, are ambiguous and may limit the validity of Aim Five, Exploratory Hypothesis One.

Adrenergic Impairment and Likelihood of the Hyperadrenergic POTS Subtype

Distribution of adrenergic impairment, as reflected by the adrenergic component of the CASS across the ERSs, was statistically significant in POTS patients (*p*=0.026) (Supplemental Table 25). The adrenergic sensitivity analysis (ASA) of results from the Valsalva tests reveal a significant difference in the distribution of POTS patients with a computable PRT across the ERSs (*p*=0.008) (Supplemental Table 25). The patients with POTS that displayed the Transient tonic electrodermal response pattern, had the shortest median PRT (1.9 ± 2.7; 1.0*), while the patients with POTS that exhibited the Delayed tonic electrodermal response pattern, had the most prolonged average PRT (5.2 ± 6.4; 2.2*) (see Table 10). The presence of a shortened PRT suggests the likelihood of HA-POTS (Table 10 and Supplemental Table 22). Whereas the presence of a prolonged PRT indicates some degree of adrenergic impairment (Table 10 and Supplemental Table 22). Note that the asterisk symbols above, refer to the origin of such labelled results, which are from a sub-sample (n=62) of the larger group of 75 POTS cases. These POTS cases are those that underwent a full ARS. Another smaller sub-sample of the main group of 75 POTS cases (n=13), only underwent head up tilt-table testing of the state of their autonomic function at the UCLA Cardiac Arrhythmia Center's Autonomic Lab. Because these sample of patients did not undergo the full battery of autonomic function tests, their HUTT was 20-minutes long, which is double the duration of the HUTTs

administered to patients that underwent all four autonomic function challenges. These results support Aim Five, Exploratory Hypothesis One.

Appraisal of adrenergic impairment in the 62 fully screened UCLA CAC POTS patients revealed that 11 of these 62 patients (or 17.7% of them) who also displayed the Persistent tonic electrodermal response pattern, had some degree of impairment in adrenergic function. In total 29 patients with POTS showed some adrenergic impairment (Supplemental Table 22). Note that the PRT was not computable in all 62 of the fully screened patients diagnosed with POTS, because some of them could not maintain an interpretable expiratory effort during the Valsalva maneuver (Table 10, Supplemental Tables 22 and 23). Whenever PRT was computed (i.e., in 58 of the 62 fully screened POTS patients and all controls), the results of such patients' adrenergic sensitivity analysis, revealed differences (some of them significant) in the distribution of their PRT values and types (i.e., a shortened vs. a normal vs a prolonged PRT), across the groups and tonic electrodermal response subtypes, with p-values of p=0.072; p=0.015; and p<0.001, respectively (Table 10, and Supplemental Tables 22 and 23). Of the 11 fully screened patients with POTS that displayed the Persistent tonic electrodermal response pattern (ERS 4), 42.3% showed evidence of some form of adrenergic impairment (Supplemental Table 22). A similar percentage (42.9%) of the 9 fully screened patients with POTS that displayed the Transient tonic electrodermal response pattern (ERS 1), showed evidence of some form of adrenergic impairment (Supplemental Table 22). Of the 5 fully screened patients with POTS that displayed the Absent tonic electrodermal response pattern (ERS 2), 45.5% showed evidence of some form of adrenergic impairment (Supplemental Table 22). Finally, of the 4 fully screened patients with POTS that displayed the Delayed tonic electrodermal response pattern (ERS 1), 100.0% showed evidence of some form of adrenergic impairment (Supplemental Table 22). Aim Five, Exploratory Hypothesis One, is at least partially supported by each of these results.

Part Two: Relationships Between Tonic Electrodermal Indices and Autonomic Reflex Screening Parameters in Patients with Postural Orthostatic Tachycardia Syndrome

Correlations Between Tonic Electrodermal Indices and Some Reference Standard Autonomic Reflex Screening Parameters, and Also Among Certain Autonomic Reflex Screening Parameters in Controls

An appraisal of certain of the novel test measures and the gold standard ARS based diagnostic parameters in the sample of controls, revealed very strong correlations among the following indices. The 'Latency of the PR Equivalent of the Maximum HR During the HUT Period' and the 'Time from Tilt-up to the Time of the Maximum HR During the HUT Period' (very strong: 0.976; $p<0.001$), the 'PR Equivalent of the Maximum HR During the HUT Period' and the 'Maximum HR During the HUT Period' (very strong: 0.889; $p<0.001$), as well as the 'PR Equivalent of the Maximum HR During the HUT Period' and the 'HR at Minimum SBP During the HUT Period' (very strong: 0.823; $p<0.001$). Examinations of other associations among certain other novel and standard ARS parameters, yielded the following strong correlations. The 'Tilt-up PR' and the '30-seconds Pre-Tilt Baseline HR' (strong: 0.785; $p<0.001$), the 'PR Equivalent of the Maximum HR During the HUT Period' and the 'Minimum HR During the HUT Period' (strong: 0.756; $p<0.001$), the 'PR Equivalent of the Maximum HR During the HUT Period' and the '30-seconds Pre-Tilt Baseline HR' (strong: 0.746; $p<0.001$), the 'Tilt-up PR' and the 'Post HUT HR' (strong: 0.744; $p<0.001$), the 'Tilt-up PR' and the 'Minimum HR During the HUT Period' (strong: 0.731; $p<0.001$), the 'Tilt-down PR' and the 'HR at the Minimum SBP During the HUT Period' (strong: 0.720; $p<0.001$), as well as the 'Tilt-up PR' and the 'Maximum HR During the HUT Period' (strong: 0.713; $p<0.001$) (Table 15). These results are fully in support of Aim Five, Exploratory Hypothesis One.

Similarly, an assessment of certain correlations between tonic electrodermal indices and standard autonomic reflex screening parameters, revealed strong or moderate correlations in the controls for indices, such as the 'Difference Between the Arc of the EDA Area During the HUT Period and the Arc of the EDA Area During the Post HUT Period' and the Heart Rate Difference (strong: -0.639;

p<0.001), the ‘Pre HUT EDA Sum’ and the ‘Minimum Phase 3 Rate of the Adrenergic Sensitivity Analysis of the Valsalva Test Results’ (strong: 0.628; *p*<0.001), the ‘Pre HUT EDA Average’ and the ‘Minimum Phase 3 Rate of the Adrenergic Sensitivity Analysis of the Valsalva Test Results’ (strong: 0.617; *p*=0.001), the ‘Pre HUT EDA Integral’ and the ‘Minimum Phase 3 Rate of the Adrenergic Sensitivity Analysis of the Valsalva Test Results’ (strong: 0.617; *p*=0.001), the ‘Pre-Tilt EDA Area’ and the ‘Difference Between the HR at the Minimum SBP and the Pre HUT HR’ (strong: 0.609; *p*=0.001), the ‘Arc of the Pre-Tilt EDA Area’ and the ‘Difference Between the HR at the Minimum SBP During the HUT Period and the Pre HUT HR’ (strong: 0.609; *p*=0.001), the ‘Post HUT EDA Average’ and the ‘Number of Chronotropic Medications not Held 48-hours Before Testing’ (strong: -0.605; *p*=0.001), the ‘Difference Between the EDA Integral During the Post HUT Period and the EDA Integral During the HUT Period’ and the ‘Number of Chronotropic Medications not Held 48-hours Before Testing’ (moderate: 0.590; *p*=0.002), the ‘Pre HUT Peak-to-Peak EDA’ and the ‘Minimum Phase 3 Rate of the Adrenergic Sensitivity Analysis of the Valsalva Test Results’ (moderate: 0.587; *p*=0.003), the ‘Difference Between the Post HUT EDA Integral and the EDA Integral During the HUT Period’ and the ‘Difference Between the Minimum Phase 3 Rate of the Adrenergic Sensitivity Analysis of the Valsalva Test Results and the Baseline Rate’ (moderate: -0.587; *p*=0.003), the ‘Pre-Tilt EDA Area’ and the ‘Difference Between the Minimum HR During the HUT Period and the HR at the Minimum SBP During the HUT Period’ (moderate: -0.584; *p*=0.002), the ‘Arc of the Pre-Tilt EDA Area’ and the ‘Difference Between the Minimum HR During the HUT Period and the HR at the Minimum SBP During the HUT Period’ (moderate: -0.584; *p*=0.002), as well as the ‘Pre HUT EDA Average’ and the ‘Difference Between the Minimum Phase 3 Rate of the Adrenergic Sensitivity Analysis of the Valsalva Test Results and the Baseline Rate’ (strong: 0.580; *p*=0.002) (Table 15). These results are fully in support of Aim Five, Exploratory Hypothesis One. Other correlations of novel tonic EDA indices and gold standard ARS parameters, all of which had moderate correlation coefficients, have been listed in Table 15. Each of these results are fully in support of Aim Five, Exploratory Hypothesis One.

Specific Correlations Between Tonic Electrodermal Indices and Gold Standard Autonomic Reflex Screening Parameters, and Also Among Certain Autonomic Reflex Screening Parameters in POTS Cases

Specific correlations between certain gold standard autonomic reflex screening parameters and pertinent tonic electrodermal response derived indices, are listed in Tables 14 and 16. There were very strong correlations between the 'HUT Maximum HR' (a standard ARS measure) and the 'PR Equivalent of Maximum HR' (a novel test measure), 'Time from Tilt to HUT Maximum HR' (a standard ARS measure) and 'Latency of PR Equivalent of Maximum HR' (a novel test measure), 'HUT Minimum HR' (a standard ARS measure) and 'Tilt-up PR' (a novel test measure), as well as between 'Baseline HR' (a standard ARS measure) and 'Tilt-up PR' (a novel test measure). These results fully support Aim Five, Exploratory Hypothesis One.

Strong correlations were found between gold standard ARS parameters such as 'HUT Minimum HR' and novel test measures such as 'PR Equivalent of Maximum HR', 'HUT Maximum HR' vs 'Tilt-up PR', 'Baseline HR' vs 'PR Equivalent of Maximum HR', 'HUT HR at the HUT Minimum SBP' vs 'PR Equivalent of Maximum HR', and 'Post HUT HR' vs 'Tilt-up PR''. These results fully support Aim Five, Exploratory Hypothesis One.

Moderate as well as weak correlations of interest to this study were also found between various gold standard ARS parameters and novel test measures. One example of a moderate correlation in POTS cases, is the correlation between the 'Number of Data Sets During HUT' and the 'EDA HUT Frequency'. The correlation coefficient for this relationship is $r = 0.527$ ($p<0.001$ and $q<0.05$), which indicates there is a high probability of the existence of a positive (albeit moderately strong) association between both of these measures. Similarly, an example of a weak correlation in POTS cases, is the correlation between the 'ASALine1Phase2ERateDifference' and 'EDAdurationHeadupTilt'. The correlation coefficient for this relationship is $r = -0.397$ ($p<0.001$ and $q<0.05$), which indicates that there is a high probability of the existence of a negative (but weak) association between both of these measures. A full listing of all of the

other moderate and weak correlations between gold standard ARS parameters and potentially pertinent novel test measures, may be found in Tables 14 and 16. Each of these results, are fully in support of Aim Five, Exploratory Hypothesis One, specifically in those instances when the q-values obtained from running tests with Storey's method for testing multiple hypotheses, are statistically significant (i.e., when $q<0.05$). Note that the use of Storey's Method in selecting the correlations reported in Tables 14, 15 and 16, helped to minimize the False Discovery Rate (FDR), firstly because it is a validated approach to the task of multiple testing correction, and secondly, because it is also a less conservative approach to this task, than either the Bonferroni Adjustment, or Tukey's Method (Lee & Lee, 2018; Noble, 2009).

Part Three: Characterization of Postural Orthostatic Tachycardia Syndrome Using Skin Conductance Responses, and Symptoms Observed During Tilt Table Testing

Comparisons Within and Across Groups Stratified by Autonomic Function Test Type

Appraisal of indices of phasic electrodermal activity observed across conditions as well as study participants, revealed the following. The numbers of the event related SCRs detected in both of the focus areas corresponding to administration of the HRDB 1 and 2 tests, differed significantly between the controls and POTS cases, with p-values of $p=0.032$ and $p=0.049$, respectively (Table 23). This result supports Aim Four, Exploratory Hypothesis One. Also, an examination of the numbers of unspecified SCRs located during the period of Valsalva maneuver 2, show a significant variation in such numbers between the controls and the POTS cases ($p=0.045$) (Table 23). This result also supports Aim Four, Exploratory Hypothesis One.

There were marked differences in the frequency of the SCRs during VM2 between the groups ($p<0.001$) (Table 23), and even though the following result does not quite meet the specified statistical significance threshold of a $p<0.05$, the p-values for comparison of the ratio of the amplitudes of the event related SCR to their respective rise times during the VM1 test came close to this threshold (or cut-off p-value), because it had a $p=0.085$ (Table 23). Furthermore, the average minimum SCL in the entire

EDA signal trace, had a p=0.069 (Table 23), which is notable, albeit not statistically significant. With regard to Aim Four, Exploratory Hypothesis One, this result is ambiguous, because it is a comparison by group (i.e., controls vs POTS cases), rather than a comparison by tonic electrodermal response subtypes.

Examination of Z-score and T-score standardized phasic EDA indices, reveal notable deviations from their respective standardized mean values of 0.000 and 50.000 respectively, with respect to the average medians, maxima, minima, peak-to-peak values, and standard deviations of their transformed raw SCR amplitudes (Tables 18, 19, 20, 21, 22, and 24). The results in these tables either fully support or partially support Aims One, Two, Three, Four, Five and Six, and their respective associated exploratory hypotheses, refute one or more of these aims and exploratory hypotheses, or else they are ambiguous (a specific breakdown will be given in subsequent paragraphs after each set of related results).

Comparison of the medians of the log transformed Z-scores during the first heart rate deep breathing test (or HRDB1), reveals that the log transformed Z-score during DB1 is -0.518 for the controls, and -0.264 in the POTS cases, which shows that the Z-scores of the POTS cases are closer to the mean than those of the controls. Similarly, during DB2, the average median of the logged Z-scores for the controls is -0.402, whereas that of the POTS cases is -0.060 (Table 18). These results partially support Aim Four, Exploratory Hypothesis One, as well as Aim Six, Exploratory Hypotheses One and Two.

Juxtaposition of the peak-to-peak variations in Z-scores and T-scores for the controls and POTS cases, reveal a blunting of these values in the POTS cases vs the controls during the 2-minutes long pre-ARS testing baseline period (2.813 vs 2.510, and 28.132 vs 25.096 respectively), which is an increase in their respective values for the POTS cases vs the controls during the 2-minutes right after tilt-up (2.879 vs 3.089, and 28.793 vs 30.890), and then blunting in the POTS cases vs the controls during the period of the first 2-minutes of sustained SCL rise subsequent to the tilting-up event and orthostatic stimulus (3.158 vs 2.922, and 31.577 vs 29.220, respectively) (Table 20). These results are partially (because they do not include variations by the ERSs) in support of Aim Four, Exploratory Hypothesis One. Also, similar

differences between the controls and the POTS cases, are evident in the peak-to-peak variations assessed from SCRs appraised across the various focus areas of interest, such as the baseline, DB1, DB2, VM1, VM2, VM3, HUTT, 30-seconds pre tilt-up, 30-seconds right after tilt-up, 30-seconds right after tilt-down, 2-minutes right after tilt-up, and during the first 2-minutes of sustained SCL elevation in HUTT after tilt-up (Tables, 18, 19, 20, 21, and 22).

With respect to comparison of the peak-to-peak differences in the log transformed Z-scores and T-scores during DB1, DB2, VM1, VM2, VM3, 2-minutes right after Tilt-up, the first 2-minutes of sustained SCL elevation in HUTT after Tilt-up, the 30-seconds right before Tilt-up, 30-seconds right after Tilt-up, 30-seconds right after Tilt-down, the ERSCR at Tilt-up and ERSCR at Tilt-down, between the controls and POTS cases, we got the following results. For DB1 (2.765 vs 3.175, and 27.651 vs 31.754), which indicates an increase of these values in the pathological (or POTS) cases. This is flipped around during DB2 (3.275 vs 2.928, and 32.753 vs 29.276), where we have a blunting of these values in POTS cases vs the controls. For VM1 (2.902 vs 2.684, and 29.014 vs 26.844), there is a blunting in the values.

During VM2 (3.034 vs 2.936, and 30.341 vs 29.364), there is a blunting in the values, and also during VM3 (3.225 vs 2.948, and 32.247 vs 29.483) there is a blunting in the values. In the 2-minutes right after Tilt-up (2.879 vs 3.089, and 28.793 vs 30.890), there is an increase in the values, and during the first 2-minutes of sustained SCL elevation in HUTT after Tilt-up (3.158 vs 2.922, and 31.577 vs 29.220), which flips around the previous trend and represents a blunting of the values in the POTS cases (Table 20). During the 30-seconds period right before Tilt-up (3.344 vs 3.182, and 33.436 vs 31.821), there is a blunting in the values. Also, in the 30-seconds right after Tilt-up period (2.997 vs 2.967, 29.974 vs 29.670), there is a blunting in the values. However, during 30-seconds right after Tilt-down period (2.730 vs 3.259, and 27.299 vs 32.589), there is an increase of the values POTS cases (Table 21). For the time of the ERSCR at Tilt-up (2.769 vs 3.401, and 27.690 vs 34.011), there is an increase of the values in POTS cases, and at the time of the ERSCR at Tilt-down (3.579 vs 3.028, and 35.789 vs 30.282), there is a

blunting of the values in the POTS cases (Table 22). Each of these sets of results partially support Aim Four, Exploratory Hypothesis One.

The numbers of event-related SCRs differed between the controls and the POTS cases, with an observable trend of the presence of a fewer number of ER-SCRs in the POTS cases vs the controls. For example, while 4 ± 3; 3 ER-SCRs were located in the controls during the DB1 test, only 2 ± 2; 1 ER-SCRs were found in the group of POTS cases during administration of the same test. Similarly, while 5 ± 3; 4 ER-SCRs were located in the controls during the DB2 test, only 3 ± 2; 2 ER-SCRs were found in the group of POTS cases during administration of the very same test (Table 18). These results partially support Aim Four, Exploratory Hypothesis One.

There was a reversal in this trend though with the Valsalva maneuvers, wherein the frequency of occurrence of the SCRs was higher in the POTS cases, than they were in the controls (5 ± 3; 4 vs 6 ± 4; 5, 5 ± 2; 3 vs 7 ± 3; 7, and 5 ± 3; 4 vs 6 ± 2; 5, for VM1, VM2, and VM3 respectively) (Table 19). Contrast of the median of the Logarithmically Transformed Raw Z-score between the controls and POTS cases, reveals a median of -0.677 in the controls vs a median of -0.157 in the POTS cases (Table 45). In DB1, the difference was -0.518 vs -0.264, in DB2 it is -0.402 vs -0.060, in VM1 it was -0.397 vs -0.032, and in VM2, this difference was -0.438 vs -0.340 (Table 45). These results partially support Aim Four, Exploratory Hypothesis One. Notable standardized Z-cores and T-scores for relevant indices are outlined in Table 24.

With respect to the event-related SCR related index 'T-score of the Amplitude of the ER-SCR in VM3' in the POTS cases when stratified by tonic electrodermal response subtype, there was a significant difference in values across the ERSs (p=0.029) (Table 27). Also, with respect to another event-related SCR index 'T-score of the Amplitude of the ER-SCR at TU' in the patients with POTS, when stratified by tonic electrodermal response subtype, there was a statistically significant difference in values across the ERSs (p=0.018) (Table 27). These results are fully in support of Aim Four, Exploratory Hypothesis One. Additionally, estimates for the Z-score transformed indices ZscrPrcsng1st2mFhuttMxZ-core(LoggedData)

and ZscrPrcsngOFerscrTDmxZ-score(LoggedData), are -3.79 and -0.288, respectively, from the results of running a logistic regression on samples for the controls and POTS cases.

Characterization with a Logistics Regression Model

Similarly, their resultant logistic regression statistics are -1.23 and -0.242, respectively (Table 28). For the indices ZscrPrcsngBslnMxZ-score(LoggedData), ZscrPrcsng2mFhuttMxZ-score(LoggedData), and ZscrPrcsngOFerscrTUmxZ-score(LoggedData), their respective logistic regression estimates, and related test statistics are as follows, 0.0299, 1.97, and 2.45, as well as 0.0493, 0.967, and 0.869 (Table 28). From the results in the column labelled "Estimate", we can see that there is a positive association with the selection of controls from the overall study sample, with respect to indices such as the Log-Transformed Z-score of the Raw Amplitude of the SCR with the Maximum SCL During the 2-minutes of Pre-ARS Testing Baseline, Log-Transformed Z-score of the Raw Amplitude of the SCR with the Maximum SCL During the 2-minutes Focused Area Right After the Tilt-up Stimulus Event, and Log-Transformed Z-score of the Raw Amplitude of the Tilt-up Generated Event Related SCR (Table 28). Whereas there is a negative association with the selection of controls (ergo a positive association in selection of the POTS cases) from the overall study sample, with respect to indices such as the Log-Transformed Z-score of the Raw Amplitude of the SCR with the Maximum SCL During the First 2-minutes of the Sustained Elevation in the SCL After the Tilt-up Stimulus Event, and Log-Transformed Z-score of the Raw Amplitude of the Tilt-down Generated Event Related SCR (Table 28). The non-statistically significant p-values (p=0.961, p=0.333 and p=0.371 vs p=0.218 and p=0.809, respectively), which correspond to each of these five estimates, are a limitation on the validity of the appropriateness of including each of these five indices in the logistics model, as potential measures for distinguishing members of one group from the other. Thus these results, are ambiguous with regard to validation of Aim Four, Exploratory Hypothesis One.

Part Four: Relationships Between Phasic Electrodermal Indices and Autonomic Reflex Screening Parameters in Controls and Patients with Postural Orthostatic Tachycardia Syndrome

Overview of Associations Among Indices of Skin Conductance Response and Reference ARS Variables

Certain indicia of phasic electrodermal response, such as the ratio standardized parameters of the amplitudes of event-related SCRs occurring during focus areas corresponding to the various deep breathing tests, Valsalva maneuvers, tilt-up and tilt-down, displayed moderate, strong, and occasionally very strong correlations with key reference diagnostic variables that were measured during the various tests of autonomic function. Results are presented in Tables 25 and 26, for the controls and POTS cases, respectively. Some notable results are as follows. In the groups of controls, there is evidence of strong positive and negative correlations between HRΔ and the T-score of the amplitudes of the SCRs with either a maximum SCL in the focus area of interest (e.g., baseline or HUTT) (Tables 25), or the event-related stimulus of a Valsalva maneuver, tilt-up, or tilt-down, which ranged from a Correlation Coefficient of -0.602 to 0.653 (Table 46).

Moderate correlational strengths, ranged from 0.415 to 0.549 (and the associated p-values, ranged from p=0.008 to p<0.001). The minimum systolic blood pressure during HUTT correlated strongly (albeit negatively) with the number of medications not withheld as directed, for at least 48-hours before autonomic function testing (Table 25). The range of Coefficients of Correlation for the associations between the minimum systolic blood pressure during HUTT and the novel phasic EDA indices, range from the least moderate coefficient of 0.415, to the strong association of -0.620 between the minimum SBP in HUTT, and the numbers of medications not held prior to ARS (p-values range from a p=0.004 to a p<0.001). (Table 25).

The strongest association between a phasic electrodermal parameter and a standard ARS measure in the group of controls, the correlation coefficient of 0.891 (p<0.001) for the relationships between the average heart rate difference during the deep breathing test, and the log-transformed T-

scores of the magnitudes of the raw amplitudes of the SCRs with either the maximum SCL, or stimulus driven SCR, during the respective focus periods of (1), the first 2-minutes of sustained SCL elevation after tilt-up, or (2), the 2-minutes period immediately after the tilting-up event and its associated orthostatic stimulus (Table 25).

Strengths of associations between various novel phasic EDA parameters and some standard ARS variables for the group of POTS cases, are detailed in Table 26. Notable among these, are the correlation between HRΔ and the log transformed T-score of the magnitude of the raw amplitude of the DB1 generated event-related SCR (Coefficient of Correlation 'r' = 0.657; $p<0.001$) (Table 26). For the gold standard ARS diagnostic variable "change in the minimum SBP in HUTT from its average 30-seconds pre tilt-up value", the strongest association was the negative association (Correlation Coefficient r = -0.644) with the log transformed T-score of the magnitude of the raw amplitude of the event-related VM3, with a $p<0.001$ (Table 26). Interestingly, the greatest HR ratio during the Valsalva maneuvers, was very strongly (and also directly or positively) associated with, the adrenergic component of the CASS, with a correlational coefficient of r = 0.898 ($p<0.001$). Interestingly, the body mass index (BMI), was quite very strongly correlated with the cardiovagal component of the CASS, in patients with POTS, in that their correlation coefficient 'r' = 0.926 (with a $p<0.001$) (Table 26).

Specific Correlations Between Certain Phasic Electrodermal Indices and Gold Standard Autonomic Reflex Screening Parameters, and Among Autonomic Reflex Screening Parameters in Controls.

Tests for the strength of association between variables/indices, revealed strong correlations between the variable Heart Rate, and skin conductance response (SCR) derived indices, such as the log transformed T-scores, of the raw amplitudes of certain SCRs that were measured over the period of time across certain focus areas, including indices such as the 'SCR with Max Amplitude 2-minutes After Tilt-up in HUTT', 'the SCR with the Max SCL's Amplitude in the 30-seconds Right Before Tilt-up', 'the SCR with the Maximum SCL located within the 1st 2-minutes of the HUTT focus area', and the 'Average Minimum

SCL of the Entire EDA Signal Trace' (Table 25). These results fully support Aim Five, Exploratory Hypothesis One. The strength of the correlations between Heart Rate and indices such as 'the SCR with Max SCL's Amplitude in the 30-seconds Right After Tilt-up', 'log-transformed T-score of 2-minutes of pre-ARS testing baseline', 'the Ratio of the Event Related SCR's Amplitude to Rise Time During the Valsalva Maneuver 2 Test', 'Tilt Up T-score Logged', and 'the log-transformed T-score of the DB 1 Test', were moderate (Table 25). Each of these results fully support Aim Five, Exploratory Hypothesis One.

There was a strong correlation between the 'Minimum Systolic Blood Pressure in HUTT' and the 'Number of Medications Not Held Before the Autonomic Reflex Screen' (Table 25). Furthermore, there were moderate correlations between the 'Minimum Systolic Blood Pressure in HUTT', and indices such as 'Frequency of the Number of SCRs During the Valsalva Maneuver 2 Test', 'Ratio of the Event Related SCR's Amplitude to the Rise Time During the Valsalva Maneuver 3 Test', 'VM3 T-score Logged', 'TD T-score Logged', and the 'T-score Logged of the SCR with Max SCL's Amplitude's in the 30-seconds After Tilt-down'. These results support Aim Five, Hypothesis One.

Similarly, there were strong correlations between the index 'Minimum Change of Systolic Blood Pressure from Pre-Tilt Values in HUTT', and 'Ratio of the Event Related SCR's Amplitude to Rise Time During the Valsalva Maneuver 1 Test', as well as 'DB2 T-score Logged' (Table 25). Moderate correlations were found between the 'Minimum Change of Systolic Blood Pressure from Pre-Tilt Values in HUTT', and indices such as 'Number of Symptoms at Tilt-up', 'VM1 T-score Logged', 'DB1 T-score Logged', 'Average Maximum SCL of the Entire EDA Signal Trace', 'Frequency of the Number of SCRs During the Valsalva Maneuver 2 Test', and 'Number of Non-specific SCRs During the Valsalva Maneuver 2' (Table 25). These results fully support Aim Five, Exploratory Hypothesis One.

There were strong correlations between 'Maximum Heart Rate in HUTT', and 'Number of Non-specific SCRs During the Valsalva Maneuver 2', 'DB1 T-score Logged', as well as the '1st 2-minutes in HUTT's SCR with Max SCL Amplitude's T-score Logged' (Table 25). These results are fully in support of

Aim Five, Exploratory Hypothesis One. Furthermore, there are moderate correlations between the gold standard reference variable 'Maximum Heart Rate in HUTT', and indices such as 'Number of Symptoms at Tilt-up', 'Number of Medications Not Held Before the Autonomic Reflex Screen', 'Number of Event Related SCRs During the Deep Breathing Test 2', 'Number of Symptoms at Tilt-down', '2-minutes in After Tilt-up in HUTT's SCR with Max SCL Amplitude's T-score Logged', 'Frequency of the Number of SCRs During the Valsalva Maneuver 2 Test', 'Total Number of Symptoms in HUTT', 'T-score logged of the SCR with Max SCL's Amplitude's in 30-seconds Before Tilt-up', 'T-score Logged of the SCR with Max SCL's Amplitude's in 30-seconds After Tilt-up', 'Baseline T-score Logged', and 'Number of Non-specific SCRs During the Valsalva Maneuver 1' (Table 25). These results fully support Aim Five, Exploratory Hypothesis One.

'Body Mass Index' correlated very strongly with the 'QSWEAT Total Forearm Sweat Volume', and there were strong correlations between the 'QSWEAT Total Forearm Sweat Volume', and indices such as 'Frequency of the Number of SCRs During the Valsalva Maneuver 1 Test', 'Number of Non-specific SCRs During the Valsalva Maneuver 1', 'Average Maximum SCL of the Entire EDA Signal Trace', 'Age', 'Ratio of the Event Related SCR's Amplitude to Rise Time During the Valsalva Maneuver 3 Test', 'VM3 T-score Logged', 'DB2 T-score Logged', and the 'Ratio of the Event Related SCR's Amplitude to Rise Time During the Valsalva Maneuver 1 Test' (Table 25). These results fully support Aim Five, Exploratory Hypothesis One. Also, we found moderate correlations between 'QSWEAT Total Forearm Sweat Volume', and indices such as the 'VM1 T-score Logged', 'VM2 T-score Logged', 'Ratio of the Event Related SCR's Amplitude to Rise Time During the Valsalva Maneuver 2 Test', 'Number of Medications Not Held Before the Autonomic Reflex Screen', 'TU T-score Logged', 'Baseline T-score Logged', and 'Average Minimum SCL of the Entire EDA Signal Trace' (Table 25). These results fully support Aim Five, Exploratory Hypothesis One.

There were very strong correlations between the gold standard ARS variable 'Average Heart

Rate Difference During the Deep breathing Test', and indices such as the '1st 2-minutes in HUTT's SCR with Max SCL Amplitude's T-score Logged', '2-minutes in After Tilt-up in HUTT's SCR with Max SCL Amplitude's T-score Logged', 'Baseline T-score Logged', 'T-score Logged of the SCR with Max SCL's Amplitude's in 30-seconds Before Tilt-up ', 'T-score Logged of the SCR with Max SCL's Amplitude's in 30-seconds After Tilt-up', 'DB1 T-score Logged', 'Average Minimum SCL of the Entire EDA Signal Trace', and 'Ratio of the Event Related SCR's Amplitude to Rise Time During the Valsalva Maneuver 2 Test' (Table 25). These results fully support Aim Five, Exploratory Hypothesis One. Furthermore, there were strong correlations between the variable 'Average Heart Rate Difference During the Deep breathing Test', and the variables 'Average Maximum SCL of the Entire EDA Signal Trace', 'TU T-score Logged", 'VM1 T-score Logged', as well as the 'Number of Symptoms at Tilt-down' (Table 25). These results fully support Aim Five, Exploratory Hypothesis One.

There were moderate correlations between the index 'Average Heart Rate Difference During the Deep breathing Test', and indices such as the 'Frequency of the Number of SCRs During the Valsalva Maneuver 1 Test', 'Ratio of the Event Related SCR's Amplitude to Rise Time During the Valsalva Maneuver 3 Test', 'Number of Symptoms at Tilt-up', 'Number of Event Related SCRs During the Deep Breathing Test 2', 'Number of Non-specific SCRs During the Valsalva Maneuver 2', and the 'Ratio of the Event Related SCR's Amplitude to Rise Time During the Valsalva Maneuver 1 Test' (Table 25). These results fully support Aim Five, Exploratory Hypothesis One.

There was one very strong correlation between the 'Greatest Heart Rate Ratio During the Valsalva Maneuver', and the 'Average Heart Rate Ratio During the Valsalva Maneuver, bpm' (Table 25). This result fully supports Aim Five, Exploratory Hypothesis One. Also, there were very strong correlations between the variable 'Average Maximum Heart Rate During the Valsalva Maneuver', and the '1st 2-minutes in HUTT's SCR with Max SCL Amplitude's T-score Logged', 'HRDB Expiration to Inspiration Ratio', '2-minutes in After Tilt-up in HUTT's SCR with Max SCL Amplitude's T-score Logged', 'Average Heart Rate

Difference During the Deep breathing Test', 'Delta HR During the Heart Rate Deep Breathing Test', 'TU T-score Logged', 'VM2 T-score Logged', and the 'T-score Logged of the SCR with Max SCL's Amplitude's in 30-seconds After Tilt-up' (Table 25). These results fully support Aim Five, Exploratory Hypothesis One.

Strong correlations were found between 'Average Maximum Heart Rate During the Valsalva Maneuver', and the 'T-score Logged of the SCR with Max SCL's Amplitude's in 30-seconds Before Tilt-up', 'Baseline T-score Logged', 'Number of Symptoms at Tilt-down', of the SCR with Max SCL's Amplitude's in 30-seconds Before Tilt-up ', 'Maximum Heart Rate in HUTT', 'DB1 T-score Logged', 'Number of Symptoms at Tilt-up', 'Average Minimum SCL of the Entire EDA Signal Trace', 'Average Maximum Heart Rate During the Deep Breathing Test', 'Ratio of the Event Related SCR's Amplitude to Rise Time During the Valsalva Maneuver 2 Test', 'Total Number of Symptoms in HUTT', and the 'Heart Rate Delta' (Table 25). These results are fully in support of Aim Five, Exploratory Hypothesis One. There were moderate correlations between the index Average Maximum Heart Rate During the Valsalva Maneuver', and the Number of Event Related SCRs During the Deep Breathing Test 2', 'Number of Non-specific SCRs During the Valsalva Maneuver 2', 'Average Maximum SCL of the Entire EDA Signal Trace', 'Heart Rate at the Minimum Systolic Blood Pressure in HUTT', and the 'VM1 T-score Logged' (Table 25). These results are fully in support of Aim Five, Exploratory Hypothesis One.

Specific Correlations Between Certain Phasic Electrodermal Indices and Gold Standard Autonomic Reflex Screening Parameters, and Among Autonomic Reflex Screening Parameters in POTS Cases.

There were five strong correlations of 'Heart Rate Delta' with the Number of Event Related SCRs During the Deep Breathing Test 1', '2-minutes After Tilt-up in HUTT's SCR with Max Amplitude's T-score Logged', '1st 2-minutes in HUTT's SCR with Max SCL Amplitude's T-score Logged', 'TU T-score Logged', and 'DB2 T-score Logged', respectively (Table 26). These results fully support Aim Five, Exploratory Hypothesis One. Correlations between 'Heart Rate Delta', and 'VM3 T-score Logged', 'TD T-score Logged', 'T-score Logged of the SCR with Max SCL's Amplitude in the 30-seconds Right After Tilt-up',

‘T-score Logged of the SCR with Max SCL's Amplitude's in 30-seconds After Tilt-down’, ‘Baseline T-score Logged’, ‘Ratio of the Event Related SCR’s Amplitude to Rise Time During the Valsalva Maneuver 3 Test’, and the ‘Average Minimum SCL of the Entire EDA Signal Trace’, were moderate (Table 26). These results fully support Aim Five, Exploratory Hypothesis One.

Three strong correlations were found between the ‘Minimum Systolic Blood Pressure in HUTT’, and ‘Baseline T-score Logged’, ‘DB2 T-score Logged’, and ‘Number of Non-specific SCRs During the Valsalva Maneuver 1’ (Table 26). These results fully support Aim Five, Exploratory Hypothesis One. There were also seven moderate correlations between and ‘Frequency of the Number of SCRs During the Valsalva Maneuver 3 Test’, ‘Ratio of the Event Related SCR’s Amplitude to Rise Time During the Valsalva Maneuver 3 Test’, ‘Average Minimum SCL of the Entire EDA Signal Trace’, ‘DB1 T-score Logged’, ‘VM3 T-score Logged’, ‘1st 2-minutes in HUTT's SCR with Max SCL Amplitude's T-score Logged’, and ‘2-minutes in After Tilt-up in HUTT's SCR with Max SCL Amplitude's T-score Logged’ (Table 26). These results fully support Aim Five, Exploratory Hypothesis One.

Additional correlations of gold standard ARS variables such as the ‘Minimum Change of Systolic Blood Pressure from Pre-Tilt Values in HUTT ‘, ‘Maximum Heart Rate in HUTT’, ‘Heart Rate at the Minimum Systolic Blood Pressure in HUTT’, ‘QSWEAT Total Forearm Sweat Volume’, ‘Average Heart Rate Difference During the Deep breathing Test’, ‘Greatest Heart Rate Ratio During the Valsalva Maneuver’, ‘Average Maximum Heart Rate During the Valsalva Maneuver’, ‘Cardiovagal Component of the Composite Autonomic Severity Score’, ‘Adrenergic Component of the Composite Autonomic Severity Score’, ‘Sudomotor Component of the Composite Autonomic Severity Score’, ‘Total of the Components of the Composite Autonomic Severity Score (or CASS)’, with other gold standard ARS diagnostic variables, had correlative strengths that range from moderate to very strong. These correlations may be found in Table 26. Each of these results fully support Aim Five, Exploratory Hypothesis One.

Part Five: Additional Results from Another Measure of Autonomic Function

Indicia of Autonomic Function from the Photoplethysmogram of a Patient with POTS

Although photoplethysmogram or photoplethysmography (PPG) signal traces, were recorded concurrently with the electrodermal signal traces obtained during ARS, and the tertiary pulse rate (PR) signal traces evident in the AcqKnowledge files used to extract PR data reported in this dissertation were derived from the PPG traces, an analysis of PPG data is not the focus of this study. Rather, such analysis has been left to a future study. However, a cursory exploration of the rich cornucopia of PPG data, which is potentially available, yielded the PPG data that have been reported in Supplemental Table 24, as well as the PPG signal traces that have been presented in Supplemental Figure 12.

In the same patient diagnosed with POTS, the maximum, minimum, peak-to-peak, and average values of PPG recorded during the 1-minute pre HUT, HUT and 1-minute post HUT periods, are 1-minute pre HUT (0.287, -0.178, 0.466 and 0.030), HUT (0.292, -0.203, 0.495 and 0.030) and 1-minute post HUT (0.449, -0.198, 0.647 and 0.030). Note that the unit of each of the datums in parentheses above is volts. Interestingly, the mean PPG value measured across each period of autonomic function testing time is 0.030 volts, despite the differences in duration of each focus area. This suggests the average PPG value may not be a good indicator of SNS responses to orthostatic challenges/changes, whereas the variations in PPG maxima, minima and peak-to-peak indices, suggests such parameters may be more sensitive to changes in autonomic function, during the same time periods.

From the representative tracings of PPG based finger pulse volume (FPV), EDA and PR before, during and after a HUTT in the same POTS case depicted in Supplemental Figure 12, who exhibited the Absent tonic electrodermal response subtype, the PPG trace during the 1-minute right after tilt-down, appears to be a mirror image of the PPG trace 1-minute before tilt-up. This trend in the PPG signal trace is akin to the patterns observed in both the tonic EDA waveforms pre and post HUT and the PPG derived PR signal traces over the same time periods. The similarity in trend, all three of these electrophysiologic

signal traces, suggests that each of them are sensitive to underlying pathological conditions, and as such may have some utility as proxies of autonomic function, thus serving as mirrors of, as well as windows into, currently poorly understood underlying mechanisms of sympathetic nervous system (SNS) activity.

While the aforementioned variations in certain indices across the three distinct time periods and postural changes (i.e., the movement of the patient from a supine, to tilted, then back down to a supine position), demonstrate an autonomic response to orthostasis. Because there is no comparison with data from another patient undergoing similar testing, these data are not sufficient to either generalize across subjects, or to support or refute any of the hypotheses of this dissertation project. As such, these results are ambiguous vis-à-vis the specific aims and exploratory hypotheses of this study. Therefore, a much more detailed extraction of data from the PPG signal traces, coupled with a deeper exploration and further analyses of the PPG data thereby acquired, is required to fully elucidate the potential utility of PPG signal traces, as a measure of autonomic function in subtypes of POTS.

Table 8

Baseline Demographics of the Study Population and Hemodynamic Responses to Upright Tilt

	Controls (n=25)	POTS (n=75)	p-value
Age, years	44 ± 19; 45	28 ± 12; 25	<0.001
Females Sex[1], N (%)	19 (76.0)	57 (76.0)	>0.999
Height, cm	165.6 ± 8.3; 165.1	168.8 ± 10.7; 167.6	0.116
Weight, kg	74.4 ± 21.6; 72.1	65.5 ± 15.1; 63.1	0.046
Body Mass Index, kg/m^2	27.1 ± 7.1; 25.7	23.0 ± 4.9; 21.8	0.006
Supine SBP, mmHg	119.7 ± 18.8; 121.0	109.5 ± 19.3; 108.0	0.025
Supine DBP, mmHg	73.3 ± 10.3; 76.0	67.4 ± 11.2; 67.7	0.016
Supine HR, bpm	75.3 ± 12.1; 75.6	76.3 ± 13.3; 74.9	0.852
Medications withheld[1], %	36.0	41.3	0.814
HR Change, bpm	26.6 ± 7.4; 26.1	54.8 ± 10.4; 52.7	<0.001
SBP Change, mmHg	-9.6 ± 7.4; -11.0	-11.5 ± 6.0; -12.4	0.272
Maximum HR During Tilt, bpm	99.2 ± 14.9; 100.0	126.2 ± 14.9; 125.0	<0.001
Minimum HR During Tilt, bpm	72.4 ± 12.6; 75.5	71.4 ± 11.8; 69.4	0.753
HR at Minimum SBP During Tilt, bpm	86.8 ± 13.9; 86.3	100.2 ± 19.1; 97.6	<0.001
Post-Tilt SBP, mmHg	130.0 ± 22.2; 127.2	115.0 ± 32.6; 115.3	0.020
Post-Tilt DBP, mmHg	71.9 ± 10.9; 70.5	65.9 ± 18.9; 64.6	0.041
Post-Tilt HR, bpm	80.3 ± 11.4; 79.2	83.0 ± 18.9; 81.3	0.562
Symptoms Reported[1], %	64.0	92.0	<0.001

Note. Values reported as mean ± SD; median, or number (n, percentage). Abbreviations: DBP, diastolic blood pressure; HR, heart rate; POTS, postural orthostatic tachycardia syndrome; SBP, systolic blood pressure. Groups were compared using the Kruskal-Wallis Test, except where noted as 1=Fishers Exact test.

Table 9

Distribution of EDA Response Subtypes in Controls and POTS Subjects

Entire study population			
EDA response subtype	Controls, n (%)	POTS cases, n (%)	p-value
Transient	18 (72.00)	21 (28.00)	<0.001
Absent	5 (20.00)	14 (18.67)	
Delayed	2 (8.00)	8 (10.67)	
Persistent	0 (0.00)	32 (42.67)	
	25	75	
Age and sex-matched subset			
EDA response subtype	Controls, n (%)	POTS cases, n (%)	p-value
Transient	14 (77.78)	3 (16.67)	<0.001
Absent	2 (11.11)	6 (33.33)	
Delayed	2 (11.11)	1 (5.60)	
Persistent	0 (0.00)	8 (44.44)	
	18	18	

Note. Values are reported as number (n, percentage). Note that for the entire study population, POTS=75 and controls=25, while for the age and sex matched subset of the entire study population, POTS=18 and controls=18. Abbreviations: EDA, electrodermal activity; ERS, EDA response subtype; POTS, postural orthostatic tachycardia syndrome. Groups were compared using Fishers Exact Test.

Table 10

Demographic, Electrodermal, and Hemodynamic characteristics of ERS Subtypes in Control and POTS Patients

	Controls				POTS				
	Transient (n=18)	Absent (n=5)	Delayed (n=2)	p-value	Transient (n=21)	Absent (n=14)	Delayed (n=8)	Persistent (n=32)	p-value
Age (all), years	44 ± 18; 46	54 ± 18; 59	27 ± 19; 27	0.259	28.3 ± 13.5; 25	27.6 ± 9.1; 26	23.1 ± 6.5; 26	28.0 ± 13.8; 24	0.832
Age (≥ 20) years	49 ± 15; 46	54 ± 18; 59	40 ± 0; 40	0.817	35.1 ± 11.4; 35	29.6 ± 8.2;28	27.6 ± 1.8; 28	33.1 ± 13.1; 29	0.573
Age (≤ 19) years	16 ± 2; 17	0 ± 0.0; 0	13 ± 0; 13	Indeterminable[2]	14.7 ± 2.3; 15	15.5 ± 2.1; 16	15.7 ± 3.1; 15	15.0 ± 1.5; 15	0.978
Female sex, N (%) Male sex, N (%)	14 (77.8) 4 (22.2)	3 (60.0) 2 (40.0)	2 (100.0) 0 (0.0)	<0.001[1]	17 (81.0) 4 (19.0)	12 (85.7) 2 (14.3)	5 (62.5) 3 (37.5)	23 (71.9) 9 (28.1)	0.555
Height, cm	166.6 ± 8.9; 166.4	161.5 ± 7.3; 160.0	166.4 ± 0.0; 166.4	0.610	166.1 ± 13.6; 167.6	170.2 ± 9.1; 171.5	174.0 ± 10.6; 170.2	168.6 ± 8.9; 167.6	0.333
Weight, kg	71.5 ± 20.5; 68.7	80.8 ± 17.5; 75.3	83.9 ± 48.1; 83.9	0.506	66.5 ± 20.8; 61.2	63.6 ± 8.7; 63.0	66.7 ± 14.3; 63.5	65.4 ± 13.6; 63.3	0.932
Body Mass Index, kg/m^2	25.6 ± 5.8; 25.2	31.1 ± 7.3; 28.7	30.2 ± 16.8; 30.2	0.271	24.2 ± 7.5; 21.6	22.0 ± 1.9; 21.6	21.9 ± 2.4; 21.6	22.9 ± 4.1; 22.3	0.863
Medications Held, N (%) Medications Taken N (%)	8 (44.4) 10 (55.6)	0 (0.0) 5 (100.0)	1 (50.0) 1 (50.0)	<0.001	9 (42.9) 12 (57.1)	8 (57.1) 6 (42.9)	2 (25.0) 6 (75.0)	12 (37.5) 20 (62.5)	0.488
Supine SBP, mmHg	118.8 ± 20.7; 124.5	124.1 ± 14.1; 118.0	116.6 ± 17.8; 116.6	0.911	108.8 ± 22.4; 108.0	109.0 ± 12.7; 111.3	102.9 ± 25.2; 105.3	111.9 ± 18.3; 109.4	0.682
Supine DBP, mmHg	72.2 ± 11.5; 76.1	78.6 ± 5.3; 80.0	69.7 ± 0.4; 69.7	0.326	66.7 ± 13.7; 71.1	66.8 ± 9.5; 65.1	64.3 ± 7.8; 65.7	69.0 ± 11.1; 68.3	0.702
Supine HR, bpm	74.3 ± 8.5; 75.3	72.5 ± 17.5; 73.0	91.4 ± 21.8; 91.4	0.398	75.8 ± 11.22; 74.9	75.8 ± 13.1; 76.1	78.8 ± 14.5; 76.0	76.1 ± 14.8; 74.3	0.968
HR Change, bpm	28.0 ± 6.7; 28.4	20.2 ± 7.1; 22.1	30.8 ± 8.9; 30.8	0.118	54.0 ± 7.8; 51.4	56.7 ± 14.2; 53.5	64.7 ± 9.5; 64.1	52.0 ± 8.8; 50.6	0.021
SBP Change, mmHg	-8.8 ± 7.5; -10.6	-12.5 ± 6.7; -12.5	-9.4 ± 9.9; -9.4	0.594	-11.1 ± 7.3; -12.7	-11.5 ± 6.1; -12.2	-11.8 ± 5.9; -8.9	-11.7 ± 5.3; -11.9	>0.999
Symptoms Reported, N (%) Symptoms Not Reported, N (%)	11 (61.1) 7 (38.9)	3 (60.0) 2 (40.0)	2 (100.0) 0 (0.0)	<0.001[1]	19 (90.5) 2 (9.5)	12 (85.7) 2 (14.3)	8 (100) 0 (0.0)	30 (93.8) 2 (6.2)	0.743
Disorientation Reported, N (%) Disorientation Not Reported, N (%)	0 (0.0) 18 (100.0)	0 (0.0) 5 (100.0)	0 (0.0) 2 (100.0)	>0.999	2 (9.5) 19 (90.5)	1 (7.1) 13 (92.9)	4 (50.0) 4 (50.0)	1 (3.1) 31 (96.9)	0.006
PRT, sec	5.3 ± 12.8; 1.4	2.9 ± 3.0; 1.0	17.8 ± 24.1; 17.8	0.886	1.9 ± 2.7; 1.0	1.5 ± 0.9; 1.4	5.2 ± 6.4; 2.2	2.7 ± 3.1; 1.5	0.015
EDA at Tilt-up, µsiemens	4.44 ± 5.94; 2.04	0.25 ± 0.29; 0.15	1.15 ± 1.46; 1.15	0.024	5.98 ± 7.35; 3.00	1.58 ± 4.30; 0.42	1.46 ± 1.78; 0.66	5.37 ± 6.31; 3.00	<0.001
EDA at Tilt Down, µsiemens	4.78 ± 6.34; 2.77	0.27 ± 0.29; 0.15	3.10 ± 2.62; 3.10	0.031	6.68 ± 7.47; 3.20	1.52 ± 3.56; 0.60	2.93 ± 2.45; 2.47	8.99 ± 7.08; 6.88	<0.001
EDA Maximum, µsiemens	10.25 ± 11.32; 5.90	0.31 ± 0.29; 0.16	4.25 ± 1.53; 4.25	0.012	11.89 ± 11.30; 8.16	3.09 ± 5.13; 0.92	5.64 ± 5.04; 4.07	13.41 ± 9.92; 10.14	<0.001
EDA Minimum, µsiemens	3.48 ± 4.8; 1.65	0.20 ± 0.30; 0.07	0.08 ± 0.07; 0.08	0.011	4.81 ± 6.46; 2.63	0.93 ± 3.08; 0.26	0.87 ± 1.00; 0.64	4.64 ± 5.88; 2.00	<0.001
EDA Difference, µsiemens	6.77 ± 7.62; 4.53	0.11 ± 0.15; 0.05	4.17 ± 1.61; 4.17	0.004	6.81 ± 5.65; 4.76	2.16 ± 3.66; 0.40	4.77 ± 4.73; 3.69	8.78 ± 6.98; 7.03	<0.001

Note: Values reported either as mean ± SD; median, or number (n, percentage). All of the Delayed values in the controls, were omitted from the computation of the p-values because there is just one patient in this subgroup. The distribution of females between groups, is POTS: n=57* and controls: n=19**. Abbreviations: DBP, diastolic blood pressure; EDA, electrodermal activity; ERS, EDA response subtype; HR, heart rate; POTS, postural orthostatic tachycardia syndrome; SBP, systolic blood pressure. The PRT values for POTS patients (*) are mean ± SD for the 58 (out of 75) POTS patients with a determinable PRT, whereas for controls (**), the values are mean ± SD for the 24 (out of the 25) controls with a

determinable PRT. Abbreviations: PRT, pressure recovery time; POTS, postural orthostatic tachycardia syndrome. Subgroups (i.e., EDA response subtypes) were compared using the Kruskal-Wallis Test, except where noted as 1=Fishers Exact Test, or 2=Mann-Whitney U Test.

Table 11

Symptoms in Controls Versus POTS Patients

	Controls (n=25)	POTS (n=75)	p-value
Presence of HUTT Symptoms, n (%)	16 (64.00)	69 (92.0)	<0.001
Average Number of Symptoms[1], #	1.8 ± 2.2; 1.0	4.6 ± 3.7; 4.0	<0.001
Total Number of Symptoms[1], #	46	347	<0.001
Presence of Tilt-up Symptoms, n (%)	8 (32.0)	50 (66.7)	<0.001
Average Number of Tilt-up Symptoms[2], #	0.6 ± 1.0; 0.0	1.2 ± 1.2; 1.0	0.006
Number of Tilt-up Symptoms[2], #	14	89	0.006
Presence of Tilt-down Symptoms, n (%)	9 (36.0)	54 (72.0)	<0.001
Average Number of Tilt-down Symptoms[1], #	0.4 ± 0.7; 0.0	3.4 ± 3.4; 3.0	<0.001
Number of Tilt-down Symptoms[1], #	11	253	<0.001
Trend of HUTT Symptoms			
No Symptoms, n (%)	9 (36.0)	6 (8.0)	<0.001
Asymptomatic Until Tilt-down, n (%)	0 (0.0)	2 (2.7)	0246
Decrease in Number of Symptoms and/or Severity of Symptoms, n (%)	7 (28.0)	11 (14.7)	0.038
Same Number of Symptoms or Level of Severity of Symptoms, n (%)	5 (20.0)	4 (5.33)	0.002
Increase in Number of Symptoms and/or Severity of Symptoms, n (%)	4 (16.0)	52 (69.3)	<0.001
Symptoms Quality and Ranking			
Not Applicable Because of the Absence of Symptoms, n (%)	9 (36.0)	6 (8.0)	<0.001
Transient Symptoms, n (%)	0 (0.0)	1 (1.3)	>0.999
Mild Symptoms, n (%)	8 (32.0)	17 (22.7)	0.205
Moderate Symptoms, n (%)	6 (24.0)	19 (25.3)	>0.999
Severe Symptoms, n (%)	2 (8.0)	32 (42.7)	<0.001

Note. Values are reported either as single numbers, or else as mean plus or minus standard deviation; median. Abbreviations: HUTT, head-up tilt-table test; POTS, postural orthostatic tachycardia syndrome. Key for interpreting the Scale for the Quantification of HUTT Symptoms: The five respective scores listed under the symptoms scoring scalar item titled “Symptoms Severity Trend”, are as follows: No Symptoms Ξ (0), Asymptomatic Until Tilt Down Ξ (1), Decreased Ξ (2), Same Ξ (3), and Increased Ξ (4). For the scalar item titled “Symptoms Quality and Ranking”,

the five respective scores represent the following: Not Applicable (because the patient did not report any symptoms) Ξ (0), Transient Ξ (1), Mild Ξ (2), Moderate Ξ (3), and Severe Ξ (4). Groups were compared using Fishers Exact Test, except where noted as 1= the Kruskal-Wallis Test, and 2=the Mann Whitney U Test.

Table 12

Symptoms in Controls Versus POTS Patients Stratified by Electrodermal Response Subtype

	Controls				POTS				
	ERS 1 n=18	ERS 2 n=5	ERS 3 n=2	p-value	ERS 1 n=21	ERS 2 n=14	ERS 3 n=8	ERS 4 n=32	p-value
Presence of HUTT Symptoms, n (%)	11 (61.1)	3 (60.0)	2 (100.0)	<0.001	19 (90.5)	12 (85.7)	8 (100)	30 (93.8)	<0.001
Average Number of Symptoms[1], #	1.7 ± 2.0; 1.0	0.8 ± 0.8; 1.0	5.5 ± 3.5; 5.5	0.143	5.1 ± 4.9	4.1 ± 3.3	5.4 ± 3.7	4.4 ± 3.1	0.890
Total Number of Symptoms[1], #	31	4	11	0.143	107	56	43	141	0.890
Presence of Tilt-up Symptoms, n (%)	5 (27.8)	1 (20.0)	2 (100.0)	<0.001	13 (61.9)	9 (64.3)	6 (75.0)	22 (68.8)	0.200
Average Number of Tilt-up Symptoms[1], #	0.6 ± 1.1; 0.0	0.2 ± 0.4; 0.0	1.5 ± 0.7; 1.5	0.119	1.0 ± 1.0	1.4 ± 1.3	1.6 ± 1.2	1.2 ± 1.3	0.446
Total Number of Tilt-up Symptoms[1], #	10	1	3	0.119	20	19	13	37	0.446
Presence of Tilt-down Symptoms, n (%)	5 (27.8)	3 (60.0)	1 (50.0)	<0.001	13 (61.9)	9 (64.3)	8 (100.0)	24 (75.0)	<0.001
Average Number of Tilt-down Symptoms[1], #	0.3 ± 0.6; 0.0	0.6 ± 0.5; 1.0	1.0 ± 1.4; 1.0	0.389	3.1 ± 3.7	3.1 ± 3.5	3.5 ± 3.8	3.7 ± 3.2	0.823
Total Number of Tilt-down Symptoms[1], #	6	3	2	0.389	65	43	28	117	0.823
Trend of HUTT Symptoms									
No Symptoms, n (%)	7 (38.9)	2 (40.0)	0 (0.0)	<0.001	2 (9.5)	2 (14.3)	0 (0.0)	2 (6.3)	<0.001
Asymptomatic Until Tilt-down, n (%)	0 (0.0)	0 (0.0)	0 (0.0)	>0.999	0 (0.0)	0 (0.0)	1 (12.5)	1 (3.1)	<0.001
Decrease in Number of Symptoms and/or Severity of Symptoms, n (%)	5 (27.8)	2 (40.0)	1 (50.0)	<0.006	5 (23.8)	3 (21.4)	0 (0.0)	3 (9.4)	<0.001
Same Number of Symptoms or Level of Severity of Symptoms, n (%)	4 (22.2)	0 (0.0)	1 (50.0)	<0.001	1 (4.8)	0 (0.0)	0 (0.0)	3 (9.4)	<0.001
Increase in Number of Symptoms and/or Severity of Symptoms, n (%)	2 (11.1)	1 (20.0)	1 (50.0)	<0.001	13 (61.9)	9 (64.3)	7 (87.5)	23 (71.9)	<0.001
Symptoms Quality and Ranking									
Not Applicable Because of the Absence of Symptoms, n (%)	7 (38.9)	2 (40.0)	0 (0.0)	<0.001	2 (9.5)	2 (14.3)	0 (0.0)	2 (6.3)	<0.001
Transient Symptoms, n (%)	0 (0.0)	0 (0.0)	0 (0.0)	>0.999	0 (0.0)	0 (0.0)	0 (0.0)	1 (3.1)	0.061
Mild Symptoms, n (%)	6 (33.3)	2 (40.0)	0 (0.0)	<0.001	5 (23.8)	2 (14.3)	1 (12.5)	9 (28.1)	0.016
Moderate Symptoms, n (%)	4 (22.2)	1 (20.0)	1 (50.0)	<0.001	8 (38.1)	3 (21.4)	3 (37.5)	5 (15.6)	<0.001
Severe Symptoms, n (%)	1 (5.5)	0 (0.0)	1 (50.0)	<0.001	6 (28.6)	6 (42.9)	4 (50.0)	15 (46.9)	0.002
Certain Clinically Significant Symptoms									
Disorientation Reported, n (%)	0 (0.0)	0 (0.0)	0 (0.0)	>0.999	2 (9.5)	1 (7.1)	4 (50.0)	1 (3.1)	<0.001
Shortness of Breath Reported, n (%)	2 (11.1)	0 (0.0)	1 (50.0)	<0.001	1 (4.8)	5 (35.7)	3 (37.5)	7 (21.9)	<0.001
Lightheadedness Reported, n (%)	4 (22.2)	2 (40.0)	1 (50.0)	<0.001	12 (66.7)	9 (64.3)	6 (75.0)	23 (71.9)	0.336

Note. Values are reported either as single numbers, or else as mean plus or minus standard deviation; median. Abbreviations: ERS, EDA response subtype; HUTT, head-up tilt-table test; POTS, postural orthostatic tachycardia syndrome. Key for interpreting the Scale for the Quantification of HUTT Symptoms: The five respective scores listed under the symptoms scoring scalar item titled “Symptoms Severity Trend”, are as follows: No Symptoms Ξ (0), Asymptomatic Until Tilt Down Ξ (1), Decreased Ξ (2), Same Ξ (3), and Increased Ξ (4). For the scalar item titled “Symptoms Quality and Ranking”, the five respective scores represent the following: Not Applicable (because the patient did not report any symptoms) Ξ (0), Transient Ξ (1), Mild Ξ (2), Moderate Ξ (3), and Severe Ξ (4). Groups were compared using Fishers Exact Test, except where noted as 1= the Kruskal-Wallis Test.

Table 13

AUCs for Variations in Electrodermal Indices Between Controls and POTS Cases (N = 100)

Variable Name	Area Under the Curve (AUC)	p-value
EDA_{Mean} Post HUTT, µsiemens	0.709	0.002
$EDA_{Frequency}$ HUTT, Hz	0.702	0.003
$EDA_{Frequency}$ HUTT – $EDA_{Frequency}$ Pre HUTT, Hz	0.702	0.003
$EDA_{Frequency}$ Post HUTT – $EDA_{Frequency}$ HUTT, Hz	0.702	0.003
EDA_{Sum} Post HUTT – EDA_{SUM} Pre HUTT, µsiemens	0.701	0.003

Note. Values are reported as single numbers. Abbreviations: AUC, area under the curve; EDA_{Area} Pre Tilt, area under the EDA trace in the 30-seconds pre head-up tilt period; $EDA_{Area\text{-}normalized}$: Normalized Area under the EDA trace (normalized through division by duration in seconds); HUTT, head-up tilt-table test; POTS, postural orthostatic tachycardia syndrome. The area under the curve (AUC) values were computed from receiving-operating characteristic curves (ROCs) related statistical analyses (performed in the course of testing for the sensitivity and specificity of certain variables either in identifying both of the groups or in picking out any of the EDA response subtypes or subgroups).

Table 14

Correlational Strength of Comparisons Between Novel Test Measures and Standard Test Measures in the Cohort of POTS Cases

Novel Test Measure	Standard Test Measure	N	Correlation Coefficient	p-value	Strength of Association
PR Equivalent of Maximum HR	HUT Maximum HR	75	0.949	<0.001	Very Strong
Latency of PR Equivalent of Maximum HR	Time from Tilt to HUT Maximum HR	75	0.872	<0.001	Very Strong
Tilt-up PR	HUT Minimum HR	75	0.850	<0.001	Very Strong
Tilt-up PR	Baseline HR	75	0.848	<0.001	Very Strong
PR Equivalent of Maximum HR	HUT Minimum HR	75	0.718	<0.001	Strong
Tilt-up PR	HUT Maximum HR	75	0.657	<0.001	Strong
PR Equivalent of Maximum HR	Baseline HR	75	0.649	<0.001	Strong
PR Equivalent of Maximum HR	HUT HR at the HUT Minimum SBP	75	0.607	<0.001	Strong
Tilt-up PR	Post HUT HR	75	0.604	<0.001	Strong
Tilt-down PR	HUT Maximum HR	75	0.595	<0.001	Moderate
Tilt-down PR	HUT Minimum HR	75	0.557	<0.001	Moderate
Tilt-up PR	HUT HR at the HUT Minimum SBP	75	0.556	<0.001	Moderate
PR Equivalent of Maximum HR	Post HUT HR	75	0.550	<0.001	Moderate
EDA HUT Frequency	Number of Data Sets During HUT	75	0.527	<0.001	Moderate
HUT EDA Frequency – Baseline EDA Frequency	Number of Data Sets During HUT	75	0.527	<0.001	Moderate
Post HUT EDA Frequency – HUT EDA Frequency	Number of Data Sets During HUT	75	0.527	<0.001	Moderate
PR Equivalent of Maximum HR	HUT HR Delta	75	0.504	<0.001	Moderate
HUT EDA BPM	Valsalva Phase 3 Minimum Rate – Baseline	75	-0.494	<0.001	Moderate
HUT EDA BPM – Baseline EDA BPM	Valsalva Phase 3 Minimum Rate – Baseline	75	-0.494	<0.001	Moderate
Post HUT EDA BPM– HUT EDA BPM	Valsalva Phase 3 Minimum Rate – Baseline	75	0.494	<0.001	Moderate
HUT EDA BPM	Time from Tilt to HUT Maximum HR	75	-0.477	<0.001	Moderate
EDA BPM HUT – Baseline EDA BPM	Time from Tilt to HUT Maximum HR	75	-0.477	<0.001	Moderate
Post HUT EDA BPM – HUT EDA BPM	Time from Tilt to HUT Maximum HR	75	0.477	<0.001	Moderate
Tilt-down PR	Post HUT HR	75	0.466	<0.001	Moderate
HUT EDA BPM	Valsalva Phase 3 Rate Difference	75	0.466	<0.001	Moderate
HUT EDA BPM – Baseline EDA BPM	Valsalva Phase 3 Rate Difference	75	0.466	<0.001	Moderate
Post HUT EDA BPM – HUT EDA BPM	Valsalva Phase 3 Rate Difference	75	-0.466	<0.001	Moderate

HUT EDA BPM	0.75 of Phase 3 Rate Difference During Valsalva	75	0.466	<0.001	Moderate
HUT EDA BPM – Baseline EDA BPM	0.75 of Phase 3 Rate Difference During Valsalva	75	0.466	<0.001	Moderate
Post HUT EDA BPM – HUT EDA BPM	0.75 of Phase 3 Rate Difference During Valsalva	75	-0.466	<0.001	Moderate
HUT EDA Delta T	Valsalva Phase 3 Minimum Rate – Baseline	75	0.465	<0.001	Moderate
HUT EDA Delta S	Valsalva Phase 3 Minimum Rate – Baseline	75	0.465	<0.001	Moderate
Latency of PR Equivalent of Maximum HR	0.75 of Phase 3 Rate Difference During Valsalva	75	-0.464	<0.001	Moderate
Latency of PR Equivalent of Maximum HR	Valsalva Phase 3 Rate Difference	75	-0.464	<0.001	Moderate
PR at Tilt-down – PR at Tilt-up	Time from Tilt to HUT Minimum HR	75	-0.444	<0.001	Moderate
HUT EDA Frequency	Valsalva Phase 2E Minimum Rate – Baseline	75	0.441	<0.001	Moderate
HUT EDA Frequency – Baseline EDA Frequency	Valsalva Phase 2E Minimum Rate – Baseline	75	0.441	<0.001	Moderate
Post HUT EDA Frequency – HUT EDA Frequency	Valsalva Phase 2E Minimum Rate – Baseline	75	-0.441	<0.001	Moderate
HUT EDA Delta S	Time from Tilt to HUT Maximum HR	75	0.440	<0.001	Moderate
HUT EDA Delta T	Time from Tilt to HUT Maximum HR	75	0.440	<0.001	Moderate
PR at Tilt-down – PR at Tilt-up	HUT Maximum HR – Baseline HR	75	0.437	<0.001	Moderate
HUT EDA Delta T	Valsalva Phase 3 Rate Difference	75	-0.431	<0.001	Moderate
HUT EDA Delta T	0.75 of Phase 3 Rate Difference During Valsalva	75	-0.431	<0.001	Moderate
HUT EDA Delta S	Valsalva Phase 3 Rate Difference	75	-0.430	<0.001	Moderate
HUT EDA Delta S	0.75 of Phase 3 Rate Difference During Valsalva	75	-0.430	<0.001	Moderate
PR Equivalent of Maximum HR	HUT Maximum HR – Baseline HR	75	0.420	<0.001	Moderate
Latency of PR Equivalent of Maximum HR	QSWEAT Forearm Ending Offset – Baseline Rate	75	0.417	<0.001	Moderate
Peak-to-Peak PR	Cardiovagal Component of the CASS	75	-0.417	0.001	Moderate
HUT EDA Frequency	Valsalva Phase 2E Rate Difference	75	-0.406	<0.001	Moderate
HUT EDA Frequency – Baseline EDA Frequency	Valsalva Phase 2E Rate Difference	75	-0.406	<0.001	Moderate
Post HUT EDA Frequency – HUT EDA Frequency	Valsalva Phase 2E Rate Difference	75	0.406	<0.001	Moderate
EDAdurationHeadupTilt	ASALine1Phase2ERateDifference	75	-0.397	<0.001	Weak
EDAdeltaS_HUT	ASALine1Phase2ERateDifference	75	-0.397	<0.001	Weak
EDAHUTBPM	ASALine1Phase2ERateDifference	75	0.393	0.001	Weak
EDAHUTTBPM-EDAPreHUTTBPM	ASALine1Phase2ERateDifference	75	0.393	0.001	Weak
EDAPostHUTBPM-EDAHUTBPM	ASALine1Phase2ERateDifference	75	-0.393	0.001	Weak
RawAUCAcqKnowGenPR	HemodynamicChangesMaxHUTHR-PreHR	75	0.389	0.001	Weak
LatentAcqKnowEqARSMaxHR	ASALine1Phase2EMaxRate-Baseline	75	-0.384	0.001	Weak
RawAUCAcqKnowGenPR	TiltHRDelta	75	0.384	0.001	Weak

HRtiltDown	TiltPreHR	75	0.380	0.001	Weak
EDAHUTBPM	numDataSetsHUT	75	-0.379	0.001	Weak
EDAHUTTBPM-EDAPreHUTTBPM	numDataSetsHUT	75	-0.379	0.001	Weak
EDAPostHUTBPM-EDAHUTBPM	numDataSetsHUT	75	0.379	0.001	Weak
EDAHUTBPM	ASALine1Phase2EMinRate-Baseline	75	-0.379	0.001	Weak
EDAHUTTBPM-EDAPreHUTTBPM	ASALine1Phase2EMinRate-Baseline	75	-0.379	0.001	Weak
EDAPostHUTBPM-EDAHUTBPM	ASALine1Phase2EMinRate-Baseline	75	0.379	0.001	Weak
LatentAcqKnowEqARSMaxHR	ASALine1Phase3MinRate-Baseline	75	0.378	0.001	Weak
EDAdurationHeadupTilt	ASALine1Phase3MaxRate-Baseline	75	0.377	0.001	Weak
EDAdeltaS_HUT	ASALine1Phase3MaxRate-Baseline	75	0.377	0.001	Weak
EDAHUTFrequency	ASALine1(0.75)ofPhase3RateDifference	75	-0.376	0.001	Weak
EDAHUTFrequency-EDAPreHUTFrequency	ASALine1(0.75)ofPhase3RateDifference	75	-0.376	0.001	Weak
EDAPostHUTFrequency-EDAHUTFrequency	ASALine1(0.75)ofPhase3RateDifference	75	0.376	0.001	Weak
EDAHUTFrequency	ASALine1Phase3RateDifference	75	-0.376	0.001	Weak
EDAHUTFrequency-EDAPreHUTFrequency	ASALine1Phase3RateDifference	75	-0.376	0.001	Weak
EDAPostHUTFrequency-EDAHUTFrequency	ASALine1Phase3RateDifference	75	0.376	0.001	Weak
EDAHUTBPM	ASALine1Phase3MaxRate-Baseline	75	-0.375	0.001	Weak
EDAHUTTBPM-EDAPreHUTTBPM	ASALine1Phase3MaxRate-Baseline	75	-0.375	0.001	Weak
EDAPostHUTBPM-EDAHUTBPM	ASALine1Phase3MaxRate-Baseline	75	0.375	0.001	Weak

Note. Values are reported as single numbers. Abbreviations: 2E, early phase 2; ASA, adrenergic sensitivity analysis; BPM, beats per minute (note that this capitalized unit is not the same thing as the well-known unit of heart rate “bpm”, rather it represents the sampling rate used to record the EDA signal); CASS, composite autonomic severity score; Delta S, change in slope; Delta T, change in time; EDA, electrodermal activity; HR, heart rate; HUT, head up tilt; PR, pulse rate; PRT, pressure recovery time; QSWEAT, the manufacturer’s brand for a type of quantitative axon reflex test (QSART) device manufactured and supplied by WR Medical Electronics Co., Minnesota. Note that only weak, moderate, strong, and

very strong results with statistically significant q-values, have been reported in this table. The 27 weak correlations reported in the table above, have been included because of their potential utility in future hypotheses generation. The correlation coefficients were determined via use of the Spearman's Correlations Test. Storey's method for multiple comparisons, was used for the adjustment of p-values, maintaining a $p<0.05$ false discovery rate, with the adjusted $p<0.05$.

Table 15

Correlational Strength of Comparisons Between Novel Test Measures and Standard Test Measures in the Cohort of Controls

Novel Test Measure	Standard Test Measure	n	Correlation Coefficient	p-value	Strength of Association
Latency of PR Equivalent of Maximum HR	Time from Tilt to HUT Maximum HR	25	0.976	<0.001	Very Strong
PR Equivalent of Maximum HR	HUT Maximum HR	25	0.889	<0.001	Very Strong
PR Equivalent of Maximum HR	HUT HR at the HUT Minimum SBP	25	0.823	<0.001	Very Strong
Tilt-up PR	Baseline HR	25	0.785	<0.001	Strong
PR Equivalent of Maximum HR	HUT Minimum HR	25	0.756	<0.001	Strong
PR Equivalent of Maximum HR	Baseline HR	25	0.746	<0.001	Strong
Tilt-up PR	Post HUT HR	25	0.744	<0.001	Strong
Tilt-up PR	HUT Minimum HR	25	0.731	<0.001	Strong
Tilt-down PR	HUT HR at the HUT Minimum SBP	25	0.720	<0.001	Strong
Tilt-up PR	HUT Maximum HR	25	0.713	<0.001	Strong
Arc of EDA Area Post HUT – Arc of EDA Area HUT	Average HR Difference (HRDB)	25	-0.639	0.001	Strong
EDA Sum Pre HUT	ASA Line 1 Phase 3 Min Rate	24	0.628	0.001	Strong
EDA Mean Pre HUT	ASA Line 1 Phase 3 Min Rate	24	0.617	0.001	Strong
EDA Integral Pre HUT	ASA Line 1 Phase 3 Min Rate	24	0.617	0.001	Strong
EDA Area Pre-Tilt	HR at Min SBP – Pre HUT HR	25	0.609	0.001	Strong
Arc of EDA Area Pre-Tilt	HR at Min SBP – Pre HUT HR	25	0.609	0.001	Strong
EDA Mean Post HUT	Number of Chronotropic Meds Not Held	25	-0.605	0.001	Strong
EDA Integral Post HUT – EDA Integral HUT	Number of Chronotropic Meds Not Held	25	0.590	0.002	Moderate
EDA Peak-to-Peak Pre HUT	ASALine1Phase3MinRate	24	0.587	0.003	Moderate
EDA Integral Post HUT – EDA Integral HUT	ASA Line 1 Phase 3 Min Rate – Baseline	25	-0.587	0.002	Moderate
EDA Area Pre-Tilt	Min HUT HR – HR at Min SBP	25	-0.584	0.002	Moderate
Arc of EDA Area Pre-Tilt	Min HUT HR – HR at Min SBP	25	-0.584	0.002	Moderate
EDA Mean Pre HUT	ASA Line 1 Phase 3 Min Rate – Baseline	25	0.580	0.002	Moderate
EDA Integral Pre HUT	ASA Line 1 Phase 3 Min Rate – Baseline	25	0.580	0.002	Moderate

EDA Frequency HUT	ASA Line 1 PRT Value	24	-0.579	0.003	Moderate
EDA Frequency HUT – EDA Frequency Pre HUT	ASA Line 1 PRT Value	24	-0.579	0.003	Moderate
EDA Frequency Post HUT – EDA Frequency HUT	ASA Line 1 PRT Value	24	0.579	0.003	Moderate
EDA Max	ASA Line 1 Phase 3 Min Rate – Baseline	25	0.578	0.003	Moderate
EDA Duration HUT	ASA Line 1 PRT Value	24	0.578	0.003	Moderate
EDA Delta S HUT	ASA Line 1 PRT Value	24	0.578	0.003	Moderate
EDA Peak-to-Peak Pre HUT	Post SBP – Pre SBP	25	0.577	0.003	Moderate
EDA Sum Post HUT	Number of Chronotropic Meds Not Held	25	-0.575	0.003	Moderate
EDA Sum HUT – EDA Sum Pre HUT	ASA Line 1 Phase 3 Min Rate – Baseline	25	0.575	0.003	Moderate
EDA Min	ASALine1Phase3MinRate – Baseline	25	0.569	0.003	Moderate
EDA BPM HUT	ASA Line 1 PRT Value	24	-0.564	0.004	Moderate
EDA HUT BPM – EDA BPM Pre HUT	ASA Line 1 PRT Value	24	-0.564	0.004	Moderate
EDAPostHUTBPM-EDAHUTBPM	ASA Line 1 PRT Value	24	0.564	0.004	Moderate
Arc of EDA Area Pre-Tilt	Weight	25	-0.562	0.003	Moderate
Arc of EDA Area Pre Tilt	Weight	25	-0.562	0.003	Moderate
EDA at Tilt-Up	ASALine1Phase3MinRate	24	0.561	0.004	Moderate
EDA Area Pre Tilt	Post SBP – Pre SBP	25	0.561	0.004	Moderate
Arc of EDA Area Pre Tilt	Post SBP – Pre SBP	25	0.561	0.004	Moderate
EDA Sum Post HUT – EDA Sum HUT	ASALine1Phase3MinRate-Baseline	25	-0.560	0.004	Moderate
EDA Tilt-Up	numMedsNotHeldChronotrope	25	-0.560	0.004	Moderate
EDA Tilt-Down	numMedsNotHeldChronotrope	25	-0.560	0.004	Moderate
EDA Max	numMedsNotHeldChronotrope	25	-0.560	0.004	Moderate
EDAmean	numMedsNotHeldChronotrope	25	-0.560	0.004	Moderate
EDAmedian	numMedsNotHeldChronotrope	25	-0.560	0.004	Moderate
EDA at the PR Equivalent of the Standard Max HR	numMedsNotHeldChronotrope	25	-0.560	0.004	Moderate
EDAintegral	numMedsNotHeldChronotrope	25	-0.560	0.004	Moderate
EDAPreHUTMean	numMedsNotHeldChronotrope	25	-0.560	0.004	Moderate
EDAPreHUTIntegral	numMedsNotHeldChronotrope	25	-0.560	0.004	Moderate
EDAHUTIntegral-EDAPreHUTIntegral	numMedsNotHeldChronotrope	25	-0.560	0.004	Moderate
EDAPreHUTSum	numMedsNotHeldChronotrope	25	-0.560	0.004	Moderate
EDAHUTSum	numMedsNotHeldChronotrope	25	-0.560	0.004	Moderate
EDAHUTSum-EDAPreHUTSum	numMedsNotHeldChronotrope	25	-0.560	0.004	Moderate
EDAPostHUTSum-EDAHUTSum	numMedsNotHeldChronotrope	25	0.560	0.004	Moderate

EDAsd (EDA Standard Deviation)	HemodynamicChangesHRDBAverageHRDifference	25	0.559	0.004	Moderate
EDA_{Area} Pre Tilt	TiltHRatMinSBP	25	0.559	0.004	Moderate
EDAnormalizedAreaPreTilt	TiltHRatMinSBP	25	0.559	0.004	Moderate
EDAmedian	ASALine1Phase3MinRate-Baseline	25	0.555	0.004	Moderate
EDAreaPreTilt	BMI	25	-0.552	0.004	Moderate
EDAnormalizedAreaPreTilt	BMI	25	-0.552	0.004	Moderate
EDAtiltUp	ASALine1Phase3MinRate-Baseline	25	0.551	0.004	Moderate
EDAareaPostTilt	HemodynamicChangesPostSBP-PreSBP	25	0.545	0.005	Moderate
EDAnormalizedAreaPostTilt	HemodynamicChangesPostSBP-PreSBP	25	0.545	0.005	Moderate
EDAmin	numMedsNotHeldChronotrope	25	-0.545	0.005	Moderate
EDAmean	ASALine1Phase3MinRate-Baseline	25	0.543	0.005	Moderate
EDAHUTFrequency	ASALine1AdrenergicScore	24	0.541	0.006	Moderate
EDAHUTFrequency-EDAPreHUTFrequency	ASALine1AdrenergicScore	24	0.541	0.006	Moderate
EDAPostHUTFrequency-EDAHUTFrequency	ASALine1AdrenergicScore	24	-0.541	0.006	Moderate
EDAintegral	ASALine1Phase3MinRate-Baseline	25	0.540	0.005	Moderate
EDAHUTIntegral-EDAPreHUTIntegral	ASALine1Phase3MinRate-Baseline	25	0.540	0.005	Moderate
EDAHUTSum	ASALine1Phase3MinRate-Baseline	25	0.540	0.005	Moderate
EDAdurationHeadupTilt	ASALine1AdrenergicScore	24	-0.539	0.007	Moderate
EDAdeltaS_HUT	ASALine1AdrenergicScore	24	-0.539	0.007	Moderate
EDAmin	ASALine1Phase3MinRate	24	0.527	0.008	Moderate
EDAPostHUTTPeaktoPeak-EDAPreHUTTPeaktoPeak	ASALine(s)AvgPRTValue	17	0.527	0.030	Moderate
EDA_{Delta} HUT	ASALine1Phase2EMaxRate-Baseline	25	-0.527	0.007	Moderate
EDAHUTBPM	ASALine1AdrenergicScore	24	0.521	0.009	Moderate
EDAHUTTBPM-EDAPreHUTTBPM	ASALine1AdrenergicScore	24	0.521	0.009	Moderate
EDAPostHUTBPM-EDAHUTBPM	ASALine1AdrenergicScore	24	-0.521	0.009	Moderate
EDAatTiltDown-EDAatTiltUp	ASALine1Phase2EMaxRate-Baseline	25	-0.520	0.008	Moderate
EDAPreHUTSum	ASALine1Phase3MinRate-Baseline	25	0.518	0.008	Moderate
$EDA_{Duration}$ HUT	ASALine1Phase2EMinRate	24	-0.516	0.010	Moderate
$EDA_{Delta\ S}$ HUT	ASALine1Phase2EMinRate	24	-0.516	0.010	Moderate
EDApeakTopeak	ASALine1Phase3MinRate-Baseline	25	0.513	0.009	Moderate
EDAdiff (EDA Difference)	ASALine1Phase3MinRate-Baseline	25	0.513	0.009	Moderate
EDAPostHUTSum-EDAPreHUTSum	HemodynamicChangesMinHUTHR-PreHR	25	0.508	0.010	Moderate

EDAPostHUTPeaktoPeak-EDAHUTPeaktoPeak	HemodynamicChangesHRDBAverageHRDifference	25	-0.506	0.010	Moderate
EDAnormalizedAreaHeadupTilt	HemodynamicChangesHRDBAverageHRDifference	25	0.504	0.011	Moderate
EDApeakTopeak	HemodynamicChangesHRDBAverageHRDifference	25	0.502	0.011	Moderate
EDAdiff	HemodynamicChangesHRDBAverageHRDifference	25	0.502	0.011	Moderate
EDAreaHeadupTilt	HemodynamicChangesHRDBAverageHRDifference	25	0.502	0.011	Moderate
EDAHUTArea-EDAPreHUTArea	HemodynamicChangesHRDBAverageHRDifference	25	0.502	0.011	Moderate
EDAPostHUTArea-EDAHUTArea	HemodynamicChangesHRDBAverageHRDifference	25	-0.502	0.011	Moderate
EDAHUTMax-EDAPreHUTMean	ASALine1Phase3MinRate-Baseline	25	0.502	0.011	Moderate
EDAPreHUTSum	TiltPostSBP	24	0.501	0.013	Moderate
EDAPostHUTPeaktoPeak-EDAHUTPeaktoPeak	ASALine1Phase3MinRate-Baseline	25	-0.500	0.011	Moderate
EDAPostHUTIntegral-EDAPreHUTIntegral	numMedsNotHeldAnticholinergic	25	0.500	0.011	Moderate
EDAHUTFrequency	ASALine1Phase2EMinRate	24	0.500	0.013	Moderate
EDAHUTFrequency-EDAPreHUTFrequency	ASALine1Phase2EMinRate	24	0.500	0.013	Moderate
EDAPostHUTFrequency-EDAHUTFrequency	ASALine1Phase2EMinRate	24	-0.500	0.013	Moderate
EDAHUTBPM	TiltPostDBP	24	0.495	0.014	Moderate
EDAHUTTBPM-EDAPreHUTTBPM	TiltPostDBP	24	0.495	0.014	Moderate
EDAPostHUTBPM-EDAHUTBPM	TiltPostDBP	24	-0.495	0.014	Moderate
EDAreaPreTilt	ASALine1Phase3MinRate-Baseline	25	0.495	0.012	Moderate
EDAnormalizedAreaPreTilt	ASALine1Phase3MinRate-Baseline	25	0.495	0.012	Moderate
EDAHUTTPeaktoPeak-EDAPreHUTTPeaktoPeak	HemodynamicChangesHRDBAverageHRDifference	25	0.491	0.013	Moderate
EDAHUTMin-EDAPreHUTMean	numMedsNotHeldAnticholinergic	25	0.489	0.013	Moderate
EDAtiltUp	HemodynamicChangesMinHUTHR-HRatMinSBP	25	-0.489	0.013	Moderate
EDAarea	Hemodynamic Changes $HRDB_{Average}$ HR Difference	25	0.489	0.013	Moderate
AcqKnowEDAatEqofARSMaxHR	ASALine1Phase3MinRate	24	0.488	0.016	Moderate
EDAPreHUTSum	ASALine1Phase3MaxRate	24	0.487	0.016	Moderate
EDAPreHUTMean	ASALine1Phase3MaxRate	24	0.483	0.017	Moderate
EDAPreHUTIntegral	ASALine1Phase3MaxRate	24	0.483	0.017	Moderate
EDAHUTBPM	ASALine1AdrenergicScore(orthe)Lowest(valid)AdrenergicScore	24	0.481	0.017	Moderate

EDA_{BPM} HUT – EDA_{BPM} Pre HUT	ASALine1AdrenergicScore(orthe)Lowest(valid)AdrenergicScore	24	0.481	0.017	Moderate
EDAPostHUTBPM-EDAHUTBPM	ASALine1AdrenergicScore(orthe)Lowest(valid)AdrenergicScore	24	-0.481	0.017	Moderate
EDAPreHUTSum	ASALine1Phase2EMaxRate	24	0.480	0.018	Moderate
EDAPreHUTSum	HemodynamicChangesMinHUTHR-HRatMinSBP	25	-0.479	0.015	Moderate
EDAPostHUTSum	ASALine1Phase3MinRate-Baseline	25	0.478	0.016	Moderate
EDAPreHUTMean	TiltPostSBP	24	0.477	0.018	Moderate
EDAPreHUTIntegral	TiltPostSBP	24	0.477	0.018	Moderate
EDAHUTMin-EDAPreHUTMean	TiltHRDelta	25	-0.477	0.016	Moderate
EDAPreHUTSum	HemodynamicChangesPostSBP-PreSBP	25	0.476	0.016	Moderate
EDAPostHUTTPeaktoPeak-EDAPreHUTTPeaktoPeak	ASALine1Phase3MinRate	24	-0.476	0.019	Moderate
EDAPostHUTMean	Number Meds Not Held Antihypertensive	25	-0.474	0.017	Moderate
EDArea Pre Tilt	TiltPostSBP	24	0.474	0.019	Moderate
$EDA_{Normalized\ Area}$ Pre Tilt	Tilt Post SBP	24	0.474	0.019	Moderate
EDA tilt Up	Tilt Post SBP	24	0.470	0.021	Moderate
EDA_{SD}	ASALine1Phase3MinRate-Baseline	25	0.468	0.018	Moderate
$EDA_{Frequency}$ HUT	ASALine1AdrenergicScore(orthe)Lowest(valid)AdrenergicScore	24	0.467	0.021	Moderate
$EDA_{Frequency}$ HUT – $EDA_{Frequency}$ Pre HUT	ASALine1AdrenergicScore(orthe)Lowest(valid)AdrenergicScore	24	0.467	0.021	Moderate
$EDA_{Frequency}$ Post HUT – $EDA_{Frequency}$ HUT	ASALine1AdrenergicScore(orthe)Lowest(valid)AdrenergicScore	24	-0.467	0.021	Moderate
EDAPostHUTSum-EDAPreHUTSum	numMedsNotHeldAnticholinergic	25	0.467	0.019	Moderate
EDAPostHUTIntegral-EDAPreHUTIntegral	numMedsNotHeldAll	25	0.467	0.019	Moderate
$EDA_{Duration}$ HUT	ASA Line 1 Adrenergic Score (or the) Lowest (valid) Adrenergic Score	24	-0.466	0.022	Moderate
$EDA_{Delta\ S}$ HUT	ASALine1AdrenergicScore(orthe)Lowest(valid)AdrenergicScore	24	-0.466	0.022	Moderate
EDAPostHUTPeaktoPeak	TiltHRatMinSBP	25	0.466	0.019	Moderate
EDAPreHUTMean	ASALine1Phase2EMaxRate	24	0.464	0.022	Moderate
EDAPreHUTIntegral	ASALine1Phase2EMaxRate	24	0.464	0.022	Moderate
EDAHUTMin-EDAPreHUTMean	HemodynamicChangesMinHUTHR-HRatMinSBP	25	0.464	0.020	Moderate
EDAtiltDown	ASALine1Phase3MinRate	24	0.463	0.023	Moderate

EDAPostHUTIntegral-EDAHUTIntegral	TiltHRatMinSBP	25	-0.462	0.020	Moderate
EDAPreHUTMean	HemodynamicChangesMinHUTHR-HRatMinSBP	25	-0.462	0.020	Moderate
EDAPreHUTIntegral	HemodynamicChangesMinHUTHR-HRatMinSBP	25	-0.462	0.020	Moderate
EDAHUTNormalizedArea-EDAPreHUTNormalizedArea	HemodynamicChangesHRDBAverageHRDifference	25	0.461	0.020	Moderate
EDAHUTMax-EDAPreHUTMean	QSWEATForearmBaselineRate	25	-0.461	0.020	Moderate
EDAHUTBPM	TiltPreDBP	25	0.461	0.020	Moderate
EDAHUTTBPM-EDAPreHUTTBPM	TiltPreDBP	25	0.461	0.020	Moderate
EDAPostHUTBPM-EDAHUTBPM	TiltPreDBP	25	-0.461	0.020	Moderate
EDAPostHUTTPeaktoPeak-EDAPreHUTTPeaktoPeak	numDataSetsHUT	25	-0.460	0.021	Moderate
EDAPostHUTIntegral-EDAHUTIntegral	numMedsNotHeldAntihypertensive	25	0.460	0.021	Moderate
EDAHUTMax-EDAPreHUTMean	HemodynamicChangesHRDBAverageHRDifference	25	0.459	0.021	Moderate
AcqKnowEDAatEqofARSMaxHR	TiltHRatMinSBP	25	0.459	0.021	Moderate
EDAtiltDown	ASALine1Phase3MinRate-Baseline	25	0.458	0.021	Moderate
EDAPreHUTPeaktoPeak	ASALine1Phase3MinRate-Baseline	25	0.458	0.021	Moderate
EDAtiltUp	HemodynamicChangesPostSBP-PreSBP	25	0.457	0.022	Moderate
EDAPreHUTMean	HemodynamicChangesPostSBP-PreSBP	25	0.455	0.022	Moderate
EDAPreHUTIntegral	HemodynamicChangesPostSBP-PreSBP	25	0.455	0.022	Moderate
EDAsd	numMedsNotHeldChronotrope	25	-0.454	0.023	Moderate
AcqKnowEDAatEqofARSMaxHR	HemodynamicChangesPostSBP-PreSBP	25	0.454	0.023	Moderate
EDAPostHUTNormalizedArea-EDAHUTNormalizedArea	Age	25	0.453	0.023	Moderate
EDAtiltUp	TiltHRatMinSBP	25	0.451	0.024	Moderate
EDAPostHUTMean	TiltHRatMinSBP	25	0.450	0.024	Moderate
EDAPostHUTPeaktoPeak	HemodynamicChangesPostSBP-PreSBP	25	0.449	0.025	Moderate
EDAPostHUTSum-EDAPreHUTSum	numMedsNotHeldAll	25	0.446	0.025	Moderate
EDAPostHUTIntegral-EDAHUTIntegral	ASALine1Phase3MinRate	24	-0.446	0.029	Moderate
EDAPostHUTArea-EDAPreHUTArea	numMedsNotHeldAnticholinergic	25	0.445	0.026	Moderate
EDAPostHUTNormalizedArea-EDAPreHUTNormalizedArea	Number of Anticholinergic Meds Not Held	25	0.445	0.026	Moderate
EDAmin	ASALine1Phase3MaxRate	24	0.444	0.030	Moderate
EDAPostHUTSum-EDAHUTSum	TiltHRatMinSBP	25	-0.443	0.027	Moderate
EDAmax	HemodynamicChangesHRDBAverageHRDifference	25	0.442	0.027	Moderate
EDA_{Sum} Post HUT	Number of Antihypertensive Meds Not Held	25	-0.442	0.027	Moderate
EDAPostHUTSum-EDAHUTSum	ASALine1Phase3MinRate	24	-0.440	0.031	Moderate

EDAarea	numMedsNotHeldChronotrope	25	-0.439	0.028	Moderate
EDAreaHeadupTilt	numMedsNotHeldChronotrope	25	-0.439	0.028	Moderate
EDAnormalizedAreaHeadupTilt	numMedsNotHeldChronotrope	25	-0.439	0.028	Moderate
EDAHUTArea-EDAPreHUTArea	numMedsNotHeldChronotrope	25	-0.439	0.028	Moderate
EDAPostHUTArea-EDAHUTArea	numMedsNotHeldChronotrope	25	0.439	0.028	Moderate
EDAPostHUTPeaktoPeak	HemodynamicChangesHRDBAverageHRDifference	25	0.439	0.028	Moderate
EDAHUTTPeaktoPeak-EDAPreHUTTPeaktoPeak	QSWEATForearmBaselineRate	25	-0.437	0.029	Moderate
EDAPreHUTPeaktoPeak	TiltPostSBP	24	0.436	0.033	Moderate
EDAnormalizedAreaHeadupTilt	QSWEATForearmBaselineRate	25	-0.436	0.030	Moderate
EDAmin	TiltHRatMinSBP	25	0.435	0.030	Moderate
EDAPostHUTIntegral-EDAPreHUTIntegral	HemodynamicChangesMinHUTHR-PreHR	25	0.435	0.030	Moderate
EDAHUTTPeaktoPeak-EDAPreHUTTPeaktoPeak	ASALine(s)AvgPRTValue	17	0.434	0.082	Moderate
EDAreaHeadupTilt	QSWEATForearmBaselineRate	25	-0.432	0.031	Moderate
EDAHUTArea-EDAPreHUTArea	QSWEATForearmBaselineRate	25	-0.432	0.031	Moderate
EDAPostHUTArea-EDAHUTArea	QSWEATForearmBaselineRate	25	0.432	0.031	Moderate
EDAHUTTPeaktoPeak-EDAPreHUTTPeaktoPeak	numDataSetsHUT	25	-0.432	0.031	Moderate
EDAreaHeadupTilt	ASALine1Phase3MinRate-Baseline	25	0.431	0.032	Moderate
EDAHUTArea-EDAPreHUTArea	ASALine1Phase3MinRate-Baseline	25	0.431	0.032	Moderate
EDAPostHUTArea-EDAHUTArea	ASALine1Phase3MinRate-Baseline	25	-0.431	0.032	Moderate
AcqKnowEDAatEqofARSMaxHR	TiltPostSBP	24	0.430	0.036	Moderate
EDAPreHUTSum	TiltPostDBP	24	0.430	0.036	Moderate
EDAPostHUTNormalizedArea-EDAHUTNormalizedArea	HemodynamicChangesMaxHUTHR-PreHR	25	-0.429	0.033	Moderate
EDAareaPostTilt	TiltHRatMinSBP	25	0.428	0.033	Moderate
EDAnormalizedAreaPostTilt	TiltHRatMinSBP	25	0.428	0.033	Moderate
EDAPreHUTSum	HemodynamicChangesPostDBP-PreDBP	25	0.428	0.033	Moderate
EDAtiltDown	TiltHRatMinSBP	25	0.426	0.034	Moderate
EDAintegral	ASALine1Phase3MinRate	24	0.425	0.038	Moderate
EDAHUTIntegral-EDAPreHUTIntegral	ASALine1Phase3MinRate	24	0.425	0.038	Moderate
EDAHUTSum	ASALine1Phase3MinRate	24	0.425	0.038	Moderate
EDApeakTopeak	QSWEATForearmBaselineRate	25	-0.425	0.034	Moderate
EDAdiff	QSWEATForearmBaselineRate	25	-0.425	0.034	Moderate

EDAnormalizedAreaHeadupTilt	TiltHRatMinSBP	25	0.425	0.034	Moderate
EDAPreHUTMean	numMedsNotHeldAntihypertensive	25	-0.425	0.034	Moderate
EDAPreHUTIntegral	numMedsNotHeldAntihypertensive	25	-0.425	0.034	Moderate
EDAPreHUTSum	numMedsNotHeldAntihypertensive	25	-0.425	0.034	Moderate
EDAPostHUTPeaktoPeak	numMedsNotHeldChronotrope	25	-0.424	0.035	Moderate
EDApeakTopeak	numMedsNotHeldChronotrope	25	-0.424	0.035	Moderate
EDAdiff	numMedsNotHeldChronotrope	25	-0.424	0.035	Moderate
EDAreaPreTilt	numMedsNotHeldChronotrope	25	-0.424	0.035	Moderate
EDAnormalizedAreaPreTilt	numMedsNotHeldChronotrope	25	-0.424	0.035	Moderate
EDAHUTNormalizedArea-EDAPreHUTNormalizedArea	numMedsNotHeldChronotrope	25	-0.424	0.035	Moderate
EDAmin	TiltPostSBP	24	0.423	0.040	Moderate
EDAtiltUp	numMedsNotHeldAntihypertensive	25	-0.423	0.035	Moderate
EDAtiltDown	numMedsNotHeldAntihypertensive	25	-0.423	0.035	Moderate
EDAmax	numMedsNotHeldAntihypertensive	25	-0.423	0.035	Moderate
EDAmean	numMedsNotHeldAntihypertensive	25	-0.423	0.035	Moderate
EDAmedian	numMedsNotHeldAntihypertensive	25	-0.423	0.035	Moderate
AcqKnowEDAatEqofARSMaxHR	numMedsNotHeldAntihypertensive	25	-0.423	0.035	Moderate
EDAintegral	numMedsNotHeldAntihypertensive	25	-0.423	0.035	Moderate
EDAHUTIntegral-EDAPreHUTIntegral	numMedsNotHeldAntihypertensive	25	-0.423	0.035	Moderate
EDAHUTSum	numMedsNotHeldAntihypertensive	25	-0.423	0.035	Moderate
EDAHUTSum-EDAPreHUTSum	numMedsNotHeldAntihypertensive	25	-0.423	0.035	Moderate
EDAPostHUTSum-EDAHUTSum	numMedsNotHeldAntihypertensive	25	0.423	0.035	Moderate
EDAmedian	ASALine1Phase3MinRate	24	0.421	0.041	Moderate
EDAHUTSum-EDAPreHUTSum	ASALine1Phase3MinRate	24	0.421	0.041	Moderate
EDAintegral	TiltHRatMinSBP	25	0.420	0.037	Moderate
EDAHUTIntegral-EDAPreHUTIntegral	TiltHRatMinSBP	25	0.420	0.037	Moderate
EDAHUTSum	TiltHRatMinSBP	25	0.420	0.037	Moderate
EDAmin	HemodynamicChangesPostSBP-PreSBP	25	0.419	0.037	Moderate
EDAreaPreTilt	numMedsNotHeldAntihypertensive	25	-0.418	0.037	Moderate
EDAnormalizedAreaPreTilt	numMedsNotHeldAntihypertensive	25	-0.418	0.037	Moderate
EDAnormalizedAreaHeadupTilt	ASALine1Phase3MinRate-Baseline	25	0.418	0.037	Moderate
AcqKnowEDAatEqofARSMaxHR	ASALine1Phase3MaxRate	24	0.417	0.042	Moderate
EDAHUTTPeaktoPeak-EDAPreHUTTPeaktoPeak	Age	25	-0.417	0.038	Moderate
EDAsd	QSWEATForearmBaselineRate	25	-0.416	0.039	Moderate

EDAPostHUTSum	TiltHRatMinSBP	25	0.415	0.039	Moderate
EDAHUTSum-EDAPreHUTSum	ASALine1Phase3MaxRate-Baseline	25	0.415	0.039	Moderate
EDAHUTSum-EDAPreHUTSum	TiltHRatMinSBP	25	0.414	0.040	Moderate
EDA Post HUT Normalized Area - EDA HUT Normalized Area	QSWEAT Forearm Baseline Rate	25	0.413	0.040	Moderate
EDAPostHUTIntegral-EDAHUTIntegral	HemodynamicChangesPostSBP-PreSBP	25	-0.412	0.041	Moderate
EDAmean	ASALine1Phase3MinRate	24	0.412	0.045	Moderate
EDAPostHUTArea-EDAPreHUTArea	numMedsNotHeldAll	25	0.412	0.041	Moderate
EDAPostHUTIntegral-EDAHUTIntegral	ASALine1Phase3MaxRate-Baseline	25	-0.411	0.041	Moderate
EDAarea	QSWEATForearmBaselineRate	25	-0.410	0.042	Moderate
EDAmin	numMedsNotHeldAntihypertensive	25	-0.410	0.042	Moderate
EDAHUTNormalizedArea-EDAPreHUTNormalizedArea	QSWEATForearmBaselineRate	25	-0.410	0.042	Moderate
EDAreaHeadupTilt	TiltHRatMinSBP	25	0.409	0.042	Moderate
EDAHUTArea-EDAPreHUTArea	TiltHRatMinSBP	25	0.409	0.042	Moderate
EDAPostHUTArea-EDAHUTArea	TiltHRatMinSBP	25	-0.409	0.042	Moderate
EDAPostHUTIntegral-EDAPreHUTIntegral	ASALine1Phase2EMaxRate-Baseline	25	-0.408	0.043	Moderate
EDAPostHUTPeaktoPeak	numMedsNotHeldAntihypertensive	25	-0.406	0.044	Moderate
EDAarea	TiltHRatMinSBP	25	0.406	0.044	Moderate
EDAattiltUp	ASALine1Phase3MaxRate	24	0.406	0.049	Moderate
EDAHUTBPM	ASALine1Phase2EMinRate	24	0.405	0.049	Moderate
EDAHUTTBPM-EDAPreHUTTBPM	ASALine1Phase2EMinRate	24	0.405	0.049	Moderate
EDAPostHUTBPM-EDAHUTBPM	ASALine1Phase2EMinRate	24	-0.405	0.049	Moderate
EDAPreHUTPeaktoPeak	BMI	25	-0.405	0.044	Moderate
EDAPostHUTSum	ASALine1Phase3MinRate	24	0.404	0.050	Moderate
EDAareaPostTilt	TiltPostSBP	24	0.404	0.050	Moderate
EDAnormalizedAreaPostTilt	TiltPostSBP	24	0.404	0.050	Moderate
EDAmedian	TiltHRatMinSBP	25	0.404	0.045	Moderate
EDAtiltUp	HemodynamicChangesPostDBP-PreDBP	25	0.404	0.046	Moderate
Arc of EDA Area Post HUT – Arc of EDA Area HUT	HR at Min SBP – Pre HUT HR	25	-0.404	0.046	Moderate
EDA at the PR Equivalent of the Standard Max HR	ASA Line 1 Phase 2E Max Rate	24	0.403	0.051	Moderate
EDA at Tilt-up	ASA Line 1 Phase 2E Max Rate	24	0.403	0.051	Moderate

Arc of EDA Area HUT – Arc of EDA Area Pre HUT	ASA Line 1 Phase 3 Min Rate – Baseline	25	0.403	0.046	Moderate
EDA Standard Deviation	Number of Antihypertensive Meds Not Held	25	-0.403	0.046	Moderate
Arc of EDA Area Post HUT – Arc of EDA Area Pre HUT	Number of All Meds Not Held	25	0.402	0.047	Moderate
EDAarea	ASA Line 1 Phase 3 Min Rate – Baseline	25	0.402	0.047	Moderate
EDA Area Pre Tilt	Post DBP – Pre DBP	25	0.402	0.047	Moderate
Arc of EDA Area Pre Tilt	Post DBP – Pre DBP	25	0.402	0.047	Moderate

Note. Values are reported as single numbers. Abbreviations: 2E, early phase 2; ASA, adrenergic sensitivity analysis; BPM, beats per minute (note that this capitalized unit is not the same thing as the well-known unit of heart rate "bpm", rather it represents the sampling rate used to record the EDA signal); CASS, composite autonomic severity score; Delta S, change in slope; Delta T, change in time; EDA, electrodermal activity; HR, heart rate; HUT, head up tilt; PR, pulse rate; PRT, pressure recovery time; QSWEAT, the manufacturer's brand for a type of quantitative axon reflex test (QSART) device manufactured and supplied by WR Medical Electronics Co., Minnesota. Only the moderate, strong, and very strong correlational results, have been reported in this table. The correlation coefficients were determined via use of the Spearman's Correlations Test. Storey's method for multiple comparisons, was used for the adjustment of p-values, maintaining a $p<0.05$ false discovery rate, with the adjusted $p<0.05$.

Table 16

Correlations Between Electrodermal Test Indices and Standard Test Indices Measured During Autonomic Reflex Screening in the POTS Cases

Novel Test Measure	Standard Test Measure	Correlation Coefficient	p-value	Strength of Association
EDA HUT Frequency	Number of Data Sets During HUT	0.527	<0.001	Moderate
HUT EDA Frequency – Baseline EDA Frequency	Number of Data Sets During HUT	0.527	<0.001	Moderate
Post HUT EDA Frequency – HUT EDA Frequency	Number of Data Sets During HUT	0.527	<0.001	Moderate
HUT EDA BPM	Valsalva Phase 3 Minimum Rate – Baseline	-0.494	<0.001	Moderate
HUT EDA BPM – Baseline EDA BPM	Valsalva Phase 3 Minimum Rate – Baseline	-0.494	<0.001	Moderate
Post HUT EDA BPM– HUT EDA BPM	Valsalva Phase 3 Minimum Rate – Baseline	0.494	<0.001	Moderate
HUT EDA BPM	Time from Tilt to HUT Maximum HR	-0.477	<0.001	Moderate
EDA BPM HUT – Baseline EDA BPM	Time from Tilt to HUT Maximum HR	-0.477	<0.001	Moderate
Post HUT EDA BPM – HUT EDA BPM	Time from Tilt to HUT Maximum HR	0.477	<0.001	Moderate
HUT EDA BPM	Valsalva Phase 3 Rate Difference	0.466	<0.001	Moderate
HUT EDA BPM – Baseline EDA BPM	Valsalva Phase 3 Rate Difference	0.466	<0.001	Moderate
Post HUT EDA BPM – HUT EDA BPM	Valsalva Phase 3 Rate Difference	-0.466	<0.001	Moderate
HUT EDA BPM	0.75 of Phase 3 Rate Difference During Valsalva	0.466	<0.001	Moderate
HUT EDA BPM – Baseline EDA BPM	0.75 of Phase 3 Rate Difference During Valsalva	0.466	<0.001	Moderate
Post HUT EDA BPM – HUT EDA BPM	0.75 of Phase 3 Rate Difference During Valsalva	-0.466	<0.001	Moderate
HUT EDA Delta T	Valsalva Phase 3 Minimum Rate – Baseline	0.465	<0.001	Moderate
HUT EDA Delta S	Valsalva Phase 3 Minimum Rate – Baseline	0.465	<0.001	Moderate
HUT EDA Frequency	Valsalva Phase 2E Minimum Rate – Baseline	0.441	<0.001	Moderate
HUT EDA Frequency – Baseline EDA Frequency	Valsalva Phase 2E Minimum Rate – Baseline	0.441	<0.001	Moderate
Post HUT EDA Frequency – HUT EDA Frequency	Valsalva Phase 2E Minimum Rate – Baseline	-0.441	<0.001	Moderate
HUT EDA Delta S	Time from Tilt to HUT Maximum HR	0.440	<0.001	Moderate
HUT EDA Delta T	Time from Tilt to HUT Maximum HR	0.440	<0.001	Moderate
HUT EDA Delta T	Valsalva Phase 3 Rate Difference	-0.431	<0.001	Moderate
HUT EDA Delta T	0.75 of Phase 3 Rate Difference During Valsalva	-0.431	<0.001	Moderate
HUT EDA Delta S	Valsalva Phase 3 Rate Difference	-0.430	<0.001	Moderate
HUT EDA Delta S	0.75 of Phase 3 Rate Difference During Valsalva	-0.430	<0.001	Moderate
HUT EDA Frequency	Valsalva Phase 2E Rate Difference	-0.406	<0.001	Moderate
HUT EDA Frequency – Baseline EDA Frequency	Valsalva Phase 2E Rate Difference	-0.406	<0.001	Moderate
Post HUT EDA Frequency – HUT EDA Frequency	Valsalva Phase 2E Rate Difference	0.406	<0.001	Moderate

Note. Values are reported as single numbers. Abbreviations: 2E, early phase 2; BPM, beats per minute (note that this capitalized unit is not the same thing as the well-known unit of heart rate “bpm”, rather it represents the sampling rate used to record the EDA signal); Delta S, change in slope; Delta T, change in time; EDA, electrodermal activity; HUT, head up tilt; Only moderate correlational results, have been reported in this table. The correlation coefficients were determined via use of the Spearman’s Correlations Test. Storey’s method for multiple comparisons, was used for the adjustment of p-values, maintaining a $p<0.05$ false discovery rate, with the adjusted $p<0.05$.

Table 17

Phasic EDA Analyses Designated Age, ARS-type, and Sex Matched Subset of the Overall Study Population: Baseline Demographics and Hemodynamic Responses to Upright Tilt

	Controls (n=14)	POTS (n=14)	p-value
Age, years	39 ± 16; 38	39 ± 17; 38	0.946
Females Sex, N (%)	12 (85.7)	12 (85.7)	>0.999
Height, cm	165.9 ± 7.7; 165.1	166.6 ± 6.7; 167.6	0.639
Weight, kg	75.8 ± 28.1; 68.7	64.8 ± 16.6; 60.6	0.675
Body Mass Index, kg/m^2	27.3 ± 9.2; 24.7	23.5 ± 7.1; 22.0	0.518
Baseline SBP, mmHg	116.3 ± 19.7; 116.3	111.8 ± 23.6; 110.1	0.590
Baseline DBP, mmHg	70.0 ± 11.7; 69.7	72.4 ± 11.1; 74.5	0.571
Baseline HR, bpm	77.4 ± 12.3; 75.5	79.1 ± 14.7; 78.6	0.795
Medications withheld, %	42.9	42.9	>0.999
HR Change, bpm	28.4 ± 6.9; 26.4	56.4 ± 15.3; 56.0	<0.001
SBP Change, mmHg	-9.7 ± 8.6; -11.0	-11.5 ± 5.6; -13.0	0.667
DBP Change, mmHg	4.0 ± 10.3; 5.2	10.8 ± 9.0; 12.1	0.044
Maximum HR During Tilt, bpm	99.2 ± 14.9; 100.8	126.2 ± 14.9; 125.0	<0.001
Minimum HR During Tilt, bpm	72.4 ± 12.6; 74.8	71.4 ± 11.8; 69.6	0.388
HR at Minimum SBP During Tilt, bpm	90.8 ± 13.4; 90.2	96.9 ± 23.9; 96.0	0.418
Post-Tilt SBP, mmHg	130.9 ± 23.4; 131.9	113.8 ± 44.9; 113.8	0.375
Post-Tilt DBP, mmHg	69.3 ± 13.5; 69.1	71.6 ± 13.9; 70.2	0.329
Post-Tilt HR, bpm	80.4 ± 11.0; 77.9	84.8 ± 14.3; 81.6	0.375
Symptoms Reported, %	64.3	85.7	<0.001
Number of Symptoms Reported, #	2 ± 2; 1	6 ± 5; 5	0.011
Pre ARS Medications Withholding Adherence, %	42.9	42.9	>0.999

Note. Values are reported either as single numbers, or else they are reported as means plus or minus standard deviation; median, or as percentages. Abbreviations: bpm, beats per minute; cm, centimeter; DBP, diastolic blood pressure; HR, heart rate; kg, kilogram; mmHg, millimeters of mercury; SBP, systolic blood pressure. Groups were compared using the T-Test, T-Test with Welch's Correction, Mann-Whitney U Test, except for where 1=Chi-Square Test.

Table 18

Differences Between Controls and POTS Cases in Skin Conductance Responses and other Autonomic Responses During Deep Breathing Tests

TEST	DB1		DB2	
Group	**controls**	**POTS cases**	**controls**	**POTS cases**
SCL Values				
Average of the Means of the Individual Skin Conductance Levels, µS	2.805 ± 4.728; 1.958	3.319 ± 4.917; 2.527	2.112 ± 5.111; 1.564	3.361 ± 5.355; 3.072
Average of the Medians of Individual Skin Conductance Levels, µS	2.753 ± 4.696; 2.018	3.348 ± 4.940; 2.554	2.090 ± 5.039; 1.591	3.374 ± 5.315; 3.086
Average of the Standard Deviations of Individual Skin Conductance Levels, µS	0.353 ± 0.479; 0.098	0.348 ± 0.317; 0.213	0.315 ± 0.470; 0.111	0.427 ± 0.582; 0.140
Average of the Maximum Values of Individual Skin Conductance Levels, µS	3.317 ± 5.167; 2.068	3.688 ± 5.235; 3.045	2.540 ± 5.483; 1.837	3.825 ± 5.974; 3.117
Average of the Minimum Values of Individual Skin Conductance Levels, µS	2.351 ± 4.515; 1.548	2.970 ± 4.723; 2.132	1.668 ± 4.843; 1.358	2.843 ± 4.830; 2.739
Average of the Differences Between the SCL Values of Each of the SCRs with the Maximum SCL and Each of the SCRs with Minimum SCLs in Each DB Focus Area During ARS, µS	0.966 ± 1.250; 0.243	0.718 ± 0.817; 0.353	0.872 ± 1.328; 0.309	0.981 ± 1.569; 0.192
Average of the Rise Times of the SCR with the Maximum SCL Within the DB Focus Areas, seconds	2.735 ± 3.012; 2.046	1.776 ± 1.950; 1.254	3.230 ± 1.877; 2.994	2.687 ± 1.629; 2.948
Average of the Half Recovery Times of the SCR with the Maximum SCL Within the DB Focus Areas, seconds	1.104 ± 0.657; 0.978	1.142 ± 0.979; 0.920	1.246 ± 0.705; 1.082	0.941 ± 0.657; 0.748

SCR Values				
Average Raw Amplitude of the Task Based SCR, µS	0.946 ± 1.335; 0.234	0.835 ± 0.911; 0.483	0.887 ± 2.077; 0.139	0.829 ± 0.869; 0.629
Mean of the Logged Z-score Standardized Amplitude of the Task Based SCR, µS	0.000 ± 1.000	0.000 ± 1.000	0.003 ± 1.039	0.000 ± 1.000
Mean of the Logged T-score Standardized Amplitude of the Task Based SCR, µS	50.000 ± 10.000	50.000 ± 10.000	50.025 ± 10.392	50.000 ± 10.000
Median of the Logged Z-scores, µS	-0.518	-0.264	-0.402	-0.060
Median of the Logged T-scores, µS	44.821	47.365	45.980	49.400
Maxima of the Logged Z-scores, µS	1.891	2.031	2.699	1.826
Maxima of the Logged T-scores, µS	68.909	70.314	76.991	68.264
Minima of the Logged Z-scores, µS	-0.874	-1.144	-0.576	-1.101
Minima of the Logged T-scores, µS	41.258	38.560	44.238	38.988
Peak to Peak of the Logged Z-scores, µS	2.765	3.175	3.275	2.928
Peak to Peak of the Logged T-scores, µS	27.651	31.754	32.753	29.276
Average Times of the Task Based Event Related SCR				
Rise Times, seconds	5.570 ± 3.451; 5.610	4.185 ± 2.449; 4.600	3.961 ± 1.697; 3.656	5.187 ± 2.969; 4.828
Numbers and Frequencies of Each of the Various Types of SCRs				
Number of Potential Event Related SCRs, #	4 ± 3; 3	2 ± 2; 1	5 ± 3; 4	3 ± 2; 2
Average Number of the Total number of the Individual SCRs in the Focus Area, #	5 ± 4; 6	6 ± 3; 7	4 ± 4; 4	5 ± 3; 7
Average Frequency of the individual SCRs, #	4 ± 3; 4	4 ± 2; 5	3 ± 3; 3	4 ± 2; 5

Note. Values are reported either as single numbers, or else they are reported as means plus or minus standard deviation; median. Abbreviations: DB, deep breathing, POTS, postural orthostatic tachycardia syndrome; SCL, skin conductance level; SCR, skin conductance response.

Table 19

Differences Between Controls and POTS Cases in Skin Conductance Responses and other Autonomic Responses During Valsalva Maneuver Tests

TEST	VM1		VM2		VM3	
Group	**controls**	**POTS cases**	**controls**	**POTS cases**	**controls**	**POTS cases**
SCL Values						
Average of the Means of the Individual Skin Conductance Levels, µS	4.072 ± 6.472; 2.438	7.675 ± 8.419; 7.103	4.631 ± 6.947; 2.855	9.610 ± 8.237; 8.148	2.861 ± 5.253; 2.000	6.851 ± 6.016; 6.356
Average of the Medians of Individual Skin Conductance Levels, µS	4.153 ± 6.533; 2.438	7.654 ± 8.339; 7.103	4.631 ± 6.947; 2.855	9.633 ± 8.289; 8.148	2.861 ± 5.253; 2.000	6.838 ± 5.984; 6.356
Average of the Standard Deviations of Individual Skin Conductance Levels, µS	0.739 ± 0.807; 0.196	0.579 ± 0.827; 0.172	0.261 ± 0.242; 0.267	0.537 ± 0.571; 0.378	0.731 ± 0.423; 0.987	0.433 ± 0.104; 0.430
Average of the Maximum Values of Individual Skin Conductance Levels, µS	4.454 ± 6.939; 2.438	8.029 ± 9.032; 7.103	4.703 ± 7.019; 2.855	9.976 ± 8.402; 8.278	3.120 ± 5.260; 0.774	7.011 ± 6.181; 6.493
Average of the Minimum Values of Individual Skin Conductance Levels, µS	3.619 ± 5.996; 2.438	7.334 ± 7.908; 7.103	4.557 ± 6.877; 2.855	9.196 ± 8.015; 8.017	2.603 ± 5.268; 0.220	6.704 ± 5.884; 6.218
Average of the Differences Between the SCL Values of Each of the SCRs with the Maximum SCL and Each of the SCRs with Minimum SCLs in Each VM Focus Area During ARS, µS	0.835 ± 1.424; 0.099	0.695 ± 1.373; 0.107	0.147 ± 0.273; 0.000	0.779 ± 1.030; 0.261	0.376 ± 0.617; 1.802	0.307 ± 0.390; 0.096
Average of the Rise Times of the SCR with the Maximum SCL Within the VM Focus Areas, seconds	6.645 ± 7.665; 5.184	4.372 ± 4.107; 2.904	5.390 ± 5.447; 3.656	5.103 ± 3.608; 3.544	5.867 ± 5.740; 4.844	5.410 ± 3.509; 3.784
Average of the Half Recovery	0.714 ± 0.667; 0.560	0.258 ± 1.110; 0.396	0.843 ± 1.230; 0.388	0.526 ± 0.444; 0.468	0.217 ± 0.318; 0.000	0.688 ± 0.655; 0.690

Times of the SCR with the Maximum SCL Within the VM Focus Areas, seconds						
SCR Values						
Average Raw Amplitude of the Task Based SCR, µS	1.713 ± 2.538; 0.499	2.275 ± 2.068; 1.402	1.347 ± 2.088; 0.433	2.344 ± 2.767; 1.402	1.848 ± 3.138; 0.629	1.485 ± 1.848; 0.816
Mean of the Logged Z-score Standardized Amplitude of the Task Based SCR, µS	0.000 ± 1.000	0.000 ± 1.000	0.000 ± 1.000	0.000 ± 1.000	0.000 ± 1.000	0.000 ± 1.000
Mean of the Logged T-score Standardized Amplitude of the Task Based SCR, µS	50.000 ± 10.000	50.000 ± 10.000	50.000 ± 10.000	50.000 ± 10.000	50.000 ± 10.000	50.000 ± 10.000
Median of the Logged Z-scores, µS	-0.397	-0.032	-0.386	-0.114	-0.354	-0.210
Median of the Logged T-scores, µS	46.032	49.678	46.136	48.865	46.463	47.902
Maxima of the Logged Z-scores, µS	2.007	1.360	2.104	1.815	2.218	1.867
Maxima of the Logged T-scores, µS	70.066	63.599	71.040	68.154	72.181	68.671
Minima of the Logged Z-scores, µS	-0.895	-1.324	-0.930	-1.121	-1.007	-1.081
Minima of the Logged T-scores, µS	41.052	36.755	40.698	38.790	39.933	39.188
Peak to Peak of the Logged Z-scores, µS	2.902	2.684	3.034	2.936	3.225	2.948
Peak to Peak of the Logged T-scores, µS	29.014	26.844	30.341	29.364	32.247	29.483
Average Times of the Task Based Event Related SCR						
Rise Times, seconds	9.266 ± 7.424; 7.578	6.287 ± 2.565;	6.377 ± 4.879; 5.580	7.033 ± 2.813; 7.756	7.447 ± 3.278; 6.934	6.067 ± 3.087; 5.318
Numbers and Frequencies of Each of the Various Types of SCRs						
Number of Potential Event Related SCRs, #	1	1	1	1	1	1
Average Number of the Total	2 ± 2; 2	2 ± 2; 2	2 ± 1; 1	2 ± 1; 2	1 ± 1; 1	2 ± 1; 2

number of the Individual SCRs in the Focus Area. #						
Average Frequency of the individual SCRs, #	5 ± 3; 4	6 ± 4; 5	5 ± 2; 3	7 ± 3; 7	5 ± 3; 4	6 ± 2; 5

Note. Values are reported either as single numbers, or else they are reported as means plus or minus standard deviation; median. Abbreviations: POTS, postural orthostatic tachycardia syndrome; SCL, skin conductance level; SCR, skin conductance response; VM, Valsalva maneuver.

Table 20

Differences Between Controls and POTS Cases in Skin Conductance Responses and other Autonomic Responses During the 2-minutes of Pre ARS-Baseline, the 2-minutes After Tilt-up in HUTT, and the First 2-minutes of Sustained Tonic EDA Trace Elevation in HUTT, Focus Areas.

TEST	2 MINUTES BASELINE		2 MINUTES AFTER TILT-UP IN HUTT		2 MINUTES OF A SUSTAINED ELEVATION IN THE SKIN CONDUCTANCE LEVEL AFTER TILT-UP IN HUTT	
Group	**controls**	**POTS cases**	**controls**	**POTS cases**	**controls**	**POTS cases**
SCL Values						
Average of the Means of the Individual Skin Conductance Levels, µS	2.322 ± 3.788; 1.539	2.612 ± 4.448; 2.308	5.060 ± 6.404; 3.773	7.432 ± 8.022; 4.759	5.497 ± 6.484; 3.869	8.824 ± 8.029; 5.811
Average of the Medians of Individual Skin Conductance Levels, µS	2.256 ± 3.637; 1.515	2.577 ± 4.433; 2.285	5.177 ± 6.582; 3.830	7.295 ± 7.981; 4.655	5.627 ± 6.664; 3.886	8.665 ± 8.007; 5.725
Average of the Standard Deviations of Individual Skin Conductance Levels, µS	0.549 ± 0.735; 0.132	0.319 ± 0.328; 0.155	0.684 ± 0.971; 0.288	1.385 ± 1.951; 0.914	0.749 ± 0.986; 0.357	1.639 ± 2.028; 0.992
Average of the Maximum Values of Individual Skin Conductance Levels, µS	3.102 ± 4.529; 1.688	3.093 ± 4.859; 2.876	6.196 ± 7.972; 4.153	9.621 ± 10.383; 5.222	6.739 ± 8.074; 4.512	11.432 ± 10.370; 6.443
Average of the Minimum Values of Individual Skin Conductance Levels, µS	1.697 ± 3.460; 1.410	2.269 ± 4.184; 2.002	3.758 ± 4.743; 3.129	5.423 ± 5.160; 3.780	4.075 ± 4.808; 3.227	6.448 ± 5.038; 4.976
Average of the Differences Between the SCL Values of Each of the SCRs with the Maximum SCL and Each of the SCRs with Minimum SCLs in Each Focus Area During ARS, µS	1.405 ± 2.074; 0.304	0.824 ± 1.032; 0.342	2.438 ± 4.010; 0.947	4.198 ± 5.562; 2.721	2.663 ± 4.103; 0.968	4.984 ± 5.724; 3.341
Average of the Rise Times of the SCR with the Maximum SCL Within the Focus Areas, seconds	1.809 ± 1.866; 0.794	2.634 ± 2.367; 2.144	4.354 ± 4.505; 2.708	6.624 ± 4.956; 5.148	5.402 ± 4.180; 5.754	5.111 ± 4.890; 5.148

Average of the Half Recovery Times of the SCR with the Maximum SCL Within the Focus Areas, seconds	3.339 ± 1.799; 3.648	4.009 ± 1.901; 3.820	0.842 ± 0.860; 0.588	0.771 ± 1.086; 0.332	0.565 ± 0.533; 0.406	0.524 ± 0.695; 0.332
SCR Values						
Average Raw Amplitude of the SCR with a Maximum SCL, or of the Task Based SCR in Each Focus Area, µS	0.951 ± 2.004; 0.045	0.574 ± 0.845; 0.042	1.964 ± 3.962; 0.239	5.226 ± 9.248; 1.463	2.142 ± 4.084; 0.276	6.246 ± 9.787; 1.901
Mean of the Logged Z-score Standardized Amplitude of the SCR with a Maximum SCL, or of that of the Task Based SCR, µS	0.000 ± 1.000	0.000 ± 1.000	-0.276 ± 0.910	0.081 ± 0.958	0.004 ± 1.030	0.002 ± 0.937
Mean of the Logged T-score Standardized Amplitude of the SCR with a Maximum SCL, µS	50.000 ± 10.000	50.000 ± 10.000	47.237 ± 9.099	50.814 ± 9.577	50.037 ± 10.302	50.018 ± 9.367
Median of the Logged Z-score Standardized Amplitude of the SCR with a Maximum SCL, µS	-0.486	-0.633	-0.677	-0.157	-0.518	-0.287
Median of the Logged T-score Standardized Amplitude of the SCR with a Maximum SCL, µS	45.142	43.674	43.232	48.427	44.818	47.128
Maxima of the Logged Z-score Standardized Amplitude of the SCR with a Maximum SCL, µS	2.264	1.791	1.883	2.143	2.371	1.869
Maxima of the Logged T-score Standardized Amplitude of the SCR with a Maximum SCL, µS	72.639	67.909	68.827	71.430	73.706	68.689
Minima of the Logged Z-score Standardized Amplitude of the SCR with a Maximum SCL, µS	-0.549	-0.719	-0.997	-0.946	-0.787	-1.053
Minima of the Logged T-score Standardized Amplitude of the SCR with a Maximum SCL, µS	44.508	42.814	40.034	40.540	42.129	39.469
Peak to Peak of the Logged Z-score Standardized Amplitude of the SCR with a Maximum SCL, µS	2.813	2.510	2.879	3.089	3.158	2.922
Peak to Peak of the Logged T-score Standardized Amplitude of the SCR with a Maximum SCL, µS	28.132	25.096	28.793	30.890	31.577	29.220
Average Times of the SCR with a Maximum SCL in Each Focus Area						
Rise Times, seconds	1.809 ± 1.866; 0.794	2.634 ± 2.367; 2.144	4.354 ± 4.505; 2.708	6.624 ± 4.956; 5.148	5.402 ± 4.180; 5.754	6.504 ± 4.595; 5.148

Numbers and Frequencies of Each of the Various Types of SCRs						
Number of Potential Event Related SCRs, #	0	0	1	1	1	1
Average Number of the Total number of the Individual SCRs in the Focus Area, #	6 ± 6; 4	5 ± 3; 6	9 ± 5; 11	9 ± 5; 8	11 ± 4; 12	11 ± 4; 11
Average Frequency of the Individual SCRs, #	3 ± 3; 2	2 ± 2; 3	5 ± 3; 5	5 ± 3; 4	5 ± 3; 5	4 ± 3; 4

Note. Values are reported as single numbers, or means plus or minus standard deviation; median. Abbreviations: EDA, electrodermal activity; HUTT, head-up tilt-table test; POTS, postural orthostatic tachycardia syndrome; SCL, skin conductance level; SCR, skin conductance response.

Table 21

Differences Between Controls and POTS Cases in Skin Conductance Responses and other Autonomic Responses During the 30-seconds of Pre-Tilt-up In-HUTT-Baseline Period, the 30-seconds After Tilt-up In-HUTT Period, and the 30-seconds After Tilt-down HUT-Stimulus Winding-down Period.

TEST	30 SECONDS PRIOR TO TILT-UP		30 SECONDS AFTER TILT-UP		30 SECONDS AFTER TILT-DOWN	
Group	**controls**	**POTS cases**	**controls**	**POTS cases**	**controls**	**POTS cases**
SCL Values						
Average of the Means of the Individual Skin Conductance Levels, µS	3.649 ± 5.484; 1.923	4.609 ± 3.900; 4.091	4.897 ± 6.398; 3.312	9.384 ± 10.043; 4.796	5.310 ± 6.633; 4.111	8.260 ± 8.284; 6.046
Average of the Medians of Individual Skin Conductance Levels, µS	3.653 ± 5.525; 1.923	4.653 ± 4.011; 4.091	4.522 ± 6.000; 3.312	9.666 ± 10.474; 4.822	5.346 ± 6.648; 4.093	8.372 ± 8.518; 6.046
Average of the Standard Deviations of Individual Skin Conductance Levels, µS	0.360 ± 0.491; 0.166	0.422 ± 0.497; 0.260	1.219 ± 2.467; 0.175	1.403 ± 2.100; 1.159	0.284 ± 0.341; 0.131	0.895 ± 1.237; 0.319
Average of the Maximum Values of Individual Skin Conductance Levels, µS	3.900 ± 5.860; 2.035	4.825 ± 4.202; 4.414	5.896 ± 8.077; 3.495	10.094 ± 10.601; 5.128	5.602 ± 6.723; 4.361	8.971 ± 9.190; 6.148
Average of the Minimum Values of Individual Skin Conductance Levels, µS	3.395 ± 5.078; 1.813	4.350 ± 3.497; 3.997	4.273 ± 5.595; 3.129	8.146 ± 9.057; 4.725	4.975 ± 6.496; 3.455	7.437 ± 7.174; 5.945
Average of the Differences Between the SCL Values of Each of the SCRs with the Maximum SCL and Each of the SCRs with Minimum SCLs in Each Focus Area During ARS, µS	0.505 ± 0.879; 0.152	0.475 ± 0.815; 0.097	1.508 ± 3.733; 0.091	1.948 ± 3.984; 0.241	0.627 ± 0.826; 0.234	1.534 ± 2.338; 0.559
Average of the Rise Times of the SCR with the Maximum SCL Within the Focus Areas, seconds	3.753 ± 2.806; 3.578	3.669 ± 2.461; 4.104	4.585 ± 3.488; 3.436	6.246 ± 4.515; 4.948	4.097 ± 4.192; 2.492	4.061 ± 3.640; 3.312
Average of the Half Recovery Times of the SCR with the Maximum SCL Within the Focus Areas, seconds	1.088 ± 0.976; 1.025	1.377 ± 0.946; 1.196	1.033 ± 1.120; 0.524	0.864 ± 0.984; 0.506	1.005 ± 0.624; 0.894	1.281 ± 1.408; 0.796

SCR Values						
Average Raw Amplitude of the SCR with the Maximum SCL in the 30-seconds Pre Tilt-up, or of the Task Based SCR in Each Focus Area, µS	0.721 ± 1.715; 0.142	0.550 ± 0.839; 0.217	2.152 ± 3.949; 0.121	5.392 ± 9.662; 1.276	0.709 ± 0.929; 0.318	2.200 ± 4.391; 0.834
Mean of the Logged Z-score Standardized Amplitude of the Task Based SCR	0.000 ± 1.000	0.000 ± 1.000	0.000 ± 1.000	0.000 ± 1.000	0.000 ± 1.000	0.000 ± 1.000
Mean of the Logged T-score Standardized Amplitude of the Task Based SCR	50.000 ± 10.000	50.000 ± 10.000	50.000 ± 10.000	50.000 ± 10.000	50.000 ± 10.000	50.000 ± 10.000
Median of the Logged Z-scores	-0.353	-0.357	-0.636	-0.242	-0.355	-0.145
Median of the Logged T-scores	46.474	46.426	43.637	47.585	46.452	48.553
Maxima of the Logged Z-scores	2.763	2.372	2.236	2.040	1.809	2.395
Maxima of the Logged T-scores	77.626	73.718	72.356	70.402	68.091	73.949
Minima of the Logged Z-scores	-0.581	-0.810	-0.762	-0.927	-0.921	-0.864
Minima of the Logged T-scores	44.190	41.897	42.382	40.732	40.792	41.361
Peak to Peak of the Logged Z-scores	3.344	3.182	2.997	2.967	2.730	3.259
Peak to Peak of the Logged T-scores	33.436	31.821	29.974	29.670	27.299	32.589
Average Times of Either the SCR with the Maximum SCL in the Respective Focus Area, or the Task Based Event Related SCR						
Rise Times, seconds	3.753 ± 2.806; 3.578	3.669 ± 2.461; 4.104	4.585 ± 3.488; 3.436	6.246 ± 4.515; 4.948	4.097 ± 4.192; 2.492	4.061 ± 3.640; 3.312
Numbers and Frequencies of Each of the Various Types of SCRs						
Number of Potential Event Related SCRs, #	0	0	1	1	1	1
Average Number of the Total number of the Individual SCRs in the Focus Area, #	2 ± 2; 2	2 ± 1; 2	2 ± 1; 2	2 ± 1; 2	3 ± 2; 2	2 ± 2; 2
Average Frequency of the individual SCRs, #	4 ± 3; 4	3 ± 2; 3	4 ± 2; 4	4 ± 2; 4	5 ± 4; 4	4 ± 3; 4

Note. Values are reported either as single numbers, or else they are reported as mean plus or minus standard deviation; median. Abbreviations: HUTT, head-up tilt-table test; POTS, postural orthostatic tachycardia syndrome; SCL, skin conductance level; SCR, skin conductance response.

Table 22

Differences Between Controls and POTS Cases in Skin Conductance Responses and other Autonomic Responses at Tilt-up and at Tilt-down.

TEST	DATA FOCUSED ON THE EVENT RELATED SKIN CONDUCTANCE RESPONSE AT TILT-UP		DATA FOCUSED ON THE EVENT RELATED SKIN CONDUCTANCE RESPONSE AT TILT-DOWN	
Group	**controls**	**POTS cases**	**controls**	**POTS cases**
SCL Values				
Average of the Means of the Individual Skin Conductance Levels, µS	3.984 ± 5.433; 2.174	5.550 ± 5.881; 4.042	5.310 ± 6.633; 4.111	8.260 ± 8.284; 6.046
Average of the Medians of Individual Skin Conductance Levels, µS	3.606 ± 5.213; 1.868	5.427 ± 4.011; 4.182	5.346 ± 6.648; 4.093	8.372 ± 8.518; 6.046
Average of the Standard Deviations of Individual Skin Conductance Levels, µS	1.343 ± 1.394; 0.494	1.488 ± 2.200; 0.757	0.284 ± 0.341; 0.284	0.895 ± 1.237; 0.319
Average of the Maximum Values of Individual Skin Conductance Levels, µS	6.798 ± 8.594; 4.512	9.421 ± 10.071; 6.065	5.602 ± 6.723; 4.361	8.971 ± 9.190; 6.148
Average of the Minimum Values of Individual Skin Conductance Levels, µS	2.360 ± 3.900; 0.860	3.468 ± 4.095; 2.102	4.975 ± 6.496; 3.455	7.437 ± 7.174; 5.945
Average of the Differences Between the SCL Values of Each of the SCRs with the Maximum SCL and Each of the SCRs with Minimum SCLs in Each Focus Area During ARS, µS	4.398 ± 5.272; 1.252	5.954 ± 8.448; 3.674	0.627 ± 0.826; 0.234	1.534 ± 2.338; 0.559
Average of the Rise Times of the SCR with the Maximum SCL Within the Focus Areas, seconds	4.575 ± 4.786; 2.215	4.266 ± 4.509; 2.024	4.097 ± 4.192; 2.492	4.061 ± 3.640; 3.312
Average of the Half Recovery Times of the SCR with the Maximum SCL Within the Focus Areas, seconds	1.048 ± 1.048; 0.872	1.384 ± 1.331; 1.132	1.005 ± 0.624; 0.894	1.281 ± 1.408; 0.796
SCR Values				
Average Raw Amplitude of the Task Based SCR in Each of the Two Focus Areas (i.e., the HUTT Focus Area as well as the 30-seconds After Tilt-down Focus Area), µS	2.869 ± 4.925; 0.423	5.170 ± 8.815; 1.682	0.945 ± 2.649; 0.098	0.981 ± 1.376; 0.263
Mean of the Logged Z-score Standardized Amplitude of the Event Related SCR in Each Focus Area, µS	0.000 ± 1.000	0.000 ± 1.000	0.000 ± 1.000	0.000 ± 1.000
Mean of the Logged T-score Standardized Amplitude of the Event Related SCR in Each Focus Area, µS	50.000 ± 10.000	50.000 ± 10.000	50.000 ± 10.000	50.000 ± 10.000
Median of the Logged Z-scores of the SCR with the Event Related SCR in	-0.472	-0.235	-0.376	-0.487

Each Focus Area, µS				
Median of the Logged T-scores of the SCR with the Event Related SCR in Each Focus Area, µS	45.284	47.648	46.237	45.125
Maxima of the Logged Z-scores of the SCR with the Event Related SCR in Each Focus Area, µS	1.937	2.216	3.084	2.149
Maxima of the Logged T-scores of the SCR with the Event Related SCR in Each Focus Area, µS	69.366	72.156	80.844	71.491
Minima of the Logged Z-scores of the SCR with the Maximum SCL in Each Focus Area, µS	-0.832	-1.186	-0.495	-0.879
Minima of the Logged T-scores of the SCR with the Event Related SCR in Each Focus Area, µS	41.676	38.145	45.055	41.209
Peak to Peak of the Logged Z-scores of the SCR with the Maximum SCL in Each Focus Area, µS	2.769	3.401	3.579	3.028
Peak to Peak of the Logged T-scores of the Event Related SCR in Each Focus Area, µS	27.690	34.011	35.789	30.282
Average Times of the Task Based Event Related SCR				
Rise Times, seconds	6.260 ± 3.364; 6.186	6.891 ± 5.060; 5.798	3.899 ± 4.082; 2.072	5.203 ± 5.953; 2.668
Numbers and Frequencies of Each of the Various Types of SCRs				
Number of Potential Event Related SCRs, #	1	1	1	1
Average Number of the Total number of the Individual SCRs in the Focus Area, #	40 ± 27; 45	41 ± 24; 48	3 ± 2; 2	2 ± 2; 2
Average Frequency of the individual SCRs, #	4 ± 3; 4	4 ± 2; 5	5 ± 4; 4	4 ± 3; 4

Note. Values are reported either as single numbers, or else they are reported as means plus or minus standard deviation; median. Abbreviations: HUTT, head-up tilt-table test; POTS, postural orthostatic tachycardia syndrome; SCL, skin conductance level; SCR, skin conductance response.

Table 23

Other Notable Phasic EDA Results Across Testing Conditions and-or Focus Areas Within the EDA Signal Trace

Variable Name	controls	POTS cases	p-values
Number of Event Related SCRs During the Deep Breathing 1 Test, #	4 ± 3; 3	2 ± 2; 1	0.032
Number of Event Related SCRs During the Deep Breathing 2 Test, #	5 ± 3; 4	3 ± 2; 2	0.049
Number of Non-Specific SCRs During the Valsalva Maneuver 1 Test, #	2 ± 2; 2	2 ± 2; 2	0.489
Number of Non-Specific SCRs During the Valsalva Maneuver 2 Test, #	2 ± 1; 1	2 ± 1; 2	0.045
Ratio of the Event Related SCR's Amplitude to Rise Time During the Deep Breathing 1 Test, µS/sec	0.173 ± 0.256; 0.059	0.230 ± 0.313; 0.098	0.796
Ratio of the Event Related SCR's Amplitude to Rise Time During the Deep Breathing 2 Test, µS/sec	0.157 ± 0.313; 0.065	0.205 ± 0.292; 0.097	0.432
Ratio of the Event Related SCR's Amplitude to Rise Time During the Valsalva Maneuver 1 Test, µS/sec	0.202 ± 0.398; 0.042	0.349 ± 0.332; 0.231	0.085
Ratio of the Event Related SCR's Amplitude to Rise Time During the Valsalva Maneuver 2 Test, µS/sec	0.211 ± 0.327; 0.062	0.362 ± 0.401; 0.181	0.119
Ratio of the Event Related SCR's Amplitude to Rise Time During the Valsalva Maneuver 3 Test, µS/sec	0.213 ± 0.247; 0.135	0.231 ± 0.226; 0.154	0.879
Frequency of the Number of SCRs During the Valsalva Maneuver 1 Test, #/sec	5 ± 3; 4	6 ± 4; 5	0.236
Frequency of the Number of SCRs During the Valsalva Maneuver 2 Test, #/sec	5 ± 2; 3	7 ± 3; 7	0.007
Frequency of the Number of SCRs During the Valsalva Maneuver 3 Test, #/sec	5 ± 3; 4	6 ± 2; 5	0.869
Average Maximum SCL of the Entire EDA Signal Trace, µS	9.665 ± 7.799; 7.474	9.999 ± 10.466; 6.735	0.839
Average Minimum SCL of the Entire EDA Signal Trace, µS	-2.176 ± 6.048; 0.004	0.565 ± 3.533; 0.493	0.069

Note. Values have been reported as mean plus or minus standard deviation; median. Abbreviations: EDA, electrodermal activity; POTS, postural orthostatic tachycardia syndrome; SCL, skin conductance level; SCRs, skin conductance responses. Groups were compared with an application of the Kruskal-Wallis Test (i.e., the Wilcoxon Rank Test), except for where 1=the Mann-Whitney U Test, 2=the T-Test, and 3=the T-Test with Welch's Correction.

Table 24

Notable Standardized Z-score and T-score Results

Focus Area and-or Test	Variable	control	POTS cases
2-mins of the Pre-ARS Testing Baseline Period	Median of the Raw Z-score, µS	-0.452	-0.629
2-mins of the Pre-ARS Testing Baseline Period	Median of the Raw T-score, µS	45.477	43.711
2-mins of the Pre-ARS Testing Baseline Period	Median of the Logarithmically Transformed Raw Z-score, µS	-0.486	-0.633
2-mins of the Pre-ARS Testing Baseline Period	Median of the Logarithmically Transformed Raw T-score, µS	45.142	43.674
1st 2-mins of Sustained SCL Elevation in HUTT	Median of the Raw Z-score, µS	-0.485	-0.481
1st 2-mins of Sustained SCL Elevation in HUTT	Median of the Raw T-score, µS	45.149	45.185
1st 2-mins of Sustained SCL Elevation in HUTT	Median of the Logarithmically Transformed Raw Z-score, µS	-0.518	-0.287
1st 2-mins of Sustained SCL Elevation in HUTT	Median of the Logarithmically Transformed Raw T-score, µS	44.818	47.128
2-mins of Sustained SCL Elevation in HUTT After the 70-degrees Tilt-up	Median of the Raw Z-score, µS	-0.371	-0.417
2-mins of Sustained SCL Elevation in HUTT After the 70-degrees Tilt-up	Median of the Raw T-score, µS	46.294	45.829
2-mins of Sustained SCL Elevation in HUTT After the 70-degrees Tilt-up	Median of the Logarithmically Transformed Raw Z-score, µS	-0.677	-0.157
2-mins of Sustained SCL Elevation in HUTT After the 70-degrees Tilt-up	Median of the Logarithmically Transformed Raw T-score, µS	43.232	48.427
Deep Breathing Task 1	Median of the Raw Z-score, µS	-0.533	-0.386
Deep Breathing Task 1	Median of the Raw T-score, µS	44.666	46.137
Deep Breathing Task 1	Median of the Logarithmically Transformed Raw Z-score, µS	-0.518	-0.264
Deep Breathing Task 1	Median of the Logarithmically Transformed Raw T-score, µS	44.821	47.365
Deep Breathing Task 2	Median of the Raw Z-score, µS	-0.378	-0.232
Deep Breathing Task 2	Median of the Raw T-score, µS	46.220	47.684
Deep Breathing Task 2	Median of the Logarithmically Transformed Raw Z-score, µS	-0.402	-0.060
Deep Breathing Task 2	Median of the Logarithmically Transformed Raw T-score, µS	45.980	49.400
Valsalva Maneuver 1	Median of the Raw Z-score, µS	-0.478	-0.330
Valsalva Maneuver 1	Median of the Raw T-score, µS	45.216	46.700
Valsalva Maneuver 1	Median of the Logarithmically Transformed Raw Z-score, µS	-0.397	-0.032
Valsalva Maneuver 1	Median of the Logarithmically Transformed Raw T-score, µS	46.032	49.678
Valsalva Maneuver 2	Median of the Raw Z-score, µS	-0.438	-0.340

Valsalva Maneuver 2	Median of the Raw T-score, µS	45.622	46.596
Valsalva Maneuver 2	Median of the Logarithmically Transformed Raw Z-score, µS	-0.386	-0.114
Valsalva Maneuver 2	Median of the Logarithmically Transformed Raw T-score, µS	46.136	48.865
Valsalva Maneuver 3	Median of the Raw Z-score, µS	-0.388	-0.362
Valsalva Maneuver 3	Median of the Raw T-score, µS	46.116	46.376
Valsalva Maneuver 3	Median of the Logarithmically Transformed Raw Z-score, µS	-0.354	-0.210
Valsalva Maneuver 3	Median of the Logarithmically Transformed Raw T-score, µS	46.463	47.902
Tilt-up Effect Period	Median of the Raw Z-score, µS	-0.497	-0.396
Tilt-up Effect Period	Median of the Raw T-score, µS	45.034	46.043
Tilt-up Effect Period	Median of the Logarithmically Transformed Raw Z-score, µS	-0.472	-0.235
Tilt-up Effect Period	Median of the Logarithmically Transformed Raw T-score, µS	45.284	47.648
Tilt-down Effect Period	Median of the Raw Z-score, µS	-0.320	-0.521
Tilt-down Effect Period	Median of the Raw T-score, µS	46.802	44.786
Tilt-down Effect Period	Median of the Logarithmically Transformed Raw Z-score, µS	-0.376	-0.487
Tilt-down Effect Period	Median of the Logarithmically Transformed Raw T-score, µS	46.237	45.125
30-secs Prior to Tilt-up	Median of the Raw Z-score, µS	-0.338	-0.397
30-secs Prior to Tilt-up	Median of the Raw T-score, µS	46.624	46.028
30-secs Prior to Tilt-up	Median of the Logarithmically Transformed Raw Z-score, µS	-0.353	-0.357
30-secs Prior to Tilt-up	Median of the Logarithmically Transformed Raw T-score, µS	46.474	46.426
30-secs After Tilt-up	Median of the Raw Z-score, µS	-0.514	-0.426
30-secs After Tilt-up	Median of the Raw T-score, µS	44.858	45.740
30-secs After Tilt-up	Median of the Logarithmically Transformed Raw Z-score, µS	-0.636	-0.242
30-secs After Tilt-up	Median of the Logarithmically Transformed Raw T-score, µS	43.637	47.585
30-secs After Tilt-down	Median of the Raw Z-score, µS	-0.421	-0.311
30-secs After Tilt-down	Median of the Raw T-score, µS	45.793	46.888
30-secs After Tilt-down	Median of the Logarithmically Transformed Raw Z-score, µS	-0.355	-0.145
30-secs After Tilt-down	Median of the Logarithmically Transformed Raw T-score, µS	46.452	48.553

Note. Values are reported as single numbers. Abbreviation: HUTT, head-up tilt-table test; SCL, skin conductance level.

Table 25

Correlational Strength of Comparisons Between Indices of Skin Conductance Response and Other Indexes of Autonomic Response in Controls

Novel Test Measure	Standard Test Measure	n	Correlation Coefficient	p-value	Strength of Association
2-minutes After Tilt-up in HUTT's SCR with Max Amplitude's T-score Logged	Heart Rate Delta	47	0.653	<0.001	Strong
T-score Logged of the SCR with Max SCL's Amplitude in the 30-seconds Right Before Tilt-up	Heart Rate Delta	47	0.645	<0.001	Strong
1st 2-minutes in HUTT's SCR with Max SCL Amplitude's T-score Logged	Heart Rate Delta	47	0.643	<0.001	Strong
Average Minimum SCL of the Entire EDA Signal Trace, µS	Heart Rate Delta	47	-0.602	<0.001	Strong
T-score Logged of the SCR with Max SCL's Amplitude in the 30-seconds Right After Tilt-up	Heart Rate Delta	47	0.549	<0.001	Moderate
Baseline T-score Logged	Heart Rate Delta	47	0.508	<0.001	Moderate
Ratio of the Event Related SCR's Amplitude to Rise Time During the Valsalva Maneuver 2 Test	Heart Rate Delta	47	0.463	<0.002	Moderate
TU T-score Logged	Heart Rate Delta	47	0.420	0.005	Moderate
DB1 T-score Logged	Heart Rate Delta	47	0.415	0.006	Moderate
Number of Medications Not Held Before the Autonomic Reflex Screen, #	Minimum Systolic Blood Pressure in HUTT	47	-0.620	<0.001	Strong
Frequency of the Number of SCRs During the Valsalva Maneuver 2 Test, #/minute	Minimum Systolic Blood Pressure in HUTT	47	0.465	0.002	Moderate
Ratio of the Event Related SCR's Amplitude to Rise Time During the Valsalva Maneuver 3 Test	Minimum Systolic Blood Pressure in HUTT	47	-0.512	0.004	Moderate
VM3 T-score Logged	Minimum Systolic Blood Pressure in HUTT	47	-0.597	<0.001	Moderate
TD T-score Logged	Minimum Systolic Blood Pressure in HUTT	47	-0.540	<0.001	Moderate
T-score Logged of the SCR with Max SCL's Amplitude's in 30-seconds After Tilt-down	Minimum Systolic Blood Pressure in HUTT	47	-0.540	<0.001	Moderate
Ratio of the Event Related SCR's Amplitude to Rise Time During the Valsalva Maneuver 1 Test	Minimum Change of Systolic Blood Pressure from Pre-Tilt Values in HUTT	47	0.644	<0.001	Strong
DB2 T-score Logged	Minimum Change of Systolic Blood Pressure from Pre-Tilt Values in HUTT	47	0.613	<0.001	Strong
Number of Symptoms at Tilt-up	Minimum Change of Systolic Blood Pressure from Pre-Tilt Values in HUTT	47	-0.565	<0.001	Moderate

VM1 T-score Logged	Minimum Change of Systolic Blood Pressure from Pre-Tilt Values in HUTT	47	0.517	<0.001	Moderate
DB1 T-score Logged	Minimum Change of Systolic Blood Pressure from Pre-Tilt Values in HUTT	47	0.425	0.005	Moderate
Average Maximum SCL of the Entire EDA Signal Trace, µS	Minimum Change of Systolic Blood Pressure from Pre-Tilt Values in HUTT	47	0.458	<0.001	Moderate
Frequency of the Number of SCRs During the Valsalva Maneuver 2 Test, #/minute	Minimum Change of Systolic Blood Pressure from Pre-Tilt Values in HUTT	47	0.442	0.003	Moderate
Number of Non-specific SCRs During the Valsalva Maneuver 2, #	Minimum Change of Systolic Blood Pressure from Pre-Tilt Values in HUTT	47	0.402	0.007	Moderate
Number of Non-specific SCRs During the Valsalva Maneuver 2, #	Maximum Heart Rate in HUTT, bpm	47	-0.718	<0.001	Strong
DB1 T-score Logged	Maximum Heart Rate in HUTT, bpm	47	-0.617	<0.001	Strong
1st 2-minutes in HUTT's SCR with Max SCL Amplitude's T-score Logged	Maximum Heart Rate in HUTT, bpm	47	-0.600	<0.001	Strong
Number of Symptoms at Tilt-up	Maximum Heart Rate in HUTT, bpm	47	0.560	<0.001	Moderate
Number of Medications Not Held Before the Autonomic Reflex Screen, #	Maximum Heart Rate in HUTT, bpm	47	0.553	<0.001	Moderate
Number of Event Related SCRs During the Deep Breathing Test 2	Maximum Heart Rate in HUTT, bpm	47	0.550	<0.001	Moderate
Number of Symptoms at Tilt-down	Maximum Heart Rate in HUTT, bpm	47	0.513	<0.001	Moderate
2-minutes in After Tilt-up in HUTT's SCR with Max SCL Amplitude's T-score Logged	Maximum Heart Rate in HUTT, bpm	47	-0.540	<0.001	Moderate
Frequency of the Number of SCRs During the Valsalva Maneuver 2 Test, #/minute	Maximum Heart Rate in HUTT, bpm	47	-0.523	0.003	Moderate
Total Number of Symptoms in HUTT, #	Maximum Heart Rate in HUTT, bpm	47	0.522	<0.001	Moderate
T-score Logged of the SCR with Max SCL's Amplitude's in 30-seconds Before Tilt-up	Maximum Heart Rate in HUTT, bpm	47	-0.468	0.002	Moderate
T-score Logged of the SCR with Max SCL's Amplitude's in 30-seconds After Tilt-up	Maximum Heart Rate in HUTT, bpm	47	-0.451	0.002	Moderate
Baseline T-score Logged	Maximum Heart Rate in HUTT, bpm	47	-0.430	0.004	Moderate
Number of Non-specific SCRs During the Valsalva Maneuver 1, #	Maximum Heart Rate in HUTT, bpm	47	0.401	0.008	Moderate
Number of Non-specific SCRs During the Valsalva Maneuver 1, #	Heart Rate at the Minimum Systolic Blood Pressure in HUTT	47	0.562	<0.001	Moderate

Number of Medications Not Held Before the Autonomic Reflex Screen, #	Heart Rate at the Minimum Systolic Blood Pressure in HUTT	47	0.516	<0.001	Moderate
Total Number of Symptoms in HUTT, #	Heart Rate at the Minimum Systolic Blood Pressure in HUTT	47	0.496	0.001	Moderate
Number of Non-specific SCRs During the Valsalva Maneuver 2, #	Heart Rate at the Minimum Systolic Blood Pressure in HUTT	47	-0.470	0.001	Moderate
Number of Event Related SCRs During the Deep Breathing Test 2	Heart Rate at the Minimum Systolic Blood Pressure in HUTT	47	0.460	0.002	Moderate
Number of Symptoms at Tilt-down	Heart Rate at the Minimum Systolic Blood Pressure in HUTT	47	0.435	0.004	Moderate
Frequency of the Number of SCRs During the Valsalva Maneuver 2 Test, #/minute	Heart Rate at the Minimum Systolic Blood Pressure in HUTT	47	-0.431	0.004	Moderate
Body Mass Index, pounds/inches squared	QSWEAT Total Forearm Sweat Volume, µL	47	0.825	<0.001	Very Strong
Frequency of the Number of SCRs During the Valsalva Maneuver 1 Test, #/minute	QSWEAT Total Forearm Sweat Volume, µL	47	-0.714	<0.001	Strong
Number of Non-specific SCRs During the Valsalva Maneuver 1, #	QSWEAT Total Forearm Sweat Volume, µL	47	-0.660	<0.001	Strong
Average Maximum SCL of the Entire EDA Signal Trace, µS	QSWEAT Total Forearm Sweat Volume, µL	47	-0.653	<0.001	Strong
Age, years	QSWEAT Total Forearm Sweat Volume, µL	47	0.617	<0.001	Strong
Ratio of the Event Related SCR's Amplitude to Rise Time During the Valsalva Maneuver 3 Test	QSWEAT Total Forearm Sweat Volume, µL	47	-0.613	<0.001	Strong
VM3 T-score Logged	QSWEAT Total Forearm Sweat Volume, µL	47	-0.609	<0.001	Strong
DB2 T-score Logged	QSWEAT Total Forearm Sweat Volume, µL	47	-0.607	<0.001	Strong
Ratio of the Event Related SCR's Amplitude to Rise Time During the Valsalva Maneuver 1 Test	QSWEAT Total Forearm Sweat Volume, µL	47	-0.604	<0.001	Strong
VM1 T-score Logged	QSWEAT Total Forearm Sweat Volume, µL	47	-0.569	<0.001	Moderate
VM2 T-score Logged	QSWEAT Total Forearm Sweat Volume, µL	47	-0.550	<0.001	Moderate
Ratio of the Event Related SCR's Amplitude to Rise Time During the Valsalva Maneuver 2 Test	QSWEAT Total Forearm Sweat Volume, µL	47	-0.546	<0.001	Moderate
Number of Medications Not Held Before the Autonomic Reflex Screen, #	QSWEAT Total Forearm Sweat Volume, µL	47	-0.535	<0.001	Moderate
TU T-score Logged	QSWEAT Total Forearm Sweat Volume, µL	47	-0.470	0.001	Moderate
Baseline T-score Logged	QSWEAT Total Forearm Sweat Volume, µL	47	-0.453	0.002	Moderate
Average Minimum SCL of the Entire EDA Signal Trace, µS	QSWEAT Total Forearm Sweat Volume, µL	47	0.410	0.006	Moderate
1st 2-minutes in HUTT's SCR with Max SCL Amplitude's T-score Logged	Average Heart Rate Difference During the Deep breathing Test, bpm	47	0.891	<0.001	Very Strong

2-minutes in After Tilt-up in HUTT's SCR with Max SCL Amplitude's T-score Logged	Average Heart Rate Difference During the Deep breathing Test, bpm	47	0.891	<0.001	Very Strong
Baseline T-score Logged	Average Heart Rate Difference During the Deep breathing Test, bpm	47	0.891	<0.001	Very Strong
T-score Logged of the SCR with Max SCL's Amplitude's in 30-seconds Before Tilt-up	Average Heart Rate Difference During the Deep breathing Test, bpm	47	0.870	<0.001	Very Strong
T-score Logged of the SCR with Max SCL's Amplitude's in 30-seconds After Tilt-up	Average Heart Rate Difference During the Deep breathing Test, bpm	47	0.866	<0.001	Very Strong
DB1 T-score Logged	Average Heart Rate Difference During the Deep breathing Test, bpm	47	0.861	<0.001	Very Strong
Average Minimum SCL of the Entire EDA Signal Trace, µS	Average Heart Rate Difference During the Deep breathing Test, bpm	47	-0.866	<0.001	Very Strong
Ratio of the Event Related SCR’s Amplitude to Rise Time During the Valsalva Maneuver 2 Test	Average Heart Rate Difference During the Deep breathing Test, bpm	47	0.852	<0.001	Very Strong
VM2 T-score Logged	Average Heart Rate Difference During the Deep breathing Test, bpm	47	0.795	<0.001	Strong
Average Maximum SCL of the Entire EDA Signal Trace, µS	Average Heart Rate Difference During the Deep breathing Test, bpm	47	0.792	<0.001	Strong
TU T-score Logged	Average Heart Rate Difference During the Deep breathing Test, bpm	47	0.777	<0.001	Strong
VM1 T-score Logged	Average Heart Rate Difference During the Deep breathing Test, bpm	47	0.713	<0.001	Strong
Number of Symptoms at Tilt-down	Average Heart Rate Difference During the Deep breathing Test, bpm	47	-0.616	<0.001	Strong
Frequency of the Number of SCRs During the Valsalva M aneuver 1 Test, #/minute	Average Heart Rate Difference During the Deep breathing Test, bpm	47	0.588	<0.001	Moderate
Ratio of the Event Related SCR’s Amplitude to Rise Time During the Valsalva Maneuver 3 Test	Average Heart Rate Difference During the Deep breathing Test, bpm	47	0.496	0.001	Moderate
Number of Symptoms at Tilt-up	Average Heart Rate Difference During the Deep breathing Test, bpm	47	-0.495	0.001	Moderate
Number of Event Related SCRs During the Deep Breathing Test 2	Average Heart Rate Difference During the Deep breathing Test, bpm	47	-0.487	0.001	Moderate
Number of Non-specific SCRs During the Valsalva Maneuver 2, #	Average Heart Rate Difference During the Deep breathing Test, bpm	47	0.456	0.002	Moderate
Ratio of the Event Related SCR’s Amplitude to Rise Time During the Valsalva Maneuver 1 Test	Average Heart Rate Difference During the Deep breathing Test, bpm	47	0.423	0.005	Moderate

Average Heart Rate Ratio During the Valsalva Maneuver, bpm	Greatest Heart Rate Ratio During the Valsalva Maneuver	47	0.833	<0.001	Very Strong
1st 2-minutes in HUTT's SCR with Max SCL Amplitude's T-score Logged	Average Maximum Heart Rate During the Valsalva Maneuver, bpm	47	-0.869	<0.001	Very Strong
HRDB Expiration to Inspiration Ratio	Average Maximum Heart Rate During the Valsalva Maneuver, bpm	47	-0.858	<0.001	Very Strong
2-minutes in After Tilt-up in HUTT's SCR with Max SCL Amplitude's T-score Logged	Average Maximum Heart Rate During the Valsalva Maneuver, bpm	47	-0.840	<0.001	Very Strong
Average Heart Rate Difference During the Deep breathing Test, bpm	Average Maximum Heart Rate During the Valsalva Maneuver, bpm	47	-0.815	<0.001	Very Strong
Delta HR During the Heart Rate Deep Breathing Test, bpm	Average Maximum Heart Rate During the Valsalva Maneuver, bpm	47	-0.815	<0.001	Very Strong
T-score Logged of the SCR with Max SCL's Amplitude's in 30-seconds Before Tilt-up	Average Maximum Heart Rate During the Valsalva Maneuver, bpm	47	-0.751	<0.001	Strong
Baseline T-score Logged	Average Maximum Heart Rate During the Valsalva Maneuver, bpm	47	-0.728	<0.001	Strong
TU T-score Logged	Average Maximum Heart Rate During the Valsalva Maneuver, bpm	47	-0.678	<0.001	Very Strong
VM2 T-score Logged	Average Maximum Heart Rate During the Valsalva Maneuver, bpm	47	-0.640	<0.001	Very Strong
T-score Logged of the SCR with Max SCL's Amplitude's in 30-seconds After Tilt-up	Average Maximum Heart Rate During the Valsalva Maneuver, bpm	47	-0.809	<0.001	Very Strong
Number of Symptoms at Tilt-down	Average Maximum Heart Rate During the Valsalva Maneuver, bpm	47	0.797	<0.001	Strong
Maximum Heart Rate in HUTT, bpm	Average Maximum Heart Rate During the Valsalva Maneuver, bpm	47	0.789	<0.001	Strong
DB1 T-score Logged	Average Maximum Heart Rate During the Valsalva Maneuver, bpm	47	-0.695	<0.001	Strong
Number of Symptoms at Tilt-up	Average Maximum Heart Rate During the Valsalva Maneuver, bpm	47	0.665	<0.001	Strong
Average Minimum SCL of the Entire EDA Signal Trace, µS	Average Maximum Heart Rate During the Valsalva Maneuver, bpm	47	0.660	<0.001	Strong
Average Maximum Heart Rate During the Deep Breathing Test, bpm	Average Maximum Heart Rate During the Valsalva Maneuver, bpm	47	-0.660	<0.001	Strong
Ratio of the Event Related SCR's Amplitude to Rise Time During the Valsalva Maneuver 2 Test	Average Maximum Heart Rate During the Valsalva Maneuver, bpm	47	-0.646	<0.001	Strong

Total Number of Symptoms in HUTT, #	Average Maximum Heart Rate During the Valsalva Maneuver, bpm	47	0.631	<0.001	Strong
Heart Rate Delta	Average Maximum Heart Rate During the Valsalva Maneuver, bpm	47	-0.609	<0.001	Strong
Number of Event Related SCRs During the Deep Breathing Test 2	Average Maximum Heart Rate During the Valsalva Maneuver, bpm	47	0.597	<0.001	Moderate
Number of Non-specific SCRs During the Valsalva Maneuver 2, #	Average Maximum Heart Rate During the Valsalva Maneuver, bpm	47	-0.581	<0.001	Moderate
Average Maximum SCL of the Entire EDA Signal Trace, µS	Average Maximum Heart Rate During the Valsalva Maneuver, bpm	47	-0.540	<0.001	Moderate
Heart Rate at the Minimum Systolic Blood Pressure in HUTT	Average Maximum Heart Rate During the Valsalva Maneuver, bpm	47	0.539	<0.001	Moderate
VM1 T-score Logged	Average Maximum Heart Rate During the Valsalva Maneuver, bpm	47	-0.499	0.001	Moderate

Note. Abbreviations: CASS, composite autonomic severity score; HR, heart rate; HRDB, heart rate deep breathing; HUTT, head-up tilt-table test; SCL, skin conductance level; SCR, skin conductance response; VM, Valsalva maneuver. Only moderate, strong, and very strong associations of the novel variables (which pertain either to the new HUTT symptoms scoring scale, or the standardized EDA related variables), and established ARS reference variables, have been reported in the table above. Only moderate, strong, and very strong associations, with p-values that are either at, or less than the chosen statistical significance level of a $p<0.05$, have been reported in Table 46. In some instances where such data are of clinical interest, an association between two reference (or gold standard) variables, have been included, because of their pertinence to this study. One example of such an instance, is the strong correlation between the variables "QSWEAT Total Forearm Volume, µL" and "Sudomotor Component of the Composite Autonomic Severity Score." These results were generated by use of the Spearman's Correlations Test. These p-values have not been adjusted for multiple comparisons. As such, the occurrence of Type I Errors may be more likely. Yet, a correction for multiple comparisons, may result in a higher occurrence of Type II Errors.

Table 26

Correlational Strength of Comparisons Between Indices of Skin Conductance Response and Other Indexes of Autonomic Response in POTS Cases

Novel Test Measure	Standard Test Measure	n	Correlation Coefficient	p-value	Strength of Association
Number of Event Related SCRs During the Deep Breathing Test 1	Heart Rate Delta	47	-0.644	<0.001	Strong
2-minutes After Tilt-up in HUTT's SCR with Max Amplitude's T-score Logged	Heart Rate Delta	47	-0.616	<0.001	Strong
1st 2-minutes in HUTT's SCR with Max SCL Amplitude's T-score Logged	Heart Rate Delta	47	-0.628	<0.001	Strong
TU T-score Logged	Heart Rate Delta	47	-0.614	<0.001	Strong
DB2 T-score Logged	Heart Rate Delta	47	0.657	<0.001	Strong
VM3 T-score Logged	Heart Rate Delta		0.545	<0.001	Moderate
TD T-score Logged	Heart Rate Delta	47	-0.569	<0.001	Moderate
T-score Logged of the SCR with Max SCL's Amplitude in the 30-seconds Right After Tilt-up	Heart Rate Delta	47	-0.597	<0.001	Moderate
T-score Logged of the SCR with Max SCL's Amplitude's in 30-seconds After Tilt-down	Heart Rate Delta	47	-0.569	<0.001	Moderate
Baseline T-score Logged	Heart Rate Delta	47	0.502	<0.001	Moderate
Ratio of the Event Related SCR's Amplitude to Rise Time During the Valsalva Maneuver 3 Test	Heart Rate Delta	47	0.435	<0.001	Moderate
Average Minimum SCL of the Entire EDA Signal Trace, µS	Heart Rate Delta	47	0.466	0.001	Moderate
Baseline T-score Logged	Minimum Systolic Blood Pressure in HUTT	47	-0.6100	<0.001	Strong
DB2 T-score Logged	Minimum Systolic Blood Pressure in HUTT	47	-0.6431	<0.001	Strong
Number of Non-specific SCRs During the Valsalva Maneuver 1, #	Minimum Systolic Blood Pressure in HUTT	47	-0.627	<0.001	Strong
Frequency of the Number of SCRs During the Valsalva Maneuver 3 Test, #/minute	Minimum Systolic Blood Pressure in HUTT	47	-0.580	<0.001	Moderate
Ratio of the Event Related SCR's Amplitude to Rise Time During the Valsalva Maneuver 3 Test	Minimum Systolic Blood Pressure in HUTT	47	-0.441	0.002	Moderate
Average Minimum SCL of the Entire EDA Signal Trace, µS	Minimum Systolic Blood Pressure in HUTT	47	-0.478	0.001	Moderate
DB1 T-score Logged	Minimum Systolic Blood Pressure in HUTT	47	-0.450	0.002	Moderate
VM3 T-score Logged	Minimum Systolic Blood Pressure in HUTT	47	-0.517	<0.001	Moderate
1st 2-minutes in HUTT's SCR with Max SCL Amplitude's	Minimum Systolic Blood Pressure in HUTT	47	0.513	<0.001	Moderate

T-score Logged					
2-minutes in After Tilt-up in HUTT's SCR with Max SCL Amplitude's T-score Logged	Minimum Systolic Blood Pressure in HUTT	47	0.439	0.002	Moderate
VM3 T-score Logged	Minimum Change of Systolic Blood Pressure from Pre-Tilt Values in HUTT	47	-0.644	<0.001	Strong
Ratio of the Event Related SCR's Amplitude to Rise Time During the Valsalva Maneuver 3 Test	Minimum Change of Systolic Blood Pressure from Pre-Tilt Values in HUTT	47	-0.625	<0.001	Strong
Ratio of the Event Related SCR's Amplitude to Rise Time During the Valsalva Maneuver 2 Test	Minimum Change of Systolic Blood Pressure from Pre-Tilt Values in HUTT	47	-0.503	<0.001	Moderate
Ratio of the Event Related SCR's Amplitude to Rise Time During the Valsalva Maneuver 1 Test	Minimum Change of Systolic Blood Pressure from Pre-Tilt Values in HUTT	47	-0.429	0.003	Moderate
Number of Symptoms at Tilt-up	Minimum Change of Systolic Blood Pressure from Pre-Tilt Values in HUTT	47	-0.518	<0.001	Moderate
Baseline T-score Logged	Minimum Change of Systolic Blood Pressure from Pre-Tilt Values in HUTT	47	-0.451	0.002	Moderate
DB2 T-score Logged	Minimum Change of Systolic Blood Pressure from Pre-Tilt Values in HUTT	47	-0.524	<0.001	Moderate
VM1 T-score Logged	Minimum Change of Systolic Blood Pressure from Pre-Tilt Values in HUTT	47	-0.450	0.002	Moderate
VM2 T-score Logged	Minimum Change of Systolic Blood Pressure from Pre-Tilt Values in HUTT	47	-0.415	0.004	Moderate
VM3 T-score Logged	Maximum Heart Rate in HUTT, bpm		0.617	<0.001	Strong
DB2 T-score Logged	Maximum Heart Rate in HUTT, bpm	47	0.578	<0.001	Moderate
Ratio of the Event Related SCR's Amplitude to Rise Time During the Valsalva Maneuver 3 Test	Maximum Heart Rate in HUTT, bpm	47	0.562	<0.001	Moderate
Number of Event Related SCRs During the Deep Breathing Test 1	Maximum Heart Rate in HUTT, bpm	47	-0.539	0.047	Moderate
Number of Symptoms at Tilt-up	Maximum Heart Rate in HUTT, bpm	47	0.514	<0.001	Moderate
Number of Symptoms at Tilt-down	Maximum Heart Rate in HUTT, bpm	47	0.506	<0.001	Moderate
Baseline T-score Logged	Maximum Heart Rate in HUTT, bpm	47	0.411	<0.001	Moderate
VM1 T-score Logged	Maximum Heart Rate in HUTT, bpm	47	0.411	<0.001	Moderate
VM1 T-score Logged	Heart Rate at the Minimum Systolic Blood Pressure in HUTT	47	0.711	<0.001	Strong
Ratio of the Event Related SCR's Amplitude to Rise Time During the Valsalva Maneuver 2 Test	Heart Rate at the Minimum Systolic Blood Pressure in HUTT	47	0.656	<0.001	Strong

Ratio of the Event Related SCR's Amplitude to Rise Time During the Valsalva Maneuver 1 Test	Heart Rate at the Minimum Systolic Blood Pressure in HUTT	47	0.628	<0.001	Strong
Number of Symptoms at Tilt-up	Heart Rate at the Minimum Systolic Blood Pressure in HUTT	47	0.621	<0.001	Strong
Baseline T-score Logged	Heart Rate at the Minimum Systolic Blood Pressure in HUTT	47	0.460	0.030	Moderate
VM2 T-score Logged	Heart Rate at the Minimum Systolic Blood Pressure in HUTT	47	0.589	<0.001	Moderate
Sudomotor Component of the Composite Autonomic Severity Score	QSWEAT Total Forearm Sweat Volume, µL	47	-0.785	<0.001	Strong
Total of the Components of the Composite Autonomic Severity Score	QSWEAT Total Forearm Sweat Volume, µL	47	-0.653	<0.001	Strong
Total Number of Symptoms in HUTT, #	QSWEAT Total Forearm Sweat Volume, µL	47	-0.618	<0.001	Strong
Frequency of the Number of SCRs During the Valsalva Maneuver 3 Test, #/minute	QSWEAT Total Forearm Sweat Volume, µL	47	0.762	<0.001	Strong
Number of Non-specific SCRs During the Valsalva Maneuver 1, #	QSWEAT Total Forearm Sweat Volume, µL	47	0.733	<0.001	Strong
Average Maximum Heart Rate During the Deep Breathing Test, bpm	QSWEAT Total Forearm Sweat Volume, µL	47	-0.615	<0.001	Strong
Age, years	QSWEAT Total Forearm Sweat Volume, µL	47	-0.534	<0.001	Moderate
Number of Symptoms at Tilt-down	QSWEAT Total Forearm Sweat Volume, µL	47	-0.538	<0.001	Moderate
VM3 T-score Logged	QSWEAT Total Forearm Sweat Volume, µL	47	0.441	0.002	Moderate
1st 2-minutes in HUTT's SCR with Max SCL Amplitude's T-score Logged	QSWEAT Total Forearm Sweat Volume, µL	47	-0.478	0.001	Moderate
Age, years	Average Heart Rate Difference During the Deep breathing Test, bpm	47	-0.692	<0.001	Strong
DB2 T-score Logged	Average Heart Rate Difference During the Deep breathing Test, bpm	47	0.673	<0.001	Strong
Number of Medications Not Held Before the Autonomic Reflex Screen, #	Average Heart Rate Difference During the Deep breathing Test, bpm	47	0.660	<0.001	Strong
Ratio of the Event Related SCR's Amplitude to Rise Time During the Valsalva Maneuver 3 Test	Average Heart Rate Difference During the Deep breathing Test, bpm	47	0.629	<0.001	Strong
VM3 T-score Logged	Average Heart Rate Difference During the Deep breathing Test, bpm	47	0.616	<0.001	Strong
Body Mass Index, pounds/inches squared	Average Heart Rate Difference During the Deep breathing Test, bpm	47	-0.571	<0.001	Moderate

1st 2-minutes in HUTT's SCR with Max SCL Amplitude's T-score Logged	Average Heart Rate Difference During the Deep breathing Test, bpm	47	-0.474	0.001	Moderate
Average Minimum SCL of the Entire EDA Signal Trace, µS	Average Heart Rate Difference During the Deep breathing Test, bpm	47	0.473	0.001	Moderate
2-minutes in After Tilt-up in HUTT's SCR with Max SCL Amplitude's T-score Logged	Average Heart Rate Difference During the Deep breathing Test, bpm	47	-0.429	0.003	Moderate
Number of Event Related SCRs During the Deep Breathing Test 1	Average Heart Rate Difference During the Deep breathing Test, bpm	47	-0.413	0.004	Moderate
Average Heart Rate Ratio During the Valsalva Maneuver, bpm	Greatest Heart Rate Ratio During the Valsalva Maneuver	47	0.949	<0.001	Very Strong
Adrenergic Component of the Composite Autonomic Severity Score	Greatest Heart Rate Ratio During the Valsalva Maneuver	47	0.898	<0.001	Very Strong
Average Minimum SCL of the Entire EDA Signal Trace, µS	Greatest Heart Rate Ratio During the Valsalva Maneuver	47	-0.786	<0.001	Strong
TU T-score Logged	Greatest Heart Rate Ratio During the Valsalva Maneuver	47	0.704	<0.001	Strong
Number of Non-specific SCRs During the Valsalva Maneuver 2, #	Greatest Heart Rate Ratio During the Valsalva Maneuver	47	0.692	<0.001	Strong
Frequency of the Number of SCRs During the Valsalva M aneuver 2 Test, #/minute	Greatest Heart Rate Ratio During the Valsalva Maneuver	47	0.682	<0.001	Strong
TD T-score Logged	Greatest Heart Rate Ratio During the Valsalva Maneuver	47	0.671	<0.001	Strong
T-score Logged of the SCR with Max SCL's Amplitude's in 30-seconds After Tilt-down	Greatest Heart Rate Ratio During the Valsalva Maneuver	47	0.671	<0.001	Strong
Average Maximum SCL of the Entire EDA Signal Trace, µS	Greatest Heart Rate Ratio During the Valsalva Maneuver	47	0.662	<0.001	Strong
T-score Logged of the SCR with Max SCL's Amplitude's in 30-seconds After Tilt-up	Greatest Heart Rate Ratio During the Valsalva Maneuver	47	0.661	<0.001	Strong
Average Maximum Heart Rate During the Valsalva Maneuver, bpm	Greatest Heart Rate Ratio During the Valsalva Maneuver	47	0.648	<0.001	Strong
1st 2-minutes in HUTT's SCR with Max SCL Amplitude's T-score Logged	Greatest Heart Rate Ratio During the Valsalva Maneuver	47	0.648	<0.001	Strong
2-minutes in After Tilt-up in HUTT's SCR with Max SCL Amplitude's T-score Logged	Greatest Heart Rate Ratio During the Valsalva Maneuver	47	0.617	<0.001	Strong
Total Number of Symptoms in HUTT, #	Greatest Heart Rate Ratio During the Valsalva Maneuver	47	0.594	<0.001	Moderate

Number of Event Related SCRs During the Deep Breathing Test 2	Greatest Heart Rate Ratio During the Valsalva Maneuver	47	-0.594	<0.001	Moderate
Ratio of the Event Related SCR's Amplitude to Rise Time During the Valsalva Maneuver 1 Test	Greatest Heart Rate Ratio During the Valsalva Maneuver	47	0.577	<0.001	Moderate
Number of Symptoms at Tilt-up	Greatest Heart Rate Ratio During the Valsalva Maneuver	47	0.557	<0.001	Moderate
VM1 T-score Logged	Greatest Heart Rate Ratio During the Valsalva Maneuver	47	0.507	<0.001	Moderate
Baseline T-score Logged	Greatest Heart Rate Ratio During the Valsalva Maneuver	47	-0.480	0.001	Moderate
Number of Event Related SCRs During the Deep Breathing Test 1	Greatest Heart Rate Ratio During the Valsalva Maneuver	47	0.466	0.001	Moderate
Ratio of the Event Related SCR's Amplitude to Rise Time During the Valsalva Maneuver 2 Test	Greatest Heart Rate Ratio During the Valsalva Maneuver	47	0.439	0.002	Moderate
VM2 T-score Logged	Greatest Heart Rate Ratio During the Valsalva Maneuver	47	0.436	0.002	Moderate
Total of the Components of the Composite Autonomic Severity Score	Greatest Heart Rate Ratio During the Valsalva Maneuver	47	0.409	0.004	Moderate
Average Heart Rate Ratio During the Valsalva Maneuver, bpm	Average Maximum Heart Rate During the Valsalva Maneuver, bpm	47	0.719	<0.001	Strong
Adrenergic Component of the Composite Autonomic Severity Score	Average Maximum Heart Rate During the Valsalva Maneuver, bpm	47	0.683	<0.001	Strong
Greatest Heart Rate Ratio During the Valsalva Maneuver	Average Maximum Heart Rate During the Valsalva Maneuver, bpm	47	0.648	<0.001	Strong
Number of Event Related SCRs During the Deep Breathing Test 2	Average Maximum Heart Rate During the Valsalva Maneuver, bpm	47	-0.570	<0.001	Moderate
Frequency of the Number of SCRs During the Valsalva Maneuver 2 Test, #/minute	Average Maximum Heart Rate During the Valsalva Maneuver, bpm	47	0.520	<0.001	Moderate
Number of Non-specific SCRs During the Valsalva Maneuver 2, #	Average Maximum Heart Rate During the Valsalva Maneuver, bpm	47	0.516	<0.001	Moderate
Number of Medications Not Held Before the Autonomic Reflex Screen, #	Average Maximum Heart Rate During the Valsalva Maneuver, bpm	47	0.492	<0.001	Moderate
Sudomotor Component of the Composite Autonomic Severity Score	Average Maximum Heart Rate During the Valsalva Maneuver, bpm	47	-0.459	0.001	Moderate
VM1 T-score Logged	Average Maximum Heart Rate During the Valsalva Maneuver, bpm	47	0.426	0.003	Moderate

Number of Symptoms at Tilt-up	Average Maximum Heart Rate During the Valsalva Maneuver, bpm	47	0.415	0.004	Moderate
Ratio of the Event Related SCR's Amplitude to Rise Time During the Valsalva Maneuver 2 Test	Average Maximum Heart Rate During the Valsalva Maneuver, bpm	47	0.408	0.004	Moderate
Body Mass Index, pounds/inches squared	Cardiovagal Component of the Composite Autonomic Severity Score	47	0.926	<0.001	Very Strong
DB2 T-score Logged	Cardiovagal Component of the Composite Autonomic Severity Score	47	-0.682	<0.001	Strong
VM3 T-score Logged	Cardiovagal Component of the Composite Autonomic Severity Score	47	-0.673	<0.001	Strong
Ratio of the Event Related SCR's Amplitude to Rise Time During the Valsalva Maneuver 3 Test	Cardiovagal Component of the Composite Autonomic Severity Score	47	-0.665	<0.001	Strong
Baseline T-score Logged	Cardiovagal Component of the Composite Autonomic Severity Score	47	-0.524	<0.001	Moderate
VM1 T-score Logged	Cardiovagal Component of the Composite Autonomic Severity Score	47	-0.506	<0.001	Moderate
Ratio of the Event Related SCR's Amplitude to Rise Time During the Valsalva Maneuver 2 Test	Cardiovagal Component of the Composite Autonomic Severity Score	47	-0.501	0.001	Moderate
DB1 T-score Logged	Cardiovagal Component of the Composite Autonomic Severity Score	47	-0.461	0.001	Moderate
VM2 T-score Logged	Cardiovagal Component of the Composite Autonomic Severity Score	47	-0.458	0.002	Moderate
Number of Symptoms at Tilt-up	Cardiovagal Component of the Composite Autonomic Severity Score	47	-0.453	0.002	Moderate
Number of Symptoms at Tilt-down	Cardiovagal Component of the Composite Autonomic Severity Score	47	-0.437	0.003	Moderate
Ratio of the Event Related SCR's Amplitude to Rise Time During the Valsalva Maneuver 1 Test	Cardiovagal Component of the Composite Autonomic Severity Score	47	-0.428	0.003	Moderate
Greatest Heart Rate Ratio During the Valsalva Maneuver	Adrenergic Component of the Composite Autonomic Severity Score	47	0.898	<0.001	Very Strong
Average Heart Rate Ratio During the Valsalva Maneuver, bpm	Adrenergic Component of the Composite Autonomic Severity Score	47	0.851	<0.001	Very Strong
TU T-score Logged	Adrenergic Component of the Composite Autonomic Severity Score	47	0.701	<0.001	Strong
Number of Non-specific SCRs During the Valsalva Maneuver 2, #	Adrenergic Component of the Composite Autonomic Severity Score	47	0.687	<0.001	Strong

Average Maximum Heart Rate During the Valsalva Maneuver, bpm	Adrenergic Component of the Composite Autonomic Severity Score	47	0.683	<0.001	Strong
Frequency of the Number of SCRs During the Valsalva Maneuver 2 Test, #/minute	Adrenergic Component of the Composite Autonomic Severity Score	47	0.656	<0.001	Strong
TD T-score Logged	Adrenergic Component of the Composite Autonomic Severity Score	47	0.653	<0.001	Strong
T-score Logged of the SCR with Max SCL's Amplitude's in 30-seconds After Tilt-down	Adrenergic Component of the Composite Autonomic Severity Score	47	0.653	<0.001	Strong
Average Minimum SCL of the Entire EDA Signal Trace, µS	Adrenergic Component of the Composite Autonomic Severity Score	47	-0.650	<0.001	Strong
Average Maximum SCL of the Entire EDA Signal Trace, µS	Adrenergic Component of the Composite Autonomic Severity Score	47	0.638	<0.001	Strong
Ratio of the Event Related SCR's Amplitude to Rise Time During the Valsalva Maneuver 1 Test	Adrenergic Component of the Composite Autonomic Severity Score	47	0.629	<0.001	Strong
Number of Symptoms at Tilt-up	Adrenergic Component of the Composite Autonomic Severity Score	47	0.620	<0.001	Strong
T-score Logged of the SCR with Max SCL's Amplitude's in 30-seconds After Tilt-up	Adrenergic Component of the Composite Autonomic Severity Score	47	0.608	<0.001	Strong
2-minutes in After Tilt-up in HUTT's SCR with Max SCL Amplitude's T-score Logged	Adrenergic Component of the Composite Autonomic Severity Score	47	0.590	<0.001	Moderate
Total Number of Symptoms in HUTT, #	Adrenergic Component of the Composite Autonomic Severity Score	47	0.581	<0.001	Moderate
Ratio of the Event Related SCR's Amplitude to Rise Time During the Valsalva Maneuver 2 Test	Adrenergic Component of the Composite Autonomic Severity Score	47	0.565	<0.001	Moderate
VM1 T-score Logged	Adrenergic Component of the Composite Autonomic Severity Score	47	0.558	<0.001	Moderate
1st 2-minutes in HUTT's SCR with Max SCL Amplitude's T-score Logged	Adrenergic Component of the Composite Autonomic Severity Score	47	0.551	<0.001	Moderate
	Adrenergic Component of the Composite Autonomic Severity Score	47	-0.547	<0.001	Moderate
VM2 T-score Logged	Adrenergic Component of the Composite Autonomic Severity Score	47	0.510	<0.001	Moderate
Number of Event Related SCRs During the Deep Breathing Test 1	Adrenergic Component of the Composite Autonomic Severity Score	47	0.468	0.001	Moderate
QSWEAT Total Forearm Sweat Volume, µL	Sudomotor Component of the Composite Autonomic Severity Score	47	-0.785	<0.001	Strong

Total of the Components of the Composite Autonomic Symptom Score	Sudomotor Component of the Composite Autonomic Severity Score	47	0.684	<0.001	Strong
Age, years	Sudomotor Component of the Composite Autonomic Severity Score	47	0.486	0.001	Moderate
VM3 T-score Logged	Sudomotor Component of the Composite Autonomic Severity Score	47	-0.494	<0.001	Moderate
Number of Non-specific SCRs During the Valsalva Maneuver 1, #	Sudomotor Component of the Composite Autonomic Severity Score	47	-0.468	0.001	Moderate
Average Maximum Heart Rate During the Valsalva Maneuver, bpm	Sudomotor Component of the Composite Autonomic Severity Score	47	-0.459	0.001	Moderate
Ratio of the Event Related SCR's Amplitude to Rise Time During the Valsalva Maneuver 3 Test	Sudomotor Component of the Composite Autonomic Severity Score	47	-0.448	0.002	Moderate
Frequency of the Number of SCRs During the Valsalva Maneuver 3 Test, #/minute	Sudomotor Component of the Composite Autonomic Severity Score	47	-0.424	0.003	Moderate
Number of Symptoms at Tilt-up	Sudomotor Component of the Composite Autonomic Severity Score	47	-0.401	0.005	Moderate
1st 2-minutes in HUTT's SCR with Max SCL Amplitude's T-score Logged	Total of the Components of the Composite Autonomic Severity Score (or CASS)	47	0.693	<0.001	Strong
Sudomotor Component of the Composite Autonomic Severity Score	Total of the Components of the Composite Autonomic Severity Score (or CASS)	47	0.684	<0.001	Strong
Total Number of Symptoms in HUTT, #	Total of the Components of the Composite Autonomic Severity Score (or CASS)	47	0.660	<0.001	Strong
QSWEAT Total Forearm Sweat Volume, µL	Total of the Components of the Composite Autonomic Severity Score (or CASS)	47	-0.653	<0.001	Strong
T-score Logged of the SCR with Max SCL's Amplitude's in 30-seconds After Tilt-up	Total of the Components of the Composite Autonomic Severity Score (or CASS)	47	0.628	<0.001	Strong
Age, years	Total of the Components of the Composite Autonomic Severity Score (or CASS)	47	0.568	<0.001	Moderate
VM3 T-score Logged	Total of the Components of the Composite Autonomic Severity Score (or CASS)	47	-0.567	<0.001	Moderate
Heart Rate Delta	Total of the Components of the Composite Autonomic Severity Score (or CASS)	47	-0.552	<0.001	Moderate
2-minutes in After Tilt-up in HUTT's SCR with Max SCL Amplitude's T-score Logged	Total of the Components of the Composite Autonomic Severity Score (or CASS)	47	0.549	<0.001	Moderate
Ratio of the Event Related SCR's Amplitude to Rise Time During the Valsalva Maneuver 3 Test	Total of the Components of the Composite Autonomic Severity Score (or CASS)	47	-0.514	<0.001	Moderate

Body Mass Index, pounds/inches squared	Total of the Components of the Composite Autonomic Severity Score (or CASS)	47	0.510	<0.001	Moderate
Baseline T-score Logged	Total of the Components of the Composite Autonomic Severity Score (or CASS)	47	-0.496	<0.001	Moderate
DB2 T-score Logged	Total of the Components of the Composite Autonomic Severity Score (or CASS)	47	-0.489	<0.001	Moderate
Maximum Heart Rate in HUTT, bpm	Total of the Components of the Composite Autonomic Severity Score (or CASS)	47	-0.484	<0.001	Moderate
Frequency of the Number of SCRs During the Valsalva M aneuver 3 Test, #/minute	Total of the Components of the Composite Autonomic Severity Score (or CASS)	47	-o.462	0.001	Moderate
Minimum Change of Systolic Blood Pressure from Pre-Tilt Values in HUTT	Total of the Components of the Composite Autonomic Severity Score (or CASS)	47	0.458	0.001	Moderate
Average Heart Rate Ratio During the Valsalva Maneuver, bpm	Total of the Components of the Composite Autonomic Severity Score (or CASS)	47	0.454	0.001	Moderate
Cardiovagal Component of the Composite Autonomic Severity Score	Total of the Components of the Composite Autonomic Severity Score (or CASS)	47	0.449	0.002	Moderate
Number of Non-specific SCRs During the Valsalva Maneuver 1, #	Total of the Components of the Composite Autonomic Severity Score (or CASS)	47	-0.443	0.002	Moderate
Average Maximum Heart Rate During the Deep Breathing Test, bpm	Total of the Components of the Composite Autonomic Severity Score (or CASS)	47	0.431	0.002	Moderate
Minimum Systolic Blood Pressure in HUTT	Total of the Components of the Composite Autonomic Severity Score (or CASS)	47	0.422	0.003	Moderate
Average Minimum SCL of the Entire EDA Signal Trace, µS	Total of the Components of the Composite Autonomic Severity Score (or CASS)	47	-0.410	0.004	Moderate
Greatest Heart Rate Ratio During the Valsalva Maneuver	Total of the Components of the Composite Autonomic Severity Score (or CASS)	47	0.409	0.002	Moderate

Note. Abbreviations: CASS, composite autonomic severity score; HR, heart rate; HRDB, heart rate deep breathing; HUTT, head up tilt-table test; SCL, skin conductance level; SCR, skin conductance response; VM, Valsalva maneuver. Only moderate, strong, and very strong associations of the novel variables (which pertain either to the new HUTT symptoms scoring scale, or the standardized EDA related variables), and established ARS reference variables, have been reported in the table above. Only moderate, strong, and very strong associations, with p-values that are either at,

or less than the chosen statistical significance level of a $p<0.05$, have been reported in Table 47. In some instances where such data are of clinical interest, an association between two reference (or gold standard) variables, have been included, because of their pertinence to this study. One example of such an instance, is the strong correlation between the variables “QSWEAT Total Forearm Volume, µL” and “Sudomotor Component of the Composite Autonomic Severity Score.” These results were generated by use of the Spearman’s Correlations Test. These p-values have not been adjusted for multiple comparisons. As such, the occurrence of Type I Errors may be more likely. Yet, a correction for multiple comparisons, may result in a higher occurrence of Type II Errors.

Table 27

T-score Transformed Raw Amplitudes of the Phasic EDA Signal Trace Derived ER-SCR Identified in the DB, VM and HUTT Segments of the ARS

	Controls				POTS				
	Transient (n=10)	Absent (n=2)	Delayed (n=2)	p-value	Transient (n=3)	Absent (n=4)	Delayed (n=1)	Persistent (n=6)	p-value
T-score of the Amplitude of the ER-SCR in DB1	50.743 ± 10.310; 44.824		43.311 ± 0.000; 43.311	Undeterminable[1]	48.253 ± 5.891; 48.664	44.795 ± 12.418; 38.598	61.518 ± 0.000; 61.518	52.424 ± 9.824; 49.643	0.364
T-score of the Amplitude of the ER-SCR in DB2	50.736 ± 10.874; 47.347		44.344 ± 0.000; 44.344	Undeterminable[1]	43.491 ± 6.987; 39.946	49.323 ± 14.281; 49.323	68.264 ± 0.000; 68.264	50.436 ± 8.194; 49.574	0.259
T-score of the Amplitude of the ER-SCR in VM1	51.664 ± 10.182; 48.360	42.307 ± 0.000; 42.307	41.052 ± 0.000; 41.052	0.167	46.307 ± 9.919; 41.035	43.437 ± 11.304; 37.067	61.257 ± 0.000; 61.257	52.490 ± 10.463; 51.521	0.171
T-score of the Amplitude of the ER-SCR in VM2	52.818 ± 10.506; 49.809	43.982 ± 4.644; 43.982	41.927 ± 1.689; 41.927	0.090	43.154 ± 5.170; 41.808	47.518 ± 7.115; 49.958	53.514 ± 3.554; 53.518	54.893 ± 10.876; 51.738	0.220
T-score of the Amplitude of the ER-SCR in VM3	50.664 ± 10.609; 47.566	45.354 ± 0.000; 45.354		Indeterminable[1]	42.702 ± 1.491; 42.702	39.188 ± 0.000; 39.188	68.671 ± 0.000; 68.671	51.684 ± 6.176; 49.194	0.029
T-score of the Amplitude of the ER-SCR at TU	51.845 ± 10.573; 45.807	48.721 ± 9.112; 45.173	44.015 ± 1.950; 44.015	0.607	53.725 ± 6.707; 51.465	40.341 ± 3.368; 38.978	45.700 ± 0.000; 45.700	55.294 ± 10.719; 51.743	0.018
T-score of the Amplitude of the ER-SCR at TD	50.386 ± 10.945; 46.237		48.069 ± 3.586; 48.069	0.758[1]	48.189 ± 5.610; 46.948	41.775 ± 0.811; 41.457	52.141 ± 0.000; 52.141	56.032 ± 12.097; 60.023	0.127

Note. Abbreviations: ARS, autonomic reflex screen; ER-SCR, event related skin conductance response; HR, heart rate; HRDB, heart rate deep breathing; HUTT, head up tilt-table test; SCL, skin conductance level; SCR, skin conductance response; VM, Valsalva maneuver. Groups were compared using the Kruskal-Wallis Test, except where noted as 1=the Mann-Whitney U Test.

Table 28

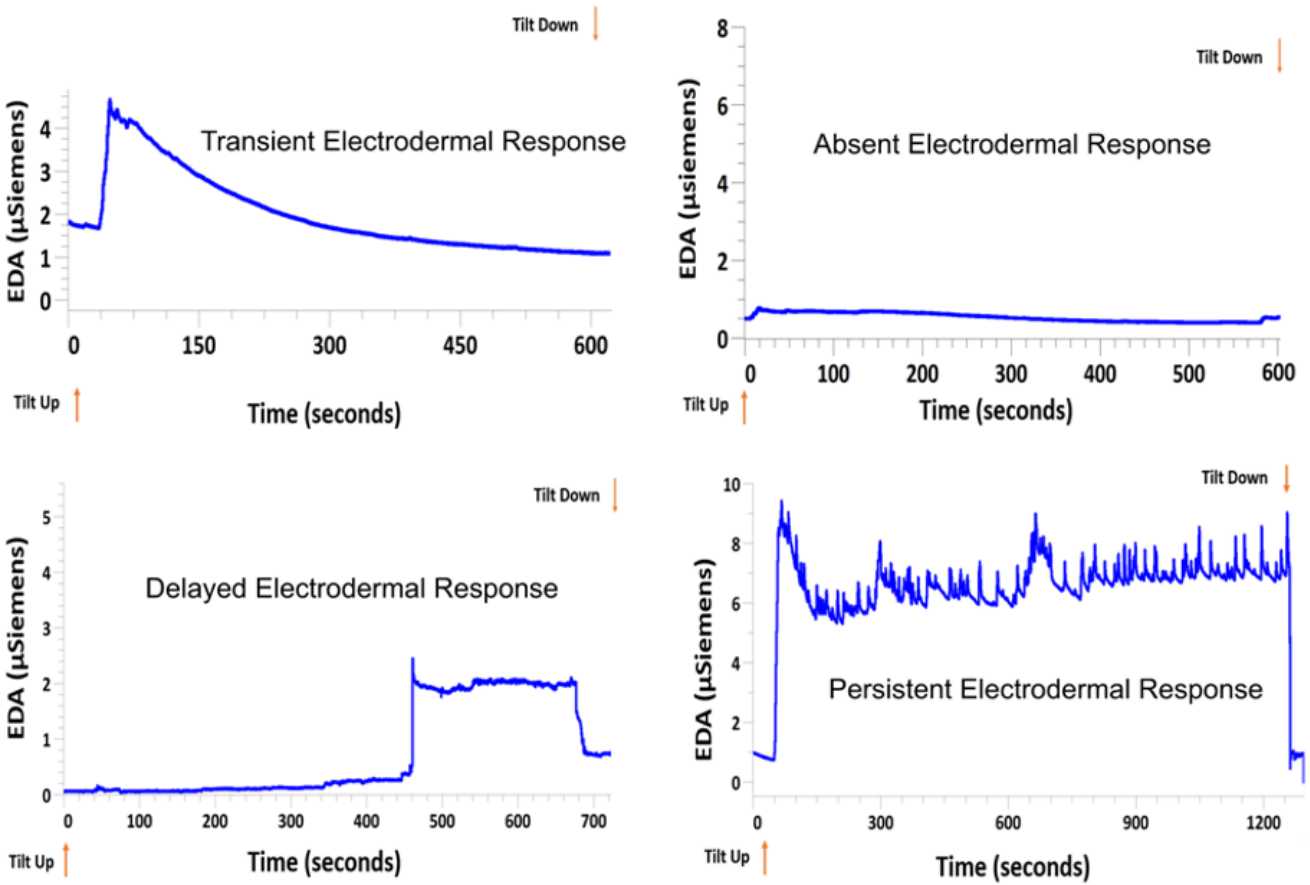
Results of a Logistic Regression of Five Z-score Transformed Raw Phasic EDA Amplitude Variables vs the Group Variable 'POTS or Controls'

Term	Estimate	Standard Error	Statistic	p-value
(Intercept)	0.67369079	0.6000682	1.12269042	0.262
Log-Transformed Z-score of the Raw Amplitude of the SCR with the Maximum SCL During the 2-minutes of Pre-ARS Testing Baseline	0.02989531	0.6063900	0.04930048	0.961
Log-Transformed Z-score of the Raw Amplitude of the SCR with the Maximum SCL During the First 2-minutes of the Sustained Elevation in the SCL After the Tilt-up Stimulus Event	-3.79325304	3.0815440	-1.23095859	0.218
Log-Transformed Z-score of the Raw Amplitude of the SCR with the Maximum SCL During the 2-minutes Focused Area Right After the Tilt-up Stimulus Event	1.97074880	2.0372609	0.96735219	0.333
Log-Transformed Z-score of the Raw Amplitude of the Tilt-up Generated Event Related SCR	2.4488186	2.7346272	0.89550847	0.371
Log-Transformed Z-score of the Raw Amplitude of the Tilt-down Generated Event Related SCR	-0.28780329	1.1883070	-0.24219607	0.809

Note. Abbreviations: ARS, autonomic reflex screen; SCL, skin conductance level; SCR, skin conductance response. Of the 28 study participants, 7 records were excluded by the logistic regression model in the RStudio statistical app, because of missing values. The resulting subset of just 21 complete records, is a likely reason for the lack of significance in the p-values. A larger set of samples (without missing fields) is probably needed. Values are reported as single numbers.

Figure 8

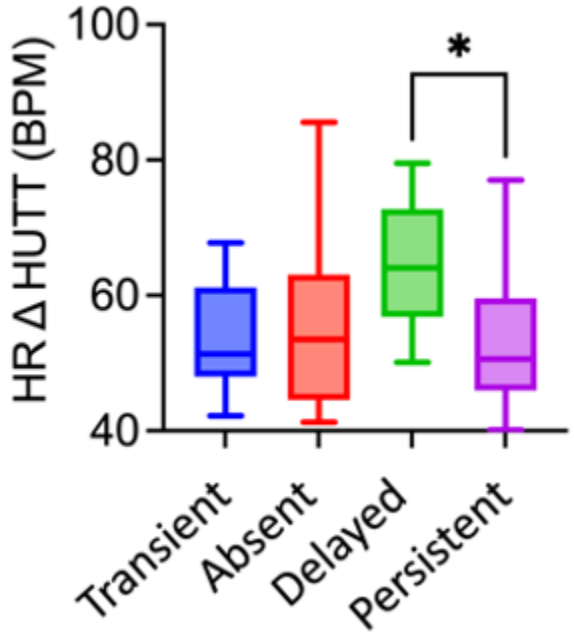
Tonic Patterns of Skin Conductance Levels Observed in HUTT



Note. Abbreviations: ERS, EDA response subtypes; HR, heart rate; HUTT, head-up tilt-table test. Electrodermal response subtypes in postural orthostatic tachycardia syndrome. Representative images of traces of the four main EDA response subtypes recorded during the various HUTTs.

Figure 9

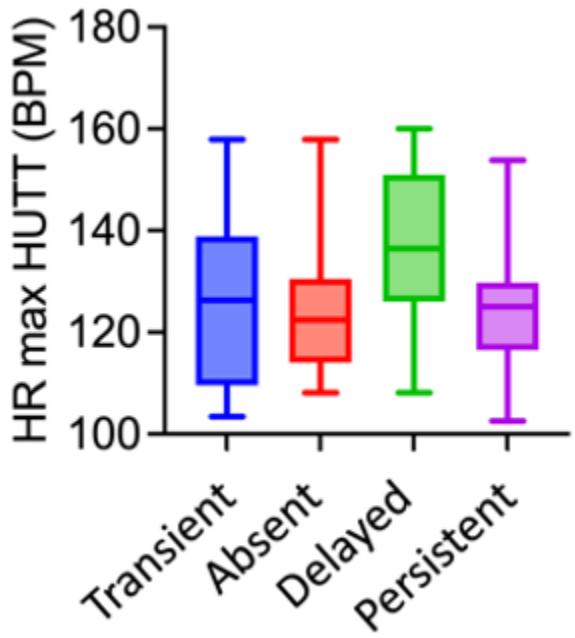
Distribution of HR Delta in HUTT by Electrodermal Response Subtypes



Note. Abbreviations: ERS, EDA response subtypes; HR, heart rate; HUTT, head-up tilt-table test. HR responses to HUTT across various ERSs. Shown above, are the heart rate changes or HR Deltas (HRΔs), which are the differences between the maximum and minimum heart rates observed during HUTTs.

Figure 10

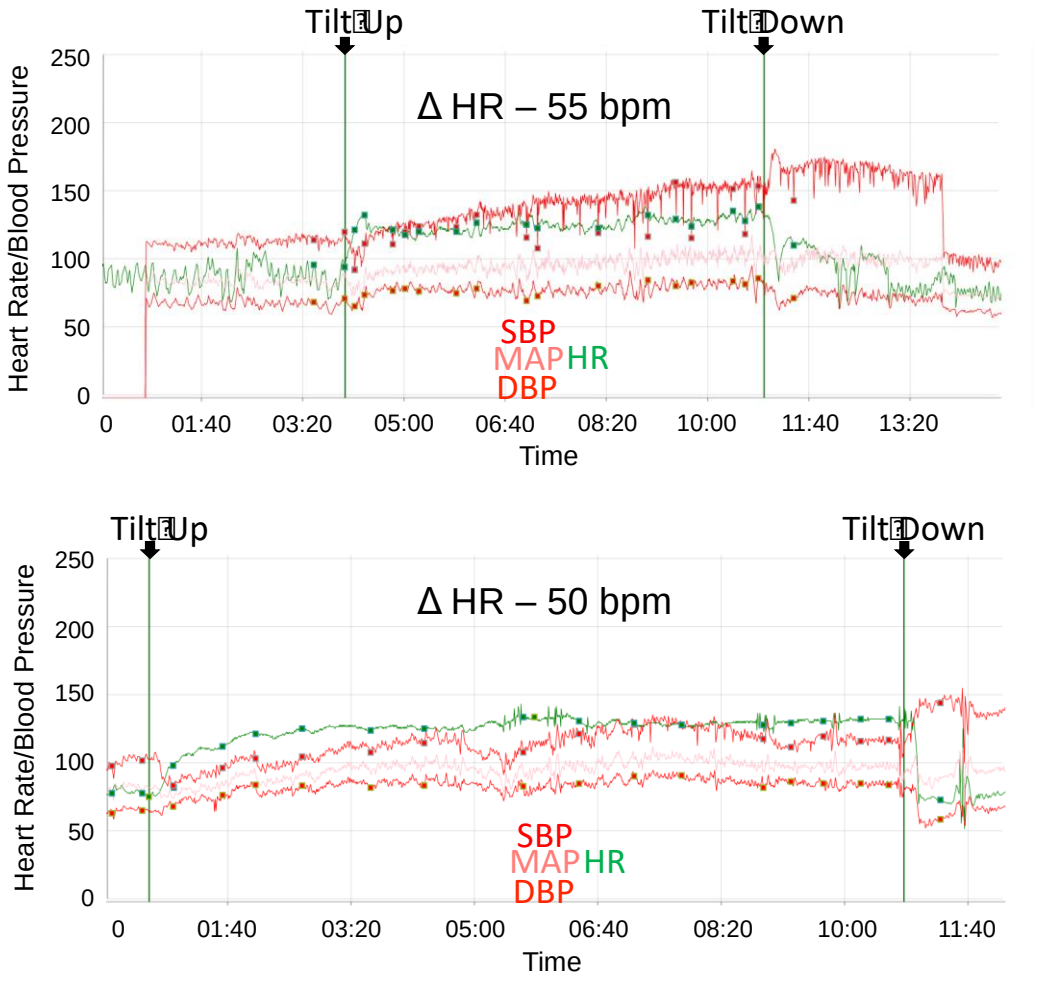
Distribution of the Maximum HR Observed During HUTT by Electrodermal Response Subtypes



Note. Abbreviations: ERS, EDA response subtypes; HR, heart rate; HUTT, head-up tilt-table test. HR responses to HUTT across various ERSs. Shown above, are the maximal heart rates achieved in response to HUTT. Heart rates are in beats per minute (BPM).

Figure 11

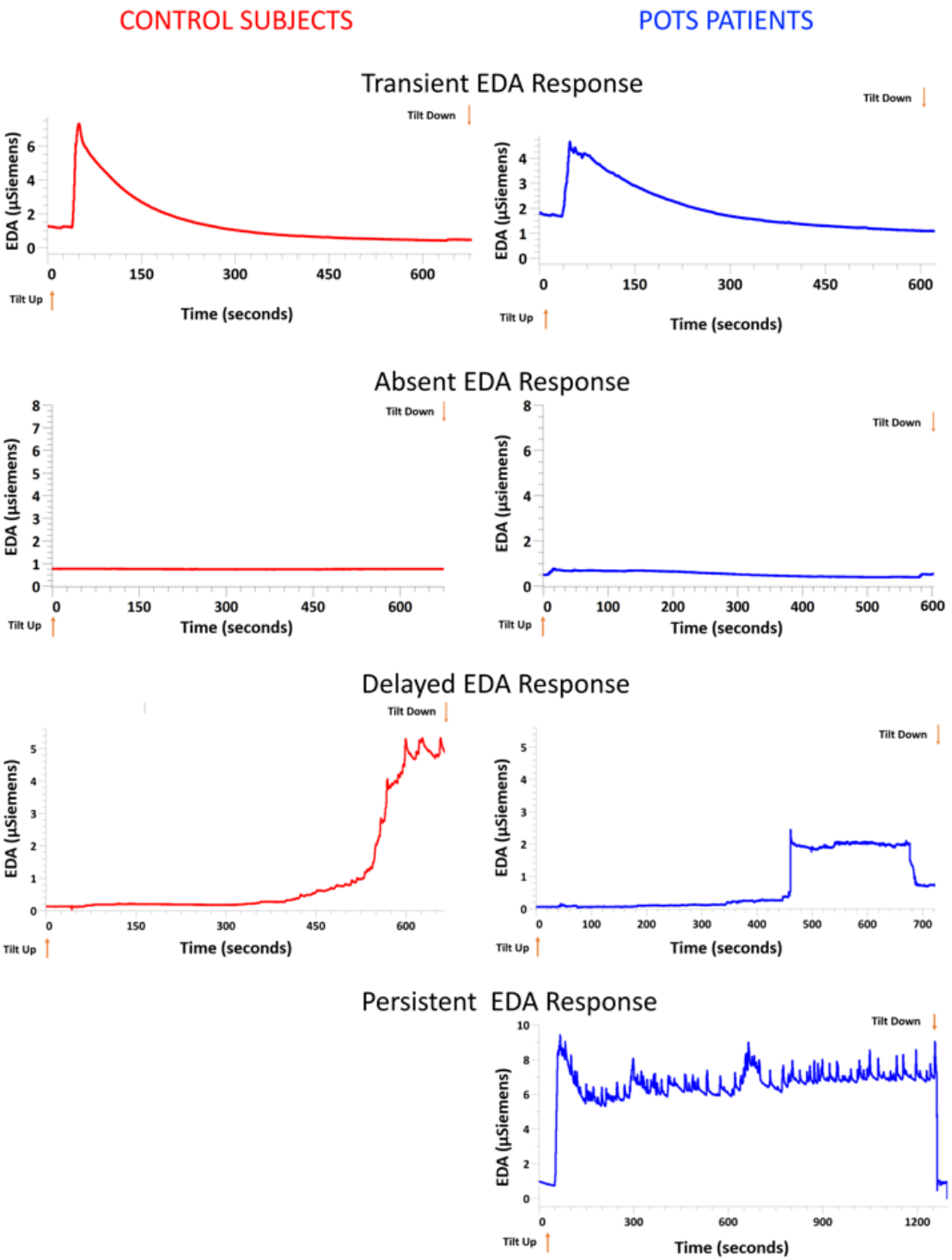
Comparison of Representative Traces of Physiologic Responses During HUTT from Two ARS Patients



Note. Abbreviation: ARS, autonomic reflex screen. Representative traces from two patients diagnosed with postural orthostatic tachycardia. Traces shown include systolic blood pressure (SBP), mean arterial pressure (MAP), diastolic blood pressure (DBP), and Heart rate (HR).

Figure 12

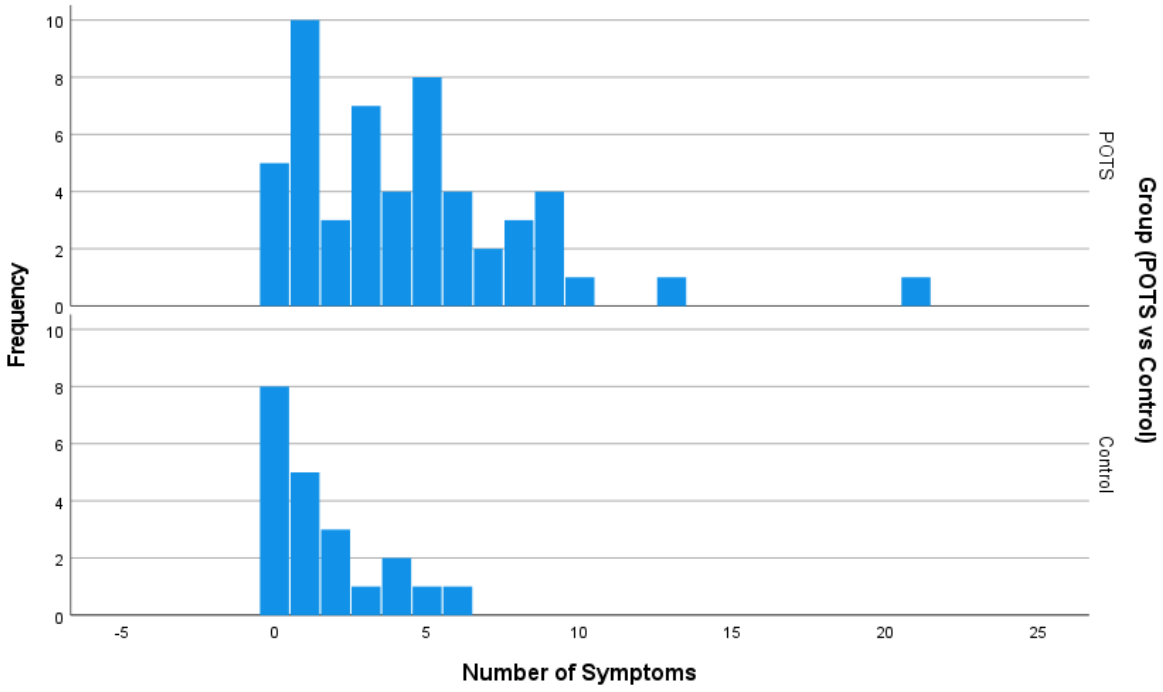
Comparison of Electrodermal Response Subtypes (ERSs) Between POTS Cases and Controls



Note. Comparison of EDA response subtypes (ERSs) between POTS cases and controls. **A**, Images of each of the ERSs in POTS patients. **B**, Images of three of the ERSs in controls. Note that ERS 4 was not observed in any of the controls. Furthermore, the amplitude of the EDA spikes on HUT in each POTS patient with either the ERS1 or ERS 3 tonic EDA pattern, is blunted compared with its matching control. Abbreviations: EDA, electrodermal activity; ERS, EDA response subtype; HUT, head up tilt; POTS, postural orthostatic tachycardia syndrome.

Figure 13

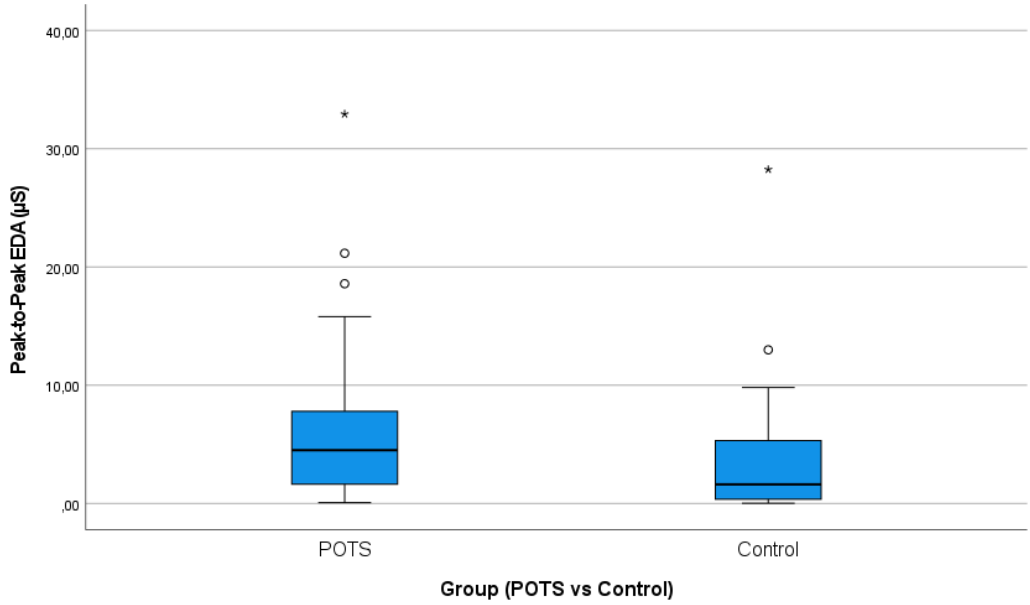
Distribution of symptoms between POTS and controls.

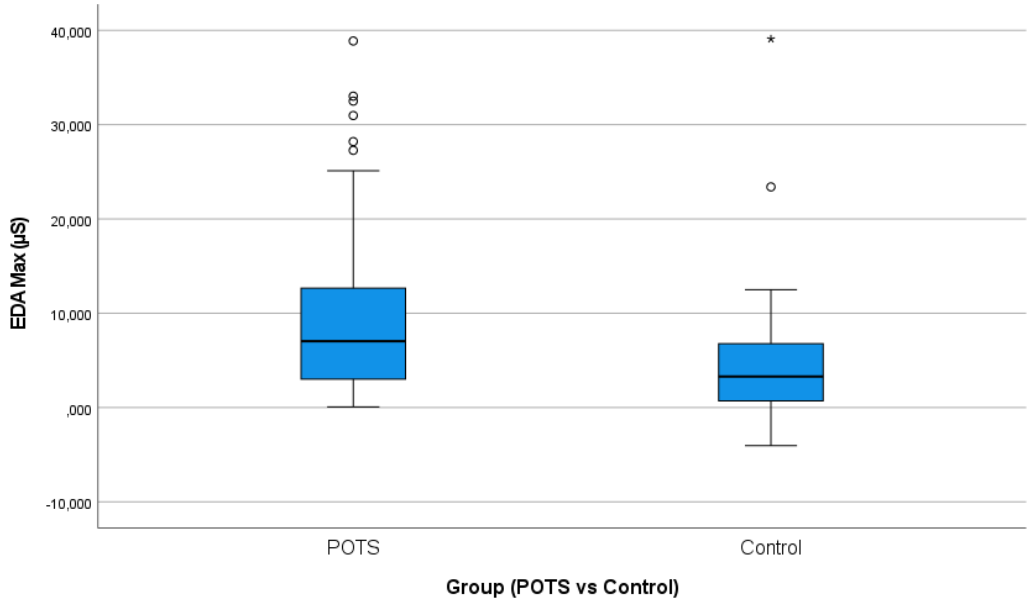


Note. Abbreviation: POTS, postural orthostatic tachycardia syndrome. Frequency distribution plots of the number of symptoms reported by the POTS patients in comparison with the controls, vs. the frequency of the occurrence of each set of numbers of symptoms, during each subject's HUTT Test. Note that the variable frequency is the same thing as the number of subjects.

Figure 14

Comparisons of Peak-to-Peak SCLs and Maximal Tonic EDA Responses in HUTT by Group

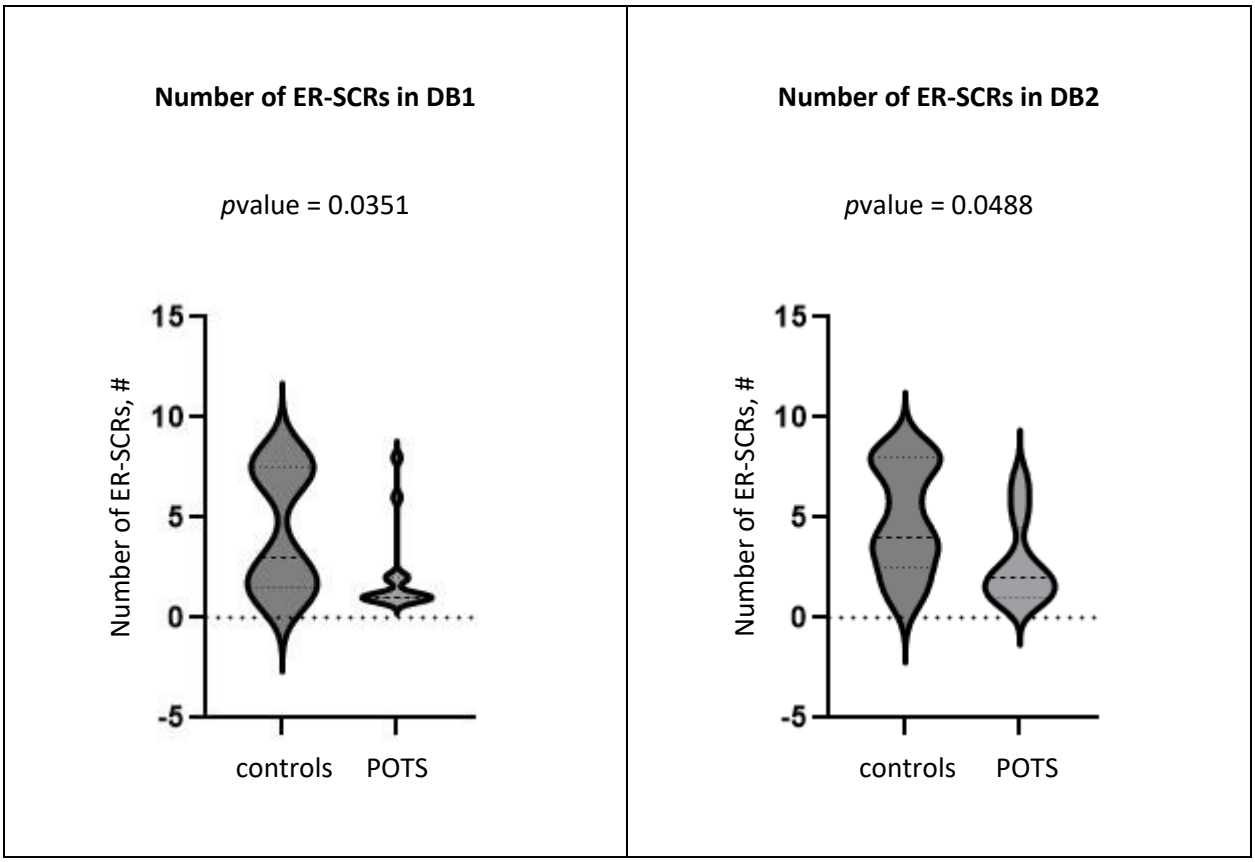




Note. Abbreviations: HUTT, head-up tilt-table test; SCL, skin conductance level. These boxplots compare the tonic EDA difference (or Peak-to-Peak EDA) and maximum SCLs in HUTT between the groups.

Figure 15

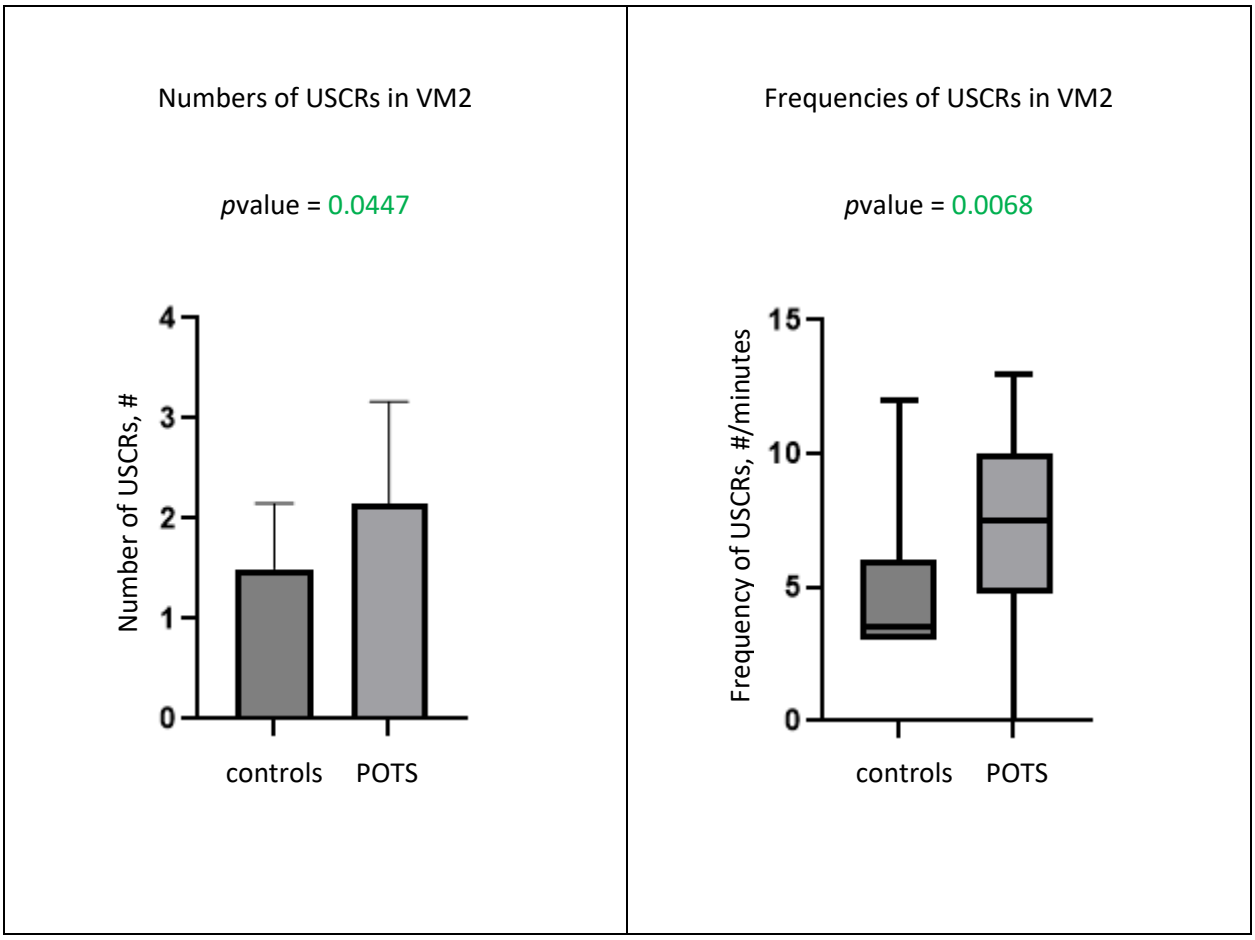
Number of Event Related Skin Conductance Responses Detected During Two Consecutive Deep Breathing Tests: A Contrast Between Controls and POTS Cases



Note. Blunting of the number of event-related SCRs is evident when controls are compared with cases.

Figure 16

Numbers and Frequencies of Unspecified SCRs Measured During Valsalva Maneuver 2 in Controls and POTS



Note. The average number of the unspecified SCRs located during the second Valsalva maneuver is markedly higher in the cases with POTS, than they are in the controls. Similarly, the frequency of the unspecified SCRs occurring during the second Valsalva maneuver was higher than the frequency seen in the controls.

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CHAPTER 6

DISCUSSION: - INTERPRETATIONS, CONCLUSIONS AND FUTURE DIRECTIONS

Chapter 6: Discussion:- Interpretations, Conclusions and Future Directions

Discussion

The main findings of the study are the following : (1) four EDA response patterns (Transient, Absent, Delayed, and Persistent) reflecting different sympathetic responses occur during HUTT; (2) the Persistent response subtype was most common in POTS patients but was not seen in any of the controls. Instead, the Transient response was most common in control patients; (3) POTS patients exhibiting the Persistent subtype had the greatest sympathetic response to upright tilt; (4) patients with the Delayed subtype exhibited the highest increase in heart rate and most frequently experienced the feeling of disorientation; and (5) parasympathetic responses differed between POTS patients and controls, and also by tonic EDA subtype nor between the electrodermal subtypes seen in POTS; (6) nonetheless there was no difference in parasympathetic dysfunction between POTS patients and controls, nor a difference in parasympathetic dysfunction in the tonic electrodermal subtypes seen in the controls; (7) however, parasympathetic dysfunction did differ between the tonic electrodermal subtypes seen in POTS cases; (8) the trend toward a decrease in the number of symptoms and/or the severity of symptoms during the course of upright tilt differed between patients with POTS and controls, as did the trend toward an increase in the number of symptoms and/or the severity of symptoms during HUTT; (9) these trends differed in both POTS cases and controls by electrodermal response subtype; (10) disorientation and shortness of breath differed between the electrodermal subtypes in POTS cases; (11) however, it was only lightheadedness and shortness of breath that differed by electrodermal subtype in the controls; (12) multiple positive and negative correlations with associative strengths that range from weak through moderate to strong and very strong were noted among novel tonic EDA vs gold standard test measures, as well as gold standard vs gold standard test measures in controls and patients with POTS; (13) similarly multiple positive and negative correlations with correlation coefficients that range from weak through moderate to strong and very strong were appraised among the novel phasic EDA test indices vs the gold

standard ARS test parameters, as well as between certain gold standard test parameters and other gold standard test parameters, in controls as well as patients with POTS; (14) sudomotor dysfunction differed between controls and POTS cases, as well as by tonic electrodermal subtype in the patients with POTS; (15) the Absent electrodermal subtype showed high specificity in distinguishing pulse rate in POTS cases in the 20-years or older age range, the Delayed subtype showed high sensitivity in distinguishing heart rate peak-to-peak differences in POTS cases in the 20-years or older age range, as well as in delineation of the maximum heart rate during upright tilt in the patients with POTS that were 20-years-old or older; (16) amplitudes, frequencies and numbers of skin conductance responses, differed between POTS cases and controls, and also by tonic electrodermal response subtypes during deep breathing and Valsalva. These findings confirm the involvement of the sympathetic nervous system in a subset of POTS patients, and indicate an association of both excessive and attenuated sympathetic responses with POTS.

Brief Description of Postural Orthostatic Tachycardia Syndrome

Despite being challenging to manage clinically; little is known about the etiology and subtypes of POTS. The rise in heart rate seen in persons with POTS has implicated sympathetic excess or dysfunction in its etiology. This form of POTS is referred to as hyperadrenergic POTS, and is associated with elevated levels of circulating catecholamines in response to upright tilt. It is usually managed via administration of beta blockers and Ivabradine, medications that counter chronotropic responses. Immune dysfunction is also associated with POTS, particularly, excessive degranulation of mast cells. This leads to an enhanced release of inflammatory mediators e.g., tryptase and histamine, which are vasodilators known to reduce blood pressure and reflexively increase heart rate. POTS has also been related to peripheral autonomic neuropathy. However, the mechanistic underpinnings involved remain poorly understood. Across these reported causes of POTS, diagnosis often requires phlebotomy to measure a circulating biomarker, or speculation about a neuropathic etiology (Aboseif et al., 2023; Gunning et al., 2019; Rodriguez et al., 2020; Moon et al., 2018; Taub et al., 2021; Thanavaro & Thanavaro, 2011; Thijs, et al., 2021).

Although this study focused on sympathetic function measured by electrodermal responses, its findings made it possible to delineate the role of reflex sympathetic responses in POTS. Specifically, the data shows that nearly half of the patients with POTS, exhibited enhanced phasic and tonic electrodermal responses, which is an indication of sympathoexcitation. Importantly, more than half of the POTS patients in the present study did not demonstrate enhanced sympathetic function, highlighting the complex and multifactorial nature of POTS, and suggesting other mechanisms could be at play. These mechanisms may (or may) not involve the parasympathetic nervous system, as certain known measures of parasympathetic function (i.e., certain indices from the HRDB and VM tests) neither differed between control and POTS patients, although such indices did exhibit differences when stratified between the various tonic electrodermal response subtypes in patients with POTS.

When analyses of skin conductance responses (SCRs), which reflect the faster-moving and higher frequency components of the overall EDA complex are considered, notable differences in the amplitudes, frequencies and numbers of the SCRs, were noted between the groups of controls and POTS cases respectively. The discernibility of such contrasts, when viewed through the sharper lens of phasic electrodermal responses (rather than solely through the broader panoramic view of tonic electrodermal responses), by revealing contrasting effects on amplitudes, frequencies and numbers (depending on the specific autonomic test administered), suggests the possibility of some parasympathetic nervous system involvement.

Interpretations

Management of POTS

This study highlights some important points regarding pharmacotherapy for POTS. First, the broad and empiric use of pharmacological agents that blunt sympathetic responses and heart rate, may be counterproductive in subtypes of POTS that are not sympathetically mediated. Furthermore, in the Absent and Delayed electrodermal response subtypes, it is possible that certain chronotropic responses

diagnosed as POTS, are related to impairment of the adrenergic nervous system. In such patients, use of agents that blunt chronotropic responses likely impair any remaining heart rate reserve in such patients, and consequently worsen their symptoms. This may partially explain why some patients with POTS may be intolerant of beta blockers, while others do benefit from beta blocker use. Certain patients with POTS benefit from the use of anticholinergic agents e.g., pyridostigmine. In such individuals, a blunting of their parasympathetic function may tip their sympathovagal balance, in favor of an appreciable enhancement of sympathetic-mediated increases in heart rate during postural change, e.g., during upright tilt.

Electrodermal Measures of Sympathetic Function

Recent literature indicates a growing interest in the use of EDA as an alternative way to appraise sympathovagal responses, because sweating is related to SNS activity (Raj, 2006). Although the previous consensus was that only peripheral stimuli generated eccrine sweat responses via mechanisms involving cholinergic sympathetic activity (Raj, 2006), the current thinking is that EDA may be blunted (or muted) by pharmacological agents with central depressant action (Raj, 2006). Apparently, EDA patterns reflect various sympathetic responses triggered by the stressor of upright tilt. These EDA patterns are signal traces that contain both the slow-changing background tonic component (i.e., skin conductance and its spontaneous variations that result from a subject's state of arousal), as well as the higher-frequency and rapidly-changing phasic component (skin conductance responses).

These components reflect a subject's basal sympathetic state and also captures autonomic responses (Raj & Levine, 2013). In this study, each of the four tonic EDA response subtypes (i.e., the Transient, Absent, Delayed, and Persistent subtypes), correspond to various autonomic reflex responses or lack thereof amongst all patients. The tonic EDA response most common in control patients was the Transient electrodermal subtype, which may reflect the generalized sympathetic response to postural change, as well as the attenuation of that response once hemodynamic homeostasis has been attained and maintained. Additionally, the possibility of an anxiety related response to upright tilt, either because

of the unusual sensation of being tilted up, or the fear of recrudescent symptoms in those patients that have had prior significant events with postural change or unpleasant experiences of orthostatic changes, cannot be ruled out.

In patients exhibiting Absent EDA responses, this finding may be due to the lack of a generalized sympathetic response, which is either due to a neuropathic cause, or one that occurs simply because the patient's hemodynamics were maintained following upright tilt, such that a sympathetic response is not needed. Although patients' medications were held for 5 half-lives, one cannot exclude the possibility of medications blunting this response. This may be in contrast to the Delayed EDA response subtype, which reflects the capability of mounting such a response, yet which is delayed, due to reasons similar to what has been stated previously. The high prevalence of symptoms in this tonic EDA response subtype of the POTS sub-population, suggests that the Delay observed in this EDA subtype is likely pathologic.

Finally, the Persistent EDA response subtype, may be reflective of an excessive and longstanding generalized sympathetic response to upright tilt. That this subtype was the most common (i.e., 42.7%) in patients with POTS, is in keeping with the common assumption that POTS is associated with sympathetic excess. However, in this case, we demonstrate that both the amplitude and duration of the response are increased. It is particularly striking that none of the patients in the control group exhibited this response, which emphasizes the pathologic nature of this finding.

Limitations

Among the limitations of this present study, are its retrospective aspects, despite its having been originally conceived with a prospective observational cohort design (Talari & Goyal, 2020). Also, this present study does not include patient outcomes by EDA response subtype, neither does it include responses to pharmacotherapy. The inclusion of control patients referred for autonomic testing, rather than primarily healthy volunteers recruited from the general population, may introduce some degree of referral bias. However, the extensive nature of the exclusions used to define the sample of controls, is a

significant mitigating factor. It should be noted that as a consequence, the application of such stringent exclusion criteria, limited the number of controls included in the study. Nonetheless, even though the number of POTS cases was greater than the number of controls, when they were matched for age, sex, and BMI with the POTS cases, the results remained essentially unchanged. It is possible though that the sample size of the records included this PhD dissertation study, may not be adequate for finding small or moderate associations.

Limitations of Certain Statistical Results. Storey's method for multiple comparisons, was used for adjustment of p-values from the Spearman's Correlation tests that were run to explore associations between tonic EDA indices and other ARS test indices or measures. The p-value adjustments were done, maintaining a $p<0.05$ false discovery rate. For these p-values, the threshold for statistical significance, was a $p<0.05$. However, the p-values from running correlations tests (i.e., either Pearson's Correlations or Spearman's Correlations), are unadjusted p-values. Failure to correct for multiple comparisons, makes an occurrence of Type I Errors more likely. However, correcting for multiple comparisons, leads to a loss of power to detect actual differences, i.e., making it easier to generate Type II Errors (GraphPad, 2024).

Conclusions and Future Directions

Presented herein, are four novel tonic EDA patterns identified during HUTT in certain patients diagnosed with POTS. These findings may yield new insights into some of the underlying sympathovagal mechanisms of POTS, and serve as potential indicators of responses to postural stress in POTS (Posada-Quintero et al., 2018; Nagai et al., 2019). However, further studies are needed, to validate our findings in independent cohorts, and also to explore the potential diagnostic, mechanistic and prognostic value of EDA in POTS, to increase understanding of the heterogeneous etiology of POTS.

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Appendix A

Supplemental Material A1

This appendix contains the supplemental material related to the first manuscript related (which is currently under review by JAMA Cardiology), as well as the supplemental material pertaining to items within the main body of the dissertation draft, and certain of the other pertinent remaining dissertation project related supplemental material. The remaining supplemental materials that are too large to be included herein, such as large Excel data spreadsheets (e.g., Dataset #1 and Dataset #2), will be made available by publication in the ProQuest archive for electronic theses and dissertations, or elsewhere.

Supplemental Methods

Data Acquisition

Test measures included sweat response, which is another index of SNS activity. EDA was measured by placing two BIOPAC Inc. manufactured electrodes on the palm of patient's right-hand, as they lay supine on a motorized tilt table. These were either connected to an EDA100C Amplifier Module by cables (Dusi et al., 2020), or wirelessly via BIOPAC's BioNomadix Transmitter (BIOPAC Systems Inc., 2023), which communicates EDA data wirelessly to BIOPAC's wireless receiver (the PPGED-R Module) (Srivastav et al., 2022). Data acquired from this equipment were recorded using various versions of Acq*Knowledge*; a software application designed by BIOPAC Systems Inc. Versions of Acq*Knowledge* used, include AcqKnowledge 4.0.0 and AcqKnowledge 5.0.0. Finger-cuff beat-to-beat blood pressure (BP), upper-arm non-invasive BP (NIBP), beat-to-beat electrocardiography (ECG), palmar EDA, and photoplethysmography-based finger pulse volume (FPV), were measured concurrently during each AFT (Dusi et al., 2020). Such measures were taken before application of each stressor and afterwards (Dusi et al., 2020). The stressors were a HRDB test, VM test, HUTT, and QSART. An administration of all four of these AFTs constitutes the full testing protocol of an ARS. However, some of the patients assessed at the UCLA CAC, only underwent a HUTT. Such patients had a 20-minutes-long HUTT, versus full ARS patients,

who underwent a 10-minutes-long HUTT (Low, et al., 2009; Raj & Levine, 2013; Sheldon, et al., 2015; Sletten, et al., 2010). The protocol used for each AFT is outlined in the guide titled “A Fancruft Guide to the Autonomic Reflex Screening” (Hale, 2018). Some of the content in this guide was derived from BIOPAC’s manuals for recording EDA and FPV measures, the pre-procedure patient education instructions for ARS testing outlined in the UCLA CAC’s patient instruction handouts titled “UCLA Autonomic Nervous System (ANS) Testing Instructions 2018” and “Autonomic Lab Medication to Hold”, and manuals from WR Medical Electronics Co. [BIOPAC Systems Inc., 2012; CNSystems, 2012; UCLA CAC, 2018; WR Med., 2018a; WR Med., 2018b; WR Med., 2017; WR Med., 2016; USDHHS, 2020). For key autonomic responses measured, see Supplemental Table 1.

Autonomic Testing

To stimulate autonomic responses, the following stressors were employed during the administration of autonomic reflex screens (ARSs); namely, heart rate deep breathing (HRDB) tests, Valsalva Maneuver (VM) tests, head up tilt (HUT) tests, and quantitative sudomotor axon reflex tests (QSARTs) (Grubb, 2008; Grubb et al., 2006; Kavi et al., 2012; Low et al., 2009; Novak, 2011; Raj et al., 2020; Raj & Levine, 2013; Sheldon et al., 2015; Feigofsky, & Fedorowski, 2020; Freeman et al., 2011; Kanjwal et al., 2011; Taub et al., 2021; Revlock, 2018; Seeley & Lau, 2021; Eftekari et al., 2021; Raj, 2006). These tests were administered by trained operators of autonomic function testing equipment, based upon established testing protocols (Grubb, 2008; Grubb et al., 2006; Kavi et al., 2012; Low et al., 2009; Novak, 2011; Raj et al., 2020; Raj & Levine, 2013; Sheldon et al., 2015; Feigofsky, & Fedorowski, 2020; Freeman et al., 2011; Kanjwal et al., 2011; Taub et al., 2021; Revlock, 2018; Seeley & Lau, 2021; Eftekari et al., 2021; Raj, 2006; Thijs, 2021; Balegh, 2019; Edwards et al., 2004; Arnold, et al., 2018; Sletten, et al., 2010; Illigens & Gibbons, 2009; Dusi et al., 2020; Hale, 2018; UCLA CAC, 2018; WR Med., 2018a; WR Med., 2018b; WR Med., 2017; WR Med., 2016), which were implemented during the administration of such autonomic function tests (AFTs). While a majority of the ARS reports reviewed for

this study, are of patients who underwent the complete ARS battery of gold standard ARS testing (i.e., patients that underwent all of the four reference standard autonomic reflex screening tests, which are the HRDB, VM, HUT and QSART tests) (Grubb, 2008; Grubb et al., 2006; Kavi et al., 2012; Low et al., 2009; Novak, 2011; Raj et al., 2020; Raj & Levine, 2013; Sheldon et al., 2015; Feigofsky, & Fedorowski, 2020; Freeman et al., 2011; Kanjwal et al., 2011; Taub et al., 2021; Revlock, 2018; Seeley & Lau, 2021; Eftekari et al., 2021; Raj, 2006), a minority of the patients that were screened for dysautonomia at the UCLA CAC, only underwent HUT-testing.

Before administration of any of the screening tests, baseline recordings were acquired in the supine position, with the patients lying on a tilt table (Hale, 2018) Thereafter, each test was performed, and finally after the end of each test (inclusive of the immediate period subsequent to tilt-down), valuable post-test data was passively acquired via means of electrophysiologic sensors (Hale, 2018). These post-ARS-test periods also served the dual purpose of assisting in stabilization of a patient's physiologic state, before proceeding to the next AFT (Hale, 2018). Isometric handgrip and/or cognitive stressor tests (such as a mental arithmetic or mathematical task related test, or a Stroop test, etc.) were not included in any of the AFT testing protocols (Ali et al., 2022; Isen et al., 2010; Abi-Samra et al., 1988; Adkinson & Benditt, 2017; Anderson et al., 2012; Benditt et al., 1996; Edwards et al., 2004; Forleo et al., 2013; Freeman et al., 2011; Frey & Wyckliffe, 1988; Fu et al., 2004; Giada et al., 2005; Kenny et al., 1986; Linzer et al., 1988; Massimini et al., 2012; Oribe et al., 1997; Flessas et al., 1976; Surono et al., 2021; Zhao & Tran, 2022; Naliboff et al., 1976; Aydin et al., 2017; Williams et al., 2004). The primary postural challenge employed consisted of either 10 minutes of HUT-testing, or 20 minutes of head up tilt (Hale, 2018). With a one patient who could not tolerate HUT-testing, an alternative arm-raise while sitting upright test was performed, in addition to an administration of the standard head up tilt test (HUTT). No pharmacological stress inducers were utilized in any of the testing sessions (Grubb et al., 2006; Thijs, 2021; Arnold et al., 2018; Sletten et al., 2010; Dusi et al., 2020; Hale, 2018; WR Med., 2016; Ali et al.,

2022; Naliboff et al., 1976; Williams et al., 2004).

Definition of Certain Key Variables

Heart rate delta (HRΔ) is the difference between the maximum and minimum HR during HUT. Heart Rate at minimum tilt systolic BP ($HR_{min\_HUT\_SBP}$) is the HR during the lowest systolic BP during HUT. Pressure recovery time (PRT) is the time in seconds between the nadir of Phase 3 and the end of the Phase 4 Overshoot during a VM. It is a useful indicator of adrenergic function (Vogel et al., 2005). The EDA Difference is the same as the Peak-to-Peak EDA, and is the difference between maximum and minimum EDA during upright tilt. Change in minimum SBP (ΔSBP_{Min}), is the difference between the minimum SBP during the HUT test, and the baseline minimum SBP. A Phase 4 Overshoot is the BP overshoot above the baseline during a VM, and a result of resumption of regular venous return to the heart triggered by the SNS in the second phase of a VM. The BP overshoot results in baroreflex stimulation, bradycardia, and a restoration of baseline BP (Low & Singer, 2023; Elgendi, 2012).

Skin conductance levels (SCLs), refer to levels of the slower-moving component of the EDA trace, and are also known as levels of Tonic EDA. They are different from the Phasic EDA responses, which are event-stimuli driven faster-moving segments of the broader, slower-moving tonic EDA complex (Edwards et al., 2004; Braithwaite, et al., 2015; Boucsein, 2012; Boucsein, et al., 2012; Critchley, 2002; Dawson, et al., 2001; Cheshire, et al., 2021; Benedek & Kaernbach, 2010). Phasic EDA responses are also known as skin conductance responses (or SCRs), and could be classified further as either event-related SCRs, or as non-specific SCRs (Edwards et al., 2004; Braithwaite, et al., 2015; Boucsein, 2012; Boucsein, et al., 2012; Critchley, 2002; Dawson, et al., 2001; Cheshire, et al., 2021; Benedek & Kaernbach, 2010).

Finger pulse volume (FPV), which is also generally referred to as blood volume pulse (BVP), is a photoplethysmography (PPG) based electrophysiologic measure (Elgendi, 2012). Although the utility of PPG in exploratory investigation of POTS was not the focus of this PhD dissertation project, it should be

noted that measures of FPV were recorded concurrently with the EDA measures recorded on each study participant during the course of their ARS appointments at the UCLA CAC. Therefore, a brief description of photoplethysmography is given below.

Photoplethysmography (PPG) is used for estimating the volume of blood flowing through the skin via means of infrared light (Elgendi, 2012). Researchers from a broad spectrum of scientific disciplines have taken a growing interest in PPG usages in both clinical practice and research, because of its benefits as a convenient, inexpensive, and non-invasive diagnostic tool. A photoplethysmogram measures the oxygen saturation, cardiac output, and BP, and therefore it is used to assess autonomic functions (Elgendi, 2012).

Although PPG shows promise as a new method for the early screening of several atherosclerotic pathologies, and may enhance routine patient assessment, a complete comprehension of the diagnostic worth of its various features remains lacking. Recent studies have explored the potential wealth of data embedded in PPG traces, with an eye on future uses beyond pulse oximetry, BP and HR measurements. One such study examined various types of characteristic PPG artifacts and current indexes to evaluate its utility in diagnoses (Elgendi, 2012). Similarly, we have started exploring the potential utility of PPG based measures of FPV, in the diagnosis, mechanism and prognosis of POTS. This exploration remains ongoing, and when it is completed, its findings will be covered in another report.

Supplemental Table 1

Chapter 2: Review of the Literature Related:- Meaning of the Acronyms or Symbols Used in the Associated Tables

Acronyms or Symbols	Meaning
:ti,ab	Article Title, Abstract (a combination of EMBASE acronyms listed under Field Labels)
/exp	Explosion in Emtree (this is the EMBASE equivalent to a MeSH Term in Medline, PubMed or PubMed Central)
AFTs	Autonomic Function Tests
ALL	All Fields (a Web of Science Acronym)
ApEnQT	Approximate Entropy of QT Intervals
ApEnRR	Approximate Entropy of R-R Intervals
ARES	Augmented REality Sandtable
EDA	Electrodermal Activity
EDALFn	Electrodermal Activity Low Frequency normalized (i.e., normalized power within the frequency band from 0.045 to 0.15 Hz)
EDAV	Electrodermal Activity Variability
GIFT	Generalized Intelligent Framework for Tutoring
GSR	Galvanic Skin Response
HA-POTS	Hyper Adrenergic POTS
HCP	Highly Cited Paper
HUT	Head Up Tilt
HUTT	Head Up Tilt Table
HRV	Heart Rate Variability
Mesh	Medical Subject Headings (a PubMed Acronym)
POTS	Postural Orthostatic Tachycardia Syndrome
Pt	Patient
PTE	Prior to Export (i.e., such papers were excluded prior to export out of the database)
Pts	Patients
SSR	Sympathetic Skin Response
TS	Topic Search (a Web of Science Acronym)
TX	Title and Abstract (a CINAHL Acronym)
QSART	Quantitative Sudomotor Axon Reflex Test
QTvi	Beat-to-beat QT Variability Index

Supplemental Table 2

Concepts Identified and Search Strings Used in Review of the Literature: Databases Searched Include CINAHL, EMBASE, PubMed, and Web of Science

PubMed	CINAHL	EMBASE	Web of Science
Concept 1: **Diagnosis** *Headings:* Diagnosis[Title/Abstract] *Keywords & phrases:* Diagnos*[Title/Abstract] OR Diagnosis[Title/Abstract] OR "Diagnostic Tests"[Title/Abstract] OR "Diagnostic Utility"[Title/Abstract] OR "Clinical Laboratory Techniques"[Mesh] OR "Diagnosis"[Mesh] OR "Diagnostic Equipment"[Mesh] OR "Diagnostic Screening Programs"[Mesh] OR "Diagnostic Techniques and Procedures"[Mesh] OR "Diagnostic Techniques, Cardiovascular"[Mesh] OR "Diagnostic Techniques, Neurological"[Mesh] OR "Diagnostic Tests, Routine"[Mesh]	**Concept 1:** **Diagnosis** *Headings:* TX(Diagnosis) *Keywords & phrases:* TX("Clinical Laboratory Techniques") OR TX(Diagnos*) OR TX(Diagnosis) OR TX("Diagnostic Tests") OR TX("Diagnostic Utility") OR TX("Diagnostic Equipment") OR TX("Diagnostic Screening Programs") OR TX("Diagnostic Techniques and Procedures") OR TX("Cardiovascular Diagnostic Techniques") OR TX("Neurological Diagnostic Techniques") OR (MH "Diagnosis, Laboratory+") OR (MH "Diagnostic Tests, Routine") OR (MH "Diagnosis, Cardiovascular+") AND (MH "Electrophysiology Laboratories") OR (MH "Diagnosis, Neurologic+") AND (MH "Electrodiagnosis+") AND (MH "Monitoring, Physiologic+")	**Concept 1:** **Diagnosis** *Headings:* Diagnosis:ti,ab *Keywords & phrases:* Diagnos*:ti,ab OR Diagnosis:ti,ab OR 'Diagnostic Screening Programs':ti,ab OR 'Diagnostic Tests':ti,ab OR 'Diagnostic Utility':ti,ab OR 'Cardiovascular System Examination'/exp OR 'Diagnosis'/exp OR 'Diagnostic Equipment'/exp OR 'Diagnostic Procedure'/exp OR 'laboratory technique'/exp OR 'Neurological Examination'/exp OR 'Diagnostic Tests'/exp	**Concept 1:** **Diagnosis** *Headings:* TS=(Diagnosis) *Keywords & phrases:* ((((((((((TS=(Diagnos*)) OR TS=(Diagnosis)) OR TS=(Diagnostic Tests)) OR TS=(Diagnostic Utility)) OR ALL=(Clinical Laboratory Techniques)) OR ALL=(Diagnosis)) OR ALL=(Diagnostic Equipment)) OR ALL=(Diagnostic Screening Programs)) OR ALL=(Diagnostic Techniques and Procedures)) OR ALL=(Cardiovascular Diagnostic Techniques)) OR ALL=(Neurological Diagnostic Techniques)) OR ALL=(Routine Diagnostic Tests)

Concept 2: **Electrodermal Activity**	**Concept 2:** **Electrodermal Activity**	**Concept 2:** **Electrodermal Activity**	**Concept 2:** **Electrodermal Activity**
Headings: "Electrodermal Activity"[Title/Abstract]	*Headings:* TX("Electrodermal Activity")	*Headings:* 'Electrodermal Activity':ti,ab	*Headings:* TS=(Electrodermal Activity)
Keywords & phrases: EDA[Title/Abstract] OR "EDA Biofeedback"[Title/Abstract] OR "EDA Level"[Title/Abstract] OR "EDA Measurements"[Title/Abstract] OR "Electrochemical Skin Conductance"[Title/Abstract] OR "Electrodermal Activity"[Title/Abstract] OR "Electrodermal Activity Measurements"[Title/Abstract] OR "Electrodermal Measurement"[Title/Abstract] OR "Electrodermal Measurements"[Title/Abstract] OR "Electrodermal Response"[Title/Abstract] OR "Electrodermal Responses"[Title/Abstract] OR "Galvanic Skin Response"[Title/Abstract] OR "GSR"[Title/Abstract] OR "Non Specific Skin Conductance Responses"[Title/Abstract] OR "Phasic EDA"[Title/Abstract] OR "Psychogalvanic Reflex"[Title/Abstract] OR "Skin Admittance"[Title/Abstract] OR "Skin	*Keywords & phrases:* TX(EDA) OR TX("EDA Biofeedback") OR TX("EDA Level") OR TX("EDA Measurements") OR TX("Electrochemical Skin Conductance") OR TX("Electrodermal Activity") OR TX("Electrodermal Activity Measurements") OR TX("Electrodermal Measurement") OR TX("Electrodermal Measurements") OR TX("Electrodermal Response") OR TX("Galvanic Skin Response") OR TX("GSR") OR TX("Non Specific Skin Conductance Responses") OR TX("Phasic EDA") OR TX("Psychogalvanic Reflex") OR TX("Skin Admittance") OR TX("Skin Conductance") OR TX("Skin Conductance Level") OR TX("Skin Conductance Measurements") OR TX("Skin Conductance Responses") OR TX("Skin Electric Conductance") OR TX("Skin Impedance") OR TX("Skin Potential") OR TX("Skin Potential Response") OR TX("Skin Resistance Level") OR TX("Skin Resistance Response") OR TX("Skin Response") OR TX("Skin Susceptance") OR TX("Skin Susceptance Response") OR TX("Specific Skin Conductance Responses") OR TX("Sympathetic Skin Responses") OR TX("Tonic EDA") OR ((MH "Skin+/PP/PH") AND (MH "Electric Impedance/ES/MT/PH/UT/TD/TU/PF") AND (MH "Reflex+/ES/EV/MT/PH/PF/TD/UT") AND (MH "Electrochemical Techniques+/ES/EV/MT/NU/PF/TD/UT"))	*Keywords & phrases:* EDA:ti,ab OR 'EDA Biofeedback':ti,ab OR 'EDA Level':ti,ab OR 'EDA Measurements':ti,ab 'Electrochemical Skin Conductance':ti,ab OR 'Electrodermal Activity':ti,ab OR 'Electrodermal Activity Measurements':ti,ab OR 'Electrodermal Measurement':ti,ab OR 'Electrodermal Measurements':ti,ab OR 'Electrodermal Response':ti,ab OR 'Electrodermal Responses':ti,ab OR 'Galvanic Skin Response':ti,ab OR GSR:ti,ab OR 'Non Specific Skin Conductance Responses':ti,ab OR 'Phasic EDA':ti,ab OR 'Psychogalvanic Reflex':ti,ab OR 'Skin Admittance':ti,ab OR 'Skin Conductance':ti,ab OR	*Keywords & phrases:* ((((((((((((((((((((((((((((((TS=(EDA)) OR TS=(EDA Biofeedback)) OR TS=(EDA Level)) OR TS=(EDA Measurements)) OR TS=(Electrochemical Skin Conductance)) OR TS=(Electrodermal Activity)) OR TS=(Electrodermal Activity Measurements)) OR TS=(Electrodermal Measurement)) OR TS=(Electrodermal Measurements)) OR TS=(Electrodermal Response)) OR TS=(Electrodermal Responses)) OR TS=(Galvanic Skin Response)) OR TS=(GSR)) OR TS=(Non Specific Skin Conductance Responses)) OR TS=(Phasic EDA)) OR TS=(Psychogalvanic Reflex)) OR TS=(Skin Admittance)) OR TS=(Skin Conductance)) OR TS=(Skin Electric Conductance)) OR TS=(Skin Conductance Level)) OR TS=(Skin Conductance Measurements)) OR TS=(Skin Conductance Responses)) OR TS=(Skin Impedance)) OR TS=(Skin Potential)) OR TS=(Skin Potential Response)) OR TS=(Skin Resistance Level)) OR TS=(Skin Resistance Response)) OR TS=(Skin Response))

Conductance"[Title/Abstract] OR "Skin Electric Conductance"[Title/Abstract] OR "Skin Conductance Level"[Title/Abstract] OR "Skin Conductance Measurements"[Title/Abstract] OR "Skin Conductance Responses"[Title/Abstract] OR "Skin Impedance"[Title/Abstract] OR "Skin Potential"[Title/Abstract] OR "Skin Potential Response"[Title/Abstract] OR "Skin Resistance Level"[Title/Abstract] OR "Skin Resistance Response"[Title/Abstract] OR "Skin Response"[Title/Abstract] OR "Skin Susceptance"[Title/Abstract] OR "Skin Susceptance Response"[Title/Abstract] OR "Specific Skin Conductance Responses"[Title/Abstract] OR "Sympathetic Skin Responses"[Title/Abstract] OR "Tonic EDA"[Title/Abstract] OR "Galvanic Skin Response"[Mesh]		'Skin Electric Conductance':ti,ab OR 'Skin Conductance Level':ti,ab OR 'Skin Conductance Measurements':ti,ab OR 'Skin Conductance Responses':ti,ab OR 'Skin Impedance':ti,ab OR 'Skin Potential':ti,ab OR 'Skin Potential Response':ti,ab OR 'Skin Resistance Level':ti,ab OR 'Skin Resistance Response':ti,ab OR 'Skin Response':ti,ab OR 'Skin Susceptance':ti,ab OR 'Skin Susceptance Response':ti,ab OR 'Specific Skin Conductance Responses':ti,ab OR 'Sympathetic Skin Responses':ti,ab OR 'Tonic EDA':ti,ab OR 'Electrodermal Response'/exp	OR TS=(Skin Susceptance)) OR TS=(Skin Susceptance Response)) OR TS=(Specific Skin Conductance Responses)) OR TS=(Sympathetic Skin Responses)) OR TS=(Tonic EDA)) OR ALL=(Electrodermal Response)
Concept 3: Mechanisms *Headings:* Mechanisms[Title/Abstract] *Keywords & phrases:*	**Concept 3: Mechanisms** *Headings:* TX(Mechanisms) *Keywords & phrases:*	**Concept 3: Mechanisms** *Headings:* Mechanisms:ti,ab *Keywords & phrases:*	**Concept 3: Mechanisms** *Headings:* TS=(Mechanisms) *Keywords & phrases:*

Mechanisms[Title/Abstract] OR "Cardiac Electrophysiology"[Mesh]	TX(Mechanisms) OR TX("Cardiac Electrophysiology") OR ((MH "Cardiovascular System+/PP/PH") AND (MH "Electrophysiology/ES/EV/MT/PH/PF/UT/TD"))	Mechanisms:ti,ab OR 'Heart Electrophysiology'/exp	(TS=(Mechanisms)) OR ALL=(Cardiac Electrophysiology)
Concept 4: Postural Orthostatic Tachycardia Syndrome *Headings:* Postural Orthostatic Tachycardia Syndrome [Title/Abstract] *Keywords & phrases:* "Hyperadrenergic POTS"[Title/Abstract] OR "Orthostatic Tachycardia"[Title/Abstract] OR POTS[Title/Abstract] OR "Postural Orthostatic Tachycardia Syndrome"[Title/Abstract] OR "Postural Tachycardia"[Title/Abstract] OR "Postural Orthostatic Tachycardia Syndrome"[Mesh]	**Concept 4: Postural Orthostatic Tachycardia Syndrome** *Headings:* TX(Postural Orthostatic Tachycardia Syndrome) *Keywords & phrases:* TX("Hyperadrenergic POTS") OR TX("Orthostatic Tachycardia") OR TX(POTS) OR TX("Postural Orthostatic Tachycardia Syndrome") OR TX("Postural Tachycardia") OR (MH "Postural Orthostatic Tachycardia Syndrome")	**Concept 4: Postural Orthostatic Tachycardia Syndrome** *Headings:* Postural Orthostatic Tachycardia Syndrome:ti,ab *Keywords & phrases:* 'Hyperadrenergic POTS':ti,ab OR 'Orthostatic Tachycardia':ti,ab OR POTS:ti,ab OR 'Postural Orthostatic Tachycardia Syndrome':ti,ab OR 'Postural Tachycardia':ti,ab OR 'Postural Orthostatic Tachycardia Syndrome'/exp	**Concept 4: Postural Orthostatic Tachycardia Syndrome** *Headings:* TS=(Postural Orthostatic Tachycardia Syndrome) *Keywords & phrases:* (((((TS=(Hyperadrenergic POTS)) OR TS=(Orthostatic Tachycardia)) OR TS=(POTS)) OR TS=(Postural Orthostatic Tachycardia Syndrome)) OR TS=(Postural Tachycardia)) OR ALL=(Postural Orthostatic Tachycardia Syndrome)
Concept 5: Prognosis *Headings:* Prognos*[Title/Abstract] *Keywords & phrases:*	**Concept 5: Prognosis** *Headings:* TX(Prognos*) *Keywords & phrases:*	**Concept 5: Prognosis** *Headings:* Prognos*:ti,ab *Keywords & phrases:*	**Concept 5: Prognosis** *Headings:* TS=(Prognosis) *Keywords & phrases:*

Prognos*[Title/Abstract] OR “Prognostic Utility”[Title/Abstract] OR "Prognosis"[Mesh]	TX(Prognos*) OR TX(“Prognostic Utility”) OR (MH "Prognosis+")	Prognos*:ti,ab OR ‘Prognostic Utility’:ti,ab OR ‘Prognosis’/exp	((TS=(Prognos*)) OR TS=(Prognostic Utility)) OR ALL=(Prognosis)
Concept 6: Utility *Headings:* Utilit*[Title/Abstract] *Keywords & phrases:* Utilit*[Title/Abstract] OR "Evaluation Study" [Publication Type]	**Concept 6: Utility** *Headings:* TX(Utilit*) *Keywords & phrases:* TX(Utilit*) OR PT("Evaluation Study")	**Concept 6: Utility** *Headings:* Utilit*:ti,ab *Keywords & phrases:* Utilit*:ti,ab OR ‘Evaluation Study’:it	**Concept 6: Utility** *Headings:* TS=(Utilit*) *Keywords & phrases:* TS=(Utilit*)

Supplemental Table 3

Results of Initial CINAHL Searches

Search Number	Query	Results	Remarks
#1	**Diagnosis** TX("Clinical Laboratory Techniques") OR TX(Diagnos*) OR TX(Diagnosis) OR TX("Diagnostic Tests") OR TX("Diagnostic Utility") OR TX("Diagnostic Equipment") OR TX("Diagnostic Screening Programs") OR TX("Diagnostic Techniques and Procedures") OR TX("Cardiovascular Diagnostic Techniques") OR TX("Neurological Diagnostic Techniques") OR (MH "Diagnosis, Laboratory+") OR (MH "Diagnostic Tests, Routine") OR (MH "Diagnosis, Cardiovascular+") AND (MH "Electrophysiology Laboratories") OR (MH "Diagnosis, Neurologic+") AND (MH "Electrodiagnosis+") AND (MH "Monitoring, Physiologic+")	1,948,267	These Results Were Used to Generate More Focused and Narrower Searches Which Yielded More Precise Results (See Combined Searches)
#2	**Electrodermal Activity** TX(EDA) OR TX("EDA Biofeedback") OR TX("EDA Level") OR TX("EDA Measurements") OR TX("Electrochemical Skin Conductance") OR TX("Electrodermal Activity") OR TX("Electrodermal Activity Measurements") OR TX("Electrodermal Measurement") OR TX("Electrodermal Measurements") OR TX("Electrodermal Response") OR TX("Galvanic Skin Response") OR TX("GSR") OR TX("Non Specific Skin Conductance Responses") OR TX("Phasic EDA") OR TX("Psychogalvanic Reflex") OR TX("Skin Admittance") OR TX("Skin Conductance") OR TX("Skin Conductance Level") OR TX("Skin Conductance Measurements") OR TX("Skin Conductance Responses") OR TX("Skin Electric Conductance") OR TX("Skin Impedance") OR TX("Skin Potential") OR TX("Skin Potential Response") OR TX("Skin Resistance Level") OR TX("Skin Resistance Response") OR TX("Skin Response") OR TX("Skin Susceptance") OR TX("Skin Susceptance Response") OR TX("Specific Skin Conductance Responses") OR TX("Sympathetic Skin Responses") OR TX("Tonic EDA") OR ((MH "Skin+/PP/PH") AND (MH "Electric Impedance/ES/MT/PH/UT/TD/TU/PF") AND (MH "Reflex+/ES/EV/MT/PH/PF/TD/UT") AND (MH "Electrochemical Techniques+/ES/EV/MT/NU/PF/TD/UT"))	6,960	Same as Above
#3	**Mechanisms** TX(Mechanisms) OR TX("Cardiac Electrophysiology") OR ((MH "Cardiovascular System+/PP/PH") AND (MH "Electrophysiology/ES/EV/MT/PH/PF/UT/TD"))	496,433	Same as Above
#4	**POTS** TX("Hyperadrenergic POTS") OR TX("Orthostatic Tachycardia") OR TX(POTS) OR TX("Postural	13,307	Same as Above

	Orthostatic Tachycardia Syndrome") OR TX("Postural Tachycardia") OR (MH "Postural Orthostatic Tachycardia Syndrome")		
#5	**Prognosis** TX(Prognos*) OR TX(“Prognostic Utility”) OR (MH "Prognosis+")	738,089	Same as Above
#6	**Utility** TX(Utilit*) OR PT("Evaluation Study")	140,183	Same as Above
#7	**Combination of Baseline Searches 1: Utility of EDA in Diagnosis of POTS** #6 AND #2 AND #1 AND #4	29	Potential Evidence of Paucity of EDA-POTS Studies
#8	**Combination of Baseline Searches 2: Utility of EDA in Diagnosis** #6 AND #2 AND #1	424	These Results Were Selected for Screening
#9	**Combination of Baseline Searches 3: EDA and Diagnosis** #2 AND #1	3,198	Prescreened Only for Classic, Classical or Seminal Status
#10	**Combination of Baseline Searches 4: Utility of EDA in Prognosis of POTS** #6 AND #2 AND #5 AND #4	20	Potential Evidence of Paucity of EDA-POTS Studies
#11	**Combination of Baseline Searches 5: Utility of EDA in Prognosis** #6 AND #2 AND #5	182	These Results Were Selected for Screening
#12	**Combination of Baseline Searches 5: EDA and Prognosis** #2 AND #5	967	Prescreened Only for Classic, Classical or Seminal Status
#13	**Combination of Baseline Searches 6: Utility of EDA in Mechanistic Study of POTS** #6 AND #2 AND #3 AND #4	25	Potential Evidence of Paucity of EDA-POTS Studies
#14	**Combination of Baseline Searches 7: Utility of EDA in Mechanistic Studies** #6 AND #2 AND #3	340	These Results Were Selected for Screening
#15	**Combination of Baseline Searches 8: EDA and Mechanistic Studies** #2 AND #3	2,165	Prescreened Only for Classic, Classical or Seminal Status
#16	**Combination of Baseline Searches 9: Utility of EDA in Exploration of POTS** #6 AND #2 AND #4	31	Potential Evidence of Paucity of EDA-POTS Studies
#17	**Combination of Baseline Searches 10: EDA and POTS** #2 AND #4	69	These Results Were Selected for Screening

#18	**Combination of Baseline Searches: Diagnosis of POTS** #1 AND #4	4,413	Prescreened Only for Classic, Classical or Seminal Status
Total Number of Search Results		3,355,102	

Note. Initial CINAHL searches yielded 3,355,102 results. Yet only 11,863 items from combinations of the six baseline search strings, were eligible for pre-screening based on their relevance to the six concepts of utility, electrodermal activity, mechanisms, postural orthostatic tachycardia syndrome and prognosis.

Supplemental Table 4

Results of Subsequent Sets of CINAHL Searches

Search Number	Query	Peer-Reviewed Articles Published Within the Past Five Years	Classical and-or Historical Articles	Articles Selected for Screening Before Removal of Duplicates
#7	**Hybrid Search 1** #6 AND #2 AND #1 AND #4	7		7
#8	**Hybrid Search 2** #6 AND #2 AND #1	127		127
#9	**Hybrid Search 3** #2 AND #1	981		981
#10	**Hybrid Search 4** #6 AND #2 AND #5 AND #4	3		3
#11	**Hybrid Search 5** #6 AND #2 AND #5	44		44
#12	**Hybrid Search 6** #2 AND #5	340		340
#13	**Hybrid Search 7** #6 AND #2 AND #3 AND #4	6		6
#14	**Hybrid Search 8** #6 AND #2 AND #3	94		94
#15	**Hybrid Search 9** #2 AND #3	610		610
#16	**Hybrid Search 10** #6 AND #2 AND #4	8		8
#17	**Hybrid Search 11** #2 AND #4	15		15
#18	**Hybrid Search 12** #1 AND #4	1,024		1,024
Totals		3,259		3,259

Supplemental Table 5

Results of Initial EMBASE Searches

Search Number	Query	Results	Remarks
#1	**Diagnosis** Diagnos*:ti,ab OR Diagnosis:ti,ab OR 'Diagnostic Screening Programs':ti,ab OR 'Diagnostic Tests':ti,ab OR 'Diagnostic Utility':ti,ab OR 'Cardiovascular System Examination'/exp OR 'Diagnosis'/exp OR 'Diagnostic Equipment'/exp OR 'Diagnostic Procedure'/exp OR 'laboratory technique'/exp OR 'Neurological Examination'/exp OR 'Diagnostic Tests'/exp	22,280,071	These Results Were Used to Generate More Focused and Narrower Searches Which Yielded More Precise Results (See Combined Searches)
#2	**Electrodermal Activity** EDA:ti,ab OR 'EDA Biofeedback':ti,ab OR 'EDA Level':ti,ab OR 'EDA Measurements':ti,ab 'Electrochemical Skin Conductance':ti,ab OR 'Electrodermal Activity':ti,ab OR 'Electrodermal Activity Measurements':ti,ab OR 'Electrodermal Measurement':ti,ab OR 'Electrodermal Measurements':ti,ab OR 'Electrodermal Response':ti,ab OR 'Electrodermal Responses':ti,ab OR 'Galvanic Skin Response':ti,ab OR GSR:ti,ab OR 'Non Specific Skin Conductance Responses':ti,ab OR 'Phasic EDA':ti,ab OR 'Psychogalvanic Reflex':ti,ab OR 'Skin Admittance':ti,ab OR 'Skin Conductance':ti,ab OR 'Skin Electric Conductance':ti,ab OR 'Skin Conductance Level':ti,ab OR 'Skin Conductance Measurements':ti,ab OR 'Skin Conductance Responses':ti,ab OR 'Skin Impedance':ti,ab OR 'Skin Potential':ti,ab OR 'Skin Potential Response':ti,ab OR 'Skin Resistance Level':ti,ab OR 'Skin Resistance Response':ti,ab OR 'Skin Response':ti,ab OR 'Skin Susceptance':ti,ab OR 'Skin Susceptance Response':ti,ab OR 'Specific Skin Conductance Responses':ti,ab OR 'Sympathetic Skin Responses':ti,ab OR 'Tonic EDA':ti,ab OR 'Electrodermal Response'/exp	17,980	Same as Above
#3	**Mechanisms** Mechanisms:ti,ab OR 'Heart Electrophysiology'/exp	2,108,708	Same as Above
#4	**POTS** 'Hyperadrenergic POTS':ti,ab OR 'Orthostatic Tachycardia':ti,ab OR POTS:ti,ab OR 'Postural Orthostatic Tachycardia Syndrome':ti,ab OR 'Postural Tachycardia':ti,ab OR 'Postural Orthostatic Tachycardia Syndrome'/exp	6,924	Same as Above
#5	**Prognosis** Prognos*:ti,ab OR 'Prognostic Utility':ti,ab OR 'Prognosis'/exp	1,418,507	Same as Above
#6	**Utility**	358,814	Same as Above

	Utilit*:ti,ab		
#7	**Combination of Baseline Searches 1: Utility of EDA in Diagnosis of POTS** #6 AND #2 AND #1 AND #4	0	Potential Evidence of a Paucity of EDA-POTS Studies
#8	**Combination of Baseline Searches 2: Utility of EDA in Diagnosis** #6 AND #2 AND #1	165	These Results Were Selected for Screening
#9	**Combination of Baseline Searches 3: EDA and Diagnosis** #2 AND #1	9,700	Prescreened Only for Classic, Classical, Historical, Pertinent, or Seminal Status
#10	**Combination of Baseline Searches 4: Utility of EDA in Prognosis of POTS** #6 AND #2 AND #5 AND #4	0	Potential Evidence of a Paucity of EDA-POTS Studies
#11	**Combination of Baseline Searches 5: Utility of EDA in Prognosis** #6 AND #2 AND #5	5	These Results Were Selected for Screening
#12	**Combination of Baseline Searches 5: EDA and Prognosis** #2 AND #5	202	Prescreened Only for Classic, Classical, Historical, Pertinent, or Seminal Status
#13	**Combination of Baseline Searches 6: Utility of EDA in Mechanistic Study of POTS** #6 AND #2 AND #3 AND #4	0	Potential Evidence of a Paucity of EDA-POTS Studies
#14	**Combination of Baseline Searches 7: Utility of EDA in Mechanistic Studies** #6 AND #2 AND #3	21	These Results Were Selected for Screening
#15	**Combination of Baseline Searches 8: EDA and Mechanistic Studies** #2 AND #3	1,738	Prescreened Only for Classic, Classical, Historical, Pertinent, or Seminal Status
#16	**Combination of Baseline Searches 9: Utility of EDA in Exploration of POTS** #6 AND #2 AND #4	0	Potential Evidence of a Paucity of EDA-POTS Studies
#17	**Combination of Baseline Searches 10: EDA and POTS** #2 AND #4	18	These Results Were Selected for Screening
#18	**Combination of Baseline Searches: Diagnosis of POTS** #1 AND #4	3,730	Prescreened Only for Classic, Classical, Historical, Pertinent, or Seminal Status

Total Number of Search Results		26,206,583	

Note. Initial EMBASE searches yielded 26,206,583 results. Yet only 15,574 items from combinations of the six baseline search strings, were eligible for pre-screening based on their relevance to the six concepts of utility, electrodermal activity, mechanisms, postural orthostatic tachycardia syndrome and prognosis.

Supplemental Table 6

Results of Subsequent Sets of EMBASE Searches

Search Number	Query	Peer-Reviewed Articles Published Within the Past Five Years	Classic, Classical, Historical, Pertinent, or Seminal Articles	Articles Selected for Screening Before Removal of Duplicates
#7	**Hybrid Search 1** #6 AND #2 AND #1 AND #4	0	0	0
#8	**Hybrid Search 2** #6 AND #2 AND #1	66	0	66
#9	**Hybrid Search 3** #2 AND #1	2,657	173	2,830
#10	**Hybrid Search 4** #6 AND #2 AND #5 AND #4	0	0	0
#11	**Hybrid Search 5** #6 AND #2 AND #5	1	4	5
#12	**Hybrid Search 6** #2 AND #5	64	8	72
#13	**Hybrid Search 7** #6 AND #2 AND #3 AND #4	0	0	0
#14	**Hybrid Search 8** #6 AND #2 AND #3	11	9	20
#15	**Hybrid Search 9** #2 AND #3	603	29	632
#16	**Hybrid Search 10** #6 AND #2 AND #4	0	0	0
#17	**Hybrid Search 11** #2 AND #4	3	14	17
#18	**Hybrid Search 12** #1 AND #4	1,603	7	1610
Totals		5,008	244	5,252

Supplemental Table 7

Results of the First Set of PubMed Searches

Search Number	Query	Results	Remarks
#1	**Diagnosis** Diagnos*[Title/Abstract] OR Diagnosis[Title/Abstract] OR "Diagnostic Tests"[Title/Abstract] OR "Diagnostic Utility"[Title/Abstract] OR "Clinical Laboratory Techniques"[Mesh] OR "Diagnosis"[Mesh] OR "Diagnostic Equipment"[Mesh] OR "Diagnostic Screening Programs"[Mesh] OR "Diagnostic Techniques and Procedures"[Mesh] OR "Diagnostic Techniques, Cardiovascular"[Mesh] OR "Diagnostic Techniques, Neurological"[Mesh] OR "Diagnostic Tests, Routine"[Mesh]	10,819,217	These Results Were Used to Generate More Focused and Narrower Searches Which Yielded More Precise Results (See Combined Searches)
#2	**Electrodermal Activity** EDA[Title/Abstract] OR "EDA Biofeedback"[Title/Abstract] OR "EDA Level"[Title/Abstract] OR "EDA Measurements"[Title/Abstract] OR "Electrochemical Skin Conductance"[Title/Abstract] OR "Electrodermal Activity"[Title/Abstract] OR "Electrodermal Activity Measurements"[Title/Abstract] OR "Electrodermal Measurement"[Title/Abstract] OR "Electrodermal Measurements"[Title/Abstract] OR "Electrodermal Response"[Title/Abstract] OR "Electrodermal Responses"[Title/Abstract] OR "Galvanic Skin Response"[Title/Abstract] OR "GSR"[Title/Abstract] OR "Non Specific Skin Conductance Responses"[Title/Abstract] OR "Phasic EDA"[Title/Abstract] OR "Psychogalvanic Reflex"[Title/Abstract] OR "Skin Admittance"[Title/Abstract] OR "Skin Conductance"[Title/Abstract] OR "Skin Electric Conductance"[Title/Abstract] OR "Skin Conductance Level"[Title/Abstract] OR "Skin Conductance Measurements"[Title/Abstract] OR "Skin Conductance Responses"[Title/Abstract] OR "Skin Impedance"[Title/Abstract] OR "Skin Potential"[Title/Abstract] OR "Skin Potential Response"[Title/Abstract] OR "Skin Resistance Level"[Title/Abstract] OR "Skin Resistance Response"[Title/Abstract] OR "Skin Response"[Title/Abstract] OR "Skin Susceptance"[Title/Abstract] OR "Skin Susceptance Response"[Title/Abstract] OR "Specific Skin Conductance Responses"[Title/Abstract] OR "Sympathetic Skin Responses"[Title/Abstract] OR "Tonic EDA"[Title/Abstract] OR "Galvanic Skin Response"[Mesh]	18,792	Same as Above
#3	**Mechanisms** Mechanisms[Title/Abstract] OR "Cardiac Electrophysiology"[Mesh]	1,481,300	Same as Above
#4	**Postural Orthostatic Tachycardia Syndrome**	5,524	Same as Above

	"Hyperadrenergic POTS"[Title/Abstract] OR "Orthostatic Tachycardia"[Title/Abstract] OR POTS[Title/Abstract] OR "Postural Orthostatic Tachycardia Syndrome"[Title/Abstract] OR "Postural Tachycardia"[Title/Abstract] OR "Postural Orthostatic Tachycardia Syndrome"[Mesh]		
#5	**Prognosis** Prognos*[Title/Abstract] OR "Prognostic Utility"[Title/Abstract] OR "Prognosis"[Mesh]	2,283,765	Same as Above
#6	**Utility** Utilit*[Title/Abstract] OR "Evaluation Study" [Publication Type]	512,120	Same as Above
#7	**Combination of Baseline Searches 1: Utility of EDA in Diagnosis of POTS** #6 AND #2 AND #1 AND #4	0	Potential Evidence of a Paucity of EDA-POTS Studies
#8	**Combination of Baseline Searches 2: Utility of EDA in Diagnosis** #6 AND #2 AND #1	190	These Results Were Selected for Screening
#9	**Combination of Baseline Searches 3: EDA and Diagnosis** #2 AND #1	8,639	Prescreened Only for Classic, Classical, Historical, Pertinent, or Seminal Status
#10	**Combination of Baseline Searches 4: Utility of EDA in Prognosis of POTS** #6 AND #2 AND #5 AND #4	0	Potential Evidence of a Paucity of EDA-POTS Studies
#11	**Combination of Baseline Searches 5: Utility of EDA in Prognosis** #6 AND #2 AND #5	18	These Results Were Selected for Screening
#12	**Combination of Baseline Searches 5: EDA and Prognosis** #2 AND #5	536	Prescreened Only for Classic, Classical, Historical, Pertinent, or Seminal Status
#13	**Combination of Baseline Searches 6: Utility of EDA in Mechanistic Study of POTS** #6 AND #2 AND #3 AND #4	0	Potential Evidence of a Paucity of EDA-POTS Studies
#14	**Combination of Baseline Searches 7: Utility of EDA in Mechanistic Studies** #6 AND #2 AND #3	13	These Results Were Selected for Screening
#15	**Combination of Baseline Searches 8: EDA and Mechanistic Studies** #2 AND #3	1,221	Prescreened Only for Classic, Classical, Historical, Pertinent, or Seminal Status
#16	**Combination of Baseline Searches 9: Utility of EDA in Exploration of POTS** #6 AND #2 AND #4	0	Potential Evidence of a Paucity of EDA-POTS Studies

#17	**Combination of Baseline Searches 10: EDA and POTS** #2 AND #4	5	These Results Were Selected for Screening
#18	**Combination of Baseline Searches: Diagnosis of POTS** #1 AND #4	1,234	Prescreened Only for Classic, Classical, Historical, Pertinent, or Seminal Status
Total Number of Search Results		15,132,574	

Note. Initial PubMed searches yielded 15,132,574 results. Yet only 11,856 items from combinations of the six baseline search strings, were eligible for pre-screening based on their relevance to the main study concepts of utility, electrodermal activity, mechanisms, postural orthostatic tachycardia syndrome and prognosis.

Supplemental Table 8

Results of Subsequent Sets of PubMed Searches

Search Number	Query	Peer-Reviewed Articles Published Within the Past Five Years	Classic, Classical, Historical, Pertinent, or Seminal Articles	Articles Selected for Screening Before Removal of Duplicates
#7	**Hybrid Search 1** #6 AND #2 AND #1 AND #4	0	0	0
#8	**Hybrid Search 2** #6 AND #2 AND #1	52	0	52
#9	**Hybrid Search 3** #2 AND #1	1,459 1,489 Exported (Not Clear Why)	16	1,475
#10	**Hybrid Search 4** #6 AND #2 AND #5 AND #4	0	0	0
#11	**Hybrid Search 5** #6 AND #2 AND #5	5	0	5
#12	**Hybrid Search 6** #2 AND #5	147	2	149
#13	**Hybrid Search 7** #6 AND #2 AND #3 AND #4	0	0	0
#14	**Hybrid Search 8** #6 AND #2 AND #3	4	0	4
#15	**Hybrid Search 9** #2 AND #3	423	2	425
#16	**Hybrid Search 10** #6 AND #2 AND #4	0	0	0
#17	**Hybrid Search 11** #2 AND #4	0	0	0
#18	**Hybrid Search 12** #1 AND #4	429	4	433
Totals		2,519	24	2,543

Note: Even though just 1,459 citations were returned by Hybrid Search 3 (or #9), 1,489 items were exported by the PubMed citation exporter for an unclear reason.

Supplemental Table 9

Results of Initial Web of Science Searches

Search Number	Query	Results	Remarks
#1	**Diagnosis** ((((((((((TS=(Diagnos*)) OR TS=(Diagnosis)) OR TS=(Diagnostic Tests)) OR TS=(Diagnostic Utility)) OR ALL=(Clinical Laboratory Techniques)) OR ALL=(Diagnosis)) OR ALL=(Diagnostic Equipment)) OR ALL=(Diagnostic Screening Programs)) OR ALL=(Diagnostic Techniques and Procedures)) OR ALL=(Cardiovascular Diagnostic Techniques)) OR ALL=(Neurological Diagnostic Techniques)) OR ALL=(Routine Diagnostic Tests)	3,395,189	These Results Were Used to Generate More Focused and Narrower Searches Which Yielded More Precise Results (See Combined Searches)
#2	**Electrodermal Activity** ((((((((((((((((((((((((((((((TS=(EDA)) OR TS=(EDA Biofeedback)) OR TS=(EDA Level)) OR TS=(EDA Measurements)) OR TS=(Electrochemical Skin Conductance)) OR TS=(Electrodermal Activity)) OR TS=(Electrodermal Activity Measurements)) OR TS=(Electrodermal Measurement)) OR TS=(Electrodermal Measurements)) OR TS=(Electrodermal Response)) OR TS=(Electrodermal Responses)) OR TS=(Galvanic Skin Response)) OR TS=(GSR)) OR TS=(Non Specific Skin Conductance Responses)) OR TS=(Phasic EDA)) OR TS=(Psychogalvanic Reflex)) OR TS=(Skin Admittance)) OR TS=(Skin Conductance)) OR TS=(Skin Electric Conductance)) OR TS=(Skin Conductance Level)) OR TS=(Skin Conductance Measurements)) OR TS=(Skin Conductance Responses)) OR TS=(Skin Impedance)) OR TS=(Skin Potential)) OR TS=(Skin Potential Response)) OR TS=(Skin Resistance Level)) OR TS=(Skin Resistance Response)) OR TS=(Skin Response)) OR TS=(Skin Susceptance)) OR TS=(Skin Susceptance Response)) OR TS=(Specific Skin Conductance Responses)) OR TS=(Sympathetic Skin Responses)) OR TS=(Tonic EDA)) OR ALL=(Electrodermal Response)	203,060	Same as Above
#3	**Mechanisms** (TS=(Mechanisms)) OR ALL=(Cardiac Electrophysiology)	4,948,003	Same as Above
#4	**Postural Orthostatic Tachycardia Syndrome** (((((TS=(Hyperadrenergic POTS)) OR TS=(Orthostatic Tachycardia)) OR TS=(POTS)) OR TS=(Postural Orthostatic Tachycardia Syndrome)) OR TS=(Postural Tachycardia)) OR ALL=(Postural Orthostatic Tachycardia Syndrome)	169,428	Same as Above
#5	**Prognosis** ((TS=(Prognos*)) OR TS=(Prognostic Utility)) OR ALL=(Prognosis)	906,814	Same as Above

#6	**Utility** TS=(Utilit*)	508,753	Same as Above
#7	**Combination of Baseline Searches 1: Utility of EDA in Diagnosis of POTS** #6 AND #2 AND #1 AND #4	3	Potential Evidence of a Paucity of EDA-POTS Studies
#8	**Combination of Baseline Searches 2: Utility of EDA in Diagnosis** #6 AND #2 AND #1	547	These Results Were Selected for Screening
#9	**Combination of Baseline Searches 3: EDA and Diagnosis** #2 AND #1	21,208	Prescreened Only for Classic, Classical, Historical, Pertinent, or Seminal Status
#10	**Combination of Baseline Searches 4: Utility of EDA in Prognosis of POTS** #6 AND #2 AND #5 AND #4	1	Potential Evidence of a Paucity of EDA-POTS Studies
#11	**Combination of Baseline Searches 5: Utility of EDA in Prognosis** #6 AND #2 AND #5	104	These Results Were Selected for Screening
#12	**Combination of Baseline Searches 5: EDA and Prognosis** #2 AND #5	4,322	Prescreened Only for Classic, Classical, Historical, Pertinent, or Seminal Status
#13	**Combination of Baseline Searches 6: Utility of EDA in Mechanistic Study of POTS** #6 AND #2 AND #3 AND #4	1	Potential Evidence of a Paucity of EDA-POTS Studies
#14	**Combination of Baseline Searches 7: Utility of EDA in Mechanistic Studies** #6 AND #2 AND #3	256	These Results Were Selected for Screening
#15	**Combination of Baseline Searches 8: EDA and Mechanistic Studies** #2 AND #3	32,653	Prescreened Only for Classic, Classical, Historical, Pertinent, or Seminal Status
#16	**Combination of Baseline Searches 9: Utility of EDA in Exploration of POTS** #6 AND #2 AND #4	5	Potential Evidence of a Paucity of EDA-POTS Studies
#17	**Combination of Baseline Searches 10: EDA and POTS** #2 AND #4	323	These Results Were Selected for Screening
#18	**Combination of Baseline Searches: Diagnosis of POTS** #1 AND #4	2,542	Prescreened Only for Classic, Classical,

			Historical, Pertinent, or Seminal Status
Total Number of Search Results		10,190,924	

Note. Initial Web of Science searches yielded 10,183,715 results. Yet only 61,965 items from combinations of the six baseline search strings, were eligible for pre-screening based on their relevance to the six concepts of utility, electrodermal activity, mechanisms, postural orthostatic tachycardia syndrome and prognosis.

Supplemental Table 10

Concepts Identified and Search Strings Used in Review of the Literature: Two Translations of Concept 2 from the PubMed Database to the Web of Science Database

PubMed	Web of Science Translation 1	Web of Science Translation 2
Concept 2: **Electrodermal Activity** *Headings:* "Electrodermal Activity"[Title/Abstract] *Keywords & phrases:* EDA[Title/Abstract] OR "EDA Biofeedback"[Title/Abstract] OR "EDA Level"[Title/Abstract] OR "EDA Measurements"[Title/Abstract] OR "Electrochemical Skin Conductance"[Title/Abstract] OR "Electrodermal Activity"[Title/Abstract] OR "Electrodermal Activity Measurements"[Title/Abstract] OR "Electrodermal Measurement"[Title/Abstract] OR "Electrodermal Measurements"[Title/Abstract] OR "Electrodermal Response"[Title/Abstract] OR "Electrodermal Responses"[Title/Abstract] OR "Galvanic Skin Response"[Title/Abstract] OR "GSR"[Title/Abstract] OR "Non Specific Skin Conductance Responses"[Title/Abstract] OR "Phasic EDA"[Title/Abstract] OR "Psychogalvanic Reflex"[Title/Abstract] OR "Skin Admittance"[Title/Abstract] OR "Skin Conductance"[Title/Abstract] OR "Skin Electric Conductance"[Title/Abstract] OR "Skin Conductance Level"[Title/Abstract] OR "Skin Conductance Measurements"[Title/Abstract] OR "Skin Conductance Responses"[Title/Abstract] OR "Skin	**Concept 2:** **Electrodermal Activity** *Headings:* TS=(Electrodermal Activity) *Keywords & phrases:* ((((((((((((((((((((((((((((((TS=(EDA)) OR TS=(EDA Biofeedback)) OR TS=(EDA Level)) OR TS=(EDA Measurements)) OR TS=(Electrochemical Skin Conductance)) OR TS=(Electrodermal Activity)) OR TS=(Electrodermal Activity Measurements)) OR TS=(Electrodermal Measurement)) OR TS=(Electrodermal Measurements)) OR TS=(Electrodermal Response)) OR TS=(Electrodermal Responses)) OR TS=(Galvanic Skin Response)) OR TS=(GSR)) OR TS=(Non Specific Skin Conductance Responses)) OR TS=(Phasic EDA)) OR TS=(Psychogalvanic Reflex)) OR TS=(Skin Admittance)) OR TS=(Skin Conductance)) OR TS=(Skin Electric Conductance)) OR TS=(Skin Conductance Level)) OR TS=(Skin Conductance Measurements)) OR	**Concept 2:** **Electrodermal Activity** *Headings:* TS=(Electrodermal Activity) *Keywords & phrases:* ((((((((((((TS=(Electrodermal Activity)) OR TS=(Electrodermal Response)) OR TS=(Galvanic Skin Response)) OR TS=(Psychogalvanic Reflex)) OR TS=(Skin Admittance)) OR TS=(Skin Conductance)) OR TS=(Skin Electric Conductance)) OR TS=(Skin Conductance Level)) OR TS=(Skin Conductance Response)) OR TS=(Skin Potential)) OR TS=(Skin Potential Response)) OR TS=(Skin Susceptance)) OR TS=(Skin Susceptance Response)

Impedance”[Title/Abstract] OR “Skin Potential”[Title/Abstract] OR “Skin Potential Response”[Title/Abstract] OR “Skin Resistance Level”[Title/Abstract] OR “Skin Resistance Response”[Title/Abstract] OR "Skin Response"[Title/Abstract] OR “Skin Susceptance”[Title/Abstract] OR “Skin Susceptance Response”[Title/Abstract] OR “Specific Skin Conductance Responses”[Title/Abstract] OR “Sympathetic Skin Responses”[Title/Abstract] OR “Tonic EDA”[Title/Abstract] OR "Galvanic Skin Response"[Mesh]	TS=(Skin Conductance Responses)) OR TS=(Skin Impedance)) OR TS=(Skin Potential)) OR TS=(Skin Potential Response)) OR TS=(Skin Resistance Level)) OR TS=(Skin Resistance Response)) OR TS=(Skin Response)) OR TS=(Skin Susceptance)) OR TS=(Skin Susceptance Response)) OR TS=(Specific Skin Conductance Responses)) OR TS=(Sympathetic Skin Responses)) OR TS=(Tonic EDA)) OR ALL=(Electrodermal Response)	
Articles Returned After Searches of PubMed and Web of Science With the Original Search String and Both of its Translations		
Original PubMed Search String	**First and Most Broad Web of Science Translation**	**Second and Narrower Web of Science Translation**
18,792	203,060	98,129

Supplemental Table 11

Results of Subsequent Sets of Web of Science Searches With the Application of Narrower Search Criteria to Identify Relevant Papers Published Over Five Years Ago

Query	Articles Published Within the Past Five Years 1	Articles Published Within the Past Five Years 2: Narrower Search Criteria Applied	Articles Published Over Five Years Ago 1	Articles Published Over Five Years Ago 2: Narrower Search Criteria Applied	Classic, Classical, Historical, Pertinent, or Seminal Articles	Articles Selected for Screening Before De-Duplication
Hybrid Search 1 #6 AND #2 AND #1 AND #4	0	Not Applicable 0 Papers Exported	3	3	0	0
Hybrid Search 2 #6 AND #2 AND #1	226	Not Applicable 226 Papers Exported	321	Not Applicable All HCPs Manually Checked	23	249
Hybrid Search 3 #2 AND #1	7,858	4,568 4,568 Papers Exported	13,344	6,315	12 1 HCP for Screening Included	4,580
Hybrid Search 4 #6 AND #2 AND #5 AND #4	0	Not Applicable 0 Papers Exported	1	0	0	0
Hybrid Search 5 #6 AND #2 AND #5	44	Not Applicable 44 Papers Exported	60	0	0	44
Hybrid Search 6 #2 AND #5	1,895	1,022 1,022 Papers Exported	2,426	1,132	15 4 HCPs Not Relevant	1,037

Hybrid Search 7 #6 AND #2 AND #3 AND #4	0	Not Applicable 0 Papers Exported	1	1	0	0
Hybrid Search 8 #6 AND #2 AND #3	100	Not Applicable 100 Papers Exported	156 5 SSR Duplicates Removed PTE	Not Applicable All HCPs Manually Checked	6	106
Hybrid Search 9 #2 AND #3	11,977	6,974 6,974 Papers Exported	20,676	9,042 53 HCPs Not Relevant	39	7,013
Hybrid Search 10 #6 AND #2 AND #4	1	1 Not Relevant 0 Paper Exported	4	4 Not Relevant	0	0
Hybrid Search 11 #2 AND #4	181	181 181 Papers Exported	142	Not Applicable All HCPs Manually Checked	10	191
Hybrid Search 12 #1 AND #4	1,301	1,301 1,301 Papers Exported	1,241	Not Applicable All HCPs Manually Checked	94 3 HCPs for Screening Included in the Above	1,395
Total Number of Search Results	23,578	14,406	38,375	16,497	199	14,615

Note. Results from application of narrower search criteria to identify studies relevant to the six core study concepts, out of papers returned from Hybrid Searches 1-12. The narrowing of the search criteria involved rephrasing the Web of Science translation of the original PubMed search string for electrodermal activity to a better and more accurate translation. The new Web of Science translated search string does not contain the

Field Tag “ALL=All Fields”. Furthermore, some constituent keywords in the first translation were removed from the new translation for betterment of accuracy, clarity and coherence (see Supplemental Table 10).

Supplemental Table 12

Table of Search Results: Number of Articles Returned Per Database

Database	Total Number of Articles Returned Per Database	Number of Articles Identified by Searches with Combinations of the Baseline Search Strings That Contain the Core Study Concepts Per Database	Number of Articles Published in the Past Five Years Per Database	Number of Articles Published More Than Five Years Ago That are Either Classic, Classical, Historical, Pertinent, or Seminal Per Database	Number of Articles Imported into Zotero for De-duplication and Secondary Screening Per Database
CINAHL	3,355,102	11,863	3,259	0	3,259 {3,703 imported} Which ⇒ 444 accessory items were imported.
EMBASE	26,206,583	15,574	5,008	244	5,252
PubMed	15,139,931	11,858	2,519 [+35 Extra Papers]	24	2,578 {2,603 imported} Which ⇒ 25 accessory items were Imported.
Web of Science	10,183,715	61,965	14,415 [+4 Extra Papers]	199	14,619 {14,642 imported} Which ⇒ 23 accessory items were imported.
Total	54,884,172	101,248	25,192	467	25,704 {26,200 imported} Which ⇒ 496 accessory documents were imported into Zotero along with the manuscripts exported from the CINAHL, PubMed and Web of Science Databases.

Supplemental Table 13

Table of Evidence: An Overview of the Characteristics of the Primary Source Studies Included in the Literature Review

	Citation	Purpose	Sample Type	Sample Size (n)	Study Type	Country	Disease(s) or Disorder(s) Studied	Role of EDA Measure(s)	EDA Related Finding(s)
Studies with Application of Electrodermal Activity in Measurements									
1	Bari, D. S., Yacoob Aldosky, H. Y., & Martinsen, Ø. G. (2020). Simultaneous measurement of electrodermal activity components correlated with age-related differences. *Journal of biological physics*, *46*(2), 177–188. https://doi.org/10.1007/s10867-020-09547-4	To explore the impact of age-related differences on EDA components via use of a novel measuring approach made up of DAQ card, a small front-end electronic box, and a laptop that runs LabVIEW software.	Human	N = 60 healthy Caucasian volunteers sorted into three study arms.	Quantitative: Cross-sectional	Iraq	Aging (which is neither a disease nor a disorder; it is a condition).	To examine the impact of age upon EDA components.	Findings indicate a need to factor age into analyses of the results of research studies wherein the overarching goal of the study, is a comparison of EDA parameters.
2	Bari, D., Aldosky, H., Tronstad, C., Kalvøy, H. & Martinsen, Ø. (2018). Electrodermal activity responses for quantitative assessment of felt pain. *Journal of Electrical Bioimpedance, 9*(1). 52-58. https://doi.org/10.2478/joeb-2018-0010	To evaluate variations in skin conductance responses (SCRs), skin potential responses (SPRs), and skin susceptance responses (SSRs) that occur concurrently as a consequence of the application of sequences of electrical (painful) stimuli delivered at different levels of intensity.	Human	N = 40 healthy volunteers . 23 male and 17 females, age range 19 to 40 yrs. (mean 25 yrs.).	Quantitative: Experimental	Iraq	Pain	The main dependent variable.	There is a linear relationship between the EDA responses, with a $p < 0.001$ for the SCRs, and SSRs with $p = 0.001$. This finding that EDA responses (particularly SCRs and SSRs) are impacted in a linear fashion by the level of the painful stimuli. EDA responses such as these, may be employed as a potentially useful biomarkers, for assessment of the degree of pain patients experience in clinical settings.
3	Bari, D. S. (2020). Gender differences in tonic and phasic electrodermal activity components. *Science Journal of*	To investigate gender variations in tonic EDA	Human	N = 60 healthy volunteers	Quantitative: Experimental	Iraq	Gender differences in phasic and	EDA measures were analyzed for variations	The results indicate that both the slow-moving tonic EDA component

	University of Zakho 8(1). 29-33. https://doi.org/10.25271/sjuoz.2020.8.1.670	components versus phasic EDA responses to some external stimulus by employment of a novel noninvasive bioimpedance system, which is dependent upon a concurrent recording of the three EDA variables of skin conductance (SC), skin potential (SP), and skin susceptance (SS), at the very same skin site.		(30 females and 30 males; with a mean age 36.5±16 years; SD=16.1 years) were recruited from the Zakho University staff and students.			tonic electrodermal activity.	by gender.	(or SCLs), and the faster moving phasic EDA component (or SCRs), display gender differences. Furthermore, females showed greater phasic and tonic EDA values than males (with the exception of their skin potential responses (SPRs)), regardless of whether they were under conditions of relaxation or those of stimulation (i.e., conditions of stress).
4	Dusi, V., Shahabi, L., Lapidus, R., Sorg, J., Naliboff, B. D., Shivkumar, K., Khalsa, S.S., & Ajijola, O. (2020). Cardiovascular autonomic reflex function following bilateral cardiac sympathetic denervation for ventricular arrhythmias. *Heart Rhythm, 1*(20). 5247-5271. doi: 10.1016/j.hrthm.2020.04.022	To assess in CMP patients, ANS responses before and after BCSD compared to healthy and matched controls.	Human	N = 26 patients (18 with CMP and undergoing BCSD, as well as 8 matched healthy controls) were recruited and studied. The 18 CMP patients with refractory ventricular arrhythmias were 54±14 years old, had an LVEF of 36±14%, and 16	Quantitative: Experimental and prospective with two time points.	USA	Cardiomyopathy	As an index of autonomic function, and adrenergic responses.	There was a blunting of EDA response with bilateral cardiac sympathetic denervation (BCSD) surgery.

				were males.					
5	Ghiasi, S., Greco, A., Barbieri, R., Scilingo, E. P., & Gaetano, V. (2020). Assessing Autonomic Function from Electrodermal Activity and Heart Rate Variability During Cold-Pressor Test and Emotional Challenge. *Scientific Reports 10*(5406). 1-13. https://doi.org/10.1038/s41598-020-62225-2	To examine novel indices of phasic autonomic regulation mechanisms via combining EDA and HRV correlates and a thorough investigation of their time-varying dynamics.	Human	N = 28 study participants.	Quantitative: Experimental	Italy	Not Applicable: Healthy volunteers.	As an index of the SNS and also as a quantifier of sympathetic dynamics.	There was a finding of significant statistical differences for the prospective indices, particularly between the response to cold-pressor elicitation and such measures at the previous resting state. Also, a 73.08% degree of accuracy was attained for the automatic emotional valence recognition. The envisaged nonlinear processing of phasic ANS markers, yields innovative insights into autonomic functioning, which may be utilized in studies that lie within the field of affective computing and psychophysiology.
6	Siepmann, M., Grossmann, J., Muck-Weymann, M., Wilhelm, K. (2003). Effects of sertraline on autonomic and cognitive functions in healthy volunteers. *Psychopharmacology 1*(168). 293-298. doi: 10.1007/s00213-003-1448-4	To contrast the impact of sertraline on autonomic and cognitive functions with those of a placebo in healthy humans.	Human	N = 12.	Quantitative: Experimental (and this was a randomized, double blind, cross over study).	Germany	Not Applicable: Healthy volunteers.	The skin conductance level (SCL) and skin conductance response (SCR) after a sudden deep respiration, were used as parameters for autonomic function.	Cognitive and psychomotor performance were not altered in the healthy humans that got multiple doses of sertraline. The drops in heart rate and SCL may have been due to the sympatho-inhibitory effect of sertraline.
7	Smyth, J., Birell, S., Woodman, R., & Jennings, (2021). Exploring the utility of EDA and skin temperature as individual physiological correlates of motion sickness. Applied Ergonomics, 92(1). 1-10. https://doi.org/10.1016/j.apergo.2020.	To examine how to measure motion sickness precisely, identify, and predict its course of severity in real time.	Human	N = 40	Quantitative: Prospective. For the first study arm (n = 14), the study was cross-	United Kingdom	Motion Sickness	To conduct in real-time a measure of the effects of motion sickness upon EDA and skin	Correlations were noted for EDA and skin temperature at the group level. However, it was also found that these physiological measures of EDA and

	103315				sectional with just one data collection point. For the second study arm, there were two data-collection points.			temperature.	skin temperature are measure that cannot be used for individual evaluations of the state of motion sickness or prognosis.
8	Wickramasuriya, D. S., & Faghih, R. T. (2020). A mixed filter algorithm for sympathetic arousal tracking from skin conductance and heart rate measurements in Pavlovian fear conditioning. *PLOS ONE 15*(4). e0231659. https://doi.org/10.1371/journal.pone.0231659	To put forward a technique for tracking a sole brain-related sympathetic arousal state from physiological signal features during fear conditioning.	Human	N = 23 (13 males, 10 females, with age 23.8 ± 3.0 years). Four study participants were excluded.	Quantitative: Experimental	United States	Pavlovian Fear Conditioning.	EDA was used to examine the impact of Pavlovian Fear Conditioning upon skin conductance, which is an EDA component.	Findings indicate an initial line of evidence for the estimation of sympathetic arousal from binary, continuous and spiking-type observations, obtained from the skin and the heart, both of which are innervated by sympathetic nerve fibers) through state-space techniques.
9	Zangróniz, R., Martínez-Rodrigo, A., Pastor, J. M., López, M. T., & Fernández-Caballero, A. (2017). Electrodermal Activity Sensor for Classification of Calm/Distress Condition. *Sensors (Basel, Switzerland)*, *17*(10), 2324. https://doi.org/10.3390/s17102324	To validate the correct operation of a wearable EDA device, via use of pictures from the International Affective Picture System in a control experiment.	Human	N = 50 study participants.	Quantitative: Experimental	Spain	Calm and Distress	EDA was used for detection of conditions of calm as contrasted with those of distress in persons wearing an EDA device.	There was a finding of 89% accuracy in the task of distinguishing a condition of calm from a condition of distress, when a wearable EDA device was used.
10	장영준, 김현옥, Jang, Y. J., & Kim, H. O. (2018). **감마나이프 수술 환자의 정위적 틀 고정을 위한 침윤 마취 시 통증 완화 중재의 효과**. *Journal of Korean Academy of Nursing, 48*(2). 221-231. https://doi.org/10.4040/jkan.2018.48.2.221 Or Jang, Y. J., & Kim, H. O. (2018). The effect of pain relieving intervention	To compare the effects of three interventions on pain, blood pressure, and pulse rate during infiltration anesthesia in patients about to undergo gamma knife surgeries.	Human	N = 30	Quantitative: Experimental	South Korea	Pain, Blood Pressure and Pulse Rate in Patients Undergoing Gamma Knife Surgeries.	Measures of GSR were taken, for the assessment of pain.	The EDA related finding, was that the GSRs during infiltration anesthesia, were significantly higher in the Lidocaine and EMLA groups than in the Vapocoolant group (with F=13.56, p<.001 and F=14.43, p<.001, respectively).

	during infiltration among gamma knife surgery patients for stereotactic frame fixation. *Journal of Korean Academy of Nursing, 48*(2). 221-231. https://doi.org/10.4040/jkan.2018.48.2.221								
11	Boyce, M., Goldberg, B. S., & Moss, J. D. (2016). Electrodermal activity analysis for training of military tactics. *Proceedings of the Human Factors and Ergonomics Society 2016 Annual Meeting 60*(1). 1339-1343. https://doi.org/10.1177/1541931213601309	To develop novel tools for training soldiers, as well as technologies for the facilitation of skill and development of learning in automatic environments, via assessing differences between 2-D and 3-D perspective displays used to train ROTC cadets.	Human	N = 19 ROTC cadets (17 male; 2 female), who were between the ages of 20 and 30 (M = 21.84, SD = 2.22).	Quantitative: Experimental	United States of America	Physiological Responses to a Military Training Task Within the Context of Human Factors Research.	SCRs (which are a type of EDA), were assessed for their utility as a means to determine if there is a difference in engagement of study participants, between ROTC cadets that were trained with a 3D perspective display and those that were trained with a 2D perspective display, as a consequence of factors like aesthetics, novelty, satisfaction, and perceived usability.	The findings were that the differences in the SCRs, between the conditions caused by the ARES and GIFT training modalities (i.e., the 3-dimensional and 2-dimensional or flat conditions), are non-significant. Past related research show positive emotional experiences may yield EDA variables that are lower in value than the baseline EDA. However, because baseline EDA was not measured this could not be assessed in this study.
12	Taylor, M. K., Barczak-Scarboro, N. E., Laver, D. C., & Hernández, L. M. (2022). Combat and blast exposure blunt sympathetic response to acute exercise stress in specialised military men. *Stress and health: Journal of the International Society for the Investigation of Stress*, *38*(1), 31–37. https://doi.org/10.1002/smi.3069	To determine if blast as well as combat exposure, modifies the EDA response to acute exercise stress, in military specialists.	Human	N = 51 men (age M = 36.1, SD = 6.5), who were a part of the Explosive Ordnance	Quantitative: Experimental	United States of America	Stress	EDA was used in this study to measure levels of stress.	The findings were that exercise stress caused observable, stepwise rises in EDA level prior to abating at a greater intensity of exercise. Blunted EDA patterns were demonstrated by persons who had more

				Disposal Operational Health Surveillance System.					substantial exposure to combat and those with blast exposure, vis-à-vis persons with low or no exposure. This blunted pattern may indicate a sub-optimal degree of sympathetic nervous system function in the cohorts of exposed individuals, and as such, it adds to the body of science on the factors that influence resilience in such men.
13	Kozel, F. A., Johnson, K. A., Laken, S. J., Grenesko, E. L., Smith, J. A., Walker, J., & George, M. S. (2009). Can simultaneously acquired electrodermal activity improve accuracy of fMRI detection of deception?, *Social Neuroscience, 4*(6). 510-517, doi: 10.1080/17470910801907168	To investigate the use of functional magnetic resonance imaging (fMRI) in detection of deception, for the development of a central yardstick for the identification of falsehood.	Human	N = 31 healthy study subjects aged 18–50 years old.	Quantitative: Experimental	United States of America	Detection of Falsehood	EDA was evaluated as an added measure to fMRI analysis, for an improvement in diagnostic ability.	The finding was that use of EDA measures in addition to fMRI measures, did not enhance exactitude of the results observed during performance of a laboratory-based deception task.
14	Posada-Quintero, H. F., & Chon, K. H. (2019). Phasic Component of Electrodermal Activity is more Correlated to Brain Activity than Tonic Component. In *2019 IEEE EMBS International Conference on Biomedical & Health Informatics (BHI)* (pp. 1017–4). IEEE. https://doi.org/10.1109/BHI.2019.8834567	To explore associations between brain activity measured by EEG and peripheral sympathetic activity measured via EDA.	Human	N = 10 healthy volunteers (7 males; ages 25 - 35) were enrolled in this study.	Quantitative: Experimental	United States of America	Association of phasic and tonic EDA, with brain activity and autonomic sympathetic activity.	EDA measures were used to investigate cheating.	The findings are that phasic components of EDA exhibited a high correlation to the power of alpha waves in all of the channels collected (with a max of r = 0.91 in the occipital point), and a high inverse correlation to delta waves, mainly in the occipital and parietal channels.
15	Posada-Quintero, H. F., Florian, J. P., Orjuela-Cañón, A. D., & Chon, K. H. (2016). Highly sensitive index of sympathetic activity based on time-frequency spectral analysis of electrodermal activity. *American Journal of Physiology-Regulatory, Integrative and Comparative Physiology*	To examine whether the power spectral density analysis of EDA would provide more consistent results than the time-domain analysis of EDA, by	Human	N = 12 subjects.	Quantitative	United States of America	Examination of Power Spectral Density EDA Analysis for its Utility vs. Time Domain EDA Analysis.	Measures of EDA were taken for an examination of the utility of EDA power spectral density.	The finding was that the sympathetic tone, which had been assessed by the power spectral density of EDA had a lower variation and more sensitivity for certain (although not

	311(3), R582-R591. https://doi.org/10.1152/ajpregu.00180.2016	performance of a variety of sympathetic tone-evoking experiments,							all), stimuli, in comparison with the time-domain analysis of EDA. The authors surmised this lack of sensitivity in certain sympathetic tone-inducing conditions with time-invariant spectral analysis of EDA, may be due to its inapplicability to the characterization of time-varying dynamics of sympathetic tone.
16	Posada-Quintero, H. F., & Chon, K. H. (2016). Frequency-domain electrodermal activity index of sympathetic function. In *2016 IEEE EMBS International Conference on Biomedical & Health Informatics (BHI)* (pp. 497–500). IEEE. https://doi.org/10.1109/BHI.2016.7455943	To quantify a person's sympathetic function, through use of electrodermal activity (EDA) variability.	Human	N = 10 study subjects.	Quantitative	United States of America	Utility of EDAV to Quantify Sympathetic Function Note: The acronym EDAV stands for electrodermal activity variability.	Measures of EDA were taken for analyses of sympathetic function.	Results indicate a significant uptick in EDALFn upon change in posture from the supine to a standing position. Also, EDALFn had lesser coefficients of variability, versus standard time-domain related indices of EDA.
17	Peleg, D., Hochman, G., Ayal, S., & Ariely, D. (2018, March). Ideological altruistic cheating – testing Robin Hood in a lie detector [Paper presentation]. 2018 OECD Global Anti-Corruption & Integrity Forum, Paris, France. 1-7. https://www.oecd.org/corruption/integrity-forum/academic-papers/Peleg.pdf	To assess effects of altruistic justification via analyses of GSRs recorded during the measurement of dishonesty in a lab with a lie detector test, if altruistic motivations increase cheating propensity, and lessens the physiological tension associated with such dishonest behavior.	Human	N is Unstated.	Quantitative Conference Paper	Israel	Effect of Altruistic Justification of Cheating on the level of cheating, and any related psychological distress.	Sympathetic Arousal Index was used as a scale in the analysis of the averaged GSRs study participants, to reveal the impact of altruistic justification of cheating, on the level of cheating behavior and its associated psychological distress.	The findings indicate that the GSRs revealed that the presence of altruistic justification increased the cheating behavior, while also blunting its associated physiological distress.

18	Kong, Y., Posada-Quintero, H. F., Tran, H., Talati, A., Acquista, T. J., Chen, I. P., & Chon, K. H. (2023). Differentiating between stress- and EPT-induced electrodermal activity during dental examination. *Computers in biology and medicine*, *155*, 106695. Advance online publication. https://doi.org/10.1016/j.compbiomed.2023.106695	To examine the use of EDA in delineating pain from stress during dental exams, including the effects of electrical pulp test (EPT).	Human	N = 51 subjects with normal or necrotic teeth.	Quantitative	United States of America	Dental Disease, Dental Pain, Effect of the Electrical Pulp Test and Stress.	Measures of EDA were analyzed for the impacts of the stimuli from the EPT and stress.	Results indicate that EDA-derived features displayed a significant difference between the residual lingering stress + EPT groups and the stress groups. Accuracy was 84.6%, sensitivity was 76.2%, and the specificity was 86.8%, with multilayer perception in differentiating betwixt pure-stress groups and stress + EPT groups. Furthermore, the EPT induced a far greater EDA amplitude and a quicker response than stress. These finding implies the machine learning approach the researchers used can distinguish effects of EPT and stressful stimuli in EDA traces.
19	Raikes, A.C., & Schaefer, S. Y. (2016). Phasic electrodermal activity during the standardized assessment of concussion (SAC). *Journal of Athletic Training, 51*(7). 533–539. doi: 10.4085/1062-6050-51.8.09	To quantify EDA variations, while conducting a standardized neurocognitive evaluation of individuals with a history of concussion and those without a history of concussion.	Human	N = 7 asymptomatic study participants with a self-reported history of sports-based concussions (with previous concussions = 1.43 ± 0.53; and the time since their most recent	Quantitative Design: Descriptive Laboratory	United States of America	The utility of EDA as an index of neurologic function in persons who have suffered a concussion.	Measures of phasic EDA were taken during a standardized neurocognitive test of asymptomatic individuals without a history of concussion and those with a history of concussion to quantify differences in their levels of neurologic function.	The study concluded that EDA is a viable biomarker for the evaluation of the effects of concussion on a concussed individual's neurologic function.

				concussion = 0.75 to 6 years; median = 3 years) and 10 study participants with no history of concussions.					
20	Wass, S. V., de Barbaro, K., & Clackson, K. (2015). Tonic and phasic co-variation of peripheral arousal indices in infants. *Biological psychology*, *111*, 26–39. https://doi.org/10.1016/j.biopsycho.2015.08.006	To evaluate infants for co-variation in their peripheral arousal indices assessed by means of EDA measures.	Human	N = 37 infants with an average age of 12.5 months (mean age in days: 387, SD: 42, range: 319–501).	Quantitative	United Kingdom	Phasic and Tonic co-variation of peripheral arousal indices in infants.	EDA measures were taken to assess indices of peripheral arousal in infants.	The study found that even though there is a high covariation amid autonomic indices in infants, EDA may only be sensitive at remarkably elevated levels of arousal.
21	Melander, C. A., Kikhia, B., Olsson, M., Wälivaara, B. M., & Sävenstedt, S. (2018). The Impact of Using Measurements of Electrodermal Activity in the Assessment of Problematic Behaviour in Dementia. *Dementia and geriatric cognitive disorders extra*, *8*(3), 333–347. https://doi.org/10.1159/000493339	To explore the effects of a sensor for the measurement of electrodermal activity (EDA), upon nursing assistants' structured evaluations of the choices of care interventions made by persons with dementia, as well as problematic behavior among such persons.	Human	N = 20 study participants with cases of dementia. 14 patients completed the study. Six dropped out (four because of death or severe disease progression and two because they refused to	Quantitative Design: Prospective	Sweden	Dementia	An EDA sensor was employed by nurses in measuring EDA levels in persons with dementia, and also in mapping out trends in time related problematic behavior.	The finding was that nurses could apply information gleaned from use of the EDA measurement sensor, to identify causes and triggers of persons with dementia more effectively, and as such make their therapeutic interventions better tailored to delivery of certain treatments at certain times, for more effective prevention and management of problematic behavior.

				wear the EDA sensors).					
22	Nandi, A., Xhafa, F., Subirats, L., & Fort, S. (2022). MDEAW: A multimodal dataset for emotion analysis through EDA and PPG signals from wireless wearable low-cost off-the-shelf devices. *arXiv:2207.06410 [cs.HC], 1*(1). 1-26. https://doi.org/10.48550/arXiv.2207.06410	To analyze emotions elicited by exercises performed by some students in a classroom scenario, via an examination of the characteristics of EDA and PPG signals recorded during the course of administering such classroom exercises.	Human	N = 10 students.	Quantitative	Spain	Analyses of Emotions	EDA was used as a measure of student-wise affect recognition.	The results indicate the prospects of using low-cost devices for affective state recognition applications.
23	Schach, S., Rings, T., Bregulla, M., Witt, J-A., Bröhl, T., Surges, R., Von Wrede, R., Lehnertz, K., & Helmstaedter, C. (2022). global characteristics of evolving functional brain networks are modified by EDA biofeedback. *Frontiers of Neuroscience, 16*(828283). . https://doi.org/10.3389/fnins.2022.828283	To investigate if the use of short-term EDA biofeedback can alter EEG-derived large-scale functional brain networks in individuals with cases of epilepsy.	Human	N = 30 study participants with cases of epilepsy.	Quantitative Design: Prospective Quasi Randomized Controlled Trial.	Germany	Epilepsy	EDA biofeedback was used as a therapeutic intervention.	The finding was that the results of this study indicate that global characteristics of evolving functional brain networks are altered by the use of EDA biofeedback, but only non-specifically.
24	Boettger, S., Puta, C., Yeragani, V. K., Donath, L. Müller, H-J., Gabriel, H. H. W., Bär, K-J. (2010) Heart rate variability, QT variability, and electrodermal activity during exercise. *Medicine & Science in Sports & Exercise 42*(3). 443-448. doi: 10.1249/MSS.0b013e3181b64db1	To assess the utility of certain measures of autonomic function taken during physical exercise, for analyzing autonomic change, connections, and the effects of physical activity.	Human	N = 23 healthy sport students (9 females, 14 males; age = 23.6 ± 1.6 years; body mass index = 22.7 ± 2.0 kg·m−2; three of whom were smokers of less than three cigarettes per day),	Quantitative	Germany	Effects of Exercise	EDA measures were recorded for use in analyses of effects of physical exercise.	One of the findings of the study was that an increase in subjects' sympathetic activity was demonstrated quite well by the EDA measures recorded. It was also found that linear and non-linear measures of R-R variability are not a sufficient index of vagal modulation. However, the results indicate that the ApEnQT/ApEnRR ratio, EDA measures, and QTvi, are good indices of an individual's sympathetic function.

				were selected for inclusion in this study.					
25	Al abdi, R. M., Alhitary, A. E., Abdul Hay, E. W., & Al-bashir, A. K. (2018). Objective detection of chronic stress using physiological parameters. *Medical & Biological Engineering & Computing, 56*(1), 2273–2286. https://doi.org/10.1007/s11517-018-1854-8	To design a system to diagnose chronic stress, based upon the blunted reactivity of the autonomic nervous system (ANS) to imposition of a cognitive load (CL).	Human	N = 58 study participants whose stress level was identified via means of use of the State-Trait Anxiety Inventory.	Quantitative	Jordan	Impact of Chronic Stress	GSR measures were taken to compare its response to imposition of a cognitive load on study participants.	This study found that the newly design system is able to objectively detect chronic stress with high accuracy, which indicates it has the ability to monitor stress for prevention of dangerous stress-related diseases. The GSR measures upon analysis, were shown to be significantly impacted by cognitive loading. There was an overall blunting of the GSR measures upon cognitive loading. But the GSR blunting, was more pronounced in the non-stressed study participants, than in stressed subjects.
26	Poh, M-Z., Swenson, N. C., & Picard, R. W. (2010). A wearable sensor for unobtrusive, long-term assessment of electrodermal activity. *IEEE Transactions on Biomedical Engineering, 57*(5). 1-10. https://affect.media.mit.edu/pdfs/10.Poh-etal-TBME-EDA-tests.pdf	To develop a wearable sensor for the continuous, long term, and widespread evaluation of EDA.	Human	N = 26 subjects (aged 18-56 years).	Quantitative Design: Prospective	United States of America	EDA Sensor Development	EDA measures were taken to assess the viability of developing a wearable EDA sensor for the assessment of EDA over a long-term period with widespread applications.	This study found evidence that the distal forearm is a viable alternative to the traditional palmar sites for measuring electrodermal activity.
27	Zamzow, R., Ferguson, B., Stichter, J., Porges, E., Ragsdale, A., Lewis, M., & Beversdorf, D. (2016). Effects of propranolol on conversational	To investigate the acute impacts of the use of propranolol on	Human	N = 20 study participants with	Quantitative: Experimental Design:	United States of America	Impact of Propranolol on Conversationa	Measures of skin conductance (SC) were	The study found that propranolol yielded a significant improvement in the performances on

	reciprocity in autism spectrum disorder: a pilot, double-blind, single-dose psychopharmacological challenge study. *Psychopharmacology*, *233*(7), 1171–1178. https://doi.org/10.1007/s00213-015-4199-0	a measure of conversational reciprocity in persons with autism spectrum disorder (ASD), and also to examine whether autonomic activity and anxiety, either mediates, or else moderates responses to propranolol, given the relationships among such variables and ASD, as well as effects of the drug.		autism spectrum disorder.	Double-Blinded Single-Dose, Within-Subject Cross Over Psychopharmacological Challenge.		l Reciprocity in Persons with ASD and the Role of Autonomic Activity and Anxiety as Mediators or Moderators of Responses to Propranolol.	recorded via use of the GSR100C made by BIOPAC Inc., to assess whether autonomic activity is a mediating or moderating factor in pts' responses to propranolol.	the conversational reciprocity task. But it did not find a similarly significant impact of autonomic activity as evidenced by mean skin conductance (SC) levels upon drug effects.
28	Edwards, M. R., Benoit, J., & Schondorf, R. (2004). Electrodermal activity in patients with neurally mediated syncope. *Clinical autonomic research : official journal of the Clinical Autonomic Research Society*, *14*(4), 228–232. https://doi.org/10.1007/s10286-004-0213-z	To conduct a study designed to test the hypothesis that like the premonitory symptoms of syncope, EDA events precede the onset of cerebral hypo-perfusion, and may be sustained beyond the timepoints of the re-establishment of cerebral perfusion.	Human	N = 77 study participants referred for recurrent syncope (n1 = 53 experienced syncope; n2 = 17 had a similar clinical profile to the syncopal patients but did not experience syncope during HUT; n3 = 7 were healthy controls).	Quantitative Design: Retrospective Study	Canada	Neurally Mediated Syncope	Measures of EDA were recorded and used to test the study hypothesis.	The study found that in most of the cases, changes in pts' EDA preceded any change in BP, PCO2 or cerebral blood volume (CBV), and were sustained well beyond the period of hemodynamic recovery subsequent to a syncopal event. Thus, even though EDA was variable, it may be an objective correlate to the clinical finding that these patients' symptoms preceded any measurable change in their cerebral perfusion.
29	Balegh, S., Ditto, B., Benoit, J., &	To investigate in	Human	N = 142	Quantitative	Canada	Vasovagal	Measures of	The study found that

	Schondorf, R. (2019c). Electrodermal activity in individuals with recurrent vasovagal syncope: Association with clinical triggers and hemodynamic mechanisms. Manuscript under review.	individuals with vasovagal syncope (VVS), the temporal characteristics of electrodermal activity (EDA), and possible associations with clinical triggers and hemodynamic processes involved in VVS.		study participants with recurrent syncope.	Design: Retrospective Study		Syncope (VVS)	EDA were recorded and used to test the study hypothesis. Which was EDA would differ among the cohorts of patients investigated in this study.	there are significant differences in EDA values, between the cohorts of patients with a purely emotion-based trigger for VVS, those with a purely orthostatic trigger for episodes of VVS, and those with a mixture of emotional triggers for their VVS events and an orthostatic trigger for their VVS episodes. However, the findings did not support the notion that clinical history and hemodynamic parameters have a strong association with EDA changes.
Studies of POTS but Without an Application of Electrodermal Activity to any of the Investigative Measurements									
1	Goldstein, D. S., Holmes, C., Frank, S. M., Dendi, R., Canon, R. O., Sharabi, Y., . . . Eisenhofer, G. (2002). Cardiac Sympathetic Dysautonomia in Chronic Orthostatic Intolerance Syndromes. *Circulation, 106*(18). 2358-2365. doi: 10.1161/01.CIR.0000036015.54619.B6	To determine if tonic cardiac sympathetic innervation and function, are involved in the pathophysiology of postural orthostatic tachycardia (POTS), as well as repeated neurocardiogenic presyncope (NCS).	Human	N = 36 subjects with POTS and N = 36 subjects with NCS.	Quantitative: Experimental	USA	NCS and POTS	EDA was not used as a measure in this study.	Not applicable because EDA was not a measure in this study. Rather neurochemical indices were the measures utilized. Findings Relevant to Mapping Out Pathophysiological Mechanisms of POTS: POTS and NCS are different in tonic cardiac sympathetic function, with increased cardiac norepinephrine release in POTS and decreased release in the NCS. Both groups had normal values for indices of function of the cell membrane

									norepinephrine transporter, norepinephrine synthesis, and density of myocardial sympathetic innervation. Because POTS and NCS show abnormalities of cardiac sympathetic function, they may be classified forms of dysautonomia.
2	Gunning III, W. T., Kvale, H., Kramer, P. M., Karabin, B. L., & Grubb, B. P. (2019). Postural Orthostatic Tachycardia Syndrome is associated with elevated G-Protein coupled receptor autoantibodies. *Journal of the American heart Association, 8(*18). 1-10. https://doi.org/10.1161/JAHA.119.013602	To explore associations of G-Protein coupled receptor autoantibodies, with postural orthostatic tachycardia syndrome.	Human	N = 55 patients with POTS and a host of comorbidities. Most of the patients were female.	Quantitative: Experimental	USA	POTS	EDA was not used as a measure in this study.	Not applicable because EDA was not a measure in this study. Rather biochemical markers (a protein and autoantibodies) were the measures utilized. <u>Findings Relevant to Diagnosis of POTS via non-EDA Means</u> Serum levels of autoantibodies were evaluated by ELISA versus 4 subtypes of G-protein coupled adrenergic receptors and 5 subtypes of G-protein coupled muscarinic acetylcholine receptors.
3	Kharraziha, I., Holm, H., Bachus, E., Melander, O., Sutton, R., Fedorowski, A., & Hamrefors, V. (2019). Monitoring of cerebral oximetry in patients with postural orthostatic tachycardia syndrome. *Europace : European pacing, arrhythmias, and cardiac electrophysiology : journal of the working groups on cardiac pacing, arrhythmias, and cardiac cellular electrophysiology of the European Society of Cardiology*, *21*(10), 1575–1583. https://doi.org/10.1093/europace/euz204	To assess SctO2 in persons with POTS and also in those with a normal response to orthostatic provocation, relative to hemodynamic parameters and symptoms.	Human	N = 34 pts with POTS (26 females; 29.1 ± 9.5 years) and also included were 34 age-/sex-matched controls with normal head-up	Quantitative	Sweden	POTS	EDA was not used as a measure in this study.	Not applicable because EDA was not a measure in this study. Yet the measure used to measure cerebral tissue saturation (SctO2), has shown promise as a tool for the evaluation of syncope, which is a symptom often reported by persons diagnosed with POTS. Furthermore, the study design is quite similar to that of this proposed

				tilt table (HUTT) tests.					study. Findings Relevant to the Study of the Utility of a Relatively Novel Measure (SctO2) in Evaluation of a Variable and Responses of Study Interest in Persons with POTS Persons with POTS have lower cerebral tissue saturation during orthostatic provocation in comparison with those with a normal hemodynamic response to HUTT testing. An orthostatic reduction in cerebral saturation only weakly correlates with an increase in heart rate, and is not predictive of a vasovagal reflex in POTS cases.
4	Taub, P. R., Zadourian, A., Lo, H. C., Ormiston, C. K., Golshan, S., & Hsu, J. C. (2021). Randomized trial of ivabradine in patients with hyperadrenergic postural orthostatic tachycardia syndrome. *Journal of the American College of Cardiology, 77*(7). 861-871. doi: 10.1016/j.jacc.2020.12.029	To investigate the effect of ivabradine (selective blocker of the Ifunny channel in the sinoatrial node) on heart rate, quality of life (QoL), and plasma norepinephrine (NE) levels in patients with hyperadrenergic POTS defined by plasma NE >600 pg/ml and abnormal tilt table test.	Human	N = 27 patients participated in the study (Of these, n = 22 aged 22.2 to 45.6 yrs.; most with HA-POTS finished the study; n = 23 were white, and n = 4 were non-white).	Quantitative: Experimental Design: A randomized, double-blinded, placebo-controlled, crossover trial.	United States of America	POTS, HA-POTS and the use of Ivabradine to treat POTS.	EDA was not used as a measure in this study.	Not applicable, as EDA was not a measure in this study. Rather gold reference tests such as a head up tilt table (HUTT) test, and other diagnostic studies such as laboratory studies, ECG, and blood draws for the measurement of plasma levels of norepinephrine (i.e., a form of catecholamine test), were utilized. Findings Relevant to the Diagnosis and the Prognosis of POTS The findings are that use of Ivabradine in patients with a predominant subtype of hyper

									adrenergic POTS, is both effective and safe, in decreasing patients' heart rate, reducing their plasma norepinephrine levels, and improving their quality of life.
5	Wang, S., Zou, R., Cai, H., & Wang, C. (2022). Predictive Value of Heart Rate and Blood Pressure on the Prognosis of Postural Tachycardia Syndrome in Children. *Frontiers in pediatrics*, *10*, 802469. https://doi.org/10.3389/fped.2022.802469	To investigate the predictive value of heart rate (HR) and blood pressure (BP) on the prognosis of postural tachycardia syndrome (POTS) in children.	Human	N = 91 children. The POTS group was comprised of nPOTS = 53 children (aged 5 to 15 years). While the controls were a group comprised of nControls = 38 children (aged 5 to 16 years). Of the 91 study participants, 45 were males, with a mean age of 11.52 ± 2.13 years.	Quantitative	China	POTS	EDA was not used as a measure in this study.	Not applicable, as EDA was not a measure in this study. Rather gold reference tests such as a head up tilt table (HUTT) test, and other diagnostic studies such as laboratory studies, and ECG measures. Findings Relevant to the Prognosis of POTS The heart rates (HRs) and the heart rate differences (HRDs), and the product of heart rate and blood pressure (RPP) that were taken at the 5th and 10th minutes, are HR 5, HR 10, HRD 5, HRD 10, RPP 5 and RPP 10 respectively, as well as the four combined indicators (HR 5, HR 10, HRD 5, and HRD 10) had predictive value for the POTS prognosis in children. The predictive value of the four combined indicators for the POTS prognosis was better than that of the single HR 5, HRD 5, and RPP 10.
6	Tao, C., Lu, X., Lin, J., Li, H., Li, X., Tang, C., Du, J., & Jin, H. (2019). Long-term outcomes of children and adolescents with postural tachycardia syndrome	To investigate long-term health related outcomes of children and	Human	N = 121 patients. Six (5.0%) of whom	Quantitative Design: Prospective	China	POTS	EDA was not used as a measure in this study.	Not applicable, as EDA was not a measure in this study. Rather gold reference tests such as a

	after conventional treatment. *Frontiers in Pediatrics, 7*(261). https://doi.org/10.3389/fped.2019.00261	adolescents with postural tachycardia syndrome, receiving standard treatments.		were lost to follow-up.					head up tilt table (HUTT) test, and other diagnostic studies such as laboratory studies, ECGs, and Findings Relevant to the Diagnosis and Prognosis of POTS in a Pediatric Population The study found benign long-term health outcomes in children as well as in those adolescents who received standard treatment. Also, the results indicate there was a gradual increase in the cumulative free rate with the passage of time. Furthermore, the authors found that prolonged duration of pt. symptoms prior to treatment, as well as a reduced maximum upright heart rate in the standing-up test, are independent risk indicators (or prognostic factors).
7	Kim, D. H., Park, J. Y., Kim, S. Y., Lee, N. M., Yi, D. Y., Yun, S. W., Lim, I. S., & Chae, S. A. (2022). Awareness of postural orthostatic tachycardia syndrome is required in adolescent syncope. *Medicine*, *101*(45), e31513. https://doi.org/10.1097/MD.0000000000031513	To establish traits of pediatric postural orthostatic tachycardia syndrome (POTS).	Human	N = 539 (147 adolescents, aged 10-19 years old; 269 adults, aged 20-59 years old; and 123 older patients, aged ≥60 years old. Of these	Quantitative	South Korea	POTS	EDA was not used as a measure in this study.	Not applicable, as EDA was not a measure in this study. Rather they used gold reference tests such as a HUTT test, ECGs, laboratory tests as well as height, weight, and BMI data. Findings Relevant to Age Related Diagnosis and Characteristics of HUTT Results Among Individuals with and Without POTS Adolescents with POTS

				patients, 70 (i.e., 13.0%) were diagnosed with POTS. Out of these patients, 61.4% were females (with a median age of 20 [17–25] years). The syndrome was more prevalent among adolescents (33 [22.4%]) than adults (37 [13.8%]) But it was absent among the set of older pts.					had a markedly lower resting diastolic blood pressure (DBP) and heart rate (HR), and also converted to their maximum HR far more rapidly than did adolescents without POTS during the passive testing phase. Adolescents with POTS demonstrated several unique characteristics versus adults with and adolescents without POTS. As such POTS may not be detected amidst syncope and presyncope patients, among which 22.4% of adolescents were diagnosed with POTS.
8	Raj, S. R., Baggioni, I. Yamahure, P. C., Black, B. K., Paranjape, S. Y., Byrne, D. W., & Robertson, D. (2005). Renin-aldosterone paradox and perturbed blood volume regulation underlying postural tachycardia syndrome. *Circulation, 111*(13). 1574-1582. https://doi.org/10.1161/01.CIR.0000160356.97313.5D	To test the hypothesis that persons with POTS are hypovolemic in comparison with healthy controls and also explore the role of aldosterone and plasma renin activity in the regulation of plasma volume.	Human	N = 29 study subjects comprised of 15 patients with POTS, and 14 healthy controls.	Quantitative	United States of America	POTS	EDA was not used as a measure in this study.	Not applicable, as EDA was not a measure in this study. Rather gold reference tests such as a head up tilt table (HUTT) test, and other diagnostic studies such as laboratory studies, ECGs, and plasma renin activity. Findings Relevant to the Diagnosis and Mechanisms of POTS The study results show

									low aldosterone as well as a paradoxically unchanged plasma renin activity in persons with POTS, as evidenced by the significant reduction in their plasma volume. The study results also showed that such pts., have a notable deficit in the volume of their red blood cells, which is regulated by the renal hormone erythropoietin. These abnormalities suggest that kidneys, may play a crucial role in POTS pathophysiology.
9	Kaye, J. M., Corrall, R. J., & Lightman, S. L. (2005). A new test for autonomic cardiovascular and neuroendocrine responses in diabetes mellitus: evidence for early vagal dysfunction. *Diabetologia*, *48*(1). 180–186. doi:10.1007/s00125-004-1615-0	To explore the autonomic, cardiac, endocrine and psychological responses of patients with diabetes to one breath of 35% CO2, regardless of their diagnostic history with autonomic neuropathy or lack of such history.	Human	N = 20 male patients with diabetes for at least three years, aged between 18 and 70 years. 11 males had diabetic autonomic neuropathy (DAN), and nine did not.	Quantitative	United Kingdom	Autonomic cardiovascular and neuroendocrine responses in diabetes mellitus, diabetic autonomic neuropathy, and vagal dysfunction.	EDA was not used as a measure in this study.	Not applicable, as EDA was not a measure in this study. Rather gold reference tests such as laboratory tests (which included blood glucose checks), autonomic function tests such as Ewing and Clarke's tests, as well as ECG tests were performed. Findings Relevant to the Diagnosis and Mechanisms of POTS The study found that a CO2 challenge can be easily and quite safely administered for an activation of the cardiac autonomic and hypothalamic–pituitary–adrenal axis, as well as emotional arousal. This test was able to distinguish pts. with cardiac autonomic neuropathy (CAN), from

									those without.
10	Yang, X., Lin, Q., Li, X., Wu, L., Xu, W., Zhu, Y., … Yao, B. (2019). Cystatin C Is an Important Biomarker for Cardiovascular Autonomic Dysfunction in Chinese Type 2 Diabetic Patients. *Journal of diabetes research*, *2019*, 1706964. doi:10.1155/2019/1706964	To investigate the relationship between Cystatin C (CysC) and cardiovascular autonomic dysfunction (CAD), in type 2 diabetic (T2D) patients without renal dysfunction.	Human	N = 161 patients with type 2 diabetes mellitus, normal serum creatinine (less than 133 μmol/l), and an estimated glomerular filtration rate (eGFR) higher than 60 ml/min per 1.73 m2.	Quantitative	China	Cardiovascular Autonomic Dysfunction and Diabetes.	EDA was not used as a measure in this study.	Not applicable, as EDA was not a measure in this study. Rather CAD was determined via an analysis of heart rate variability (HRV). This was measured by a 24-hour Holter monitor. Serum CysC was tested by particle-enhanced turbidimetric immunoassay, and the subjects were divided into three groups, based upon the tertiles of CysC. Findings Relevant to the Diagnosis and Mechanisms of POTS Serum CysC levels are associated with cardiovascular autonomic dysfunction. Results also indicate CysC may be a reliable and a convenient biomarker, for CAD detection.
11	Akbar, M., Bhandari, U., Habib, A., & Ahmad, R. (2017). Potential Association of Triglyceride Glucose Index with Cardiac Autonomic Neuropathy in Type 2 Diabetes Mellitus Patients. *Journal of Korean Medical Science*, *32*(7), 1131–1138. doi:10.3346/jkms.2017.32.7.1131	To examine the correlation of triglyceride glucose index (TyG index) in Cardiac Autonomic Neuropathy (CAN) patients, as well as the prevalence of CAN in Type 2 Diabetes Mellitus (T2DM) patients.	Human	N = 202 with T2DM (aged 18-80 years).	Quantitative	India	CAN	EDA was not used as a measure in this study.	Not applicable, as EDA was not a measure in this study. Rather the use of tests such as the triglyceride glucose index (TyG index), and other diagnostic tests, inclusive of Ewing's set of autonomic function tests, and blood draws for the glucose fasting test occurred. Findings Relevant to the Diagnosis and Mechanisms of POTS The study found that the TyG index and the

									low-cost IR index, may be used as alternative screening measures for early screening of high risk DN pts.
12	Plash, W. B., Diedrich, A., Biaggioni, I., Garland, E. M., Paranjape, S. Y., Black, B. K., Dupont, W. D., & Raj, S. R. (2013). Diagnosing postural tachycardia syndrome: comparison of tilt testing compared with standing haemodynamics. *Clinical science (London, England: 1979)*, *124*(2), 109–114. https://doi.org/10.1042/CS20120276	To test the postulate that a passive head-up tilt (HUTT) table test, would produce greater increases in HR, than an active stand test, and that this difference would cause variability in the number of patients and controls meeting the orthostatic HR criterion for the diagnosis of POTS.	Human	N = 30 study participants (aged ≥ 18 years; 15 of whom were cases, and 15 of whom were controls).	Quantitative	United States of America	POTS	EDA was not used as a measure in this study.	Not applicable, as EDA was not a measure in this study. Rather the Findings Relevant to the Diagnosis and Mechanisms of POTS The study found that orthostatic tachycardia was greater during tilt (with lower specificity for POTS diagnosis), than it was during the tests with a patient standing at the 10th and 30th min. The 30 bpm ΔHR criterion, is not beneficial with a 30-minute head-up tilt test. As such, steps for the diagnosis of POTS, should factor in criteria for orthostatic intolerance, instead of being based exclusively upon the criterion of orthostatic tachycardia, regardless of the type of test that was performed.
13	Moon, J., Kim, D. Y., Lee, W. J., Lee, H. S., Lim, J. A., Kim, T. J., Jun, J. S., Park, B., Byun, J. I., Sunwoo, J. S., Lee, S. T., Jung, K. H., Park, K. I., Jung, K. Y., Kim, M., Lee, S. K., & Chu, K. (2018). Efficacy of Propranolol, Bisoprolol, and Pyridostigmine for Postural Tachycardia Syndrome: a Randomized Clinical Trial. *Neurotherapeutics: the journal of the American Society for Experimental NeuroTherapeutics*, *15*(3), 785–795.	To evaluate the efficacy of sustained medical treatments, the pros and cons of two β-blockers, and the benefit conferred by reception of extra treatment with pyridostigmine upon persons with POTS, as well as the	Human	N = 77 study participants.	Quantitative: Experimental Design: 2 × 2 factorial design, randomized, clinical trial of a 3-month medical treatment regimen in POTS	South Korea	POTS, Medications Efficacy and Quality of Life.	EDA was not used as a measure in this study.	Not applicable, as EDA was not a measure in this study. Rather tests such as postural BPs, and the orthostatic vital sign (OVS) test were performed. Findings Relevant to Treatment, Prognosis, Mechanisms and the Diagnosis, of POTS The study found that a

	https://doi.org/10.1007/s13311-018-0612-9	effectiveness of such therapeutic regimens in reducing their depression and/or improving their quality of life.			patients.				sustained reception of medical treatment is beneficial to persons with POTS, not just for the management of their symptoms of orthostatic intolerance, but also for management of their depression and an improvement in their quality of life, despite non-use of antidepressants. The efficacy of each of these regimens in the management of individuals with POTS, was comparable.
14	Zhang, R., Mayuga, K., Shields, R., Cantrell, C., & Wilson, R. (2022). Skin Biopsy and Quantitative Sudomotor Axon Reflex Testing in Patients With Postural Orthostatic Tachycardia Syndrome. *Cureus*, *14*(11), e31021. https://doi.org/10.7759/cureus.31021	To characterize the utility of autonomic function (AF) testing methods such as skin biopsies and the quantitative axon reflex test (QSART) at a tertiary center, and also to identify any clinical features associated with abnormal testing.	Human	N = 356 patient records out of the 2,658 patients screened, met the criteria for inclusion in the study. Their mean age is 31 ± 10 years, and 90% of them are female.	Quantitative	United States of America	POTS	EDA was not used as a measure in this study.	Not applicable, as EDA was not a measure in this study. Rather the measures taken during this study include the Valsalva Maneuver (VM) test, quantitative sudomotor axon reflex test (QSART), heart rate deep breathing (HRDB) test, and ECGs. Findings Relevant to the Diagnosis and Mechanisms of POTS The study found that a subset of the patients with POTS displayed evidence of small fiber neuropathy. Such pts generally showed signs of poor cardiovascular autonomic function, but were otherwise akin to patients with no evidence of small fiber neuropathy.
15	Heyer, G. L., Harvey, R. A., & Islam, M.	To characterize and	Human	N = 150	Quantitative	United	Sweat	EDA was not	Not applicable because

	P. (2016). Sweat patterns differ between tilt-induced reflex syncope and tilt-induced anxiety among youth. *Clinical autonomic research : official journal of the Clinical Autonomic Research Society*, *26*(4), 295–302. https://doi.org/10.1007/s10286-016-0368-4	compare the sweat patterns associated with head up tilt (HUT) test induced anxiety, presyncope, syncope, and normal head up tilt testing.		study participants (15.1 ± 2.3 years; 82.9 % female) with 156 diagnoses (Patients with POTS were not included).	Design: Prospective Observational Study	States of America	Patterns in Reflex Syncope and Anxiety During HUTT Testing	used as a measure in this study.	EDA measures were not recorded during the course of this study. Rather measures of QSWEAT were taken. Findings Relevant to Diagnosis of HUTT Test Induced Dysautonomia The study found that sweat patterns related with either syncope or presyncope, differ from the sweat patterns that are associated with anxiety. The authors state that recognition of the different sweat patterns could inform the interpretation of signs and symptoms obtained from clinical orthostatic challenges.
16	Schondorf, R., Benoit, J., & Wein, T. (1997). Cerebrovascular and Cardiovascular Measurements During Neurally Mediated Syncope Induced by Head-Up Tilt. Stroke, 28(8), 1564–1568. https://doi.org/10.1161/01.STR.28.8.1564	To investigate if the autoregulation of cerebral function is intact or impaired, in individuals with recurrent neurally mediated syncope (NMS).	Human	N = 22 study participants (n1 = 12 patients with NMS and n2 = 10 controls).	Quantitative	Canada	Neurally Mediated Syncope (NMS)	EDA was not used as a measure in this study.	Not applicable because EDA measures were not recorded during the course of this study. Rather measures such as of heart rate, HR, blood pressure, BP (through use of volume clamp photoplethysmography), stroke volume (via means of impedance cardiography) as well as cerebral blood velocity, CBV (via means of transcranial Doppler sonography) were taken. Findings Relevant to Diagnosis of HUTT Test Induced Dysautonomia The study found that the declination of cerebrovascular

									resistance during NMS is indicative of the maintenance of the integrity of cerebrovascular autoregulation, despite imminence of syncope. Furthermore, the selective loss of diastolic flow during syncope, as well as the rise in pulsatility index, are likely due to a collapse of the blood vessels downstream, as the diastolic blood pressure drops below the critical closing pressure of the cerebral vessels.
Case Reports on Cardiovascular Dysautonomia without an Application of Electrodermal Activity to any of the Investigative Measurements									
1	Teng, A. E., Noor, B., Ajijola, O. A., & Yang, E. H. (2021). Chemotherapy and Radiation-Associated Cardiac Autonomic Dysfunction. *Current oncology reports*, *23*(2), 14. https://doi.org/10.1007/s11912-020-01013-7	To describe clinical features, diagnostic methods, proposed mechanisms, and readily available therapeutics for the treatment of cases of cardiovascular autonomic dysautonomia in survivors of cancer.	Human	N = 6 patient case reports.	Quantitative: Case Reports (published as a review in Current oncology reports).	United States of America	Chemotherapy and Radiation Associated Cardiac Autonomic Dysfunction (CAD)	EDA was not used as a measure in any of these cases.	Not applicable, as EDA was not a measure in this study. Rather tests such as the Baroreflex Sensitivity (BRS) test, ECGs, the Valsalva Maneuver (VM) test, Blood pressure response to standing (i.e., orthostatic blood pressures), Blood pressure response to a sustained handgrip, Blood pressure response to exercise, heart rate recovery tests (such as a continuous cardiac rhythm monitoring treadmill test), Pre-ejection Period (PEP) test, quantitative sudomotor

									axon reflex test (QSART), heart rate deep breathing (HRDB) test, HUTT, and an analysis of heart rate variability (HRV) were performed. Findings Relevant to Diagnosis, Prognosis and POTS Treatment The findings indicate that because CAD is nonspecific, tools for assessing autonomic function, may provide objective markers for diagnosis and tracking of treatment response in persons with cancer linked dysautonomia.
2	Enechukwu, M., & Blitshteyn, S. (2018). Diagnosing and treating postural orthostatic tachycardia syndrome. *Family Doctor, 6*(3). 30–31. http://www.dysautonomiaclinic.com/wp-content/uploads/2018/08/POTS-Review-Maryland-Fam-Doc-Summer-2018.pdf	To examine hands-on approaches to the diagnosis and the treatment of POTS, in clinical settings via a review of a series of case reports.	Human	N = 4 patient case reports.	Quantitative: Case Series	United States of America	POTS	EDA was not used as a measure in any of these cases.	Not applicable, as EDA was not a measure in this study. Rather tests such as were done. Findings Relevant to Diagnosis, Prognosis and POTS Treatment The authors concluded from these cases that POTS is a frequently misdiagnosed as well as underdiagnosed disorder, which leads to diagnostic delays, treatment delays, disability, poor quality of life and other adverse patient outcomes. As such they recommended education to improve awareness among healthcare providers of the clinical features of POTS to improve the time to diagnosis of

									POTS, treatment, and consequently the prognosis of persons suffering with POTS.
3	Rodriguez, B., Hoepner, R., Salmen, A., Kamber, N., & Z'Graggen, W. J. (2020). Immunomodulatory treatment in postural tachycardia syndrome: a case series. *European journal of neurology*, 10.1111/ene.14711. Advance online publication. https://doi.org/10.1111/ene.14711	To assess use of intravenous immunoglobulin (IVIG) therapy in persons with progressive and/or refractory immune-mediated POTS.	Human	N = 6 study participants with a diagnosis of neuropathic POTS, who had been receiving immunoglobulin therapy for at least 6 months.	Quantitative: Case Series	Switzerland	POTS (progressive and/or refractory immune mediated POTS).	EDA was not used as a measure in any of these cases.	Not applicable, as EDA was not a measure in this study. Rather gold reference tests such as a head up tilt table (HUTT) test, and other diagnostic studies such as laboratory studies, ECG measures, and an anhydrous sweat test. Findings Relevant to Prognosis and POTS Treatment Some of the findings of this retroactive case series (which describes via means of objective and subjective measures promising effects of IVIG therapy in POTS patients with immune-mediated dysautonomia), are that by pre-treatment with steroids and intravenous hydration, and reducing the rate of infusion, levels of tolerance might be enhanced.
6	Blitshteyn, S., & Whitelaw, S. (2021). Postural orthostatic tachycardia syndrome (POTS) and other autonomic disorders after COVID-19 infection: a case series of 20 patients. *Immunologic research*, *69*(2), 205–211. https://doi.org/10.1007/s12026-021-09185-5	To describe clinical features, diagnostic findings, treatments, and outcomes in patients with new-onset POTS and other autonomic disorders after infection with the SARS-CoV-2 (COVID-19) virus.	Human	N = 20 (70% female; median age 40 years; age range 25-65 years).	Quantitative: Case Series	USA	COVID-19 and POTS	EDA was not used as a measure in any of these cases.	Not applicable because EDA was not a measure in this study. <u>Findings Relevant to POTS as one of the Sequelae of Infection With the SARS-CoV-2 Virus</u> POTS can follow COVID-19 in previously healthy patients. Appropriate diagnostic investigations and therapies are

									necessary to identify and treat autonomic dysfunction after COVID-19.
5	Kesserwani, H. (2020). Postural Orthostatic Tachycardia Syndrome Misdiagnosed as Anxiety: A Case Report with a Review of Therapy and Pathophysiology. *Cureus*, *12*(10), e10881. https://doi.org/10.7759/cureus.10881	To present the case of a 19-year-old young woman, who reported classic POTS symptoms, yet whom had been incorrectly diagnosed as having anxiety for years.	Human	N = 1 female (19 years old).	Quantitative: Case Report	United States of America	POTS	EDA was not used as a measure in this case.	Not applicable, as EDA was not a measure in this study. Rather gold reference tests such as a head up tilt table (HUTT) test, and other diagnostic studies such as laboratory studies, EKG, and performance of a power spectra density analysis were utilized. Findings Relevant to the Differentiation of Anxiety from the Adrenergic and the Neuropathic Subtypes of POTS The increase in HR of HR Δ = 63 bpm on 70 degrees of HUT sans a drop in SBP of 30 mm of Hg established the presence of a case of POTS. Manifestation of signs and symptoms such as diaphoresis, dimming of vision, feelings of impending doom, palpitations, and light headedness, are suggestive of the presence of hyper adrenergic POTS. Yet, because signs of hyper adrenergic POTS are akin to signs of anxiety it was necessary to distinguish anxiety from hyper adrenergic POTS. The rapid but sustained increase in HR within 10

									minutes, alongside orthostatic symptoms, established a diagnosis of POTS. By means of an analysis of power spectra measured over the course of 24-hours, subtypes of POTS such as neuropathic POTS and hyper adrenergic POTS. This should be distinguished from a confounder such as pheochromocytoma, which mimics POTS.
6	Mönnig G, Ribbing M, Wasmer K, Breithardt G, & Eckardt L. (2004). Recurrent syncope triggered by inappropriate sinus tachycardia. *Pacing & Clinical Electrophysiology*, *27*(9), 1324–1326. https://doi.org/10.1111/j.1540-8159.2004.00629.x	To report a case of a patient with recurring syncopal episodes along with sinus tachycardia and examine any underlying pathophysiological mechanisms.	Human	N = 1. Female, 25 years old.	Quantitative: Case Report	Germany	IST	EDA was not used as a measure in this study.	Not applicable because EDA was not a measure in this study. Rather gold reference (or standard) tests such as a head up tilt table (HUTT) test, a stress test, a right ventricular angiogram, blood pressure measures, an electrocardiograph (ECG). Furthermore, a sinus node modulation was performed. This was followed by an AVN ablation and dual chamber pacemaker placement. Collection of electrophysiologic data was done before these procedures, during these procedures, and after a follow-up period of 12 months. Findings Relevant to Distinguishing IST from POTS and the Mechanisms of IST Which is a Confounder of POTS The findings of this case

									report indicated for the first time that the presence of a moderate degree of tachycardia in a structurally unremarkable heart might be an underlying mechanism for a patient's recurrent episodes of syncope. Yet the precise etiology of syncope in this patient remains unknown, and as such, a severe sympathovagal imbalance was implicated as the most likely pathophysiological mechanism. POTS was ruled out, because the patient's HUTT results were negative for POTS, and the patient's syncopal signs and/or symptoms, were either reported and/or observed, in both supine and upright positions.
7	Morishima, I., Sone, T., Tsuboi, H., Mukawa, H., Satoda, M., & Uesugi, M. (2004). Asymptomatic Brugada syndrome associated with postural orthostatic tachycardia syndrome: Does autonomic disorder increase propensity for future arrhythmic events? *Pacing and clinical electrophysiology : PACE*, *27*(4), 537–540. https://doi.org/10.1111/j.1540-8159.2004.00477.x	To explore the clinical implications of a concurrent case of POTS in a patient diagnosed with Asymptomatic Brugada Syndrome.	Human	N = 1. Male, 26 years old.	Quantitative: Case Report	Japan	Asymptomatic Brugada Syndrome and POTS	EDA was not used as a measure in this study.	Not applicable because EDA was not a measure in this study. Rather gold reference (or standard) tests such as a head up tilt table (HUTT) test, as well as other diagnostic studies such as echocardiography, coronary angiography, and right and left ventriculographies. Furthermore, autonomic functions were investigated by the spectral analysis of 24-

									hour heart rate variability. <u>Findings Relevant to Establishing for the First Time an Association Between Asymptomatic Brugada Syndrome and POTS</u> Despite diagnoses of concurrent cases of Asymptomatic Brugada Syndrome (ABS) and POTS, on account of the clinical presentation, POTS rather than ABS is responsible for the patient's syncopal episode.
8	Del Pozzi, A. T., Enechukwu, M., & Blitshteyn, S. (2019). Postural orthostatic tachycardia syndrome in primary care: diagnosis, treatment and a case of African-American man presenting with POTS. *BMJ Case reports, 12*(9). e229824. http://dx.doi.org/10.1136/bcr-2019-229824	To make a report on the clinical features, diagnosis, pathophysiology, and treatment of POTS, in light of the case of an individual who presented with the clinical features and evidence of POTS.	Human	N = 1 patient diagnosed with POTS (aged 29 years old.	Quantitative: Case Report	United States of America	POTS	EDA was not used as a measure in this case.	Not applicable because EDA was not a measure in this study. Rather gold reference tests such as a head up tilt table (HUTT) test, as well as diagnostic tests such as an X-ray, a set of routine blood tests, a drug screen, postural test, a 30-day cardiac monitor, a doppler ultrasound, an echocardiography, and an electrophysiologic study. Also, autonomic functions were studied by the spectral analysis of 24-hour HRV. Findings Relevant to the Promotion of Accurate and Timely Diagnosis of POTS Despite a positive HUTT test, the African American male patient was not diagnosed with POTS, because of an

									incorrect notion that POTS is a disorder experienced by young Caucasian women. So, the authors state that POTS is a disorder of the ANS, which is often misdiagnosed as an eating disorder, anemia, dehydration, a viral illness, or anxiety. It is frequently underdiagnosed because of a lack of knowledge, as well as unawareness on the part of health providers.

Note: The primary focus of this table is the use of EDA as a measure for investigating the diagnostic, mechanistic and prognostic characteristics of POTS. Some studies with no direct relation to the study of POTS are included. Yet all studies used EDA as a measure of some variable of interest.

Supplemental Table 14

Variables for Comparative Analyses (or Analyses of Differences) – Data from AcqKnowledge and TestWorks

	Variable Name	Variable Type	Data Source: Hardware	Data Source: Software	Clinical and Statistical Notes
1	ARS Testing Type: Based Upon Completeness of Each Chart Record, Number of Tests Administered During Each ARS, and Each Patient's Ability to Complete Each ARS Test Administered.	Screening Descriptor: Potentially a Categorical Predictor Variable, or a Potential Covariable.	Not Applicable	TestWorks	Nominal: ARS Testing Types 1, 2, 3, and 4.
2	ARS Type: Full ARS With a CASS, Full ARS Without a Determinable CASS, or a Partial ARS With No CASS.	Screening Descriptor: Potentially a Categorical Predictor Variable	Not Applicable	TestWorks	Nominal: Type of ARS Done and/or the Results Obtained
3	Group	Independent Variable: Primary Predictor Variable	Not Applicable	TestWorks	Nominal: Study Arms, i.e., the Control or POTS Cohorts
4	EDA Type	EDA Signal Shape	EDA100C and PPGED-R	AcqKnowledge	Nominal: Tonic EDA Waveform or Response Subtype
5	POTS Diagnostic Age Range	Demographic	Not Applicable	TestWorks	Ordinal
6	Age Group	Demographic	Not Applicable	TestWorks	Ordinal
7	Sex	Demographic	Not Applicable	TestWorks	Nominal
8	BMI Group	Demographic	Not Applicable	TestWorks	Ordinal
9	Tilt Test Symptoms	Symptom	Not Applicable	TestWorks	Categorical (No/Yes)
10	Symptom: Anxiety	Symptom	Not Applicable	TestWorks	Categorical (No/Yes)
11	Symptom: Disorientation	Symptom	Not Applicable	TestWorks	Categorical (No/Yes)
12	Symptom: Dizziness	Symptom	Not Applicable	TestWorks	Categorical (No/Yes)

13	Symptom: Falling or Floating	Symptom	Not Applicable	TestWorks	Categorical (No/Yes)
14	Symptom: Brain Cloud, Brain Cloudiness, Brain Fog, Brain Fogginess, Mind Cloud, or Mind Cloudiness.	Symptom	Not Applicable	TestWorks	Categorical (No/Yes)
15	Symptom: Empty (feelings of emptiness)	Symptom	Not Applicable	TestWorks	Categorical (No/Yes)
16	Symptom: Headache	Symptom	Not Applicable	TestWorks	Categorical (No/Yes)
17	Symptom: Heavy (feelings of heaviness)	Symptom	Not Applicable	TestWorks	Categorical (No/Yes)
18	Symptom: Nausea	Symptom	Not Applicable	TestWorks	Categorical (No/Yes)
19	Symptom: Palpitation	Symptom	Not Applicable	TestWorks	Categorical (No/Yes)
20	Symptom: Chest Tightness	Symptom	Not Applicable	TestWorks	Categorical (No/Yes)
21	Symptom: Light Headedness	Symptom	Not Applicable	TestWorks	Categorical (No/Yes)
22	Symptom: Blurred Vision	Symptom	Not Applicable	TestWorks	Categorical (No/Yes)
23	Symptom: Cloudy Vision	Symptom	Not Applicable	TestWorks	Categorical (No/Yes)
24	Symptom: Spotty Vision	Symptom	Not Applicable	TestWorks	Categorical (No/Yes)
25	Symptom: Aura	Symptom	Not Applicable	TestWorks	Categorical (No/Yes)
26	Symptom: Non-Chest Pain	Symptom	Not Applicable	TestWorks	Categorical (No/Yes)
27	Symptom: Fatigue	Symptom	Not Applicable	TestWorks	Categorical (No/Yes)
28	Symptom: Drowsy, Drowsiness, Sleepy, Sleepiness.	Symptom	Not Applicable	TestWorks	Categorical (No/Yes)
29	Symptom: Tremor	Symptom	Not Applicable	TestWorks	Categorical (No/Yes)

30	Symptom: Tingling	Symptom	Not Applicable	TestWorks	Categorical (No/Yes)
31	Symptom: Flushes, Flushing, Hot Flushes.	Symptom	Not Applicable	TestWorks	Categorical (No/Yes)
32	Symptom: Clammy, Clamminess, Sweat, Sweatiness.	Symptom	Not Applicable	TestWorks	Categorical (No/Yes)
33	Symptom: Chill, Chills.	Symptom	Not Applicable	TestWorks	Categorical (No/Yes)
34	Symptom: Cold, Coldness.	Symptom	Not Applicable	TestWorks	Categorical (No/Yes)
35	Symptom: Fever, Feverishness Temperature Rise.	Symptom	Not Applicable	TestWorks	Categorical (No/Yes)
36	Symptom: Pressure (feelings of pressure)	Symptom	Not Applicable	TestWorks	Categorical (No/Yes)
37	Symptom: Numbness	Symptom	Not Applicable	TestWorks	Categorical (No/Yes)
38	Symptom: Pins and Needles	Symptom	Not Applicable	TestWorks	Categorical (No/Yes)
39	Symptom: Itchiness	Symptom	Not Applicable	TestWorks	Categorical (No/Yes)
40	Symptom: Weakness	Symptom	Not Applicable	TestWorks	Categorical (No/Yes)
41	Symptom: Shortness of Breath	Symptom	Not Applicable	TestWorks	Categorical (No/Yes)
42	Symptom: Fast Breath (feelings of increased HR)	Symptom	Not Applicable	TestWorks	Categorical (No/Yes)
43	Symptom: Faint (feelings of fainting or syncope)	Symptom	Not Applicable	TestWorks	Categorical (No/Yes)
44	Symptom: Drool (drooling or watering mouth)	Symptom	Not Applicable	TestWorks	Categorical (No/Yes)
45	Symptom: Paralysis (feelings of paralysis)	Symptom	Not Applicable	TestWorks	Categorical (No/Yes)

46	Symptom: Other (any other sundry symptoms)	Symptom	Not Applicable	TestWorks	Categorical (No/Yes)
47	CASS Computed	CASS	Not Applicable	TestWorks	Categorical (No/Yes)
48	CASS: Raw Cardiovagal Score Nominal Type 2	CASS	Not Applicable	TestWorks	Nominal CASS Variable
49	CASS Coded Cardiovagal Score	CASS	Not Applicable	TestWorks	Nominal CASS Variable
50	CASS Raw Adrenergic Score Nominal Type 2	CASS	Not Applicable	TestWorks	Nominal CASS Variable
51	CASS Coded Adrenergic Score	CASS	Not Applicable	TestWorks	Nominal CASS Variable
52	CASS Raw Sudomotor Score Nominal Type 2	CASS	Not Applicable	TestWorks	Nominal CASS Variable
53	CASS Coded Sudomotor Score	CASS	Not Applicable	TestWorks	Nominal CASS Variable
54	CASS Raw Total Score Nominal Type 2	CASS	Not Applicable	TestWorks	Nominal CASS Variable
55	CASS Coded Total Score	CASS	Not Applicable	TestWorks	Nominal CASS Variable
56	General Autonomic Impairment	CASS	Not Applicable	TestWorks	Nominal CASS Variable
57	Adrenergic POTS	Potential POTS Subtype	Not Applicable	TestWorks	Categorical (No/Yes)
58	Adrenergic Impairment Without Hyperadrenergism	Potential POTS Subtype	Not Applicable	TestWorks	Categorical (No/Yes)
59	Hyperadrenergism	Potential POTS Subtype	Not Applicable	TestWorks	Categorical (No/Yes)
60	Pre-ARS Medications Holding Adherence	Medications Holding Adherence	Not Applicable	TestWorks	Categorical (No/Yes)
61	Pre-ARS Anticholinergic Medications Holding Adherence	Medications Holding Adherence	Not Applicable	TestWorks	Categorical (No/Yes)
62	Meds48hourHRControl	Medications Holding Adherence	Not Applicable	TestWorks	Categorical (No/Yes)

63	Meds48hourAlcoholCaffeinated	Medications Holding Adherence	Not Applicable	TestWorks	Categorical (No/Yes)
64	Meds48hourAnticholinergic	Medications Holding Adherence	Not Applicable	TestWorks	Categorical (No/Yes)
65	Meds48hourAntihypertensive	Medications Holding Adherence	Not Applicable	TestWorks	Categorical (No/Yes)
66	Meds48hourAntihypotensive	Medications Holding Adherence	Not Applicable	TestWorks	Categorical (No/Yes)
67	Meds48hourChronotrope	Medications Holding Adherence	Not Applicable	TestWorks	Categorical (No/Yes)
68	Meds48hourNSAIDsOpioidsPain	Medications Holding Adherence	Not Applicable	TestWorks	Categorical (No/Yes)
69	ASA Line 1 PRT Computed	Adrenergic Sensitivity Analysis	CNAP Equipment and NIBP Cuff	TestWorks	Pressure Recovery Time
70	ASA Line 1 (or More) Average PRT Computed	Adrenergic Sensitivity Analysis	CNAP Equipment and NIBP Cuff	TestWorks	Average Pressure Recovery Time

Note. Abbreviations: ARS, autonomic reflex screen; ASA, adrenergic sensitivity analysis; BMI, body mass index; CASS, composite autonomic severity score; CNAP, continuous non-invasive arterial pressure; EDA, electrodermal activity; NIBP, non-invasive blood pressure; POTS, postural orthostatic tachycardia syndrome; PRT, pressure recovery time.

Supplemental Table 15

Variables for Correlational Analyses – Data from AcqKnowledge and TestWorks

	Variable Name	Variable Type	Data Source: Hardware	Data Source: Software	Clinical and Statistical Notes
1	EDA Peak to Peak During HUTT Period	EDA Change	EDA100C and PPGED-R	AcqKnowledge	Continuous Numeric Variable
2	EDA at Tilt-Up During HUTT Period	EDA Fixed-Point Value	EDA100C and PPGED-R	AcqKnowledge	Continuous Numeric Variable
3	EDA at Tilt Down During HUTT Period	EDA Fixed-Point Value	EDA100C and PPGED-R	AcqKnowledge	Continuous Numeric Variable
4	EDA Max During HUTT Period	EDA Fixed-Point Value	EDA100C and PPGED-R	AcqKnowledge	Continuous Numeric Variable
5	EDA Min During HUTT Period	EDA Fixed-Point Value	EDA100C and PPGED-R	AcqKnowledge	Continuous Numeric Variable
6	EDA Difference During HUTT Period (i.e., the Difference Between {EDA Max and EDA Min} During HUTT Period)	EDA Change	EDA100C and PPGED-R	AcqKnowledge	Continuous Numeric Variable
7	EDA Mean During HUTT Period	EDA Fixed-Point Value	EDA100C and PPGED-R	AcqKnowledge	Continuous Numeric Variable
8	EDA Median During HUTT Period	EDA Fixed-Point Value	EDA100C and PPGED-R	AcqKnowledge	Continuous Numeric Variable
9	EDA Standard Deviation During HUTT Period	EDA Fixed-Point Value	EDA100C and PPGED-R	AcqKnowledge	Continuous Numeric Variable
10	EDA Area During HUTT Period	EDA Fixed-Point Value	EDA100C and PPGED-R	AcqKnowledge	Continuous Numeric Variable

11	EDA Integral During HUTT Period	EDA Fixed-Point Value	EDA100C and PPGED-R	AcqKnowledge	Continuous Numeric Variable
12	EDA Delta During HUTT Period	EDA Fixed-Point Value	EDA100C and PPGED-R	AcqKnowledge	Continuous Numeric Variable
13	EDA Area During Pre-Tilt Period	EDA Fixed-Point Value	EDA100C and PPGED-R	AcqKnowledge	Continuous Numeric Variable
14	EDA Pre-Tilt Duration (30 seconds before HUTT period starts)	EDA Time Fixed-Point Value	EDA100C and PPGED-R	AcqKnowledge	Continuous Numeric Variable
15	EDA Area During Pre-Tilt Period Per Second (#13 ÷ #14)	EDA Fixed-Point Value	EDA100C and PPGED-R	AcqKnowledge	Continuous Numeric Variable
16	EDA Area During the Head Up Tilt Test (HUTT) Period	EDA Fixed-Point Value	EDA100C and PPGED-R	AcqKnowledge	Continuous Numeric Variable
17	EDA Head Up Tilt Test Duration (a variable period of time)	EDA Time Fixed-Point Value	EDA100C and PPGED-R	AcqKnowledge	Continuous Numeric Variable
18	EDA Area During the Head Up Tilt Test (HUTT) Period Per Second (#16 ÷ #17)	EDA Fixed-Point Value	EDA100C and PPGED-R	AcqKnowledge	Continuous Numeric Variable
19	EDA Area During Post-Tilt Period	EDA Fixed-Point Value	EDA100C and PPGED-R	AcqKnowledge	Continuous Numeric Variable
20	EDA Post-Tilt Duration (30 seconds after HUTT period ends)	EDA Time Fixed-Point Value	EDA100C and PPGED-R	AcqKnowledge	Continuous Numeric Variable
21	EDA Area During Post-Tilt Period Per Second (#19 ÷ #20)	EDA Fixed-Point Value	EDA100C and PPGED-R	AcqKnowledge	Continuous Numeric Variable
22	EDA Slope During HUTT Period	EDA Fixed-Point Value	EDA100C and PPGED-R	AcqKnowledge	Continuous Numeric Variable

23	EDA Delta-Slope During HUTT Period	EDA Fixed-Point Value	EDA100C and PPGED-R	AcqKnowledge	Continuous Numeric Variable
24	EDA Area During Post-HUTT Period – EDA Area During Pre-HUTT Period	EDA Change	EDA100C and PPGED-R	AcqKnowledge	Continuous Numeric Variable
25	EDA Area During HUTT Period – EDA Area During Pre-HUTT Period	EDA Change	EDA100C and PPGED-R	AcqKnowledge	Continuous Numeric Variable
26	EDA Area During Post-HUTT Period - EDA Area During HUTT Period	EDA Change	EDA100C and PPGED-R	AcqKnowledge	Continuous Numeric Variable
27	EDA Mean During Pre-HUTT Period	EDA Fixed-Point Value	EDA100C and PPGED-R	AcqKnowledge	Continuous Numeric Variable
28	EDA Mean During Post-HUTT Period	EDA Fixed-Point Value	EDA100C and PPGED-R	AcqKnowledge	Continuous Numeric Variable
29	EDA Peak to Peak During Pre-HUTT Period	EDA Change	EDA100C and PPGED-R	AcqKnowledge	Continuous Numeric Variable
30	EDA Peak to Peak During Post-HUTT Period	EDA Change	EDA100C and PPGED-R	AcqKnowledge	Continuous Numeric Variable
31	EDA Area During Post-HUTT Period Per Second – EDA Area During Pre-HUTT Period Per Second	EDA Change	EDA100C and PPGED-R	AcqKnowledge	Continuous Numeric Variable
32	EDA Area During HUTT Period Per Second – EDA Area During Pre-HUTT Period Per Second	EDA Change	EDA100C and PPGED-R	AcqKnowledge	Continuous Numeric Variable
33	EDA Area During Post-HUTT Period Per Second – EDA Area During HUTT Period Per Second	EDA Change	EDA100C and PPGED-R	AcqKnowledge	Continuous Numeric Variable
34	EDA Max During HUTT Period – EDA Mean Pre-HUTT Period	EDA Change	EDA100C and PPGED-R	AcqKnowledge	Continuous Numeric Variable

35	EDA Min During HUTT Period – EDA Mean During Pre-HUTT Period	EDA Change	EDA100C and PPGED-R	AcqKnowledge	Continuous Numeric Variable
36	EDA Peak to Peak During Post-HUTT Period – EDA Peak to Peak During Pre-HUTT Period	EDA Change	EDA100C and PPGED-R	AcqKnowledge	Continuous Numeric Variable
37	EDA Peak to Peak During HUTT - EDA Peak to Peak During Pre-HUTT	EDA Change	EDA100C and PPGED-R	AcqKnowledge	Continuous Numeric Variable
38	EDA Peak to Peak During Post-HUTT Period - EDA Peak to Peak During HUTT Period	EDA Change	EDA100C and PPGED-R	AcqKnowledge	Continuous Numeric Variable
39	EDA Frequency During Pre-HUTT Period	EDA Fixed-Point Value	EDA100C and PPGED-R	AcqKnowledge	Continuous Numeric Variable
40	EDA Frequency During HUTT Period	EDA Fixed-Point Value	EDA100C and PPGED-R	AcqKnowledge	Continuous Numeric Variable
41	EDA Frequency During Post-HUTT Period	EDA Fixed-Point Value	EDA100C and PPGED-R	AcqKnowledge	Continuous Numeric Variable
42	EDA Frequency During Post-HUTT Period – EDA Frequency During Pre-HUTT Period	EDA Change	EDA100C and PPGED-R	AcqKnowledge	Continuous Numeric Variable
43	EDA Frequency During HUTT Period – EDA Frequency During Pre-HUTT Period	EDA Change	EDA100C and PPGED-R	AcqKnowledge	Continuous Numeric Variable
44	EDA Frequency During Post-HUTT Period – EDA Frequency During HUTT Period	EDA Change	EDA100C and PPGED-R	AcqKnowledge	Continuous Numeric Variable
45	EDA BPM During Pre-HUTT Period	EDA Fixed-Point Value	EDA100C and PPGED-R	AcqKnowledge	Continuous Numeric Variable
46	EDA BPM During HUTT Period	EDA Fixed-Point Value	EDA100C and PPGED-R	AcqKnowledge	Continuous Numeric Variable

47	EDA BPM During Post-HUTT Period	EDA Fixed-Point Value	EDA100C and PPGED-R	AcqKnowledge	Continuous Numeric Variable
48	EDA BPM During Post-HUTT Period – EDA BPM During Pre-HUTT Period	EDA Change	EDA100C and PPGED-R	AcqKnowledge	Continuous Numeric Variable
49	EDA BPM During HUTT Period – EDA During Pre-HUTT Period	EDA Change	EDA100C and PPGED-R	AcqKnowledge	Continuous Numeric Variable
50	EDA BPM During Post-HUTT Period – EDA BPM During HUTT Period	EDA Change	EDA100C and PPGED-R	AcqKnowledge	Continuous Numeric Variable
51	EDA Integral During Pre-HUTT Period	EDA Fixed-Point Value	EDA100C and PPGED-R	AcqKnowledge	Continuous Numeric Variable
52	EDA Integral During Post-HUTT Period	EDA Fixed-Point Value	EDA100C and PPGED-R	AcqKnowledge	Continuous Numeric Variable
53	EDA Integral During Post-HUTT Period – EDA Integral During Pre-HUTT Period	EDA Change	EDA100C and PPGED-R	AcqKnowledge	Continuous Numeric Variable
54	EDA Integral During HUTT Period – EDA Integral During Pre-HUTT Period	EDA Change	EDA100C and PPGED-R	AcqKnowledge	Continuous Numeric Variable
55	EDA Integral During Post-HUTT Period – EDA Integral During HUTT Period	EDA Change	EDA100C and PPGED-R	AcqKnowledge	Continuous Numeric Variable
56	EDA Sum During Pre-HUTT Period	EDA Fixed-Point Value	EDA100C and PPGED-R	AcqKnowledge	Continuous Numeric Variable
57	EDA Sum During HUTT Period	EDA Fixed-Point Value	EDA100C and PPGED-R	AcqKnowledge	Continuous Numeric Variable
58	EDA Sum During Post HUTT Period	EDA Fixed-Point Value	EDA100C and PPGED-R	AcqKnowledge	Continuous Numeric Variable

59	EDA Sum During Post HUTT Period – EDA Sum During Pre-HUTT Period	EDA Change	EDA100C and PPGED-R	AcqKnowledge	Continuous Numeric Variable
60	EDA Sum During HUTT Period – EDA Sum During Pre-HUTT Period	EDA Change	EDA100C and PPGED-R	AcqKnowledge	Continuous Numeric Variable
61	EDA Sum During Post-HUTT Period – EDA Sum During HUTT Period	EDA Change	EDA100C and PPGED-R	AcqKnowledge	Continuous Numeric Variable
62	EDA at Tilt Down During HUTT Period – EDA at Tilt Up During HUTT Period	EDA Change	EDA100C and PPGED-R	AcqKnowledge	Continuous Numeric Variable
63	EDA Value Corresponding to the AcqKnowledge Equivalent of the ARS Max HR Result Shown in TestWorks During HUTT	EDA Fixed-Point Value	EDA100C and PPGED-R	AcqKnowledge	Continuous Numeric Variable
64	AcqKnowledge Equivalent of the ARS Max HR Result Shown in TestWorks During HUTT Period	Hemodynamic Fixed-Point Variable: AcqKnowledge Equivalent of a HR Result Shown in TestWorks	EDA100C and PPGED-R	AcqKnowledge	Continuous Numeric Variable
65	Raw Area Under the Curve of the AcqKnowledge Generated Pulse Rate (PR) During HUTT Period	Hemodynamic Fixed-Point Variable: Derived from the PPG Signal Trace in AcqKnowledge Without Dependence on the HR Results in TestWorks	EDA100C and PPGED-R	AcqKnowledge	Continuous Numeric Variable
66	Area Under the Curve of the AcqKnowledge Generated Pulse Rate (PR) During HUTT Period Per Second	Hemodynamic Fixed-Point Variable: Derived from the PPG Signal Trace in AcqKnowledge Without Dependence on the HR Results in TestWorks	EDA100C and PPGED-R	AcqKnowledge	Continuous Numeric Variable

67	HR at Tilt Up During HUTT Period	Hemodynamic Fixed-Point Variable: AcqKnowledge Equivalent of a HR Result Shown in TestWorks	EDA100C and PPGED-R	AcqKnowledge	Continuous Numeric Variable
68	HR at Tilt Down During HUTT Period	Hemodynamic Fixed-Point Variable: AcqKnowledge Equivalent of a HR Result Shown in TestWorks	EDA100C and PPGED-R	AcqKnowledge	Continuous Numeric Variable
69	HR Peak to Peak During HUTT Period	Hemodynamic Change Variable in AcqKnowledge	EDA100C and PPGED-R	AcqKnowledge	Continuous Numeric Variable
70	Hemodynamic Changes: AcqKnowledge PR at Tilt Down – AcqKnowledge PR at Tilt Up During HUTT Period	Hemodynamic Change Variable in AcqKnowledge	EDA100C and PPGED-R	AcqKnowledge	Continuous Numeric Variable
71	Hemodynamic-Time: Latency of the AcqKnowledge Equivalent of the ARS Max HR Result Shown in TestWorks During HUTT Period	Hemodynamic Variable Time in AcqKnowledge	EDA100C and PPGED-R	AcqKnowledge	Continuous Numeric Variable
72	Age	Demographic	Not Applicable	TestWorks	Continuous Numeric Variable
73	Height	Demographic	Unstated Measuring Device, Ruler or Scale.	TestWorks	Continuous Numeric Variable
74	Weight	Demographic	Unstated Measuring Device, Ruler or Scale.	TestWorks	Continuous Numeric Variable
75	EDA Mean During HUTT Period ÷ EDA Difference During HUTT Period	EDA Inter and Intra Group Normalization Variable	EDA100C and PPGED-R	AcqKnowledge	Continuous Numeric Variable
76	EDA at Tilt Down – EDA at Tilt Up During HUTT Period ÷ EDA Difference During HUTT Period	EDA Inter and Intra Group Normalization Variable	EDA100C and PPGED-R	AcqKnowledge	Continuous Numeric Variable

77	EDA Max During HUTT Period ÷ EDA Min During HUTT Period	EDA Inter and Intra Group Normalization Variable	EDA100C and PPGED-R	AcqKnowledge	Continuous Numeric Variable
78	EDA Max Time During HUTT Period ÷ EDA Min Time During HUTT Period	EDA Inter and Intra Group Normalization Variable	EDA100C and PPGED-R	AcqKnowledge	Continuous Numeric Variable

Note. Abbreviations: ARS, autonomic reflex screen; EDA. Electrodermal activity; HR, heart rate; HUTT, head-up tilt-table test; PPG, photoplethysmography.

Supplemental Table 16

Additional Details on the Nomenclature of Some Variables: List of Variables With Their Regular Variable Names and Their Statistical-Analyses-Friendly Variable Names

	Regular Variable Names	**Statistical Analyses Friendly Variable Names**
1	All Medications Holding Adherence (Yes/No/Unknown)	Meds48hourChronotrope
2	Anticholinergic Medications Holding Adherence (Yes/No/Unknown)	AnticholinergicMedAdherence
3	Hemodynamic Changes: Post-SBP – Pre-SBP	HemodynamicChangesPostSBP-PreSBP
4	Hemodynamic Changes: Post-DBP – Pre-DBP	HemodynamicChangesPostDBP-PreDBP
5	Hemodynamic Changes: Post-HR – Pre-HR	HemodynamicChangesPostHR-PreHR
6	Hemodynamic Changes: Max HUT HR – Pre-HR	HemodynamicChangesMaxHUTHR-PreHR
7	Hemodynamic Changes: Min HUT HR – Pre-HR	HemodynamicChangesMinHUTHR-PreHR
8	Hemodynamic Changes: Max HUT HR - HR at Min SBP	HemodynamicChangesMaxHUTHR-HRatMinSBP
9	Hemodynamic Changes: Min HUT HR - HR at Min SBP	HemodynamicChangesMinHUTHR-HRatMinSBP
10	Hemodynamic Changes: HR at Min SBP – Pre-HR	HemodynamicChangesHRatMinSBP-PreHR
11	AcqKnowledge Heart Rate (or PR) at Tilt Down - AcqKnowledge Heart Rate (or PR) at Tilt Up	HemodynamicChangesAcqKHR(PR)atTiltDown-AcqKHR(PR)atTiltUp
12	HRDB: Average of Heart Rate Differences	HemodynamicChangesHRDBAverageHRDifference
13	EDA_{var} EDA Post HUT Area – EDA Pre Hut Area	EDAPostHUTArea-EDAPreHUTArea

14	EDA_{var} EDA HUT Area – EDA Pre Hut Area	EDAHUTArea-EDAPreHUTArea
15	EDA_{var} EDA Post HUT Area – EDA Hut Area	EDAPostHUTArea-EDAHUTArea
16	EDA_{var} Pre-HUT Mean EDA	EDAPreHUTMean
17	EDA_{var} Post-HUT Mean EDA	EDAPostHUTMean
18	EDA_{var} Pre-HUT Peak-to-Peak EDA	EDAPreHUTPeaktoPeak
19	EDA_{var} Post-HUT Peak-to-Peak EDA	EDAPostHUTPeaktoPeak
20	EDA_{var} Post-HUT EDA Area Per Second – Pre-HUT EDA Area Per Second	EDAPostHUTAreaPerSecond-EDAPreHUTAreaPerSecond
21	EDA_{var} HUT EDA Area Per Second - Pre-HUT EDA Area Per Second	EDAHUTAreaPerSecond-EDAPreHUTAreaPerSecond
22	EDA_{var} Post-HUT EDA Area Per Second - HUT EDA Area Per Second	EDAPostHUTAreaPerSecond-EDAHUTAreaPerSecond
23	EDA_{var} HUT Max EDA - Pre-HUT Mean EDA	EDAHUTMax-EDAPreHUTMean
24	EDA_{var} HUT Min EDA - Pre-HUT Mean EDA	EDAHUTMin-EDAPreHUTMean
25	EDA_{var} Post-HUT Peak-to-Peak EDA - Pre-HUT Peak-to-Peak EDA	EDAPostHUTTPeaktoPeak-EDAPreHUTTPeaktoPeak
26	EDA_{var} HUT Peak-to-Peak EDA - Pre-HUT Peak-to-Peak EDA	EDAHUTTPeaktoPeak-EDAPreHUTTPeaktoPeak
27	EDA_{var} Post-HUT Peak-to-Peak EDA - HUT Peak-to-Peak EDA	EDAPostHUTPeaktoPeak-EDAHUTPeaktoPeak
28	EDA_{var} Pre-HUT EDA Frequency	EDAPreHUTFrequency
29	EDA_{var} HUT EDA Frequency	EDAHUTFrequency
30	EDA_{var} Post-HUT EDA Frequency	EDAPostHUTFrequency
31	EDA_{var} Post-HUT EDA Frequency - Pre-HUT EDA Frequency	EDAPostHUTFrequency-EDAPreHUTFrequency

32	EDA_{var} HUT EDA Frequency - Pre-HUT EDA Frequency	EDAHUTFrequency-EDAPreHUTFrequency
33	EDA_{var} Post-HUT EDA Frequency - HUT EDA Frequency	EDAPostHUTFrequency-EDAHUTFrequency
34	EDA_{var} Pre-HUT EDA BPM	EDAPreHUTBPM
35	EDA_{var} HUT EDA BPM	EDAHUTBPM
36	EDA_{var} Post-HUT EDA BPM	EDAPostHUTBPM
37	EDA_{var} Post-HUT EDA BPM - Pre-HUT EDA BPM	EDAPostHUTBPM-EDAPreHUTBPM
38	EDA_{var} HUT EDA BPM - Pre-HUT EDA BPM	EDAHUTTBPM-EDAPreHUTTBPM
39	EDA_{var} Post-HUT EDA BPM - EDA HUT BPM	EDAPostHUTBPM-EDAHUTBPM
40	EDA_{var} EDA Pre HUT Integral	EDAPreHUTIntegral
41	EDA_{var} EDA Post HUT Integral	EDAPostHUTIntegral
42	EDA_{var} EDA Post HUT Integral - EDA Pre HUT Integral	EDAPostHUTIntegral-EDAPreHUTIntegral
43	EDA_{var} EDA HUT Integral - EDA Pre HUT Integral	EDAHUTIntegral-EDAPreHUTIntegral
44	EDA_{var} EDA Post HUT Integral - EDA HUT Integral	EDAPostHUTIntegral-EDAHUTIntegral
45	EDA_{var} EDA Pre HUT Sum	EDAPreHUTSum
46	EDA_{var} EDA HUT Sum	EDAHUTSum
47	EDA_{var} EDA Post HUT Sum	EDAPostHUTSum
48	EDA_{var} EDA Post HUT Sum - EDA Pre HUT Sum	EDAPostHUTSum-EDAPreHUTSum
49	EDA_{var} EDA HUT Sum - EDA Pre HUT Sum	EDAHUTSum-EDAPreHUTSum

50	EDA_{var} EDA Post HUT Sum - EDA HUT Sum	EDAPostHUTSum-EDAHUTSum
51	EDA_{var} EDA at Tilt Down - EDA at Tilt Up	EDAatTiltDown-EDAatTiltUp
52	Baseline from Line-1 of the Adrenergic Sensitivity Analysis of the Valsalva Maneuver Test	ASALine1Baseline
53	Phase 2E Max Rate from Line-1 of the Adrenergic Sensitivity Analysis of the Valsalva Maneuver Test	ASALine1Phase2EMaxRate
54	Phase 2E Min Rate from Line-1 of the Adrenergic Sensitivity Analysis of the Valsalva Maneuver Test	ASALine1Phase2EMinRate
55	Phase 2E Rate Difference from Line-1 of the Adrenergic Sensitivity Analysis of the Valsalva Maneuver Test	ASALine1Phase2ERateDifference
56	Phase 2E Max Rate from Line-1 of the Adrenergic Sensitivity Analysis of the Valsalva Maneuver Test - Baseline from Line-1 of the Adrenergic Sensitivity Analysis of the Valsalva Maneuver Test	ASALine1Phase2EMaxRate-Baseline
57	Phase 2E Min Rate from Line-1 of the Adrenergic Sensitivity Analysis of the Valsalva Maneuver Test - Baseline from Line-1 of the Adrenergic Sensitivity Analysis of the Valsalva Maneuver Test	ASALine1Phase2EMinRate-Baseline
58	Phase 3 Max Rate from Line-1 of the Adrenergic Sensitivity Analysis of the Valsalva Maneuver Test	ASALine1Phase3MaxRate
59	Phase 3 Min Rate from Line-1 of the Adrenergic Sensitivity Analysis of the Valsalva Maneuver Test	ASALine1Phase3MinRate-Baseline
60	Phase 3 Rate Difference from Line-1 of the Adrenergic Sensitivity Analysis of the Valsalva Maneuver Test	ASALine1Phase3RateDifference
61	0.75 of Phase 3 Rate Difference from Line-1 of the Adrenergic Sensitivity Analysis of the Valsalva Maneuver Test	ASALine1(0.75)ofPhase3RateDifference
62	Phase 3 Max Rate from Line-1 of the Adrenergic Sensitivity Analysis of the Valsalva Maneuver Test - Baseline from Line-1 of the Adrenergic Sensitivity Analysis of the Valsalva Maneuver Test	ASALine1Phase3MaxRate-Baseline

63	Phase 3 Min Rate from Line-1 of the Adrenergic Sensitivity Analysis of the Valsalva Maneuver Test - Baseline from Line-1 of the Adrenergic Sensitivity Analysis of the Valsalva Maneuver Test	ASALine1Phase3MinRate-Baseline
64	Total Difference from Line-1 of the Adrenergic Sensitivity Analysis of the Valsalva Maneuver Test	ASALine1TotalDifference
65	Adrenergic Score from Line-1 of the Adrenergic Sensitivity Analysis of the Valsalva Maneuver Test	ASALine1AdrenergicScore
66	Lowest Adrenergic Score from the Adrenergic Sensitivity Analysis of the Valsalva Maneuver Test	ASALine1AdrenergicScore(orthe)Lowest(valid)AdrenergicScore
67	QSWEAT (Forearm): Total Volume	QSWEATForearmTotalVolume
68	QSWEAT (Forearm): Response Latency	QSWEATForearmResponseLatency
69	QSWEAT (Forearm): Baseline Rate	QSWEATForearmBaselineRate
70	QSWEAT (Forearm): Ending Offset	QSWEATForearmEndingOffset
71	QSWEAT (Forearm): 5th Percentile Q-Sweat	QSWEATForearm5thPercentileQSweat
72	QSWEAT (Forearm): Ending Offset - Baseline Rate	QSWEATForearmEndingOffset-BaselineRate

Note. Abbreviations: ASA, adrenergic sensitivity analysis; DBP, diastolic blood pressure; EDA, electrodermal activity; HR, heart rate; HUT, head up tilt; PR, pulse rate; SBP, systolic blood pressure; QSWEAT, a brand name for a piece of quantitative sudomotor axon test (QSART) related physio lab testing equipment that is manufactured and sold by WR Medical Electronics Co., Maplewood, Minnesota.

Supplemental Table 17

Gold Standard Diagnostic Indices, Parameters, or Variables.

	Column	Index-Parameter-or-Variable Statistical Name	Index-Parameter-or-Variable Full Regular Name	Type
1	C	GroupPOTScases1controls2	Group: Control or Pathological Case	Categorical
2	E	EDAresponseSubtypeNewLabels	Subgroup: Tonic Electrodermal Response Subtype	Categorical
3	F	Age	Age	Continuous
4	G	POTSDiagnosticAgeRange	Diagnostic Age Range for POTS Cases	Ordinal
5	H	AgeGroup	Age Group	Categorical
6	I	Sex	Sex	Categorical
7	L	BMI	BMI	Continuous
8	P	TiltTestSymptoms	Symptoms Reported During HUTT	Categorical
9	Q	NumSymptoms	Number of Symptoms Reported During HUTT	Count
10	BC	TiltUpSymptomsPresence	Symptoms Reported at Tilt-up	Categorical
11	BD	TiltUpSymptomsNumber	Number of Symptoms Reported at Tilt-up	Count
12	BE	SymptomsSeverityTrendDuringUTilt	Trend of Symptoms Severity During HUTT	Ordinal
13	BF	TiltDownSymptomsPresence	Symptoms Reported at Tilt-down	Categorical
14	BG	TiltDownSymptomsNumber	Number of Symptoms Reported at Tilt-down	Continuous
15	BH	SymptomsQualityandRanking	Symptoms Quality and Ranking	Ordinal
16	BI	huttHRmax	Maximum HR During HUTT	Continuous
17	BK	huttHRDelta	HR Delta During HUTT	Continuous
18	BL	huttHRatSBPmin	HR at the Minimum SBP During HUTT	Continuous
19	BM	huttSBPmin	Minimum SBP During HUTT	Continuous
20	BN	huttSBPminChange	Change in Minimum SBP from Pre-HUTT to HUTT	Continuous
21	SG	CASSRawCardiovagalScrNumTyp1	Cardiovagal Component of the CASS	Continuous
22	SJ	CASSRawAdrenergicScrNumTyp1	Adrenergic Component of the CASS	Continuous
23	SM	CASSRawSudmtrScrNumTyp1	Sudomotor Component of the CASS	Continuous
24	SP	CASSRawTotalScoreNumType1	Total of the Three Components of the CASS	Continuous
25	TO	MedAdhrnc	Adherence to the Medications Withholding Requirement	Categorical
26	TP	AntchlnrgcMedAdhrnc	Anticholinergic Medications Withholding Adherence	Categorical
27	TX	numMedsNtHldAll	Number of Medications Not Withheld Before Testing	Count
28	TZ	numMedsNtHldAntchlnrgc	Number of Anticholinergic Medications Not Withheld Before Testing	Count

29	UN	HmdynmcChngsHRDBAvrgHRDffrnc	Hemodynamic Changes HRDB Average HR Difference	Continuous
30	WM	ASALn1PRTVl	Pressure Recovery Time	Continuous
31	WS	QSWEATFrrmTtlVlm	Total Volume Measured During QSART-QSWEAT	Continuous
32	WT	QSWEATFrrmRspnsLtncy	Latency of Sweat Response During QSART-QSWEAT	Continuous
33	XA	HRDBRMaxHRAvg	HRDB Average Maximum HR	Continuous
34	XC	HRDBRDltHR	HRDB Delta HR	Continuous
35	XD	HRDBEIRatio	HRDB Expiration-Inspiration Ratio HR	Continuous
36	XJ	VlslvMaxHRAvg	Maximum Valsalva Maneuver HR	Continuous
37	XL	VlslvRatioHRAvg	Average Valsalva Maneuver HR Ratio	Continuous
38	XM	VlslvRatioHRGrtst	Greatest Valsalva Maneuver HR Ratio	Continuous

Note. Abbreviations: ASA, adrenergic sensitivity analysis; CASS, composite autonomic symptoms score; EDA, electrodermal activity; HUTT, head-up tilt-table test; POTS, postural orthostatic tachycardia syndrome; QSART, quantitative sudomotor axon test; QSWEAT, quantitative sweat test.

Supplemental Table 18

Table of Variables: List of Variables, Variable Characteristics and Time of Measurement for the Variables in Dataset #1

	Variable	**Variable Type: ASA-Derived CASS, ASA Valsalva Maneuver, Demographic, EDA, EDA Group, Study Arm (or Study Cohort), Hemodynamic, Pre-ARS Medications Adherence, Number, Potential POTS Subtype, Screening Type (or Test Type), Time (including PRT), or QSART (or QSWEAT)**	**Variable Statistical Type**	**Variable Measurement Software**	**Variable Role**	**Variable Measured During Test, Pre-Test, or Post-Test**
1	Study ID	Not Applicable	Numeric (Discrete)	Not Applicable	Patient Identification	Not Applicable
2	ARS Testing Type: Fully Completed ARS Tests = 1; Fully Completed ARS Tests with Missing Results = 2; Fully Completed TT-Only Tests = 3; Partially Completed ARS Tests = 4)	Screening Type (or Test Type)	Categorical (Nominal)	TestWorks	Covariate	Not Applicable
3	Group (POTS vs Control)	Study Arm (or Study Cohort)	Categorical (Nominal)	TestWorks	Primary Predictor	Not Applicable
4	EDA Type	EDA Group	Categorical (Nominal)	AcqKnowledge	Covariate	HUTT
5	Age (years)	Demographic	Numeric (Continuous)	TestWorks	Covariate	Not Applicable
6	POTS Diagnostic Age Range: ≤ 19-years-old vs ≥ 20-years-old	Demographic	Numeric (Discrete)	TestWorks	Covariate	Not Applicable
7	Age Group Classification of All Patients (Controls & POTS): ≤ 19-years-old vs ≥ 20-years-old	Demographic	Numeric (Discrete)	TestWorks	Covariate	Not Applicable
8	Sex (female vs male)	Demographic	Categorical (Nominal)	TestWorks	Covariate	Not Applicable

9	Height (cm)	Demographic	Numeric (Continuous)	TestWorks	Covariate	Not Applicable
10	Weight (kg)	Demographic	Numeric (Continuous)	TestWorks	Covariate	Not Applicable
11	BMI (kg/m2)	Demographic	Numeric (Continuous)	TestWorks	Covariate	Not Applicable
12	BMI Interpretation (Underweight vs Healthy vs Overweight vs Obese)	Demographic	Categorical (Ordinal)	TestWorks	Covariate	Not Applicable
13	Tilt Test Symptoms (Absent/Present)	Symptom	Categorical (Nominal)	TestWorks	Outcome Variable	HUTT
14	Number of Symptoms	Symptom	Numeric (Continuous)	TestWorks	Outcome Variable	HUTT
15	Type of Symptom: Anxiety, Anxious, Stressed, Worried (Yes/No)	Symptom	Categorical (Nominal)	TestWorks	Outcome Variable	HUTT
16	Type of Symptom: Disorientation, Head Spinning, Slipping off Tilt Table, Unbalanced, Unsteady (Yes/No)	Symptom	Categorical (Nominal)	TestWorks	Outcome Variable	HUTT
17	Type of Symptom: Dizziness (Yes/No)	Symptom	Categorical (Nominal)	TestWorks	Outcome Variable	HUTT
18	Type of Symptom: Feelings of Falling, Flight, Floatiness, Hallucinations of Body Moving in Tandem with Moving Objects & Walls, Soaring, Levitation (Yes/No)	Symptom	Categorical (Nominal)	TestWorks	Outcome Variable	HUTT
19	Type of Symptom: Fogginess (Brain-Fog, Cloudiness, etc.) (Yes/No)	Symptom	Categorical (Nominal)	TestWorks	Outcome Variable	HUTT
20	Type of Symptom: Feelings of Emptiness (Yes/No)	Symptom	Categorical (Nominal)	TestWorks	Outcome Variable	HUTT
21	Type of Symptom: Headache, Head Feels Heavy, Head Hurts, Head Throbbing, Head Pounding, Head Pressure (Yes/No)	Symptom	Categorical (Nominal)	TestWorks	Outcome Variable	HUTT
22	Type of Symptom: Feels Heavy (Specific: Other Body Parts), Heaviness (Specific: Other Body Parts), "Feels heavy everywhere.",	Symptom	Categorical (Nominal)	TestWorks	Outcome Variable	HUTT

	Heavy (Non-Localized & Non-Specific), Heaviness Everywhere (Yes/No)					
23	Type of Symptom: Nausea (Yes/No)	Symptom	Categorical (Nominal)	TestWorks	Outcome Variable	HUTT
24	Type of Symptom: Chest Pounding, Chest Racing, Heart Beating faster, Heart Pounding, Heart Racing, Palpitations (Yes/No)	Symptom	Categorical (Nominal)	TestWorks	Outcome Variable	HUTT
25	Type of Symptom: Chest Discomfort, Chest Pain, Chest Pressure, Chest Tightness, Chest Throbbing, "like a brick on chest" (Yes/No)	Symptom	Categorical (Nominal)	TestWorks	Outcome Variable	HUTT
26	Type of Symptom: Light Headedness (Yes/No)	Symptom	Categorical (Nominal)	TestWorks	Outcome Variable	HUTT
27	Type of Symptom: Blurry Vision (Yes/No)	Symptom	Categorical (Nominal)	TestWorks	Outcome Variable	HUTT
28	Type of Symptom: Cloudy Vision (Yes/No)	Symptom	Categorical (Nominal)	TestWorks	Outcome Variable	HUTT
29	Type of Symptom: Spotty Vision (Yes/No)	Symptom	Categorical (Nominal)	TestWorks	Outcome Variable	HUTT
30	Type of Symptom: Aura/Halo/Lights (Yes/No)	Symptom	Categorical (Nominal)	TestWorks	Outcome Variable	HUTT
31	Type of Symptom: Pain (Not Chest Pain: Other Body Part) (Yes/No)	Symptom	Categorical (Nominal)	TestWorks	Outcome Variable	HUTT
32	Type of Symptom: Fatigue, Tiredness, or Weariness) (Yes/No)	Symptom	Categorical (Nominal)	TestWorks	Outcome Variable	HUTT
33	Type of Symptom: Drowsy, Drowsiness, Feels Sleepy, Sleepy, Sleepiness (Yes/No)	Symptom	Categorical (Nominal)	TestWorks	Outcome Variable	HUTT
34	Type of Symptom: Shaking, Trembling, or Tremors (Yes/No)	Symptom	Categorical (Nominal)	TestWorks	Outcome Variable	HUTT
35	Type of Symptom: Tingling (Yes/No)	Symptom	Categorical (Nominal)	TestWorks	Outcome Variable	HUTT
36	Type of Symptom: Flushes (Yes/No)	Symptom	Categorical (Nominal)	TestWorks	Outcome Variable	HUTT

37	Type of Symptom: Clammy, Clamminess, Sweat (Yes/No)	Symptom	Categorical (Nominal)	TestWorks	Outcome Variable	HUTT
38	Type of Symptom: Chill, Chilliness, Chilly (Yes/No)	Symptom	Categorical (Nominal)	TestWorks	Outcome Variable	HUTT
39	Type of Symptom: Coldness (Yes/No)	Symptom	Categorical (Nominal)	TestWorks	Outcome Variable	HUTT
40	Type of Symptom: Heat, Hot, Fever, or Feverish, Temperature, "Temperature fluctuating" (Yes/No)	Symptom	Categorical (Nominal)	TestWorks	Outcome Variable	HUTT
41	Type of Symptom: Pressure (Yes/No)	Symptom	Categorical (Nominal)	TestWorks	Outcome Variable	HUTT
42	Type of Symptom: Numbness (Yes/No)	Symptom	Categorical (Nominal)	TestWorks	Outcome Variable	HUTT
43	Type of Symptom: Pins and Needles (Yes/No)	Symptom	Categorical (Nominal)	TestWorks	Outcome Variable	HUTT
44	Type of Symptom: Itch, Itchy, Itchiness, Scratchy (Yes/No)	Symptom	Categorical (Nominal)	TestWorks	Outcome Variable	HUTT
45	Type of Symptom: Weakness (Yes/No)	Symptom	Categorical (Nominal)	TestWorks	Outcome Variable	HUTT
46	Type of Symptom: Breathing Harder, "Breathing more labored," Difficulty Breathing, Dyspnea, Shortness of Breath (SOB) (Yes/No)	Symptom	Categorical (Nominal)	TestWorks	Outcome Variable	HUTT
47	Type of Symptom: Feelings of Breathing Faster, Breathing More, Tachypnea (Yes/No)	Symptom	Categorical (Nominal)	TestWorks	Outcome Variable	HUTT
48	Type of Symptom: Blacking-out, Feeling Faint, Feeling like Passing Out, Greying-out, Presyncopal, Wooziness (Yes/No)	Symptom	Categorical (Nominal)	TestWorks	Outcome Variable	HUTT
49	Type of Symptom: Drooliness, Mouth Watering (Yes/No)	Symptom	Categorical (Nominal)	TestWorks	Outcome Variable	HUTT
50	Type of Symptom: Feelings of Paralysis or Partial Paralysis: Feels "Like Body Cannot Move," "Unable to	Symptom	Categorical (Nominal)	TestWorks	Outcome Variable	HUTT

	open eyes," "Cannot lift up (or hold up) head" (Yes/No)					
51	Type of Symptom: Other (Any Additional Symptom or Symptoms) (Yes/No)	Symptom	Categorical (Nominal)	TestWorks	Outcome Variable	HUTT
52	Tilt PreSBP (mmHg)	Hemodynamic	Numeric (Continuous)	TestWorks	Outcome Variable	Pre-HUTT
53	Tilt PreDBP (mmHg)	Hemodynamic	Numeric (Continuous)	TestWorks	Outcome Variable	Pre-HUTT
54	Tilt PreHR (bpm)	Hemodynamic	Numeric (Continuous)	TestWorks	Outcome Variable	Pre-HUTT
55	Tilt PostSBP (mmHg)	Hemodynamic	Numeric (Continuous)	TestWorks	Outcome Variable	Post-HUTT
56	Tilt PostDBP (mmHg)	Hemodynamic	Numeric (Continuous)	TestWorks	Outcome Variable	Post-HUTT
57	Tilt PostHR (bpm)	Hemodynamic	Numeric (Continuous)	TestWorks	Outcome Variable	Post-HUTT
58	Tilt MinSBP (mmHg)	Hemodynamic	Numeric (Continuous)	TestWorks	Outcome Variable	HUTT
59	Tilt MinSBP Time (seconds)	Time	Numeric (Continuous)	TestWorks	Outcome Variable	HUTT
60	Tilt SBPChange (mmHg)	Hemodynamic	Numeric (Continuous)	TestWorks	Outcome Variable	HUTT – Pre-HUTT
61	Tilt HRatMinSBP (bpm)	Hemodynamic	Numeric (Continuous)	TestWorks	Outcome Variable	HUTT
62	Tilt MaxHR (bpm)	Hemodynamic	Numeric (Continuous)	TestWorks	Outcome Variable	HUTT
63	Maximum HR Time from Tilt (seconds)	Time	Numeric (Continuous)	TestWorks	Outcome Variable	HUTT
64	Tilt MinHR (bpm)	Hemodynamic	Numeric (Continuous)	TestWorks	Outcome Variable	HUTT
65	Minimum HR Time from Tilt (seconds)	Time	Numeric (Continuous)	TestWorks	Outcome Variable	HUTT
66	Tilt HRDelta (bpm)	Hemodynamic	Numeric (Continuous)	TestWorks	Outcome Variable	HUTT

67	Peak-to-Peak EDA (µS)	EDA	Numeric (Continuous)	AcqKnowledge	Outcome Variable	HUTT
68	Tilt Up EDA (µS)	EDA	Numeric (Continuous)	AcqKnowledge	Outcome Variable	HUTT
69	Tilt Down EDA (µS)	EDA	Numeric (Continuous)	AcqKnowledge	Outcome Variable	HUTT
70	EDA Max (µS)	EDA	Numeric (Continuous)	AcqKnowledge	Outcome Variable	HUTT
71	EDA Min (µS)	EDA	Numeric (Continuous)	AcqKnowledge	Outcome Variable	HUTT
72	EDA Difference [Max – Min] (µS)	EDA	Numeric (Continuous)	AcqKnowledge	Outcome Variable	HUTT
73	Mean EDA (µS)	EDA	Numeric (Continuous)	AcqKnowledge	Outcome Variable	HUTT
74	Median EDA (µS)	EDA	Numeric (Continuous)	AcqKnowledge	Outcome Variable	HUTT
75	EDA Stddev (µS)	EDA	Numeric (Continuous)	AcqKnowledge	Outcome Variable	HUTT
76	AcqKnowledge Equivalent of ARS Max HR (bpm)	hemodynamic	Numeric (Continuous)	AcqKnowledge	Outcome Variable	HUTT
77	AcqKnowledge Equivalent of ARS Max HR EDA (µS)	EDA	Numeric (Continuous)	AcqKnowledge	Outcome Variable	HUTT
78	Latency of AcqKnowledge Equivalent of ARS Maximum HR (seconds)	Time	Numeric (Continuous)	AcqKnowledge	Outcome Variable	HUTT
79	EDA Integral (µS)	EDA	Numeric (Continuous)	AcqKnowledge	Outcome Variable	HUTT
80	EDA Delta (µS)	EDA	Numeric (Continuous)	AcqKnowledge	Outcome Variable	HUTT
81	EDA Area (µS-sec)	EDA	Numeric (Continuous)	AcqKnowledge	Outcome Variable	HUTT
82	CASS Computed (Yes/No)	CASS	Categorical (Nominal)	TestWorks	Outcome Variable	
83	CASS: Raw Cardiovagal Score as a Numeric Variable (For: Computed: 0 ≤ X ≤ 3; Not Applicable {TTT-Only}: Blank Cell; Not Computable	CASS	Numeric (Discrete)	TestWorks	Outcome Variable	

	{Incomplete/Non-Performable/Non-Interpretable}: Blank Cell) - Raw Data Type 1					
84	CASS: Raw Cardiovagal Score as a Nominal Variable (For: Computed = 1; Not Applicable {TTT-Only} = 2; Not Computable {Incomplete/Non-Performable/Non-Interpretable Test} = 3) - Raw Data Type 2	CASS	Categorical (Nominal)	TestWorks	Outcome Variable	
85	CASS: Coded Cardiovagal Score (For: 0 ≤ X ≥ 3, N/A, or NC) - See Legend (or Key) Below for the Data Coding Format	CASS	Categorical (Ordinal)	TestWorks	Outcome Variable	
86	CASS: Raw Adrenergic Score as a Numeric Variable (For: Computed: 0 ≤ X ≤ 4; Not Applicable {TTT-Only}: Blank Cell; Not Computable {Incomplete/Non-Performable/Non-Interpretable Test}: Blank Cell) - Raw Data Type 1	CASS	Numeric (Discrete)	TestWorks	Outcome Variable	
87	CASS: Raw Adrenergic Score as a Nominal Variable (For: Computed = 1; Not Applicable {TTT-Only} = 2; Not Computable {Incomplete/Non-Performable/Non-Interpretable Test} = 3) - Raw Data Type 2	CASS	Categorical (Nominal)	TestWorks	Outcome Variable	
88	CASS: Coded Adrenergic Score (For: 0 ≤ X ≥ 4, N/A, or NC) - See Legend (or Key) Below for the Data Coded Format	CASS	Categorical (Ordinal)	TestWorks	Outcome Variable	
89	CASS: Raw Sudomotor Score as a Numeric Variable (For: Computed: 0 ≤ X ≤ 3; Not Applicable {TTT-Only}: Blank Cell; Not Computable {Incomplete/Non-Performable/Non-Interpretable Test}: Blank Cell) - Raw Data Type 1	CASS	Numeric (Discrete)	TestWorks	Outcome Variable	

90	CASS: Raw Sudomotor Score as a Nominal Variable (For: Computed = 1; Not Applicable {TTT-Only} = 2; Not Computable {Incomplete/Non-Performable/Non-Interpretable Test} = 3) - Raw Data Type 2	CASS	Categorical (Nominal)	TestWorks	Outcome Variable	
91	CASS: Coded Sudomotor Score (For: 0 ≤ X ≥ 3, N/A, or NC) - See Legend (or Key) Below for the Data Coding Format	CASS	Categorical (Ordinal)	TestWorks	Outcome Variable	
92	CASS: Raw Total Score as a Numeric Variable (For: Computed: 0 ≤ X ≤ 10; Not Applicable {TTT-Only}: Blank Cell; Not Computable {Incomplete/Non-Performable/Non-Interpretable Test}: Blank Cell) - Raw Data Type 1	CASS	Numeric (Discrete)	TestWorks	Outcome Variable	
93	CASS: Total Score as a Nominal Variable (For: Computed = 1; Not Applicable {TTT-Only} = 2; Not Computable {Incomplete/Non-Performable/Non-Interpretable Test} = 3) - Raw Data Type 2	CASS	Categorical (Nominal)	TestWorks	Outcome Variable	
94	CASS: Coded Total Score (For: 0 ≤ X ≥ 10, N/A, or NC) - See Legend (or Key) Below for the Coded Data	CASS	Categorical (Ordinal)	TestWorks	Outcome Variable	
95	Generalized Autonomic Impairment: Normal, Present, Mild, Moderate, or Severe; or GAI Not Determined	CASS	Categorical (Ordinal)	TestWorks	Outcome Variable	
96	Likelihood of Adrenergic or Hyper-Adrenergic POTS Stated in the Interpretation and/or Conclusion of the ARS Report (Yes/No/Not Applicable); No = 0; Yes = 1; Not Applicable = 2	Potential POTS Subtype	Categorical (Nominal)	TestWorks	Outcome Variable	
97	Likely Adrenergic Impairment without Hyperadrenergism (i.e., an Adrenergic CASS without likelihood of	Potential POTS Subtype	Categorical (Nominal)	TestWorks	Outcome Variable	

	hyperadrenergism), (Yes/No/Not Applicable/Not Stated/Indeterminable); No = 0; Yes = 1; Not Applicable = 2; Not Stated = 3; Indeterminable = 4					
98	Likely Hyperadrenergism (Yes/No/Not Applicable/Not Stated); No = 0; Yes = 1; Not Applicable = 2; Not Stated = 3; Indeterminable = 4	Potential POTS Subtype	Categorical (Nominal)	TestWorks	Outcome Variable	
99	ARS Full or Partial (i.e., TTT Only): Full = 1; Partial (i.e., TTT Only) = 2; Full ARS with Indeterminable CASS = 3	Screening Type (or Test Type)	Categorical (Nominal)	TestWorks	Covariate	
100	Pre-Tilt EDA Area (µS-sec)	EDA	Numeric (Discrete)	AcqKnowledge	Outcome Variable	Pre-HUTT
101	Pre-Tilt Duration (seconds)	Time (EDA Time)	Numeric (Discrete)	AcqKnowledge	Outcome Variable	Pre-HUTT
102	Normalized Pre-Tilt EDA Area (µS)	EDA	Numeric (Discrete)	AcqKnowledge	Outcome Variable	Pre-HUTT
103	Head-Up Tilt EDA Area (µS-sec)	EDA	Numeric (Discrete)	AcqKnowledge	Outcome Variable	HUTT
104	Head-Up Tilt Duration (seconds)	Time (EDA Time)	Numeric (Discrete)	AcqKnowledge	Outcome Variable	HUTT
105	Normalized Head-Up Tilt EDA Area (µS)	EDA	Numeric (Discrete)	AcqKnowledge	Outcome Variable	HUTT
106	Post-Tilt EDA Area (µS)	EDA	Numeric (Discrete)	AcqKnowledge	Outcome Variable	Post-HUTT
107	Post-Tilt Duration (seconds)	Time (EDA Time)	Numeric (Discrete)	AcqKnowledge	Outcome Variable	Post-HUTT
108	Normalized Post-Tilt EDA Area (µS)	EDA	Numeric (Discrete)	AcqKnowledge	Outcome Variable	Post-HUTT
109	Data Sets During HUT (#)	Number	Numeric (Discrete)	TestWorks	Outcome Variable	HUTT
110	EDA Slope During HUT (µS)	EDA	Numeric (Discrete)	AcqKnowledge	Outcome Variable	HUTT
111	EDA Delta S During HUT (samples)	EDA	Numeric (Discrete)	AcqKnowledge	Outcome Variable	HUTT
112	Raw AUC of the AcqKnowledge Generated PR (or Heart Rate) (BPM-sec)	Hemodynamic	Numeric (Discrete)	AcqKnowledge	Outcome Variable	HUTT
113	Normalized AUC of the AcqKnowledge Generated HR (or Pulse Rate) (BPM)	Hemodynamic	Numeric (Discrete)	AcqKnowledge	Outcome Variable	HUTT
114	Tilt-Up Heart Rate (or Pulse Rate) (bpm)	Hemodynamic	Numeric (Discrete)	AcqKnowledge	Outcome Variable	HUTT
115	Tilt-Down Heart Rate (or Pulse Rate; Equivalent to AcqKnowledge PR Value) (bpm)	Hemodynamic	Numeric (Discrete)	AcqKnowledge	Outcome Variable	HUTT

116	Heart Rate (or Pulse rate) Peak-to-Peak (bpm)	Hemodynamic	Numeric (Discrete)	AcqKnowledge	Outcome Variable	HUTT
117	All Medications Holding Adherence (Yes/No/Unknown)	Pre-ARS Medications Adherence	Categorical (Nominal)	TestWorks	Covariate	
118	Anticholinergic Medications Holding Adherence (Yes/No/Unknown)	Pre-ARS Medications Adherence	Categorical (Nominal)	TestWorks	Covariate	
119	Medications Taken Within 48-Hours: Any Prohibited Medications or Substances (Yes = 1; No = 0; Unknown = 2)	Pre-ARS Medications Adherence	Categorical (Nominal)	TestWorks	Covariate	
120	Medications Taken Within 48-Hours: Alcohol, Coffee, Other Caffeinated Drinks and/or Wine (Yes = 1; No = 0; Unknown = 2)	Pre-ARS Medications Adherence	Categorical (Nominal)	TestWorks	Covariate	
121	Medications Taken Within 48-Hours: Anticholinergic (Yes = 1; No = 0; Unknown = 2)	Pre-ARS Medications Adherence	Categorical (Nominal)	TestWorks	Covariate	
122	Medications Taken Within 48-Hours: Antihypertensives (Yes = 1; No = 0; Unknown = 2)	Pre-ARS Medications Adherence	Categorical (Nominal)	TestWorks	Covariate	
123	Medications Taken Within 48-Hours: Antihypotensive Blood Pressure Agents (Yes = 1; No = 0; Unknown = 2)	Pre-ARS Medications Adherence	Categorical (Nominal)	TestWorks	Covariate	
124	Medications Taken Within 48-Hours: Chronotropes (Yes = 1; No = 0; Unknown = 2)	Pre-ARS Medications Adherence	Categorical (Nominal)	TestWorks	Covariate	
125	Medications Taken Within 48-Hours: NSAIDs, Opioids and Other Pain Medications (Yes = 1; No = 0; Unknown = 2)	Pre-ARS Medications Adherence	Categorical (Nominal)	TestWorks	Covariate	
126	Number of Meds Not Held: All Medications (#)	Pre-ARS Medications Adherence	Numeric (Discrete)	TestWorks	Covariate	
127	Number of Meds Not Held: Alcohol, Coffee, Other Caffeinated Drinks and/or Wine (#)	Pre-ARS Medications Adherence	Numeric (Discrete)	TestWorks	Covariate	
128	Number of Meds Not Held: Anticholinergics (#)	Pre-ARS Medications Adherence	Numeric (Discrete)	TestWorks	Covariate	

129	Number of Meds Not Held: Antihypertensives (#)	Pre-ARS Medications Adherence	Numeric (Discrete)	TestWorks	Covariate	
130	Number of Meds Not Held: Antihypotensives (#)	Pre-ARS Medications Adherence	Numeric (Discrete)	TestWorks	Covariate	
131	Number of Meds Not Held: Chronotropes (#)	Pre-ARS Medications Adherence	Numeric (Discrete)	TestWorks	Covariate	
132	Number of Meds Not Held: NSAIDs, Opioids and Other Pain Medications (#)	Pre-ARS Medications Adherence	Numeric (Discrete)	TestWorks	Covariate	
133	Hemodynamic Changes: Post-SBP - Pre-SBP	Hemodynamic Change	Numeric (Discrete)	TestWorks	Outcome Variable	HUTT
134	Hemodynamic Changes: Post-DBP - Pre-DBP	Hemodynamic Change	Numeric (Discrete)	TestWorks	Outcome Variable	HUTT
135	Hemodynamic Changes: Post-HR - Pre-HR	Hemodynamic Change	Numeric (Discrete)	TestWorks	Outcome Variable	HUTT
136	Hemodynamic Changes: Max HUT HR - Pre-HR	Hemodynamic Change	Numeric (Discrete)	TestWorks	Outcome Variable	HUTT – Pre-HUTT
137	Hemodynamic Changes: Min HUT HR - Pre-HR	Hemodynamic Change	Numeric (Discrete)	TestWorks	Outcome Variable	HUTT – Pre-HUTT
138	Hemodynamic Changes: Max HUT HR - HR at Min SBP	Hemodynamic Change	Numeric (Discrete)	TestWorks	Outcome Variable	HUTT
139	Hemodynamic Changes: Min HUT HR - HR at Min SBP	Hemodynamic Change	Numeric (Discrete)	TestWorks	Outcome Variable	HUTT
140	Hemodynamic Changes: HR at Min SBP - Pre-HR	Hemodynamic Change	Numeric (Discrete)	TestWorks	Outcome Variable	HUTT – Pre-HUTT
141	AcqKnowledge Heart Rate (or PR) at Tilt Down - AcqKnowledge Heart Rate (or PR) at Tilt Up	Hemodynamic Change	Numeric (Discrete)	AcqKnowledge	Outcome Variable	HUTT
142	HRDB: Average of Heart Rate Differences	Hemodynamic Change	Numeric (Discrete)	TestWorks	Outcome Variable	HRDB
143	EDA_{var} Post-HUT EDA Area - Pre-HUT EDA Area	EDA Change		AcqKnowledge	Outcome Variable	Post-HUTT – Pre-HUTT
144	EDA_{var} HUT EDA Area - Pre-HUT EDA Area	EDA Change	Numeric (Discrete)	AcqKnowledge	Outcome Variable	HUTT – Pre-HUTT
145	EDA_{var} Post-HUT EDA Area - HUT EDA Area	EDA Change	Numeric (Discrete)	AcqKnowledge	Outcome Variable	Post-HUTT – HUTT

146	EDA_{var} Pre-HUT Mean EDA	EDA Change	Numeric (Discrete)	AcqKnowledge	Outcome Variable	Pre-HUTT
147	EDA_{var} Post-HUT Mean EDA	EDA Change	Numeric (Discrete)	AcqKnowledge	Outcome Variable	Post-HUTT
148	EDA_{var} Pre-HUT Peak-to-Peak EDA	EDA Change	Numeric (Discrete)	AcqKnowledge	Outcome Variable	Pre-HUTT
149	EDA_{var} Post-HUT Peak-to-Peak EDA	EDA Change	Numeric (Discrete)	AcqKnowledge	Outcome Variable	Post-HUTT
150	EDA_{var} Post-HUT Normalized EDA Area - Pre-HUT Normalized EDA Area	EDA Change	Numeric (Discrete)	AcqKnowledge	Outcome Variable	Post-HUTT – Pre-HUTT
151	EDA_{var} HUT Normalized EDA Area - Pre-HUT Normalized EDA Area	EDA Change	Numeric (Discrete)	AcqKnowledge	Outcome Variable	HUTT – Pre-HUTT
152	EDA_{var} Post-HUT Normalized EDA Area - HUT Normalized EDA Area	EDA Change	Numeric (Discrete)	AcqKnowledge	Outcome Variable	Post-HUTT – HUTT
153	EDA_{var} HUT Max EDA - Pre-HUT Mean EDA	EDA Change	Numeric (Discrete)	AcqKnowledge	Outcome Variable	HUTT – Pre-HUTT
154	EDA_{var} HUT Min EDA - Pre-HUT Mean EDA	EDA Change	Numeric (Discrete)	AcqKnowledge	Outcome Variable	HUTT – Pre-HUTT
155	EDA_{var} Post-HUT Peak-to-Peak EDA - Pre-HUT Peak-to-Peak EDA	EDA Change	Numeric (Discrete)	AcqKnowledge	Outcome Variable	Post-HUTT – Pre-HUTT
156	EDA_{var} HUT Peak-to-Peak EDA - Pre-HUT Peak-to-Peak EDA	EDA Change	Numeric (Discrete)	AcqKnowledge	Outcome Variable	HUTT – Pre-HUTT
157	EDA_{var} Post-HUT Peak-to-Peak EDA - HUT Peak-to-Peak EDA	EDA Change	Numeric (Discrete)	AcqKnowledge	Outcome Variable	Post-HUTT – HUTT
158	EDA_{var} Pre-HUT EDA Frequency	EDA Change	Numeric (Discrete)	AcqKnowledge	Outcome Variable	Pre-HUTT
159	EDA_{var} HUT EDA Frequency	EDA Change	Numeric (Discrete)	AcqKnowledge	Outcome Variable	HUTT
160	EDA_{var} Post-HUT EDA Frequency	EDA Change	Numeric (Discrete)	AcqKnowledge	Outcome Variable	Post-HUTT
161	EDA_{var} Post-HUT EDA Frequency - Pre-HUT EDA Frequency	EDA Change	Numeric (Discrete)	AcqKnowledge	Outcome Variable	Post-HUTT – Pre-HUTT
162	EDA_{var} HUT EDA Frequency - Pre-HUT EDA Frequency	EDA Change	Numeric (Discrete)	AcqKnowledge	Outcome Variable	HUTT – Pre-HUTT
163	EDA_{var} Post-HUT EDA Frequency - HUT EDA Frequency	EDA Change	Numeric (Discrete)	AcqKnowledge	Outcome Variable	Post-HUTT – HUTT
164	EDA_{var} Pre-HUT EDA BPM	EDA Change	Numeric (Discrete)	AcqKnowledge	Outcome Variable	Pre-HUTT
165	EDA_{var} HUT EDA BPM	EDA Change	Numeric (Discrete)	AcqKnowledge	Outcome Variable	HUTT
166	EDA_{var} Post-HUT EDA BPM	EDA Change	Numeric (Discrete)	AcqKnowledge	Outcome Variable	Post-HUTT
167	EDA_{var} Post-HUT EDA BPM - Pre-HUT EDA BPM	EDA Change	Numeric (Discrete)	AcqKnowledge	Outcome Variable	Post-HUTT – Pre-HUTT
168	EDA_{var} HUT EDA BPM - Pre-HUT EDA BPM	EDA Change	Numeric (Discrete)	AcqKnowledge	Outcome Variable	HUTT – Pre-HUTT

169	EDA_{var} Post-HUT EDA BPM - EDA HUT BPM	EDA Change	Numeric (Discrete)	AcqKnowledge	Outcome Variable	Post-HUTT
170	EDA_{var} EDA Pre HUT Integral	EDA Change	Numeric (Discrete)	AcqKnowledge	Outcome Variable	Pre-HUTT
171	EDA_{var} EDA Post HUT Integral	EDA Change	Numeric (Discrete)	AcqKnowledge	Outcome Variable	Post-HUTT
172	EDA_{var} EDA Post HUT Integral - EDA Pre HUT Integral	EDA Change	Numeric (Discrete)	AcqKnowledge	Outcome Variable	Post-HUTT – Pre-HUTT
173	EDA_{var} EDA HUT Integral - EDA Pre HUT Integral	EDA Change	Numeric (Discrete)	AcqKnowledge	Outcome Variable	HUTT – Pre-HUTT
174	EDA_{var} EDA Post HUT Integral - EDA HUT Integral	EDA Change	Numeric (Discrete)	AcqKnowledge	Outcome Variable	Post-HUTT – HUTT
175	EDA_{var} EDA Pre HUT Sum	EDA Change	Numeric (Discrete)	AcqKnowledge	Outcome Variable	Pre-HUTT
176	EDA_{var} EDA HUT Sum	EDA Change	Numeric (Discrete)	AcqKnowledge	Outcome Variable	HUTT
177	EDA_{var} EDA Post HUT Sum	EDA Change	Numeric (Discrete)	AcqKnowledge	Outcome Variable	Post-HUTT
178	EDA_{var} EDA Post HUT Sum - EDA Pre HUT Sum	EDA Change	Numeric (Discrete)	AcqKnowledge	Outcome Variable	Post-HUTT – Pre-HUTT
179	EDA_{var} EDA HUT Sum - EDA Pre HUT Sum	EDA Change	Numeric (Discrete)	AcqKnowledge	Outcome Variable	HUTT – Pre-HUTT
180	EDA_{var} EDA Post HUT Sum - EDA HUT Sum	EDA Change	Numeric (Discrete)	AcqKnowledge	Outcome Variable	Post-HUTT
181	EDA_{var} EDA at Tilt Down - EDA at Tilt Up	EDA Change	Numeric (Discrete)	AcqKnowledge	Outcome Variable	HUTT
182	Baseline from Line-1 of the Adrenergic Sensitivity Analysis of the Valsalva Maneuver Test	ASA	Numeric (Discrete)	TestWorks	Outcome Variable	ASAVM
183	Phase 2E Max Rate from Line-1 of the Adrenergic Sensitivity Analysis of the Valsalva Maneuver Test	ASA	Numeric (Discrete)	TestWorks	Outcome Variable	ASAVM
184	Phase 2E Min Rate from Line-1 of the Adrenergic Sensitivity Analysis of the Valsalva Maneuver Test	ASA	Numeric (Discrete)	TestWorks	Outcome Variable	ASAVM
185	Phase 2E Rate Difference from Line-1 of the Adrenergic Sensitivity Analysis of the Valsalva Maneuver Test	ASA	Numeric (Discrete)	TestWorks	Outcome Variable	ASAVM
186	Phase 2E Max Rate from Line-1 of the Adrenergic Sensitivity Analysis of the Valsalva Maneuver Test - Baseline	ASA	Numeric (Discrete)	TestWorks	Outcome Variable	ASAVM

	from Line-1 of the Adrenergic Sensitivity Analysis of the Valsalva Maneuver Test					
187	Phase 2E Min Rate from Line-1 of the Adrenergic Sensitivity Analysis of the Valsalva Maneuver Test - Baseline from Line-1 of the Adrenergic Sensitivity Analysis of the Valsalva Maneuver Test	ASA	Numeric (Discrete)	TestWorks	Outcome Variable	ASAVM
188	Phase 3 Max Rate from Line-1 of the Adrenergic Sensitivity Analysis of the Valsalva Maneuver Test	ASA	Numeric (Discrete)	TestWorks	Outcome Variable	ASAVM
189	Phase 3 Min Rate from Line-1 of the Adrenergic Sensitivity Analysis of the Valsalva Maneuver Test	ASA	Numeric (Discrete)	TestWorks	Outcome Variable	ASAVM
190	Phase 3 Rate Difference from Line-1 of the Adrenergic Sensitivity Analysis of the Valsalva Maneuver Test	ASA	Numeric (Discrete)	TestWorks	Outcome Variable	ASAVM
191	0.75 of Phase 3 Rate Difference from Line-1 of the Adrenergic Sensitivity Analysis of the Valsalva Maneuver Test	ASA	Numeric (Discrete)	TestWorks	Outcome Variable	ASAVM
192	Phase 3 Max Rate from Line-1 of the Adrenergic Sensitivity Analysis of the Valsalva Maneuver Test - Baseline from Line-1 of the Adrenergic Sensitivity Analysis of the Valsalva Maneuver Test	ASA	Numeric (Discrete)	TestWorks	Outcome Variable	ASAVM
193	Phase 3 Min Rate from Line-1 of the Adrenergic Sensitivity Analysis of the Valsalva Maneuver Test - Baseline from Line-1 of the Adrenergic Sensitivity Analysis of the Valsalva Maneuver Test	ASA	Numeric (Discrete)	TestWorks	Outcome Variable	ASAVM
194	PRT of Data Set 1 Computed (Yes = 1; No = 0)	ASA	Categorical (Nominal)	TestWorks	Outcome Variable	ASAVM

195	PRT Value of Data Set 1 (if PRT of Data Set 1 was Computed)	ASA	Numeric (Discrete)	TestWorks	Outcome Variable	ASAVM
196	Average PRT of Data Sets 1 & 2 Computed (Yes = 1; No = 0)	ASA	Categorical (Nominal)	TestWorks	Outcome Variable	ASAVM
197	Average PRT Value (if Average PRT is Computed)	ASA	Numeric (Discrete)	TestWorks	Outcome Variable	ASAVM
198	Total Difference from Line-1 of the Adrenergic Sensitivity Analysis of the Valsalva Maneuver Test	ASA	Numeric (Discrete)	TestWorks	Outcome Variable	ASAVM
199	Adrenergic Score from Line-1 of the Adrenergic Sensitivity Analysis of the Valsalva Maneuver Test	ASA	Numeric (Discrete)	TestWorks	Outcome Variable	ASAVM
200	Lowest Adrenergic Score from the Adrenergic Sensitivity Analysis of the Valsalva Maneuver Test	ASA	Numeric (Discrete)	TestWorks	Outcome Variable	ASAVM
201	QSWEAT (Forearm): Total Volume	QSART (volume)	Numeric (Discrete)	TestWorks	Outcome Variable	QSWEAT
202	QSWEAT (Forearm): Response Latency	QSART (latency)	Numeric (Discrete)	TestWorks	Outcome Variable	QSWEAT
203	QSWEAT (Forearm): Baseline Rate	QSART (rate)	Numeric (Discrete)	TestWorks	Outcome Variable	QSWEAT
204	QSWEAT (Forearm): Ending Offset	QSART (rate)	Numeric (Discrete)	TestWorks	Outcome Variable	QSWEAT
205	QSWEAT (Forearm): 5th Percentile Q-Sweat	QSART (percentile)	Numeric (Discrete)	TestWorks	Outcome Variable	QSWEAT
206	QSWEAT (Forearm): Ending Offset - Baseline Rate	QSART (rate change)	Numeric (Discrete)	TestWorks	Outcome Variable	QSWEAT

Note. ARS, autonomic reflex screen; ASA, adrenergic sensitivity analysis; ASAVM, adrenergic sensitivity analysis based upon the results of the Valsalva maneuver; BMI, body mass index; CASS, composite autonomic severity score; DBP, diastolic blood pressure; EDA, electrodermal activity; EDA_{Var} , EDA variable; GAI, generalized autonomic impairment; HUT, head-up tilt; HUTT, head-up tilt-table test; HR, heart rate; NSAIDs, non-steroidal anti-inflammatory drugs; POTS, postural orthostatic tachycardia syndrome; PR, pulse rate; PRT, pressure recovery time; SBP, systolic

blood pressure; Stddev, standard deviation; QSART, quantitative sudomotor axon test; QSWEAT, a brand of QSART lab equipment manufactured and sold by WR Medical Electronics Co., Maplewood, Minnesota.

Supplemental Table 19

Certain Notable Novel Phasic EDA Analyses Related Indices, Parameters, or Variables in Dataset #2, with Their Column Labels, Statistical Names, Regular Names, and Variable Type.

	Column	Index-Parameter-or-Variable Statistical Name	Index-Parameter-or-Variable Full Regular Name	Type
1	DN	RshPrARStstnBSLNmxSCL2HUTTmxSCL	Ratio of Pre ARS Testing Baseline Maximum SCL to HUTT Maximum SCL	Ratio
2	DO	RshPrARStstnBsln2HUTTmxSCLDfrncs	Ratio of Pre-ARS Testing Baseline Peak-to-Peak SCL to HUTT Peak-to-Peak SCL	Ratio
3	DU	PreARStstnBslnNmbrUscrs	Number of SCRs During the Pre-ARS Testing Baseline Period	Count
4	DV	DB1NmbrUscrs	Number of SCRs During the Deep Breathing 1 Period	Count
5	DW	DB2NmbrUscrs	Number of SCRs During the Deep Breathing 2 Period	Count
6	EB	VM1NmbrUscrs	Number of SCRs During the Valsalva Maneuver 1 Period	Count
7	EC	VM2NmbrUscrs	Number of SCRs During the Valsalva Maneuver 2 Period	Count
8	ED	VM3NmbrUscrs	Number of SCRs During the Valsalva Maneuver 3 Period	Count
9	EH	30sPreHUTTNmbrUscrs	Number of SCRs During the 30 seconds Pre-HUTT Period	Count
10	EI	HUTTNmbrUscrs	Number of SCRs During the HUTT Period	Count
11	EJ	30sPostHUTTNmbrUscrs	Number of SCRs During the 30-seconds Post-HUTT Period	Count
12	EK	30sAfterTiltUpNmbrOfUSCRs	Number of SCRs During the 30-seconds After Tilt-up Period	Count
13	EL	2mAfterTiltUpNmbrOfUSCRs	Number of SCRs During the 2-minutes After Tilt-up Period	Count
14	EM	Frst2MinsFsclSpkRltdNmbrFuSCRs	Number of SCRs During the First 2-minutes of Sustained Tonic EDA Elevation After Tilt-up Period	Count
15	EN	RshNmbPreHUTTuSCRs2NmbHUTTuSCRs	Ratio of the Number of Pre-HUTT SCRs to the Number of HUTT SCRs	Ratio
16	EO	FrequencyOftheNumberOfBslnUSCRs	Frequency of the Number of SCRs During the Baseline Period	Ratio
17	EP	FrequencyOftheNumberOfHUTTuSCRs	Frequency of the Number of SCRs During the HUTT Period	Ratio
18	EQ	FrqncyOfNmbrOf30sPreHUTTuSCRs	Frequency of the Number of SCRs During the 30 seconds Pre-HUTT Period	Ratio
19	ER	FrqncyOfNmbrOf30sAfterTUuSCRs	Frequency of the Number of SCRs During the 30 seconds After Tilt-up Period	Ratio

20	ES	FrqF1st2mnFsclSpkRltdNmbrFuSCRs	Frequency of the Number of SCRs During the First 2-minutes of Sustained Tonic EDA Elevation After Tilt-up Period	Ratio
21	ET	RshFrqBsln2Frq1st2mSCLspkUSCRs	Ratio of Frequency of SCRs During Baseline to Frequency of SCRs During the First 2-minutes of Sustained Tonic EDA Elevation After Tilt-up	Ratio
22	FD	BSLNmaxSCRriseTime	Rise Time of the Maximum SCR During the Baseline	Time
23	FG	BSLNmaxSCRhalfRecoveryTime	Half-Recovery Time of the Maximum SCR During the Baseline	Time
24	FR	DB1MaxSCRriseTime	Rise Time of the Maximum SCR During the DB1 Period	Time
25	FU	DB1MaxSCRhalfRecoveryTime	Half-Recovery Time of the Maximum SCR During the DB1 Period	Time
26	GF	DB2MaxSCRriseTime	Rise Time of the Maximum SCR During the DB2 Period	Time
27	GI	DB2MaxSCRhalfRecoveryTime	Half-Recovery Time of the Maximum SCR During the DB2 Period	Time
28	IJ	VM1MaxSCRriseTime	Rise Time of the Maximum SCR During the VM1 Period	Time
29	IM	VM1MaxSCRhalfRecoveryTime	Half-Recovery Time of the Maximum SCR During the VM1 Period	Time
30	IX	VM2MaxSCRriseTime	Rise Time of the Maximum SCR During the VM2 Period	Time
31	JA	VM2MaxSCRhalfRecoveryTime	Half-Recovery Time of the Maximum SCR During the VM2 Period	Time
32	JL	VM3MaxSCRriseTime	Rise Time of the Maximum SCR During the VM3 Period	Time
33	JO	VM3MaxSCRhalfRecoveryTime	Half-Recovery Time of the Maximum SCR During the VM3 Period	Time
34	LB	PreHUTTMaxSCRriseTime	Rise Time of the Maximum SCR During the Pre-HUTT Period	Time
35	LE	PreHUTTMaxSCRhalfRecoveryTime	Half-Recovery Time of the Maximum SCR During the Pre-HUTT Period	Time
36	LP	HUTTMaxSCRriseTime	Rise Time of the Maximum SCR During the HUTT Period	Time
37	LS	HUTTMaxSCRhalfRecoveryTime	Half-Recovery Time of the Maximum SCR During the HUTT Period	Time
38	MD	PostHUTTMaxSCRriseTime	Rise Time of the Maximum SCR During the Post-HUTT Period	Time
39	MG	PostHUTTMaxSCRhalfRecoveryTime	Half-Recovery Time of the Maximum SCR During the Post-HUTT Period	Time
40	MR	30sAfterTiltUpMaxSCRriseTime	Rise Time of the Maximum SCR During the 30-seconds After Tilt-up Period	Time
41	MU	30sAfterTiltUpMaxSCRhalfRecoveryTime	Half-Recovery Time of the Maximum SCR During the 30-seconds After Tilt-up Period	Time

42	NF	2mAfterTiltUpMaxSCRriseTime	Rise Time of the Maximum SCR During the 2-minutes After Tilt-up Period	Time
43	NI	2mAfterTiltUpMaxSCRhalfRecoveryTime	Half-Recovery Time of the Maximum SCR During the 2-minutes After Tilt-up Period	Time
44	NT	Fst2mSCLspkRltdNmbuSCRMaxSCRrzTm	Rise Time of the Maximum SCR During the First 2-minutes of Sustained Tonic EDA Elevation After Tilt-up Period	Time
45	NW	Frst2mSCLspkRltdNmbuSCRsMxSCRhrt	Half-Recovery Time of the Maximum SCR During the First 2-minutes of Sustained Tonic EDA Elevation After Tilt-up Period	Time
46	OE	RshNrmlzdMxBsln2HUTTSCRsAmpltds	Ratio of the Amplitude of the Normalized Maximum Baseline SCR to the Amplitude of the Normalized Maximum HUTT SCR	Ratio
47	OG	FrequencyOfNmbrAcclimationUSCRs	Frequency of the Number of SCRs During the Acclimation Period	Ratio
48	OH	RngStndrdzdHUTTmxSCRonsetSCL	Range Standardized Onset SCL of the SCR with the Maximum SCL During HUTT	Ratio
49	OI	RngStndrdzdHUTTmxSCRpeakSCL	Range Standardized Peak SCL of the SCR with the Maximum SCL During HUTT	Ratio
50	OJ	RngStndrdzdHUTTmxSCRampltd	Range Standardized Amplitude of the SCR with the Maximum SCL During HUTT	Ratio
51	OK	RshHUTTmxSCRAmpl2HUTTmxSCRriseTm	Ratio of the HUTT Max SCR to the HUTT Max SCR Rise Time	Ratio
52	OL	RshHTscrRiseTm2HTscrHalfRcvryTm	Ratio of the HUTT SCR Rise Time to the HUTT Max SCR	Ratio
53	OQ	ERscrDB1SCRriseTime	Event Related SCR Rise Time During Deep Breathing 1 Test	Time
54	OT	ERscrRatioDB1SCRampltd2RiseTime	Ratio of the DB1 ERSCR SCR's Amplitude to its Rise Time	Ratio
55	OY	ERscrDB2SCRriseTime	Event Related SCR Rise Time During Deep Breathing 2 Test	Time
56	PB	ERscrRatioDB2SCRampltd2RiseTime	Ratio of the DB2 ERSCR SCR's Amplitude to its Rise Time	Ratio
57	QE	ERscrVM1SCRriseTime	Event Related SCR Rise Time During Valsalva Maneuver 1	Time
58	QH	ERscrRatioVM1SCRampltd2RiseTime	Ratio of the VM1 ERSCR SCR's Amplitude to its Rise Time	Ratio
59	QM	ERscrVM2SCRriseTime	Event Related SCR Rise Time During Valsalva Maneuver 2	Time
60	QP	ERscrRatioVM2SCRampltd2RiseTime	Ratio of the VM2 ERSCR SCR's Amplitude to its Rise Time	Ratio
61	QU	ERscrVM3SCRriseTime	Event Related SCR Rise Time During Valsalva Maneuver 3	Time
62	QX	ERscrRatioVM3SCRampltd2RiseTime	Ratio of the VM3 ERSCR SCR's Amplitude to its Rise Time	Ratio
63	RS	ERscrHUTTscrRiseTime	Event Related SCR Rise Time During the HUTT Period	Time
64	RV	ERscrRatioHUTTscrAmpltd2RiseTime	Ratio of the HUTT ERSCR SCR's Amplitude to its Rise Time	Ratio
65	SA	ERscrTDscrRiseTime	Event Related SCR Rise Time During the Tilt-down Period	Time

66	SD	ERscrRatioTDscrAmpltd2RiseTime	Ratio of the Tilt-down ERSCR SCR's Amplitude to its Rise Time	Ratio
67	YT	ZscrPrcsngBslnMxRawSCRvrMean	Baseline Maximum Raw SCR Amplitude Divided by the Mean	Ratio
68	YU	ZscrPrcsngBslnMxLogSCRvrmean	Baseline Maximum Logged SCR Amplitude Divided by the Mean	Ratio
69	YX	ZscrPrcsngBslnMxZ-scoreRaw	Baseline Z-score Raw	Z-score
70	YY	ZscrPrcsngBslnMxT-scoreRaw	Baseline T-score Raw	T-score
71	YZ	ZscrPrcsngBslnMxZ-score(LoggedData)	Baseline Z-score Log Transformed	Z-score Log Transformed
72	ZA	ZscrPrcsngBslnMxT-score	Baseline T-score Log Transformed	T-score Log Transformed
73	ZG	ZscrPrcsng1st2mFhuttMxRawSCRvrMean	Maximum Raw SCR Amplitude in the First 2-minutes of HUTT Divided by the Mean	Ratio
74	ZH	ZscrPrcsng1st2mFhuttMxLogSCRvrMean	Max Log-transformed Raw SCR Amplitude in the First 2-minutes of HUTT Divided by the Mean.	Ratio
75	ZK	ZscrPrcsng1st2mFhuttMxZ-scoreRaw	Raw Z-score of the Magnitude of the Amplitude of the SCR with the Maximum SCL During the First 2-minutes of a Sustained Elevation in the EDA Signal Trace After Tilt-up	Z-score
76	ZL	ZscrPrcsng1st2mFhuttMxT-scoreRaw	Raw T-score of the Magnitude of the Amplitude of the SCR with the Maximum SCL During the First 2-minutes of a Sustained Elevation in the EDA Signal Trace After Tilt-up	T-score
77	ZM	ZscrPrcsng1st2mFhuttMxZ-score(LoggedData)	Logged-Data of the Z-score of the Magnitude of the Amplitude of the SCR with the Maximum SCL During the First 2-minutes of a Sustained Elevation in the EDA Signal Trace After Tilt-up	Z-score Log Transformed
78	ZN	ZscrPrcsng1st2mFhuttMxT-score	Logged-Data of the T-score of the Magnitude of the Amplitude of the SCR with the Maximum SCL During the First 2-minutes of a Sustained Elevation in the EDA Signal Trace After Tilt-up	T-score Log Transformed
79	ZT	ZscrPrcsng2mFhuttMxRawSCRvrMean	Maximum Raw SCR Amplitude in the Focus Area of the 2-minutes Right After Tilt-up in HUTT Divided by the Mean	Ratio
80	ZU	ZscrPrcsng2mFhuttMxLogSCRvrMean	Max Log-transformed Raw SCR Amplitude in the Focus Area of the 2-minutes Right After Tilt-up in HUTT Divided by the Mean	Ratio
81	ZX	ZscrPrcsng2mFhuttMxZ-scoreRaw	Raw Z-score of the Magnitude of the Amplitude of the SCR with the Maximum SCL During the Period of the 2-minutes Right After Tilt-up	Z-score

82	ZY	ZscrPrcsng2mFhuttMxT-scoreRaw	Raw Z-score of the Magnitude of the Amplitude of the SCR with the Maximum SCL During the Period of the 2-minutes Right After Tilt-up	T-score
83	ZZ	ZscrPrcsng2mFhuttMxZ-score(LoggedData)	Logged-Data of the Z-score of the Magnitude of the Amplitude of the SCR with the Maximum SCL During the Period of the 2-minutes in HUTT Right After Tilt-up	Z-score Log Transformed
84	AAA	ZscrPrcsng2mFhuttMxT-score	Logged-Data of the T-score of the Magnitude of the Amplitude of the SCR with the Maximum SCL During the Period of the 2-minutes in HUTT Right After Tilt-up	T-score Log Transformed
85	AAG	ZscrPrcsngOFerscrDB1MxRawSCRvrMean	Maximum Raw SCR Amplitude in the DB1 Focus Area	Ratio
86	AAH	ZscrPrcsngOFerscrDB1MxLogSCRvrMean	Max Log-transformed Raw SCR Amplitude in the DB1 Focus Area	Ratio
87	AAK	ZscrPrcsngOFerscrDB1MxZ-scoreRaw	Raw Z-score of the Magnitude of the Amplitude of the SCR with the Maximum SCL During the DB1 Focus Area	Z-score
88	AAL	ZscrPrcsngOFerscrDB1MxT-scoreRaw	Raw T-score of the Magnitude of the Amplitude of the SCR with the Maximum SCL During the DB1 Focus Area	T-score
89	AAM	ZscrPrcsngOFerscrDB1MxZ-score(LoggedData)	Logged-Data of the Z-score of the Magnitude of the Amplitude of the SCR with the Maximum SCL During the DB1 Focus Area	Z-score Log Transformed
90	AAN	ZscrPrcsngOFerscrDB1MxT-score	Logged-Data of the T-score of the Magnitude of the Amplitude of the SCR with the Maximum SCL During the DB1 Focus Area	T-score Log Transformed
91	AAT	ZscrPrcsngOFerscrDB2MxRawSCRvrMean	Maximum Raw SCR Amplitude in the DB2 Focus Area	Ratio
92	AAU	ZscrPrcsngOFerscrDB2MxLogSCRvrMean	Max Log-transformed Raw SCR Amplitude in the DB2 Focus Area	Ratio
93	AAX	ZscrPrcsngOFerscrDB2MxZ-scoreRaw	Raw Z-score of the Magnitude of the Amplitude of the SCR with the Maximum SCL During the DB2 Focus Area	Z-score
94	AAY	ZscrPrcsngOFerscrDB2MxT-scoreRaw	Raw T-score of the Magnitude of the Amplitude of the SCR with the Maximum SCL During the DB2 Focus Area	T-score
95	AAZ	ZscrPrcsngOFerscrDB2MxZ-score(LoggedData)	Logged-Data of the Z-score of the Magnitude of the Amplitude of the SCR with the Maximum SCL During the DB2 Focus Area	Z-score Log Transformed
96	ABA	ZscrPrcsngOFerscrDB2MxT-score	Logged-Data of the T-score of the Magnitude of the Amplitude of the SCR with the Maximum SCL During the Db2 Focus Area	T-score Log Transformed
97	ACT	ZscrPrcsngOFerscrVM1MxRawSCRvrMean	Maximum Raw SCR Amplitude in the VM1 Focus Area	Ratio

98	ACU	ZscrPrcsngOFerscrVM1MxLogSCRvrMean	Max Log-transformed Raw SCR Amplitude in the VM1 Focus Area	Ratio
99	ACX	ZscrPrcsngOFerscrVM1MxZ-scoreRaw	Raw Z-score of the Magnitude of the Amplitude of the SCR with the Maximum SCL During the VM1 Focus Area	Z-score
100	ACY	ZscrPrcsngOFerscrVM1MxT-scoreRaw	Raw T-score of the Magnitude of the Amplitude of the SCR with the Maximum SCL During the VM1 Focus Area	T-score
101	ACZ	ZscrPrcsngOFerscrVM1MxZ-score(LoggedData)	Logged-Data of the Z-score of the Magnitude of the Amplitude of the SCR with the Maximum SCL During the VM1 Focus Area	Z-score Log Transformed
102	ADA	ZscrPrcsngOFerscrVM1MxT-score	Logged-Data of the T-score of the Magnitude of the Amplitude of the SCR with the Maximum SCL During the VM1 Focus Area	T-score Log Transformed
103	ADG	ZscrPrcsngOFerscrVM2MxRawSCRvrMean	Maximum Raw SCR Amplitude in the VM2 Focus Area	Ratio
104	ADH	ZscrPrcsngOFerscrVM2MxLogSCRvrMean	Max Log-transformed Raw SCR Amplitude in the VM2 Focus Area	Ratio
105	ADK	ZscrPrcsngOFerscrVM2MxZ-scoreRaw	Raw Z-score of the Magnitude of the Amplitude of the SCR with the Maximum SCL During the VM2 Focus Area	Z-score
106	ADL	ZscrPrcsngOFerscrVM2MxT-scoreRaw	Raw T-score of the Magnitude of the Amplitude of the SCR with the Maximum SCL During the VM2 Focus Area	T-score
107	ADM	ZscrPrcsngOFerscrVM2MxZ-score(LoggedData)	Logged-Data of the Z-score of the Magnitude of the Amplitude of the SCR with the Maximum SCL During the VM2 Focus Area	Z-score Log Transformed
108	ADN	ZscrPrcsngOFerscrVM2MxT-score	Logged-Data of the T-score of the Magnitude of the Amplitude of the SCR with the Maximum SCL During the VM2 Focus Area	T-score Log Transformed
109	ADT	ZscrPrcsngOFerscrVM3MxRawSCRvrMean	Maximum Raw SCR Amplitude in the VM3 Focus Area	Ratio
110	ADU	ZscrPrcsngOFerscrVM3MxLogSCRvrMean	Max Log-transformed Raw SCR Amplitude in the VM3 Focus Area	Ratio
111	ADX	ZscrPrcsngOFerscrVM3MxZ-scoreRaw	Raw Z-score of the Magnitude of the Amplitude of the SCR with the Maximum SCL During the VM3 Focus Area	Z-score
112	ADY	ZscrPrcsngOFerscrVM3MxT-scoreRaw	Raw T-score of the Magnitude of the Amplitude of the SCR with the Maximum SCL During the VM3 Focus Area	T-score
113	ADZ	ZscrPrcsngOFerscrVM3MxZ-score(LoggedData)	Logged-Data of the Z-score of the Magnitude of the Amplitude of the SCR with the Maximum SCL During the VM3 Focus Area	Z-score Log Transformed

114	AEA	ZscrPrcsngOFerscrVM3MxT-score	Logged-Data of the T-score of the Magnitude of the Amplitude of the SCR with the Maximum SCL During the VM3 Focus Area	T-score Log Transformed
115	AFG	ZscrPrcsngOFerscrTUmxRawSCRvrMean	Maximum Raw SCR Amplitude in the Tilt-up Event-related SCR in HUTT Focus Area	Ratio
116	AFH	ZscrPrcsngOFerscrTUmxLogSCRvrMean	Max Log-transformed Raw SCR Amplitude in the Tilt-up Event-related SCR in HUTT Focus Area	Ratio
117	AFK	ZscrPrcsngOFerscrTUmxZ-scoreRaw	Raw Z-score of the Magnitude of the Amplitude of the SCR with the Maximum SCL During the Tilt-up Event-related SCR in HUTT Focus Area	Z-score
118	AFL	ZscrPrcsngOFerscrTUmxT-scoreRaw	Raw T-score of the Magnitude of the Amplitude of the SCR with the Maximum SCL During the Tilt-up Event-related SCR in HUTT Focus Area	T-score
119	AFM	ZscrPrcsngOFerscrTUmxZ-score(LoggedData)	Logged-Data of the Z-score of the Magnitude of the Amplitude of the SCR with the Maximum SCL During the Tilt-up Event-related SCR in HUTT Focus Area	Z-score Log Transformed
120	AFN	ZscrPrcsngOFerscrTUmxT-score	Logged-Data of the T-score of the Magnitude of the Amplitude of the SCR with the Maximum SCL During the Tilt-up Event-related SCR in HUTT Focus Area	T-score Log Transformed
121	AFT	ZscrPrcsngOFerscrTDmxRawSCRvrMean	Maximum Raw SCR Amplitude in the Tilt-down Event-related SCR in HUTT Focus Area	Ratio
122	AFU	ZscrPrcsngOFerscrTDmxLogSCRvrMean	Max Log-transformed Raw SCR Amplitude in the Tilt-down Event-related SCR in HUTT Focus Area	Ratio
123	AFX	ZscrPrcsngOFerscrTDmxZ-scoreRaw	Raw Z-score of the Magnitude of the Amplitude of the SCR with the Maximum SCL During the Tilt-down Event-related SCR in HUTT Focus Area	Z-score
124	AFY	ZscrPrcsngOFerscrTDmxT-scoreRaw	Raw T-score of the Magnitude of the Amplitude of the SCR with the Maximum SCL During the Tilt-down Event-related SCR in HUTT Focus Area	T-score
125	AFZ	ZscrPrcsngOFerscrTDmxZ-score(LoggedData)	Logged-Data of the Z-score of the Magnitude of the Amplitude of the SCR with the Maximum SCL During the Tilt-down Event-related SCR in HUTT Focus Area	Z-score Log Transformed
126	AGA	ZscrPrcsngOFerscrTDmxT-score	Logged-Data of the T-score of the Magnitude of the Amplitude of the SCR with the Maximum SCL During the Tilt-down Event-related SCR in HUTT Focus Area	T-score Log Transformed

127	AGG	ZscrPrcsng30sB4TUmxRawSCRvrMean	Maximum Raw SCR Amplitude in the 30-seconds Before Tilt-up Focus Area	Ratio
128	AGH	ZscrPrcsng30sB4TUmxLogSCRvrMean	Max Log-transformed Raw SCR Amplitude in the 30-seconds Before Tilt-up Focus Area	Ratio
129	AGK	ZscrPrcsng30sB4TUmxZ-scoreRaw	Raw Z-score of the Magnitude of the Amplitude of the SCR with the Maximum SCL During the 30-seconds Before Tilt-up Focus Area	Z-score
130	AGL	ZscrPrcsng30sB4TUmxT-scoreRaw	Raw T-score of the Magnitude of the Amplitude of the SCR with the Maximum SCL During the 30-seconds Before Tilt-up Focus Area	T-score
131	AGM	ZscrPrcsng30sB4TUmxZ-score(LoggedData)	Logged-Data of the Z-score of the Magnitude of the Amplitude of the SCR with the Maximum SCL During the 30-seconds Before Tilt-up Focus Area	Z-score Log Transformed
132	AGN	ZscrPrcsng30sB4TUmxT-score	Logged-Data of the T-score of the Magnitude of the Amplitude of the SCR with the Maximum SCL During the 30-seconds Before Tilt-up Focus Area	T-score Log Transformed
133	AGT	ZscrPrcsng30sAftrTUmxRawSCRvrMean	Maximum Raw SCR Amplitude in the 30-seconds Right After Tilt-up Focus Area	Ratio
134	AGU	ZscrPrcsng30sAftrTUmxLogSCRvrMean	Max Log-transformed Raw SCR Amplitude in the 30-seconds Right After Tilt-up Focus Area	Ratio
135	AGX	ZscrPrcsng30sAftrTUmxZ-scoreRaw	Raw Z-score of the Magnitude of the Amplitude of the SCR with the Maximum SCL During the 30-seconds Right After Tilt-up Focus Area	Z-score
136	AGY	ZscrPrcsng30sAftrTUmxT-scoreRaw	Raw T-score of the Magnitude of the Amplitude of the SCR with the Maximum SCL During the 30-seconds Right After Tilt-up Focus Area	T-score
137	AGZ	ZscrPrcsng30sAftrTUmxZ-score(LoggedData)	Logged-Data of the Z-score of the Magnitude of the Amplitude of the SCR with the Maximum SCL During the 30-seconds Right After Tilt-up Focus Area	Z-score Log Transformed
138	AHA	ZscrPrcsng30sAftrTUmxT-score	Logged-Data of the T-score of the Magnitude of the Amplitude of the SCR with the Maximum SCL During the 30-seconds Right After Tilt-up Focus Area	T-score Log Transformed
139	AHG	ZscrPrcsng30sAftrTDmxRawSCRvrMean	Maximum Raw SCR Amplitude in the 30-seconds Right After Tilt-down Focus Area	Ratio
140	AHH	ZscrPrcsng30sAftrTDmxLogSCRvrMean	Max Log-transformed Raw SCR Amplitude in the 30-seconds Right After Tilt-down Focus Area	Ratio

141	AHK	ZscrPrcsng30sAftrTDmxZ-scoreRaw	Raw Z-score of the Magnitude of the Amplitude of the SCR with the Maximum SCL During the 30-seconds Right After Tilt-down Focus Area	Z-score
142	AHL	ZscrPrcsng30sAftrTDmxT-scoreRaw	Raw T-score of the Magnitude of the Amplitude of the SCR with the Maximum SCL During the 30-seconds Right After Tilt-down Focus Area	T-score
143	AHM	ZscrPrcsng30sAftrTDmxZ-score(LoggedData)	Logged-Data of the Z-score of the Magnitude of the Amplitude of the SCR with the Maximum SCL During the 30-seconds Right After Tilt-down Focus Area	Z-score Log Transformed
144	AHN	ZscrPrcsng30sAftrTDmxT-score	Logged-Data of the T-score of the Magnitude of the Amplitude of the SCR with the Maximum SCL During the 30-seconds Right After Tilt-down Focus Area	T-score Log Transformed
145	AHP	FrequencyOftheNumberOfDB1USCRs	Frequency of the Number of DB1 Unspecified SCRs	Ratio
146	AHR	FrequencyOftheNumberOfDB2USCRs	Frequency of the Number of DB2 Unspecified SCRs	Ratio
147	AHZ	FrequencyOftheNumberOfVM1USCRs	Frequency of the Number of VM1 Unspecified SCRs	Ratio
148	AIB	FrequencyOftheNumberOfVM2USCRs	Frequency of the Number of VM2 Unspecified SCRs	Ratio
149	AID	FrequencyOftheNumberOfVM3USCRs	Frequency of the Number of VM3 Unspecified SCRs	Ratio
150	AII	FrqncyFdNmbrF2mSCLspkAftrTUuSCRs	Frequency of the Number of TU Unspecified SCRs	Ratio
151	AIS	FrqncyOF30sPostHUTTNmbrUscrs	Frequency of the Number of 30-seconds post-HUTT Unspecified SCRs	Ratio
152	AIJ	NumberOfDB1relatedERSCRs	Number of DB1 Related Event-related SCRs	Ratio
153	AIK	NumberOfDB2relatedERSCRs	Number of DB2 Related Event-related SCRs	Ratio
154	AIQ	RshFbslnPk2PkLgd2NtreTrsPk2PLgdk	Ratio of the Log-transformed Magnitude of the Peak-to-Peak Value of the SCLs Across Segment of the EDA Signal Trace in the Period of the Pre-ARS Testing Baseline, to the Log-transformed Magnitude of the Peak-to-Peak Value of the SCLs Across the Entire EDA Signal Trace.	Ratio
155	AIR	RshBslnSCRrzTm2BslnSCRhlfRcvryTm	Ratio of the Rise Time of the SCR with the Maximum SCL During the Period of the Pre-ARS Testing Baseline, to its Half-Recovery Time.	Ratio

Note. Abbreviations: ARS, autonomic reflex screen; ASA, adrenergic sensitivity analysis; Bsln, the 2-minutes of pre-ARS testing baseline; CASS, composite autonomic severity score; DB1, deep breathing 1 test; DB2, deep breathing 2 test; EDA, electrodermal activity; ERscr, event related

skin conductance response; HUTT, head-up tilt-table test; POTS, postural orthostatic tachycardia syndrome; SCL, skin conductance level; SCR, skin conductance response; QSART, quantitative sudomotor axon test; uSCR, unspecified skin conductance response; VM1, Valsalva maneuver 1; VM2, Valsalva maneuver 2; VM3, Valsalva maneuver 3.

Supplemental Table 20

Nonstandard Abbreviations and Acronyms Related to the Results in Chapter 5

Abbreviations or Acronyms	Meaning
ΔHR	Delta Heart Rate
ANS	Autonomic Nervous System
ASA	Adrenergic Sensitivity Analysis
ARS	Autonomic Reflex Screen
CAC	Cardiac Arrhythmia Center
CASS	Composite Autonomic Severity Score
EDA	Electrodermal Activity
ERS	Eda Response Subtypes
FPV	Finger Pulse Volume
GAI	General Autonomic Impairment
GSR	Galvanic Skin Response
HA-POTS	Hyperadrenergic Postural Orthostatic Tachycardia Syndrome
HRΔ	Heart Rate Delta
HRDB	Heart Rate Deep Breathing
HUT	Head Up Tilt
HUTT	Head Up Tilt-Table Test
MPFC	Medial Prefrontal Cortex
OFC	Orbitofrontal Cortex
OH	Orthostatic Hypotension
OI	Orthostatic Intolerance
POTS	Postural Orthostatic Tachycardia Syndrome
PPG	Photoplethysmography
PRT	Pressure Recovery Time
QoL	Quality of Life
QSART	Quantitative Sudomotor Axon Reflex Test
QSWEAT	Quantitative Sweat Test Device

SC	Skin Conductance
SCL	Skin Conductance Level
SCR	Skin Conductance Response
TTT	Tilt Table Test
UCLA	University of California Los Angeles
VM	Valsalva Maneuver
VR	Valsalva Ratio

Supplemental Table 21

Autonomic Reflex Function in POTS Versus Control Subjects

Variable	Controls (n = 25)	POTS (n = 62)	p-value
ΔHR During Deep Breathing, bpm	17.1 ± 8.3; 13.1	22.8 ± 8.2; 22.8	0.002
Maximum HR During Deep Breathing, bpm[1]	84.0 ± 10.3; 85.1	89.7 ± 12.7; 89.1	0.049
Minimum HR During Deep Breathing, bpm[1]	68.1 ± 10.8; 67.7	67.6 ± 12.2; 65.6	0.843
E:I Ratio During Deep Breathing[2]	1.3 ± 0.2; 1.2	1.4 ± 0.2; 1.3	0.006
Maximum HR During Valsalva Maneuver, bpm[1]	102.4 ± 18.7; 107.1	124.2 ± 16.1; 122.4	<0.001
Minimum HR During Valsalva Maneuver, bpm	67.0 ± 17.1; 62.9	56.4 ± 9.9; 54.8	0.002
Greatest HR Ratio During Valsalva Maneuver	1.8 ± 0.2; 1.7	2.4 ± 0.5; 2.4	<0.001
Pressure Recovery Time, sec	5.9 ± 12.4; 1.4	2.4 ± 3.0; 1.4	0.934

Note. Values reported as mean ± SD; median. The number of results reported in each cohort of the study is denoted by n_x, where ncontrols = 25 and nPOTS = 62. Abbreviations: ΔHR, Delta Heart Rate; E:I, expiration:inspiration; HR, Heart Rate; HUT, Head-up Tilt; POTS, Postural Orthostatic Tachycardia Syndrome; SD, Standard Deviation. The PRT values for POTS cases (*) are the mean ± SD; median for the 58 POTS cases with reported PRTs, and the PRT values for controls (**) are the mean ± SD; median, for the 24 controls with reported PRTS. Only 62 patients with POTS underwent a full ARS. Groups were compared using the Mann-Whitney U Test, except where noted as 1=the Unpaired T-Test.

Supplemental Table 22

Autonomic Reflex Function in Fully Screened Controls and POTS Cases Stratified by Electrodermal Response Subtype

Variable	Controls (n=25)				POTS Cases (n= 62)				
	Transient (n=18)	Absent (n=5)	Delayed (n=2)	p-value	Transient (n=21)	Absent (n=11)	Delayed (n=4)	Persistent (n=26)	p-value
ΔHR During Deep Breathing[1], bpm	18.6 ± 9.0; 15.1	10.0 ± 1.6; 11.4	18.9 ± 4.9; 4.9	0.049	22.0 ± 7.3; 24.7	24.4 ± 8.2; 24.2	25.9 ± 7.0; 26.8	22.2 ± 9.2; 20.3	0.607
Patients with a Below Normal ΔHR, N (%)	0 (0.0)	0 (0.0)	0 (0.0)	>0.999	2 (9.5)	0 (0.0)	0 (0.0)	2 (7.7)	<0.001
Patients with an Above Normal ΔHR, N (%)	0 (0.0)	0 (0.0)	0 (0.0)	>0.999	0 (0.0)	1 (9.1)	0 (0.0)	1 (3.8)	<0.001
E:I Ratio During Deep Breathing[1]	1.3 ± 0.2; 1.2	1.2 ± 0.0; 1.2	1.3 ± 0.1; 1.3	0.249	1.3 ± 0.1; 1.3	1.4 ± 0.2; 1.3	1.4 ± 0.1; 1.4	1.4 ± 0.2; 1.3	0.556
Greatest HR Ratio During Valsalva Maneuver[1]	1.8 ± 0.2; 1.7	1.7 ± 0.2; 1.7	2.0 ± 0.1; 2.0	0.322	2.4 ± 0.5; 2.4	2.4 ± 0.4; 2.6	2.7 ± 0.5; 2.7	2.3 ± 0.5; 2.3	0.374
Patients with Below Normal Greatest HR Ratio During Valsalva Maneuver, N (%)	0 (0.0)	0 (0.0)	0 (0.0)	>0.999	1 (4.8)	0 (0.0)	0 (0.0)	0 (0.0)	0.004
Patients with Above Normal Greatest HR Ratio During Valsalva Maneuver, N (%)	0 (0.0)	0 (0.0)	0 (0.0)	>0.999	5 (23.8)	2 (14.3)	2 (50.0)	2 (6.3)	<0.001
Patients Without a Late Phase 2 Recovery, N (%)	0 (0.0)	0 (0.0)	0 (0.0)	>0.999	4 (19.0)	0 (0.0)	0 (0.0)	4 (17.4)	<0.001
Patients with an Absent Phase 4 Overshoot, N (%)	0 (0.0)	0 (0.0)	0 (0.0)	>0.999	1 (4.8)	0 (0.0)	0 (0.0)	0 (0.0)	0.004
Patients with an Exaggerated Phase 4 Overshoot, N (%)	0 (0.0)	0 (0.0)	0 (0.0)	>0.999	5 (23.8)	3 (27.3)	1 (25.0)	4 (15.4)	0.165
Patients with a Prolonged Pressure Recovery Time, N (%)	2 (11.1)	2 (40.0)	2 (100.0)	<0.001	2 (9.5)	(0.0)	1 (25.0)	3 (11.5)	<0.001
Patients with an Abnormal Adrenergic Function, N (%)	0 (0.0)	0 (0.0)	0 (0.0)	>0.999	9 (42.9)	5 (45.5)	4 (100.0)	11 (42.3)	<0.001
Patients with an Abnormal Cardiovagal Function, N (%)	0 (0.0)	0 (0.0)	0 (0.0)	>0.999	2 (9.5)	(0.0)	0 (0.0)	3 (11.5)	<0.001
Patients with an Abnormal Sudomotor Function, N (%)	0 (0.0)	0 (0.0)	0 (0.0)	>0.999	14 (66.7)	6 (54.5)	1 (25.0)	9 (34.6)	<0.001
Patients with General Autonomic Impairment, N (%)	0 (0.0)	0 (0.0)	0 (0.0)	>0.999	18 (85.7)	10 (90.9)	3 (75.0)	19 (73.1)	0.002

Values reported as mean ± SD; median, or percentages. The number of results reported in each of the electrodermal subgroups is denoted by n_x, where $n_{Transient} = 21$, $n_{Absent} = 11$, $n_{Delayed} = 4$, and $n_{Persistent} = 26$. Abbreviations: ΔHR, delta heart rate; E:I, expiration:inspiration; HR, heart rate; POTS, postural orthostatic tachycardia syndrome; SD, standard deviation. The PRT values for POTS cases are reported as the mean ± SD; median, for the 58 POTS cases with reported PRTs. Only 62 patients with POTS underwent a full ARS. Groups were compared with the Fisher's Exact Test, except where noted as 1= Kruskal-Wallis Test.

Supplemental Table 23

Autonomic reflex function

Variable	Controls (n = 25)	POTS (n = 62)	p-value
ΔHR During Deep Breathing[1], bpm	17.1 ± 8.3; 13.1	22.8 ± 8.2; 22.8	0.002
Percentage of Patients with a Below Normal ΔHR (%)	0.0	6.5*	0.014
Percentage of Patients with an Above Normal ΔHR (%)	0.0	3.2*	0.246
Maximum HR During Deep Breathing[1], bpm	84.0 ± 10.3; 85.1	89.7 ± 12.7; 89.1	0.049
Minimum HR During Deep Breathing[1], bpm	68.1 ± 10.8; 67.7	67.6 ± 12.2; 65.6	0.843
E:I Ratio During Deep Breathing[1]	1.3 ± 0.2; 1.2	1.4 ± 0.2; 1.3	0.006
Maximum HR During Valsalva Maneuver[1], bpm	102.4 ± 18.7; 107.1	124.2 ± 16.1; 122.4	<0.001
Minimum HR During Valsalva Maneuver[1], bpm	67.0 ± 17.1; 62.9	56.4 ± 9.9; 54.8	0.002
Greatest HR Ratio During Valsalva Maneuver[1]	1.8 ± 0.2; 1.7	2.4 ± 0.5; 2.4	<0.001
Percentage of Patients with Below Normal Greatest HR Ratio During Valsalva Maneuver (%)	0.0	1.6*	0.498
Percentage of Patients with Above Normal Greatest HR Ratio During Valsalva Maneuver (%)	0.0	17.7*	<0.001
Percentage of Patients Without a Phase 1 Response (%)	0.0	1.6*	0.498
Percentage of Patients Without a Late Phase 2 Recovery (%)	0.0	12.9*	<0.001
Percentage of Patients with an Absent Phase 4 Overshoot (%)	0.0	1.6*	0.498
Percentage of Patients with a Blunted Phase 4 Overshoot (%)	0.0	11.3*	<0.001
Percentage of Patients with an Exaggerated Phase 4 Overshoot (%)	0.0	21.0*	<0.001
Pressure Recovery Time (PRT)[1], seconds	5.9 ± 12.4; 1.4^{++}	2.4 ± 3.0; 1.4**	0.934
Percentage of Patients with a Shortened PRT (%)	40.0	27.4*	0.072
Percentage of Patients with a Prolonged PRT (%)	24.0	9.7*	0.014
Patients with an Abnormal Adrenergic Function (%)	0.0	46.8*	0.081
Patients with an Abnormal Cardiovagal Function (%)	0.0	8.1*	0.710
Patients with an Abnormal Sudomotor Function (%)	0.0	51.6*	<0.001
Patients with General Autonomic Impairment (%)	0.0	80.6*	<0.001

Note. Values are reported as mean ± SD; median, or n; where n_x is the number enrolled in each group of the study ($n_{controls}$ = 25 and n_{POTS} = 62). Abbreviations: ΔHR, delta heart rate, E:I, expiration:inspiration; HR, heart rate; HUT, head-up tilt; PRT, pressure recovery time. Note that the percentage of patients out of all of the 62 POTS cases that underwent a full autonomic reflex screen (ARS) is denoted by an asterix (*). All other percentages, are based on all of the patients in each group respectively. In patients with POTS, the PRT was only determinable in 58 out of 62 patients, and this is denoted by two asterixes (**). In the controls, the PRT was only determinable in 24 out of 25 patients, and this is denoted by two bold superscript asterixes ($^{++}$). The groups were compared with the Fisher's Exact Test, except where noted as 1= Kruskal-Wallis Test.

Supplemental Table 24

PPG values in pre-HUT, HUT, and post-HUT periods, stratified by EDA response subtype in the same patient with POTS.

Variable	Variable Value	1 Minute Pre-HUT Period	HUT Period	1 Minute Post HUT Period
PR, BPM	Maximum Value	78.125	177.514	102.739
	Minimum Value	59.288	0.000	56.390
	Peak-to-Peak Value	18.836	177.514	46.348
	Mean Value	67.859	92.923	81.190
EDA, µsiemens	Maximum Value	0.437	0.413	0.318
	Minimum Value	0.366	0.256	0.270
	Peak-to-Peak Value	0.071	0.157	0.048
	Mean Value	0.401	0.329	0.295
PPG, Volts	Maximum Value	0.287	0.292	0.449
	Minimum Value	-0.178	-0.203	-0.198
	Peak-to-Peak Value	0.466	0.495	0.647
	Mean Value	0.030	0.030	0.030

Note. Abbreviations: EDA, electrodermal activity; ; HUT, head-up tilt; POTS, postural orthostatic tachycardia syndrome; PPG, photoplethysmography; PR, pulse rate. Values are reported as means or single numbers. The datums for the maximum, minimum and peak-to-peak PR values recorded during the HUT period, may be due to artifacts in the underlying PPG signal traces, because these values, are sharp deviations from their respective equivalent values during Pre-HUT and Post-HUT, and so they may be extreme outliers.

Supplemental Table 25

Variables vs. EDA Response Subtype by Group (N = 100 – Subjects of All Ages, i.e., Aged 11-79-years old)

			EDA Response Subtype					
Group	**Variable Name**	**Level**	**Transient**	**Absent**	**Delayed**	**Persistent**	**Total**	**p-value**
POTS	Adrenergic Impairment without Surety of Hyperadrenergic POTS	0 – No	16	11	4	21	52	0.0255
	Adrenergic Impairment without Surety of Hyperadrenergic POTS	1 – Yes	5	0	0	4	9	
	Adrenergic Impairment without Surety of Hyperadrenergic POTS	2 – Not Applicable	0	3	4	6	13	
	Adrenergic Impairment without Surety of Hyperadrenergic POTS	4 – Indeterminable	0	0	0	1	1	
	Adrenergic Impairment without Surety of Hyperadrenergic POTS	Percentage of Level 0 Cases for the variable 'Adrenergic Impairment without Surety of Hyperadrenergic POTS'	76.2%	78.6%	50.0%	65.6%		
Controls	Adrenergic Impairment without Surety of Hyperadrenergic POTS	2 – Not Applicable	18	6	1	0		
	Adrenergic Impairment without Surety of Hyperadrenergic POTS	Percentage of Level 4 Cases for the variable 'Adrenergic Impairment without Surety of Hyperadrenergic POTS'	0.0%	0.0%	0.0%	0.0%		
POTS	ASA Line 1 PRT Computed	0 – No	0	4	4	9	17	0.0080
	ASA Line 1 PRT Computed	1 – Yes	21	10	4	23	58	
	ASA Line 1 PRT Computed	Percentage of ASA Line 1 PRT Computed	100.0%	71.4%	50.0%	71.9%		
Control	ASA Line 1 PRT Computed	0 – No	1	0	0	0	1	>0.9999
	ASA Line 1 PRT Computed	1 – Yes	17	6	1	0	24	
	ASA Line 1 PRT Computed	Percentage of ASA Line 1 PRT Computed	94.4%	100.0%	100.0%	0.0%		

Note. (1) Abbreviations: ASA, adrenergic sensitivity analysis; POTS, postural orthostatic tachycardia syndrome; PRT, pressure recovery time. (2) A Key of Levels for the variable labelled "Adrenergic Impairment without Surety of Hyperadrenergic POTS": Level 0 No; Level 1 Yes; Level 2 Not Applicable; Level 3 Not Stated; Level 4 Indeterminable. Groups were compared with the use of Fisher's Exact Test.

Supplemental Table 26

Variables vs. EDA Response Subtype by Group (N = 100 – Subjects of All Ages, i.e., Aged 11-79-years old)

			EDA Response Subtype					
Group	**Variable Name**	**Level**	**Transient**	**Absent**	**Delayed**	**Persistent**	**Total**	**p-value**
POTS (by detailed ARS Testing type)	ARS Testing Type	1	20	9	4	19	52	0.0330
	ARS Testing Type	2	1	2	0	4	7	
	ARS Testing Type	3	0	2	4	6	12	
	ARS Testing Type	4	0	1	0	3	4	
	ARS Testing Type	Percentage of ARS Testing Type 4	0.0%	7.1%	0.0%	9.4%		
Controls (by detailed ARS Testing type)	ARS Testing Type	1	17	6	1	0	24	>0.9999
	ARS Testing Type	2	1	0	0	0	1	
	ARS Testing Type	Percentage of ARS Testing Type 2	5.6%	0.0%	0.0%	0.0%		
POTS (by broad ARS Testing type; i.e., full or partial)	ARS Full or Partial	1 – Full	21	12	5	28	66	0.0325
	ARS Full or Partial	2 – Partial	0	2	3	4	9	
	ARS Full or Partial	Percentage of 2-partial	0.0%	14.3%	37.5%	12.5%		
Control (by broad ARS Testing type; i.e., full or partial)	ARS Full or Partial	1 – Full	18	6	1	0	25	
	ARS Full or Partial	2 – Partial	0	0	0	0	0	
	ARS Full or Partial	Percentage of ARS Full or Partial 2-partial	0.0%	0.0%	0.0%	0.0%		

Note. (1) Abbreviations: ARS, autonomic reflex screen; ERS, EDA response subtype; POTS, postural orthostatic Tachycardia Syndrome. (2) A Key of Levels for the variable labelled "ARS Testing Type": Level 1 Fully Completed ARS Tests; Level 2 Fully Completed ARS Tests with Missing Results: Applicable to Full ARS Cases Only; Level 3 Fully Completed TTT-Only ARS Tests (i.e., for those patients that underwent Tilt Table Test-Only ARS type testing during their appointments at the UCLA Cardiac Arrhythmia Center's Autonomic Testing Laboratory); Level 4 Partially Completed ARS Tests: Applicable to Full ARS Cases Only. Groups were compared with the use of Fisher's Exact Test.

Supplemental Table 27

Variables vs. EDA Response Subtype by Group (N = 100 – Subjects of All Ages, i.e., Aged 11-79-years old)

			EDA Response Subtype					
Group	**Variable Name**	**Level**	**Transient**	**Absent**	**Delayed**	**Persistent**	**Total**	**p-value**
POTS	Symptom: Disorientation	0 – No	19	13	4	31	67	0.0055
	Symptom: Disorientation	1 – Yes	2	1	4	1	8	
	Symptom: Disorientation	Percentage of Present Symptoms	9.5%	7.1%	50.0%	3.1%		
Control	Symptom: Disorientation	0 – No	18	6	1	0	25	
	Symptom: Disorientation	1 – Yes	0	0	0	0	0	
	Symptom: Disorientation	Percentage of Present Symptoms	0.0%	0.0%	0.0%	0.0%		
POTS	Symptom: Shortness of Breath	0 – No	20	9	5	25	59	0.0650
	Symptom: Shortness of Breath	1 – Yes	1	5	3	7	16	
	Symptom: Shortness of Breath	Percentage of the Number of POTS Cases that Reported Feeling Shortness of Breath	4.8%	35.7%	37.5%	21.9%		
Control	Symptom: Shortness of Breath	0 – No	16	5	1	0	22	>0.9999
	Symptom: Shortness of Breath	1 – Yes	2	1	0	0	3	
	Symptom: Shortness of Breath	Percentage of the Number of Controls that Reported Feeling Shortness of Breath	11.1%	16.7%	0.0%	0.0%		

Note. Abbreviations: EDA, electrodermal activity; ERS, EDA response subtype; POTS, postural orthostatic tachycardia syndrome. The results for "shortness of breath" is almost statistically significant (p= 0.0650). Despite the lack of statistical significance, i.e., vis-à-vis a minimum statistical significance level of $p<0.05$, this result is clinically significant. As such it has been highlighted as shown in the table above. Groups were compared with the use of Fisher's Exact Test.

Supplemental Table 28

Variables vs. EDA Response Subtype by Group (N = 100 – Subjects of All Ages, i.e., Aged 11-79-years old)

			EDA Response Subtype					
Group	**Variable Name**	**Level**	**Transient**	**Absent**	**Delayed**	**Persistent**	**Total**	**p-value**
POTS	CASS Computed	0 – No	0	3	4	6	13	0.0055
	CASS Computed	1 – Yes	21	11	4	26	62	
	CASS Computed	Percentage of Patients with a Computed CASS	100.0%	78.6%	50.0%	81.3%		
Control	CASS Computed	0 – No	18	6	1	0	25	
	CASS Computed	1 – Yes	0	0	0	0	0	
	CASS Computed	Percentage of Patients with a Computed CASS	0.0%	0.0%	0.0%	0.0%		
POTS	CASS Raw Cardiovagal Score (Nominal Type 2)	1	21	11	4	26	62	0.0085
	CASS Raw Cardiovagal Score (Nominal Type 2)	2	0	3	4	6	13	
	CASS Raw Cardiovagal Score (Nominal Type 2)	Percentage of the Number of POTS Cases with a CASS Raw Cardiovagal Score (Nominal Type 2) of Level 2	0.0%	21.4%	50.0%	18.8%		
Control	CASS Raw Cardiovagal Score (Nominal Type 2)	1	18	6	1	0	25	
	CASS Raw Cardiovagal Score (Nominal Type 2)	2	0	0	0	0	0	
	CASS Raw Cardiovagal Score (Nominal Type 2)	Percentage of the Number of POTS Cases with a CASS Raw Cardiovagal Score (Nominal Type 2) of Level 2	0.0%	0.0%	0.0%	0.0%		
POTS	CASS Raw Adrenergic Score (Nominal Type 2)	1	21	11	4	26	62	0.0150
	CASS Raw Adrenergic Score (Nominal Type 2)	2	0	3	4	6	13	
	CASS Raw Adrenergic Score (Nominal Type 2)	Percentage of the Number of POTS Cases with a CASS Raw Adrenergic Score (Nominal Type 2) of Level 2	0.0%	21.4%	50.0%	18.8%		
Control	CASS Raw Adrenergic Score (Nominal Type 2)	1	18	6	1	0	25	
	CASS Raw Adrenergic Score (Nominal Type 2)	2	0	0	0	0	0	
	CASS Raw Adrenergic Score (Nominal Type 2)	Percentage of the Number of POTS Cases with a CASS Raw Adrenergic Score (Nominal Type 2) of Level 2	0.0%	0.0%	0.0%	0.0%		

Note. Abbreviations: CASS, composite autonomic severity score; EDA, electrodermal activity; ERS, EDA response subtype; POTS, postural orthostatic tachycardia syndrome. (2) A Key of Levels for the variables labelled “CASS RAW Cardiovagal Score (Nominal Type 2)” and “CASS RAW Adrenergic Score (Nominal Type 2)”: Level 1 ; Level 2 . Groups were compared with the use of Fisher’s Exact Test.

Supplemental Table 29

Variables vs. EDA Response Subtype by Group (N = 100 – Subjects of All Ages, i.e., Aged 11-79-years old)

			EDA Response Subtype					
Group	**Variable Name**	**Level**	**Transient**	**Absent**	**Delayed**	**Persistent**	**Total**	**p-value**
POTS	CASS Raw Sudomotor Score (Nominal Type 2)	1	21	11	4	25	61	0.0135
	CASS Raw Sudomotor Score (Nominal Type 2)	2	0	3	4	6	13	
	CASS Raw Sudomotor Score (Nominal Type 2)	3	0	0	0	1	1	
	CASS Raw Sudomotor Score (Nominal Type 2)	Percentage of the Number of POTS Cases with a CASS Raw Sudomotor Score (Nominal Type 2) of Level 3	0.0%	0.0%	0.0%	3.1%		
Control	CASS Raw Sudomotor Score (Nominal Type 2)	1	18	5	2	0	25	
	CASS Raw Sudomotor Score (Nominal Type 2)	2	0	0	0	0	0	
	CASS Raw Sudomotor Score (Nominal Type 2)	3	0	0	0	0	0	
	CASS Raw Sudomotor Score (Nominal Type 2)	Percentage of the Number of POTS Cases with a CASS Raw Sudomotor Score (Nominal Type 2) of Level 3	0.0%	0.0%	0.0%	0.0%		
POTS	CASS Coded Sudomotor Score	1	7	2	3	14	26	0.0345
	CASS Coded Sudomotor Score	2	0	0	0	1	1	
	CASS Coded Sudomotor Score	3	6	4	0	1	11	
	CASS Coded Sudomotor Score	5	3	3	0	3	9	
	CASS Coded Sudomotor Score	7	5	2	1	6	14	
	CASS Coded Sudomotor Score	8	0	3	4	6	13	
	CASS Coded Sudomotor Score	9	0	0	0	1	1	
	CASS Coded Sudomotor Score	Percentage of the Number of POTS Cases with a CASS Coded Sudomotor Score of Level 9	0.0%	21.4%	50.0%	18.8%		
Control	CASS Coded Sudomotor Score	1	18	5	2	0	25	
	CASS Coded Sudomotor Score	2	0	0	0	0	0	
	CASS Coded Sudomotor Score	3	0	0	0	0	0	
	CASS Coded Sudomotor Score	5	0	0	0	0	0	
	CASS Coded Sudomotor Score	7	0	0	0	0	0	
	CASS Coded Sudomotor Score	8	0	0	0	0	0	
	CASS Coded Sudomotor Score	9	0	0	0	0	0	
	CASS Coded Sudomotor Score	Percentage of the Number of POTS Cases with a CASS Coded Sudomotor Score of Level 9	0.0%	0.0%	0.0%	0.0%		

Note. Abbreviation: CASS, composite autonomic severity score; EDA, electrodermal activity; ERS, EDA response subtype; POTS, postural orthostatic tachycardia syndrome. (2) A Key of Levels for the variable labelled “CASS RAW Sudomotor Score (Nominal Type 2)”: Level 1 ; Level 2 ; Level 3 . (3) A Key of Levels for the variables labelled “CASS Coded Sudomotor Score”: Level 1 ; Level 2 ; level 3 ; Level 4 ; Level 5 ; Level 6 ; Level 7 ; Level 8 ; level 9 . Groups were compared with the use of Fisher’s Exact Test.

Supplemental Table 30

Variables vs. EDA Response Subtype by Group (N = 100 – Subjects of All Ages, i.e., Aged 11-79-years old)

			EDA Response Subtype					
Group	**Variable Name**	**Level**	**Transient**	**Absent**	**Delayed**	**Persistent**	**Total**	**p-value**
POTS	CASS Raw Total Score (Nominal Type 2)	1	21	11	4	26	62	0.0120
	CASS Raw Total Score (Nominal Type 2)	2	0	3	4	6	13	
	CASS Raw Total Score (Nominal Type 2)	Percentage of the Number of POTS Cases with a CASS Raw Total Score of Level 2	0.0%	21.4%	50.0%	18.8%		
Control	CASS Raw Total Score (Nominal Type 2)	1	18	5	2	0	25	
	CASS Raw Total Score (Nominal Type 2)	2	0	0	0	0	0	
	CASS Raw Total Score (Nominal Type 2)	Percentage of the Number of POTS Cases with a CASS Raw Sudomotor Score of Level 2	0.0%	0.0%	0.0%	0.0%		
POTS	General Autonomic Impairment	1	3	2	3	8	16	0.0795
	General Autonomic Impairment	2	0	0	0	2	2	
	General Autonomic Impairment	3	16	9	1	15	41	
	General Autonomic Impairment	4	1	0	0	1	2	
	General Autonomic Impairment	6	1	3	4	6	14	
	General Autonomic Impairment	Percentage of the Number of POTS Cases with a General Autonomic Impairment of Level 6	0.0%	21.4%	50.0%	18.8%		
Control	General Autonomic Impairment	1	18	5	2	0	25	
	General Autonomic Impairment	2	0	0	0	0	0	
	General Autonomic Impairment	3	0	0	0	0	0	
	General Autonomic Impairment	4	0	0	0	0	0	
	General Autonomic Impairment	6	0	0	0	0	0	
	General Autonomic Impairment	Percentage of the Number of POTS Cases with a General Autonomic Impairment of Level 6	0.0%	0.0%	0.0%	0.0%		

Note. (1) Abbreviation: CASS, composite autonomic severity score; EDA, electrodermal activity; ERS, EDA response subtype; POTS, postural orthostatic tachycardia syndrome. (2) A Key of Levels for the variables labelled “CASS RAW Total Score (Nominal Type 2)”: Level 1 ; Level 2 . (3) A Key of Levels for the variable labelled “General Autonomic Impairment”: Level 1 Absent; Level 2 Present; Level 3 Mild; Level 4

Moderate; Level 5 Severe; Level 6 Unknown. Groups were compared with the use of Fisher's Exact Test.

Supplemental Table 31

Differences in Various EDA Indices Between POTS Cases and Controls Across the Entire Study Population

Variable Name	Area Under the Curve (AUC)	p-value	q-value
EDA_{Mean} Post HUTT, µsiemens	0.709	0.0018	0.0195
$EDA_{Frequency}$ HUTT	0.702	0.0025	0.0251
$EDA_{Frequency}$ HUTT – $EDA_{Frequency}$ Pre HUTT	0.702	0.0025	0.0251
$EDA_{Frequency}$ Post HUTT – $EDA_{Frequency}$ HUTT	0.702	0.0025	0.0251
EDA_{Sum} Post HUTT – EDA_{SUM} Pre HUTT,	0.701	0.0027	0.0260
EDA Delta, µsiemens	0.681	0.0070	0.0501
EDA at Tilt Down – EDA at Tilt Up, µsiemens	0.678	0.0079	0.0535
$EDA_{Integral}$ Post HUTT – $EDA_{Integral}$ Pre HUTT, µsiemens-sec	0.671	0.0109	0.0677
$EDA_{Peak\text{-}to\text{-}Peak}$ Post HUTT – $EDA_{Peak\text{-}to\text{-}Peak}$ Pre HUTT, µsiemens	0.667	0.0126	0.0748
$EDA_{Peak\text{-}to\text{-}Peak}$ HUTT – $EDA_{Peak\text{-}to\text{-}Peak}$ Pre HUTT, µsiemens	0.661	0.0162	0.0862
EDA_{Slope} HUTT	0.654	0.0208	0.0945
EDA_{Sum} HUTT – EDA_{Sum} Pre HUTT	0.655	0.0210	0.0946
EDA_{Sum} Post HUTT – EDA_{Sum} HUTT	0.646	0.0298	0.1096
EDA_{Sum} HUTT	0.643	0.0329	0.1176
EDA at Tilt Down	0.634	0.0457	0.1432
EDA_{Median}	0.634	0.0453	0.1432
EDA_{Area} Post Tilt	0.629	0.0541	0.1600
$EDA_{Area\text{-}normalized}$ Post Tilt	0.629	0.0541	0.1600

EDA_{Sum} Post HUTT	0.629	0.0541	0.1600
$EDA_{Integral}$ HUTT – $EDA_{Integral}$ Pre HUTT	0.625	0.0625	0.1801
EDA Post HUTT - $EDA_{Integral}$ HUTT	0.625	0.0636	0.1827
EDA_{Mean}	0.624	0.0648	0.1853
EDA_{Max}	0.622	0.0683	0.1917
$EDA_{Integral}$	0.621	0.0720	0.1977
EDA_{Area} Post HUTT – EDA_{Area} Pre HUTT	0.619	0.0772	0.2010
$EDA_{Area\text{-}normalized}$ Post HUTT – $EDA_{Area\text{-}normalized}$ Pre HUTT	0.619	0.0772	0.2010
EDA_{Area} During Head-up Tilt	0.617	0.0813	0.2102
EDA_{Max} HUTT – EDA_{Mean} Pre HUTT	0.616	0.0841	0.2123
EDA_{Area} HUTT – EDA_{Area} Pre HUTT	0.615	0.0870	0.2175
EDA_{Area} Post HUTT – EDA_{Area} HUTT	0.614	0.0900	0.2205
$EDA_{Peak\text{-}to\text{-}Peak}$	0.611	0.0994	0.2367
$EDA_{Difference}$	0.609	0.1044	0.2433
$EDA_{Peak\text{-}to\text{-}Peak}$ Post HUTT	0.609	0.1061	0.2457
$EDA_{Integral}$ Post HUTT	0.607	0.1114	0.2548
EDA_{Area}	0.606	0.1132	0.2581
$EDA_{Area\text{-}normalized}$ During Head-up Tilt	0.590	0.1785	0.3456
$EDA_{Standard\text{-}Deviation}$	0.587	0.1972	0.3750
$EDA_{Area\text{-}normalized}$ HUTT – $EDA_{Area\text{-}normalized}$ Pre HUTT	0.584	0.2114	0.3908
EDA_{Mean} Pre HUTT	0.577	0.2550	0.4446
EDA_{Min} HUTT – EDA_{Mean} Pre HUTT	0.573	0.2787	0.4707
$EDA_{Integral}$ Pre HUTT	0.571	0.2897	0.4847

EDA_{Min}	0.569	0.3026	0.4977
$EDA_{Peak\text{-}to\text{-}Peak}$ Post HUTT – $EDA_{Peak\text{-}to\text{-}Peak}$ HUTT	0.565	0.3315	0.5229
EDA_{Sum} Pre HUTT	0.560	0.3726	0.5638
$EDA_{Tilt\text{-}Up}$	0.557	0.4010	0.5778
EDA Pre HUTT Peak-to-Peak	0.546	0.4936	0.6488
EDA_{DeltaS} During HUTT	0.533	0.6301	0.7551
$EDA_{Duration}$ Head-up Tilt	0.532	0.6329	0.7573
$EDA_{Area\text{-}normalized}$ Post HUTT – $EDA_{Area\text{-}normalized}$ HUTT	0.530	0.6558	0.7700
EDA_{BPM} HUTT, BPM	0.483	0.7843	0.8607
EDA_{BPM} HUTT – EDA_{BPM} Pre HUTT, BPM	0.483	0.7843	0.8607
EDA_{BPM} Post HUTT – EDA_{BPM} HUTT, BPM	0.517	0.7843	0.8607
EDA_{Area} Pre Tilt	0.483	0.7989	0.8704
$EDA_{Area\text{-}normalized}$ Pre Tilt	0.483	0.7989	0.8704
Number of Data Sets During HUT	0.491	0.8838	0.9384

Note. Abbreviations: EDAArea: area under the EDA signal trace; $EDA_{Area\text{-}normalized}$: normalized area under the EDA signal trace. The EDA differences between the controls and POTS cases, were appraised with the Kruskal-Wallis test.

Supplemental Table 32

A Detailed Breakdown of the Symptoms Reported During HUTT and New Symptoms Scoring Scale Items for the Group of Controls

Study ID	EDA Response Subtype	Symptoms Remarks	Symptoms Severity Trend	Symptoms Quality and Ranking	Number of Symptoms
26.2	2	0 Asymptomatic.2 Asymptomatic.4 Asymptomatic.6 Head feels heavy.8 Head feels heavy.10 Head feels less heavy once supine.PACs noted.	Increased (4)	Moderate (3)	1
25.2	3	0 Light headed after tilting up.2 Lightheadedness decreased.4 Feeling of heaviness in bilateral legs.6 Pressure behind right eye.8 Heaviness in legs still present. Pressure behind right eye gone.10 Asymptomatic.	Same (3)	Moderate (3)	3
24.2	1	PAC noted0 A little rush feeling radiating from chest to bilateral armpits while tilting up.2 Asymptomatic. 4 Asymptomatic. 6 Asymptomatic. 8 Asymptomatic. 10 Asymptomatic.	Decreased (2)	Mild (2)	1
23.2	1	0 Asymptomatic.2 Asymptomatic.4 Asymptomatic.6 Asymptomatic.8 Asymptomatic.10 Asymptomatic.Hypertensive when tilted down. Systolic 200's.PACs and PVC noted.	No Symptoms (0)	N/A (0)	0
22.2	1	0 Asymptomatic.2 Asymptomatic.4 Asymptomatic.6 Asymptomatic.8 Asymptomatic.10 Asymptomatic.	No Symptoms (0)	N/A (0)	0
21.2	2	0 Asymptomatic.2 Asymptomatic.4 Asymptomatic.6 Asymptomatic.8 Asymptomatic.10 Asymptomatic.	No Symptoms (0)	N/A (0)	0
20.2	1	0 Asymptomatic.2 Asymptomatic.3 Head pressure in the back of her head.4 Head pressure subsided.6 Same as above.8 Same as above plus ear pressure.10 Same as above once supine.	Same (3)	Mild (2)	2
19.2	1	0 Asymptomatic.2 Asymptomatic.4 Asymptomatic.6 Asymptomatic.8 Asymptomatic.10 Asymptomatic.	No Symptoms (0)	N/A (0)	0

18.2	2	0 A little lightheaded.2 Light headedness decreasing.4 Asymptomatic.6 Asymptomatic.8 Asymptomatic.10 A little lightheaded while tilting down.	Decreased (2)	Mild (2)	1
17.2	2	0 Asymptomatic.2 Asymptomatic.4 Asymptomatic.6 Asymptomatic.8 Asymptomatic.10 Asymptomatic.	No Symptoms (0)	N/A (0)	0
16.2	2	0 A little dizzy. Feels heavy. 2 Less heavy. Tired. Feels like she's still moving. Can't breathe well. 4 Less dizzy. More tired. 6 Same as above plus nausea. 8 Left hand and both legs feel tight. Feel heart pounding. 10 Very tired and heavy,	Increased (4)	Severe (4)	8
15.2	1	0 Asymptomatic. 2 A little lightheaded. 4 A little SOB. 6 Same as above. 8 A little better. 10 Feels better.	Decreased (2)	Mild (2)	2
14.2	1	0 Asymptomatic. 2 Asymptomatic. 4 Asymptomatic. 6 Asymptomatic. 8 Asymptomatic. 10. Lightheaded coming down to supine position.	Same (3)	Mild (2)	1
13.2	1	0 Feels good. 2 Feels good. 4 Feels good. Muscle twitching in both legs. 6 Same as above. 8 Same as above. 10 Same as above.	Same (3)	Mild (2)	1
11.2	1	SR PACs. 0: Head shaking started. A little dizziness. Cognitive awareness foggy. Nausea. 2: Same as above. 4: Head shaking stopped. Cognitive awareness better. Nauseous. Head pressure. Pooping in ears. 6: Head shaking started again. 8: Nauseous.	Increased (4)	Severe (4)	6
10.2	1	0: Feeling fine 2: fine 4: fine 6: fine 8: fine 10: feeling good	No Symptoms (0)	N/A (0)	0
9.2	1	0: feeling fine 2: a little lightheadedness 4: lightheadedness getting better 6: tired, a little SOB and dizzy, heart pounding 8: getting better somehow 10: a little dizzy	Decreased (2)	Moderate (3)	5
8.2	1	0: a little weird, lightheadedness 2: sweating, a little lightheadedness 4: right arm stiff, 6: feeling fine 8: feeling fine, 10: feeling fine.	Decreased (2)	Moderate (3)	4
7.2	1	0: Dizzy and nauseated 2: Headache, a little dizzy, tired 4: Tired and nauseated 6: Tired and nauseated, better than 2 min ago 8: Tired and a little nauseated 10: Feeling fine	Same (3)	Moderate (3)	4

6.2	1	0: feeling fine, 1: kind of dizzy, 2: Dizziness getting better 4: getting better 6: feeling fine 8: feeling fine 10: feeling fine	Decreased (2)	Mild (2)	1
5.2	2	0: Felt ok. 2: Discomfort right side of anterior chest. 4: Felt ok. 6: Still has chest pain same area but a little less. 8: Chest pain gone. 10: Feels lightheaded.	Decreased (2)	Mild (2)	2
4.2	1	0: Feels lightheaded. 2: Headache has gotten worse. 4: Headache is diminishing as well as lightheadedness. 6: Feels ok. Left hand tingling. 8: Feels same. Muscle beginning to cramp. 10: Feels much better.	Increased (4)	Moderate (3)	4
3.2	1	2:00 fine 4:00 fine 6:00 fine 8:00 fine	No Symptoms (0)	N/A (0)	0
2.2	1	1:00 Fine 3:00 Fine 5:00 Fine 7:00 Fine 9:00 Fine	No Symptoms (0)	N/A (0)	0
1.2	1		No Symptoms (0)	N/A (0)	0

Note. Abbreviations: HUTT, head-up tilt-table test; PAC, premature atrial contraction; PVC, premature ventricular contraction; POTS, postural orthostatic tachycardia syndrome; SR, sinus rhythm. Scale for Quantification of HUTT Symptoms: The five respective scores listed under the symptoms scoring scalar item titled “Symptoms Severity Trend”, are as follows: No Symptoms Ξ (0), Decreased Ξ (2), Asymptomatic Until Tilt Down Ξ (1), Same Ξ (3), and Increased Ξ (4). For the scalar item titled “Symptoms Quality and Ranking”, the five respective scores represent the following: Not Applicable (because the patient did not report any symptoms) Ξ (0), Transient Ξ (1), Mild Ξ (2), Moderate Ξ (3), and Severe Ξ (4).

Supplemental Table 33

A Detailed Breakdown of the Symptoms Reported During HUTT and New Symptoms Scoring Scale Items for the Group of POTS Cases

Study ID	EDA Response Subtype	Symptoms Remarks	Symptoms Severity Trend	Symptoms Quality and Ranking	Number of Symptoms
79.1	4	0 A little lightheaded while tilting up.2 Lightheadedness decreased. Bilateral legs feel weak.4 Same as above.5:24 Dizzy.6 Legs feel better. Otherwise, same as above.8 Same as above.10 Still dizzy and now feels shaky which according to the patient "moves around."12 Dizziness increased.14 Dizziness decreased. Lightheadedness still present.16 Same as above.18 Chest tightness which made breathing harder.20 Felt a little better once supine. Breathing better,	Increased (4)	Severe (4)	7
78.1	2	0 Asymptomatic.2 Asymptomatic.4 Asymptomatic.6 Asymptomatic.8 Asymptomatic.10 Asymptomatic.	No Symptoms (0)	N/A (0)	0
77.1	3	0 A bit dizzy, lightheaded, and nauseous.2 Symptoms above decreased. Short of breath.4 Same as above plus tired.6 Same as above plus wants to lie down.8 Same as above.10 Feeling hot all over and nausea decreased. Otherwise, same as above.12 Feeling of hotness increased. Anxious. Still short of breath. Wave of nausea just now.14 Nausea comes in waves. Still feeling hot and the other symptoms above.16 Anxiety increased.18 Same as above.20 Felt better once down.	Increased (4)	Severe (4)	8
76.1	4	0 Asymptomatic.2 A little flush and uneasy.4 The feeling of flushness behind neck and a little lightheaded.6 Feeling flushed and tingling in bilateral lower legs and feet. Heart	Increased (4)	Severe (4)	10

		racing and pounding. Lightheadedness increased. A little nauseous.8 Heart not racing and pounding as much. Headache. Tingling and flushed in bilateral lower legs and feet. Still nauseated.10 Heart racing and pounding decreased. Otherwise, same as above. 12 Dizzy. Heart pounding again. Otherwise, same as above.14 Headache. Dizzy. Tingling in bilateral lower legs and feet. Nauseous.16 Lightheaded. Otherwise, same as above.18 Heart pounding gone. Otherwise, same as above.20 Same as above.Took 6 minutes for the symptoms to subside post tilt.			
75.1	3	0 Light dizziness, lightheadedness, and nausea.2 Same as above.4 Symptoms above increased a little.6 Same as above.8 Lightheadedness increased.10 Nausea increased.12 Same as above.14 Above symptoms slightly increased.16 Same as above.18 Nausea increased.20 While tilting down the patient felt disoriented. She felt like she was doing "flips."	Increased (4)	Severe (4)	5
74.1	4	0 Asymptomatic.2 Asymptomatic.4 Feels restless. Breathing deeper. He has the urge to breath deeper at times that is not triggered by anything.6 Same as above. 8 Head feels heavier. Otherwise, the same as above.10 Tired. Otherwise, the same as above.4 minutes post test he was seeing floaters in his eyes.	Increased (4)	Severe (4)	5
73.1	4	0 A little dizziness.2 Asymptomatic.4 A little dizzy and feels hot.6 Dizziness increased. Lightheaded and still hot.8 Feels a little better.10 Dizziness and feeling of hotness came back.12 Dizziness and feeling of hotness went away.14 A little dizzy.16 Dizziness increased.18 Feels hot again. Dizziness increased a little.	Increased (4)	Moderate (3)	3

		Lightheaded.20 Felt better once down.			
72.1	2	0 Feels blood moving all around.2 Same as above.4 Lethargic. Shooting pain in chest just right of center.6 Heart feels heavy. Less lethargic.8 Feels heart beating fast.10 Felt better once down.	Increased (4)	Severe (4)	5
71.1	3	0 Disoriented when tilting up. A little lightheaded as well.2 Asymptomatic.3 Nauseous.4 Coldness in bilateral shins and feet.5 Pressure bilateral ears.6 Same as above.7 Pins and needles in bilateral shins and feet.8 Feels flush and light headed.9 Feels more flush.10 Same as above. Pressure in ears increased. Feels hot.11 Bilateral arms feels chilly especially around the elbows and back of neck.12 Headache.13 Chest pain in upper chest radiating up his throat. Hot and flushed. Asked to take his goggles off and it helped with the headache.14 Still hot and flushed.15 Tingling in bilateral feet.16 Same as above. 18 Tingling and weakness in bilateral legs and feet. Respiratory chest pain.19 Chest pain increased.20 Chest pain increased while tilting down and radiating to his jaw.	Increased (4)	Severe (4)	13
70.1	4	0 Dizzy and light headed.2 Same as above.4 Lightheaded. Dizziness gone.6 Light headedness decreased. Feels better.8 Lightheadedness gone.10 Feels better once down.	Decreased (2)	Mild (2)	2
69.1	4	0 Light headed.2 Whole body shaky. Light headedness the same.4 Body shakes increased. SOB. Light headedness the same.6 SOB increased. Shakiness getting worse.8 Bilateral arms tingly and numb. Shakiness is getting worse. SOB increased.10 Felt better once supine. Shakiness gone. SOB still present.	Increased (4)	Severe (4)	5
68.1	2	0 A little lightheaded once up.2 Same as above.4 Lightheadedness disappeared.6 Asymptomatic.8	Decreased (2)	Mild (2)	1

		Asymptomatic.10 Asymptomatic.12 Asymptomatic.14 Asymptomatic.16 Asymptomatic.18 A little light headed.19 Lightheadedness disappeared.20 Asymptomatic.			
67.1	3	0 Disorientation while tilting up.2 Feels heart rate is faster. SOB.4 Feels heart rate is fast. SOB better.6 Bilateral legs feel tingly. Heart rate stlll feels fast.8 Bilateral legs feel tingly. SOB gone. Heart rate feels like it calmed down for him.10 Bilateral legs still feel tingly especially below the knee.	Increased (4)	Moderate (3)	4
66.1	4	0 A little lightheadedness.2 Lightheadedness gone.4 Asymptomatic.6 Asymptomatic.8 A little chest tightness.10 Chest tightness better when supine.	Increased (4)	Mild (2)	2
65.1	2	0 A little dizziness and lightheadedness while tilting up. SOB.2 Dizziness and SOB still present. Lightheadedness gone.4 Same as above.6 Same as above plus feels his head and heart throbbing.8 Same as above plus neck pain.10 Same as above.	Increased (4)	Severe (4)	6
63.1	4	0 A little dizziness while tilting up.2 Asymptomatic.4 Asymptomatic.6 Asymptomatic.8 Asymptomatic.10 Asymptomatic.	Decreased (2)	Mild (2)	1
62.1	1	0 Felt heart pounding. A little dizzy. Lightheaded.2 Dizziness increased. Still a little lightheaded. A little SOB. A little nauseous. Still feels heart racing.4 Same as above.6 SOB intermittent. Otherwise same as above.8 Felt better all around. Symptoms above decreased. Head pressure.10 Felt better once supine.	Increased (4)	Moderate (3)	6
61.1	1	0 A little disoriented when tilted up. Feels like he is floating.2 Both legs feel sweaty. Chest feels warm. Head feels heavy. Tingling in both feet. Feels like he is walking upstairs.3:30 Light headed.4 Sees wall moving. Feels like body is moving as well	Increased (4)	Severe (4)	21

		matching the movement of the wall. Feels like he is breathing more. Hard to keep head up.6 Feels woozy like a head high. Mouth watering. Can't keep head up. Feels like he is slipping off of the table.8 Feels llike he is falling forward.9 Drooling. Head is down and is leaning forward.10 Felt empty once down. Listless. Fatigued. Whole body feels like it can't move.			
59.1	2	0 Feels “weird”. Really lightheaded. 50 seconds: Dizzy. 2 Pressure in legs. Wants to lie down. 4 Wants to lie down and hold something, Pressure in legs more. Breathing harder. 6 Tired. Breathing harder. 7:30 Left arm tingly pressure left hand. 8 More tired. 10 Feels a little better. 11 Still tired. Legs still tingly.	Increased (4)	Severe (4)	9
58.1	2	0 Asymptomatic. 1 Lightheaded. 2 Nauseous and lightheaded. 4 Very tired. 6 Same as above. 8 More nauseous. 10 Feels better supine.	Increased (4)	Severe (4)	3
57.1	4	0 Asymptomatic. 2 Asymptomatic. 4 Slightly out of breath and uneasy. Tired. 6 Same as above plus slight chest discomfort. 8 Same as above plus uncomfortable feeling. 10 Feels better.	Increased (4)	Mild (2)	5
56.1	1	0 Asymptomatic. 2 Can feel heart pounding. 4 Asymptomatic. 6 Asymptomatic. 8 Asymptomatic. 10 Asymptomatic.	Decreased (2)	Mild (2)	1
55.1	2	0 A little dizzy and lightheaded. 2 Uncomfortable otherwise same as above. 4 Out of breath. More lightheaded. Left CP. 6 Tired. Otherwise same as above. 8 Same as above. 10 Nauseous. Otherwise, same as above. 12 Headache. Otherwise same as above. 14 Left ear pain. Otherwise same as above. 16 Same as above. 18 Feels hot and flushed. 20 Tired but better.	Increased (4)	Severe (4)	11
54.1	4	0 Lightheaded. Nauseous. Dizzy. 2 Less lightheaded. Dizziness better. Nauseous worse. Getting tired. 4	Increased (4)	Severe (4)	5

		More tired. Calves hurting. Otherwise, same as above. 6 Fatigue worse. Nausea worse. Dizziness same. LH same. 8 Really tired. LH worse. Nausea 8 and dizziness the same. 10 Feels better. T wave changes.			
53.1	4	0 A little lightheaded. 2 More lightheaded. 4 Toes tingly. Lightheadedness gone. 6 Same as above. 8 Same as above. 10 Tingly sensation gone.	Increased (4)	Mild (2)	2
52.1	1	0 Nauseous. Lightheaded. Feels heart pounding. 2 Same as above. 4 Same as above. 6 Same as above. 8 Same as above. 10 Same as above plus back hurts.	Increased (4)	Moderate (3)	4
51.1	4	0 Asymptomatic. 2 Asymptomatic. 4 A little lightheaded. 6 More lightheaded. Feels hot and cold. 8 Same as above. 10 Feels better.	Increased (4)	Moderate (3)	3
50.1	2	0 A little SOB. Head rush and lightheaded. 2 Asymptomatic. 4 Asymptomatic. 6 Asymptomatic. 8 Asymptomatic. 10 Asymptomatic.	Decreased (2)	Moderate (3)	3
49.1	2	0 Asymptomatic. 2 Asymptomatic. 4 Asymptomatic. 6 Asymptomatic. 8 Asymptomatic. 10 Asymptomatic. 12 Asymptomatic. 14 Asymptomatic. 16 Asymptomatic. 18 Asymptomatic. 20 Asymptomatic.	No Symptoms (0)	N/A (0)	0
48.1	4	Sneezed at the 4 minute baseline. 0 Dizzy. 2 More dizzy. Pain in stomach and chest. SOB. 4 Less dizzy. SOB. Head hurts. 6 Still dizzy. Headache. 8 Still dizzy. Headache. Blurry vision. Pre-syncopal. 10 Feels better when down.	Increased (4)	Severe (4)	7
47.1	4	Patient shaky prior to test. 0 Nauseous. Not feeling well. Dizzy. LH. Vision narrowed. Pre-syncopal. 2 More nauseous. Headache. 4 Weakness in legs. Nausea and LH same. 6 More nauseous. Headache. 8 Less nauseous. Knees jittery. 10 Legs significantly weaker. More nauseous. 10 Chest tightness. 12 Headache worse. More nauseous. 14 Knees	Increased (4)	Severe (4)	11

		shakier. Jittery. Vision narrowed. 16 Less nauseous. LH. 18 Less nauseous. Chest tighter. 20 Better			
46.1	1	0 Asymptomatic. 2 Asymptomatic. 4 Asymptomatic. 6 Asymptomatic. 8 Asymptomatic. 10 Asymptomatic.	No Symptoms (0)	N/A (0)	0
45.1	4	0 A little dizzy. 2 Less dizzy. A little lightheaded. 3.Patient ok. 6 Weak. Dizziness gone. A little lightheaded. 8 Same as above. 10 Same as above. 12 Same as above. 14 Same as above. 16 Same as above. 18 Weaker. 20 Same as above. 22 Same as above. 24 Same as above. 25 Tilt down. Feels better.	Increased (4)	Moderate (3)	3
44.1	4	0 A little upset stomach. 2 Same as above. 4 Upset stomach worse. 6 Upset stomach much worse. Headache. BP dropped after patient told me how she was feeling. Upright tilt then terminated. Patient stated she felt syncopal right before cessation of upright tilt.	Increased (4)	Severe (4) (Most Severe)	3
43.1	4	0 Lightheaded. Dizzy. 2 Same as above plus heaviness. 4 Same as above. 5 Feels heart rate going faster. 6 Lightheaded. Dizzy. Hip pain. No longer feeling fast heart rate. 8 Same as above. 10 Feels better.	Increased (4)	Severe (4)	5
42.1	3	0 Head hurts. Dizzy. 2 Same as above. 4 Same as above. 6 Same as above. 8 Same as above plus lightheaded. 10 A little better.	Increased (4)	Moderate (3)	3
41.1	3	0 Lightheaded. Dizzy. 2 Same as above. 4 Same as above plus nauseated. Vision blurry. 6 More nauseated. 8 Same as above. 10 Headache. Otherwise, same as above. 12 Same as above. 14 Same as above. 16 Same as above. 18 More dizzy. 20 getting better	Increased (4)	Severe (4)	5
40.1	2	0 A little lightheaded. 2 Dizzy and lightheaded. 4 Same as above. 6 Same as above. 8 Lightheaded. Less dizzy. Feels flushed. 10 Lightheaded and less flushed.	Increased (4)	Moderate (3)	3
39.1	1	0 A little dizzy. 2 Dizziness gone. Slightly lightheaded. 4 Nauseous. 6	Increased (4)	Severe (4)	6

		Nauseous and tired. Feels heavy everywhere. 8 Nauseous, tired, lightheaded, and cold. 10 Feels better.			
38.1	1	0 Lightheaded. 2 Increased light headedness. 4 Heavy. Light headedness less. 6 Dizzy and not as lightheaded. 8 Feels better. Not as dizzy. 10 Feels better.	Increased (4)	Moderate (3)	4
37.1	4	Chest pressure prior to tilt. 0 Feels ok. 2 Shaky. SOB. Dizzy and lightheaded. Unable to open eyes. 4 Same as above. 6 Anxious and hot. Otherwise, same as above. 8 Same as above. 10 Feels better.	Increased (4)	Severe (4)	8
36.1	4	0 A little dizzy. 2 Dizzy and nauseous. 3 Lightheaded. 4 Same as above. 6 Feel HR high. Otherwise, same as above. 7 Hands tingly. 8 Same as above. 10 Tired. Head spinning.	Increased (4)	Severe (4)	7
35.1	4	0 A little light headedness. 2 Same as above. 4 Feels a little better. Still lightheaded. 6 More tired. Otherwise, same as above. 8 More SOB. Chest tightness. 10 Chest tightness getting worse. After tilt table patient went to rest room.	Increased (4)	Moderate (3)	4
34.1	1	0 Feels ok. 2 Tired. Feels HR tachy. 4 Lightheaded. Slightly nauseous. 6 Same as above plus mild chest pressure. 8 Same as above and more fatigued. 10 Feels better.	Increased (4)	Moderate (3)	5
33.1	1	0 Nauseous. 2 Less nauseous. 4 Less nauseous. 6 Stomach hurts. Nausea gone. Back hurts. 8 Feels fine. Symptoms gone. 10 Feels better.	Decreased (2)	Moderate (3)	3
32.1	1	0 A little dizzy. 2 A bit unsteady. No more dizziness. 4 Feels fine. 6 Feels fine just sleepy. 8 Sleepy. 10 Feels better.	Decreased (2)	Mild (2)	3
31.1	3	Sr 68 0 Feels good. 2 Feels good. 4 Lightheaded. Breathing more labored. 6 Throat hurts. Lightheaded and SOB. 8 Lightheaded. A little SOB. 10 Feels a little better post tilt.	Increased (4)	Moderate (3)	4
30.1	4	SR 73 bpm 0: A little lightheaded. 2: Same as above. 4: Same as above. 6: Dizziness increased a little. 8: Same as	Same (3)	Mild (2)	2

		above. 10: Same as above. 12: Same as above. 14: Lightheaded and dizzy. 16: Same as above. 18: Less lightheaded. 20: Same as above.			
29.1	1	0: Nauseous. 2: A little lightheaded. Dizziness. 4: Same as above plus temperature fluctuating. 5: Heart starting to pound. 6: Tingling in lower extremities. 8: LE more tingly. Shoulder, neck, spine pain. 10: Legs itchy. Dizzy. Sleepy.	Increased (4)	Severe (4)	12
28.1	1	SR 0: Relief. Blurry vision. 2: Feels okay. 4: Weak knees. Overheated. Fatigued. 6: Feels heart beating overworked. Heart “feels pounding”. 8: Head pain “more pronounced”. Stomach “feels off”. Legs weak. 10: Feels heart is relaxed.	Increased (4)	Severe (4)	9
27.1	2	SR 0: Feels fine. 2: A little lightheaded. 4: Same as above. 6: Vision a little blurry and still a little lightheaded. 8: Dizzy and lightheaded. 10: Tired. Spotty vision. Dizzy.	Increased (4)	Moderate (3)	5
26.1	1	0: Feels fine. 2: Feels ok. 4: Feels ok. 6: Feels tired. 8: Feels fat and heart rate increase. 10: Feels fine. Feet cold.	Increased (4)	Moderate (3)	4
25.1	1	0: Really dizzy and seeing spots. 2: Same as above plus a headache and chest tightness. 4: Legs hurt. Dizzy as above. Lightheaded. Nausea. 6: Same as above. 8: Presyncopal. Joint pain. 10: Feels a bit better after tilt down. Sinus with atrial bigeminy.	Increased (4)	Severe (4)	9
24.1	2	0: Feels ok. 2: Feels nauseas. 4: Feels worse plus dizzy and lightheaded. 6: Feels worse than above. 8: Feels worse than above. Patient really struggling to stay up. 10: Patient had a really hard time. “Really nauseated”, dizzy.	Increased (4)	Severe (4)	4
23.1	2	0:VERY symptomatic once tilted. VERY lightheaded. Labored breathing. VERY dizzy. 2: Getting better. 4: Same as above. 6: Feels better but sweaty. 8; Feels better. Feels clammy. 10: Less dizzy.	Decreased (2)	Severe (4)	5

22.1	4	0: feel heavy, lightheadedness 2: lightheadedness, getting better 4: still a little lightheaded 6: feeling fine 8: feeling fine 10: feeling fine. During tilt, low R wave amplitude noted, due to patient movement.	Decreased (2)	Mild (2)	2
21.1	4	0: a little dizzy, nauseated, lightheaded, pressure in head 2: feeling fine 4: weak and tired 6: a little dizzy, weak and tired 8: leg muscle hurts, dizzy, weak and nauseate 10: dizzy, nauseate, headache Dizziness and nausea improved at 1 min post	Increased (4)	Severe (4)	9
20.1	1	0: A little lightheaded. 2: Less lightheaded. Feels heart racing. 4: Light headedness gone. Feels weak. Sweaty. 6: Feels ok. Still sweaty. 8: Sweaty but feels good. 10: Feels much better.	Increased (4)	Moderate (3)	4
19.1	4	0: Lightheaded and dyspneic. 2: Same as above. Feels harder to breath. 4: Same as above. Feels “like a brick on chest”. Right hand very cold and tingly. 6: Same as above. Malaise. Breathing harder. 8: Lower right rib pain. Same as above. 9: Symptoms better. 10: Symptoms better.	Increased (4)	Severe (4)	7
18.1	1	0: a little dizzy 2: “a little weird” 4: “a little weird” 6: “a little dizzy” 8: “a little dizzy” and lightheaded 10: feeling “weird”, but not dizzy any more	Same (3)	Mild (2)	3
17.1	4	0: Feels good. 2: Feels pretty good. 4: Feels ok. 6: Feels pretty good. 8: Feels good. 10: Felt a little lightheaded when tilted down. Only lasted a couple of seconds.	Asymptomatic Until Tilt Down (1)	Transient (1)	1
16.1	4	0: Fine 2: fine 4: fine 6: fine 8: fine 10:fine	No Symptoms (0)	N/A (0)	0
15.1	3	0: Feels ok. 2: Feels ok. 4: Feels ok. 6: Feels ok. 8: Feels good. 10: Feels disoriented when brought down.	Asymptomatic Until Tilt Down (1)	Mild (2)	1
14.1	4	lightheaded, blood drain out 2: still lightheaded, hands and feet numb 4: same as 4 minutes, heart beating faster, 6: sweat in back, felt heart	Increased (4)	Severe (4)	9

		beating slowly 8: nauseated, lightheaded, sweating 10: lightheaded, felt fever, nauseated			
13.1	1	0: a little dizzy, lightheaded 2: little dizzy, lightheaded worse, feet cold 4: lightheaded, feet cold, pressure on head, felt shaky 6: same as 4 minutes, nauseate, face heating up 8: shaky worse, pressure on forehead 10: shaky and achy.	Increased (4)	Severe (4)	9
12.1	1	0:00 Feels ok. No symptoms. 2:00 Feels ok. No symptoms. 4:00 Feels ok. No symptoms. 6:00 Legs feeling a little shaky. 8:00 Whole body feels shaky. 10:00 Feels much better.	Increased (4)	Moderate (3)	2
10.1	4	0:00 Feels a little lightheaded. 2:00 Feels like she wants to sit down. Cramp in right calf. Still dizzy. 4:00 Still dizzy. A little nausea. 6:00 Feels sleepy. Still nauseas. 8:00 Still dizzy. 10:00 Does not feel good. Presyncopal.	Increased (4)	Severe (4)	8
9.1	4	06:00 Patient felt more tired. 08:00 Patient continues to feel tired and slightly lightheaded. 10:00 Felt warm.	Increased (4)	Moderate (3)	3
8.1	4	2:00 5/10 level of dizziness 4:00 less dizzy 6:00 slightly dizzy 8:00 slightly dizzy	Same (3)	Mild (2)	1
7.1	2	2:00 slightly dizzy; 4:00 more dizzy; 6:00 about the same; 8:00 slightly worse dizziness; 2:00 post-tilt dizziness better	Increased (4)	Mild (2)	1
6.1	1	0:20 fine 1:00 not bad 3:00 ok 5:00 not bad 6:00 ok 6:30 weak legs 8:00 ok 9:00 ok	Decreased (2)	Mild (2)	1
5.1	4	7:40 - pt feels fine	No Symptoms (0)	N/A (0)	0
3.1	4	5:58 - pt feels lightheaded. (eyes are squinted closed) 10:50 - manually recalibrated BP	Same (3)	Mild (2)	1
2.1	1	5:38 - feeling a little lightheaded 9:15: not as lightheaded as earlier	Decreased (2)	Mild (2)	1
1.1	1		No Symptoms (0)	N/A (0)	0

Note. Abbreviations: HUTT, head-up tilt-table test; PAC, premature atrial contraction; PVC, premature ventricular contraction; SR, sinus rhythm. Scale for Quantification of HUTT Symptoms: The five respective scores listed under the symptoms scoring scalar item titled “Symptoms Severity Trend”, are as follows: No Symptoms Ξ (0), Decreased Ξ (2), Asymptomatic Until Tilt Down Ξ (1), Same Ξ (3), and Increased Ξ (4). For the scalar item titled “Symptoms Quality and Ranking”, the five respective scores represent the following: Not Applicable (because the patient did not report any symptoms) Ξ (0), Transient Ξ (1), Mild Ξ (2), Moderate Ξ (3), and Severe Ξ (4).

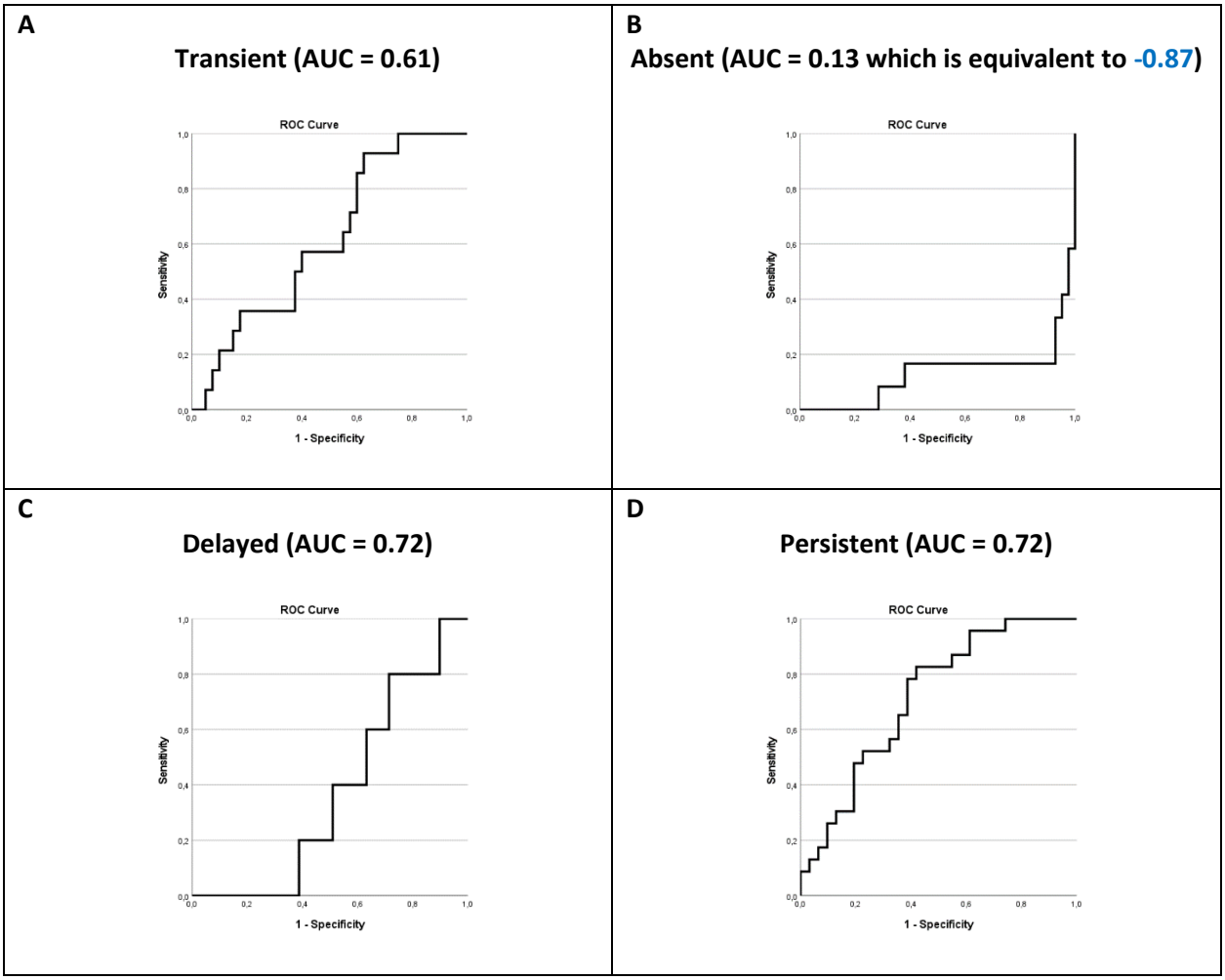
Supplemental Table 34

Study Timeline

Task Description	Start Date	Stop Date	Key Resources
Review of the Literature	01/02/2022	03/01/2023	CINAHL, Embase, PubMed and Web of Science.
Data Retrieval	08/19/2020	06/30/2023	UCLA Division of Cardiology patients' medical records.
Data Clean-up	08/19/2020	10/16/2023	UCLA Division of Cardiology patients' medical records, AcqKnowledge data acquisition and analysis software.
Data Analysis	08/19/2020	10/16/2023	UCLA Division of Cardiology patients' medical records, BIOPAC Systems Incorporated's AcqKnowledge data acquisition and analysis software, WR Medical Electronic Company's TestWorks data acquisition and analysis software, R 4.03 statistical software, and SPSS statistical software.
Review of Results by Faculty Mentors	08/19/2020	01/16/2024	Wendie Robbins, PhD, RN, Olujimi Ajijola, PhD, MD, Jeffrey Ardell, PhD, and Mary-Lynn Brecht, PhD.
Manuscript Drafting	6/22/2022	01/1/2024	John Odeh, MS, RN., Olujimi Ajijola, PhD, MD, Madeleine Johansson, PhD, MD, and various peer reviewed articles.
Abstract Drafting	03/24/2023	01/16/2024	John Odeh, MS, RN., Olujimi Ajijola, PhD, MD Madeleine Johansson, PhD, MD, and various peer reviewed articles.
Submission of Paper to a Peer Reviewed Journal for Publication	01/18/2024	01/18/2024	Review of paper and approval by John Odeh's PhD dissertation committee.
Presentation of Study Findings at Research Conferences Podcasts, Seminars, or Webinars	11/17/2023	Not Applicable	Presenter or presenters.

Supplemental Figure 1

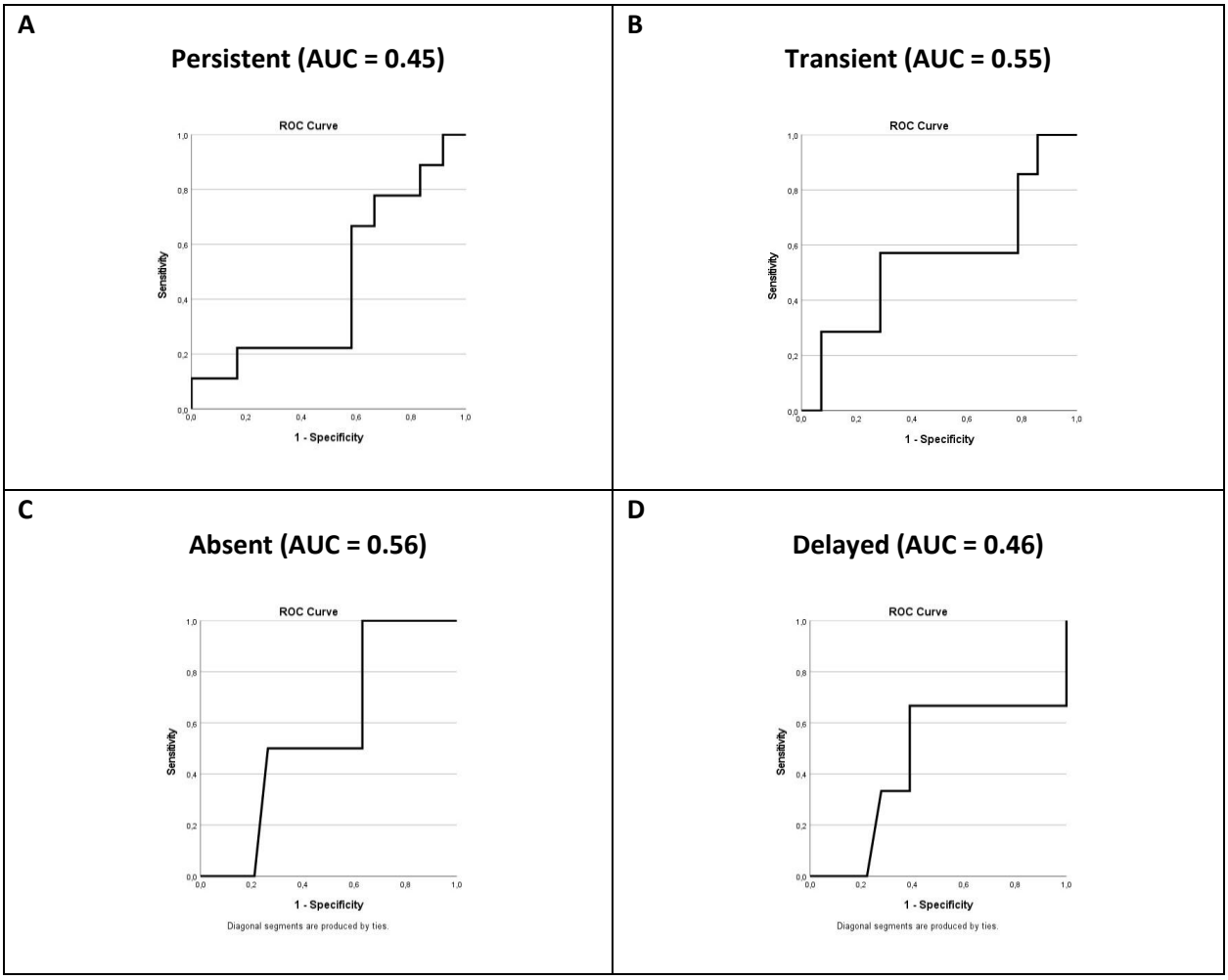
ROC Curves of Electrodermal Response Subtypes vs PR Area Per Second ($PR_{Area/sec}$) for Cases ≥20 years



Note. AUC-ROC Curves for ERS versus PR Area Per Second. **A**, Predictive value of the Transient ERS. **B**, Predictive value of the Absent ERS. **C**, Predictive value of the Delayed ERS. **D**, Predictive value of the Persistent ERS. Abbreviations: AUC, area under the curve; AUC-ROC, area under the curve of receiver operating characteristic; EDA, electrodermal activity; ERS, EDA response subtype; PR, pulse rate. ROC, receiver operating characteristic. Tests for sensitivity and specificity were done to generate these ROC curves with their associated AUCs.

Supplemental Figure 2

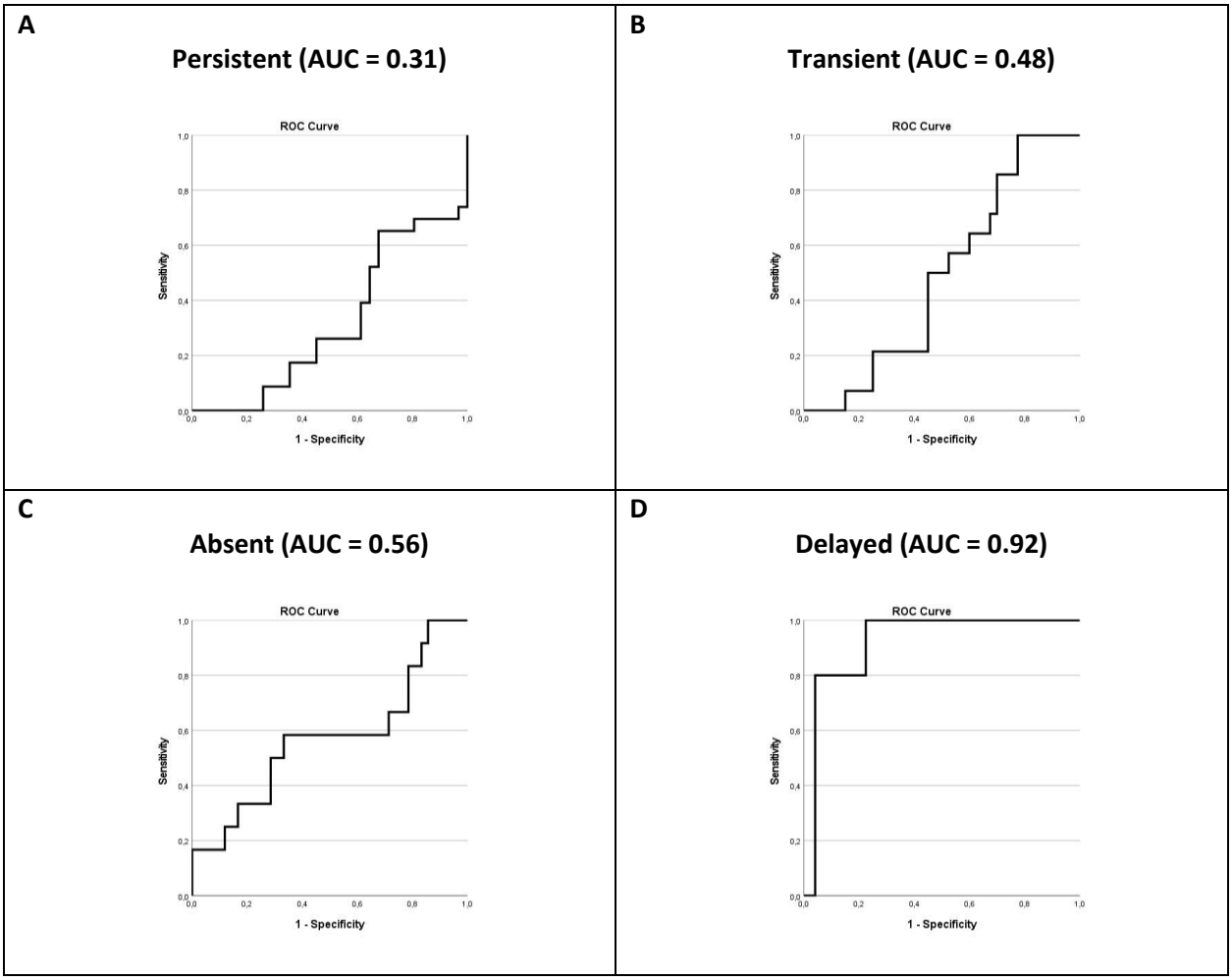
AUC-ROC Curves for ERS vs HR-Delta (HRΔ): POTS Cases ≤ 19-years-old



Note. Abbreviations: AUC-ROC, Area Under the Curve of Receiver Operating Characteristic; ERS, EDA Response Subtype; PR, Pulse Rate

Supplemental Figure 3

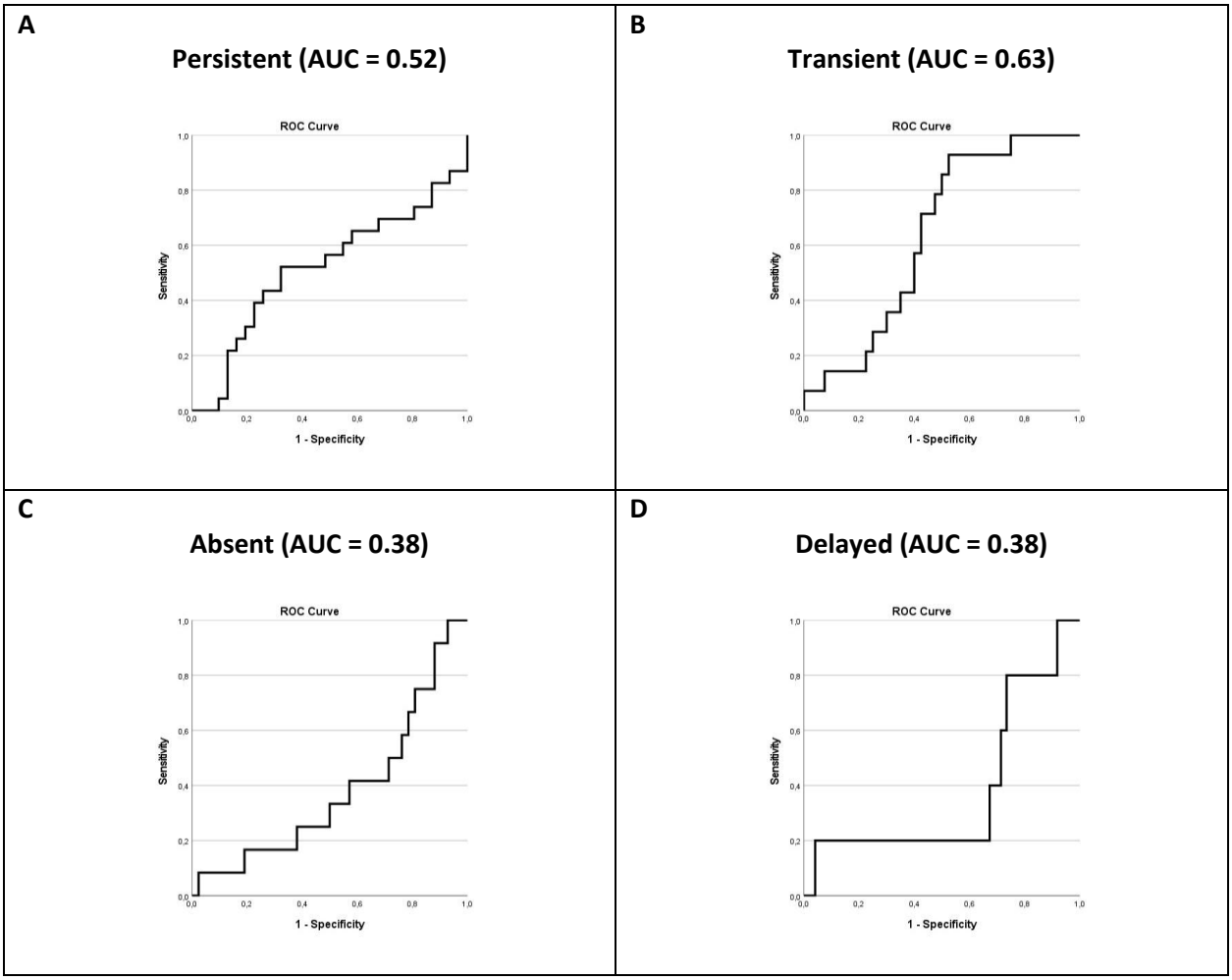
AUC-ROC Curves for ERS vs HR-Delta (HRΔ): POTS Cases ≥ 20-years-old



Note. Abbreviations: AUC-ROC, Area Under the Curve of Receiver Operating Characteristic; HR, Heart Rate; ERS, EDA Response Subtype; PR, Pulse Rate.

Supplemental Figure 4

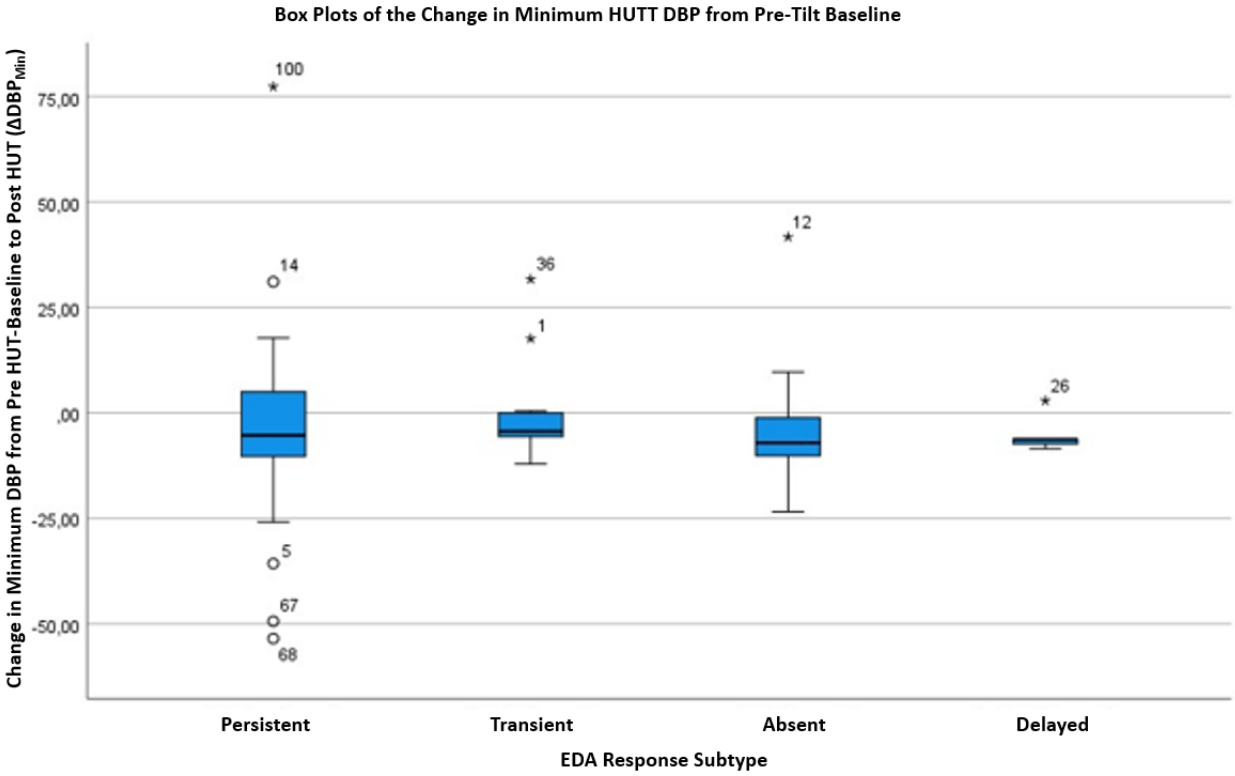
AUC-ROC Curves for ERS vs Change in Minimum SBP from Baseline (ΔSBP_{Min})



Note. Abbreviations: AUC-ROC, Area Under the Curve of Receiver Operating Characteristic; ERS, EDA Response Subtype; PR, Pulse Rate; SBP, Systolic Blood Pressure.

Supplemental Figure 5

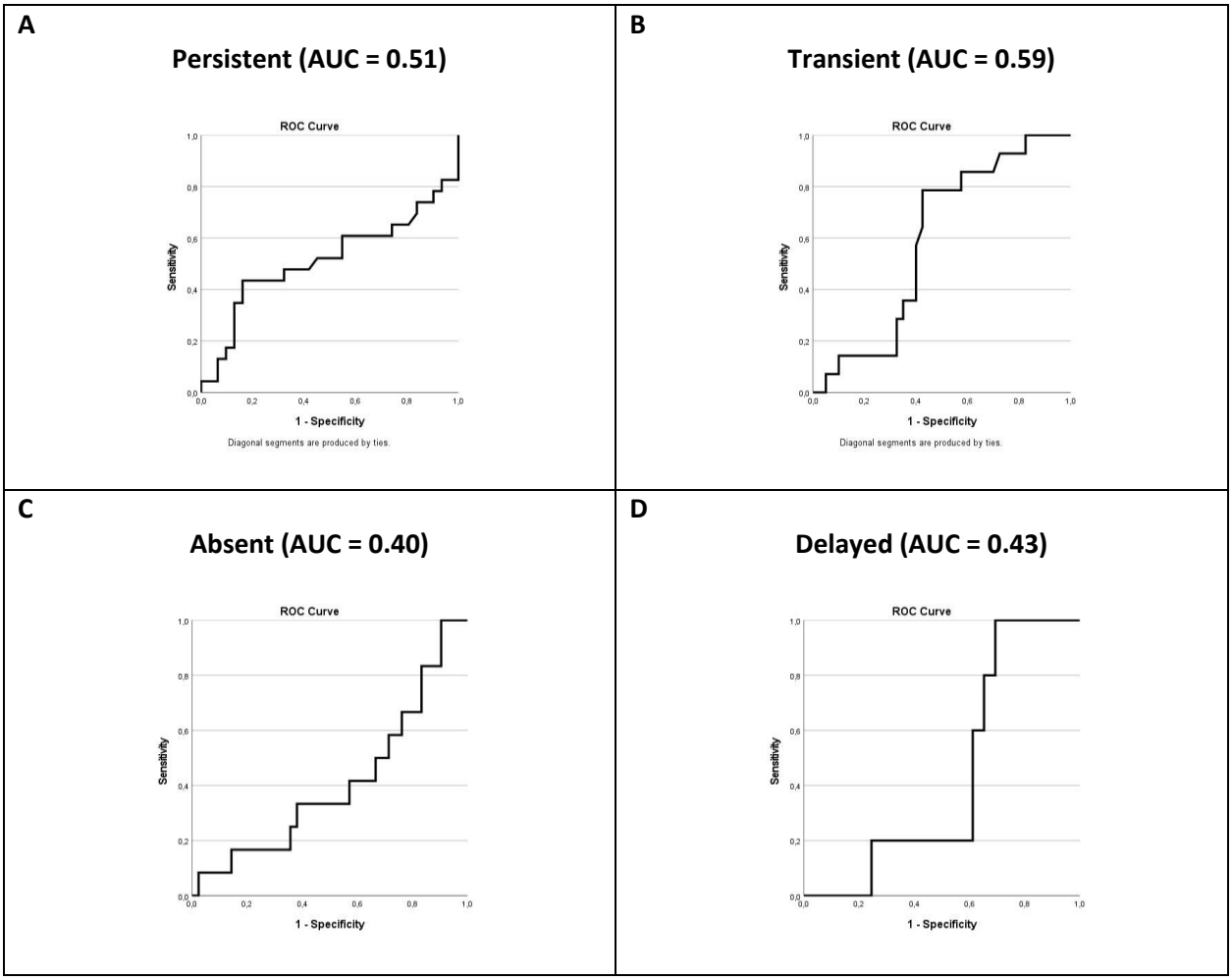
Change in the Minimum Diastolic Blood Pressure During Upright Tilt from Pre-Tilt Baseline to Post-Tilt



Note. Abbreviations: HUT, head up tilt; HUTT, head up tilt-table testing; DBP, diastolic blood pressure.

Supplemental Figure 6

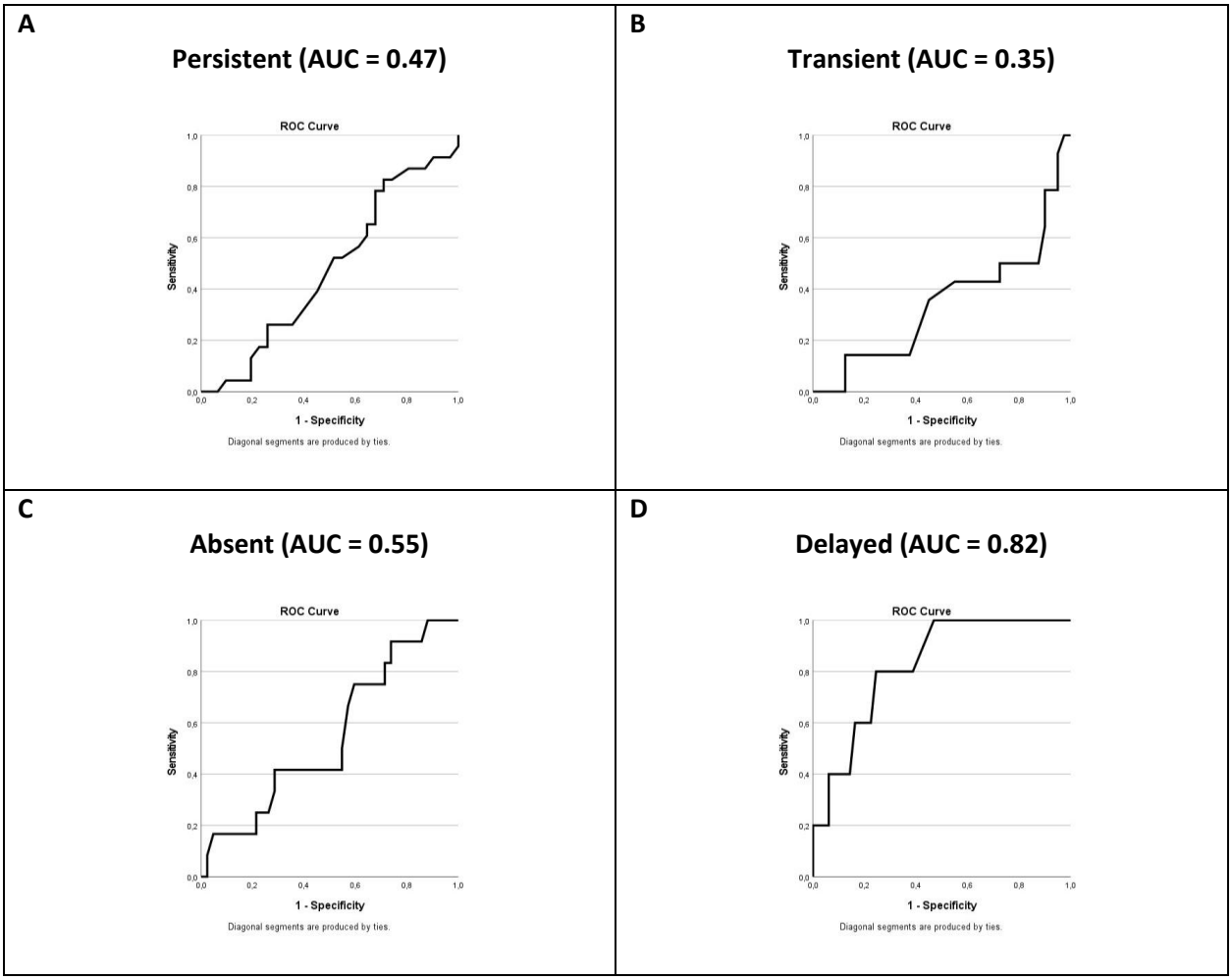
AUC-ROC Curves for ERS vs Difference in the Minimum Post Tilt DBP from Baseline (ΔDBP_{Min})



Note. Abbreviations: AUC-ROC, Area Under the Curve of Receiver Operating Characteristic; DBP, Diastolic Blood Pressure; ERS, EDA Response Subtype; PR, Pulse Rate.

Supplemental Figure 7

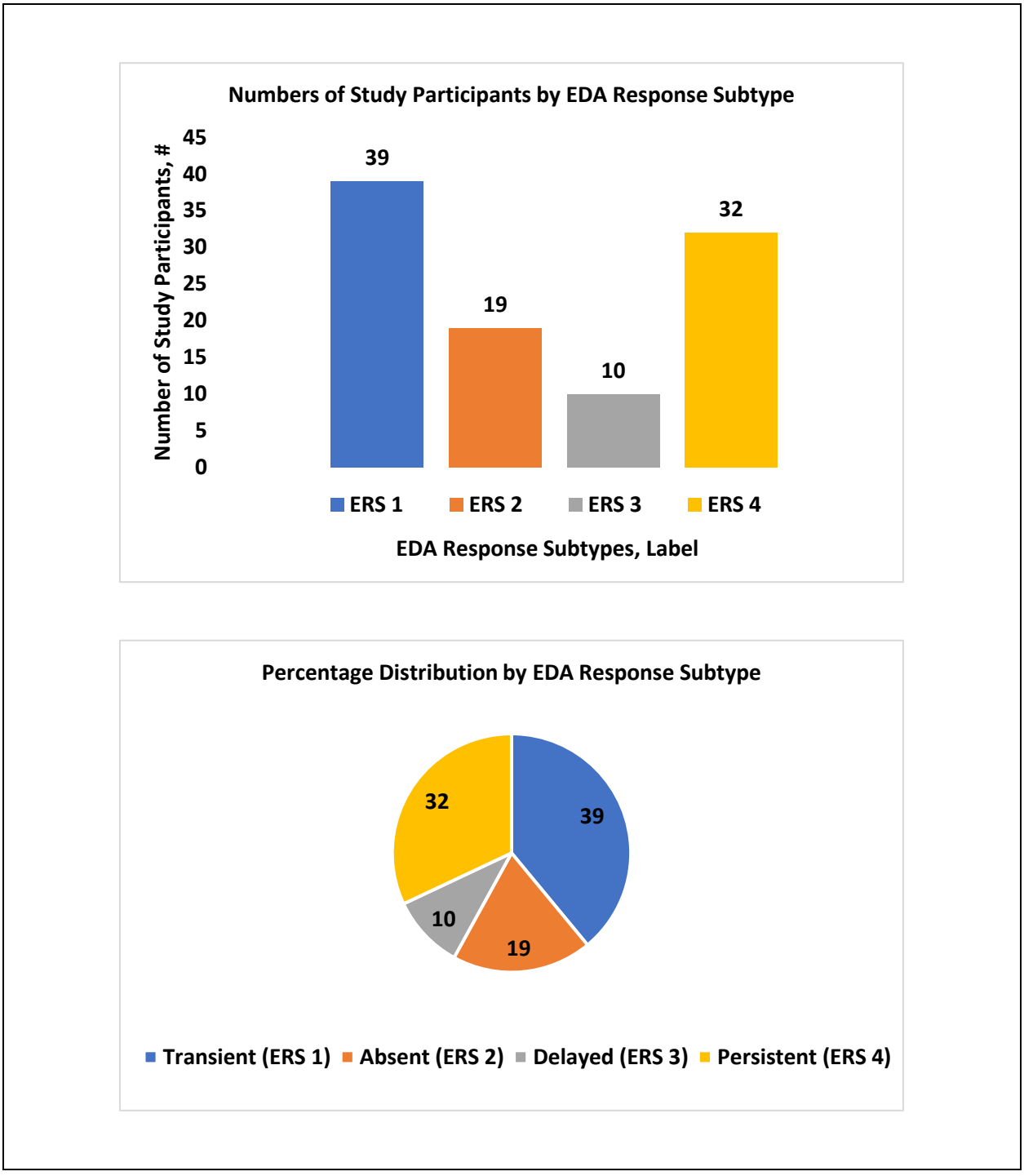
AUC-ROC Curves for ERS vs HR Maximum in HUT (HR_{Max})



Note. Abbreviations: AUC-ROC, Area Under the Curve of Receiver Operating Characteristic; ERS, EDA Response Subtype; HR, Heart Rate; HUT, Head Up Tilt; PR, Pulse Rate.

Supplemental Figure 8

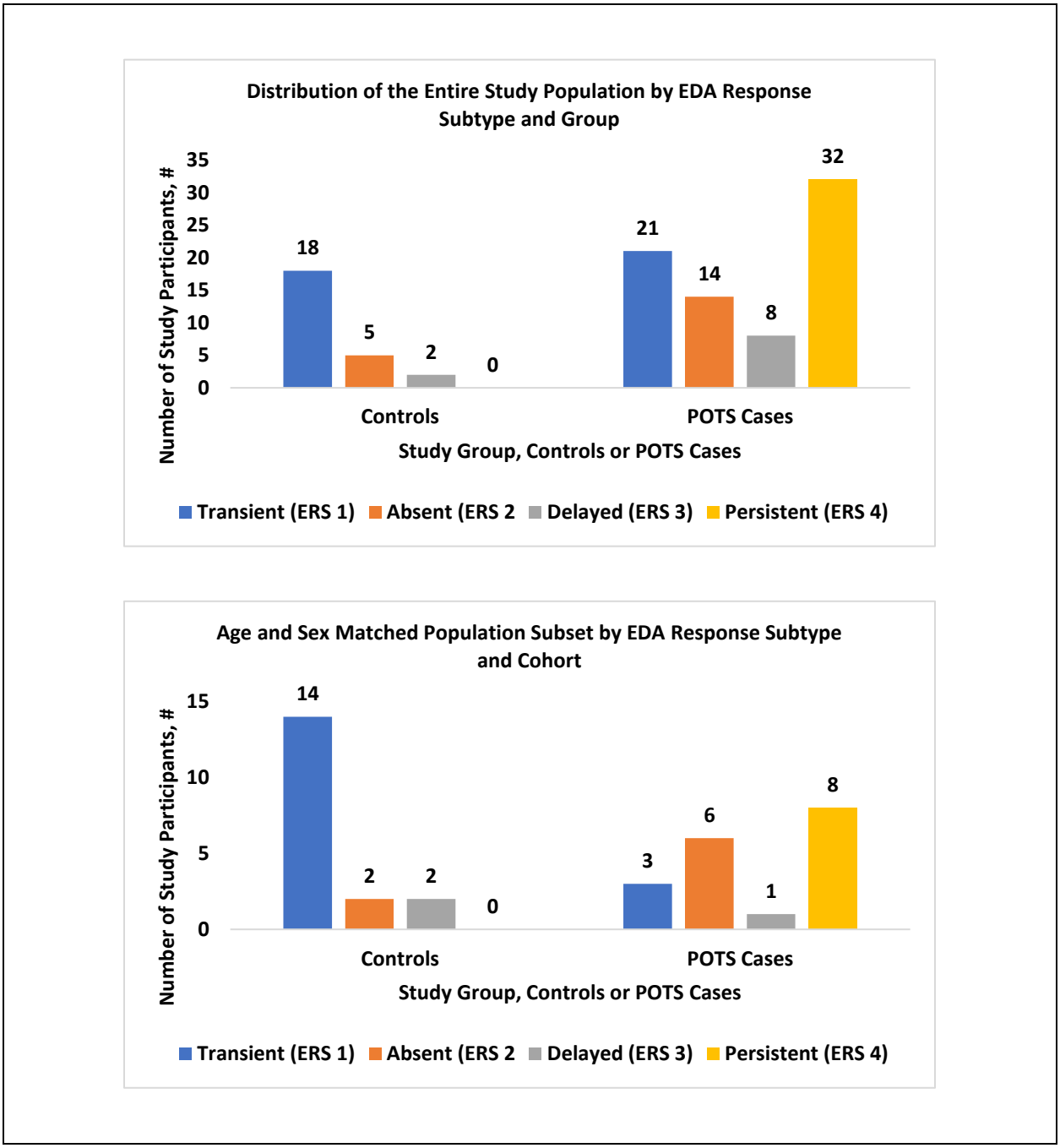
Distribution of Patients in Study Population by EDA Response Subtype



Note. Abbreviations: EDA, electrodermal activity; ERS, EDA response subtype.

Supplemental Figure 9

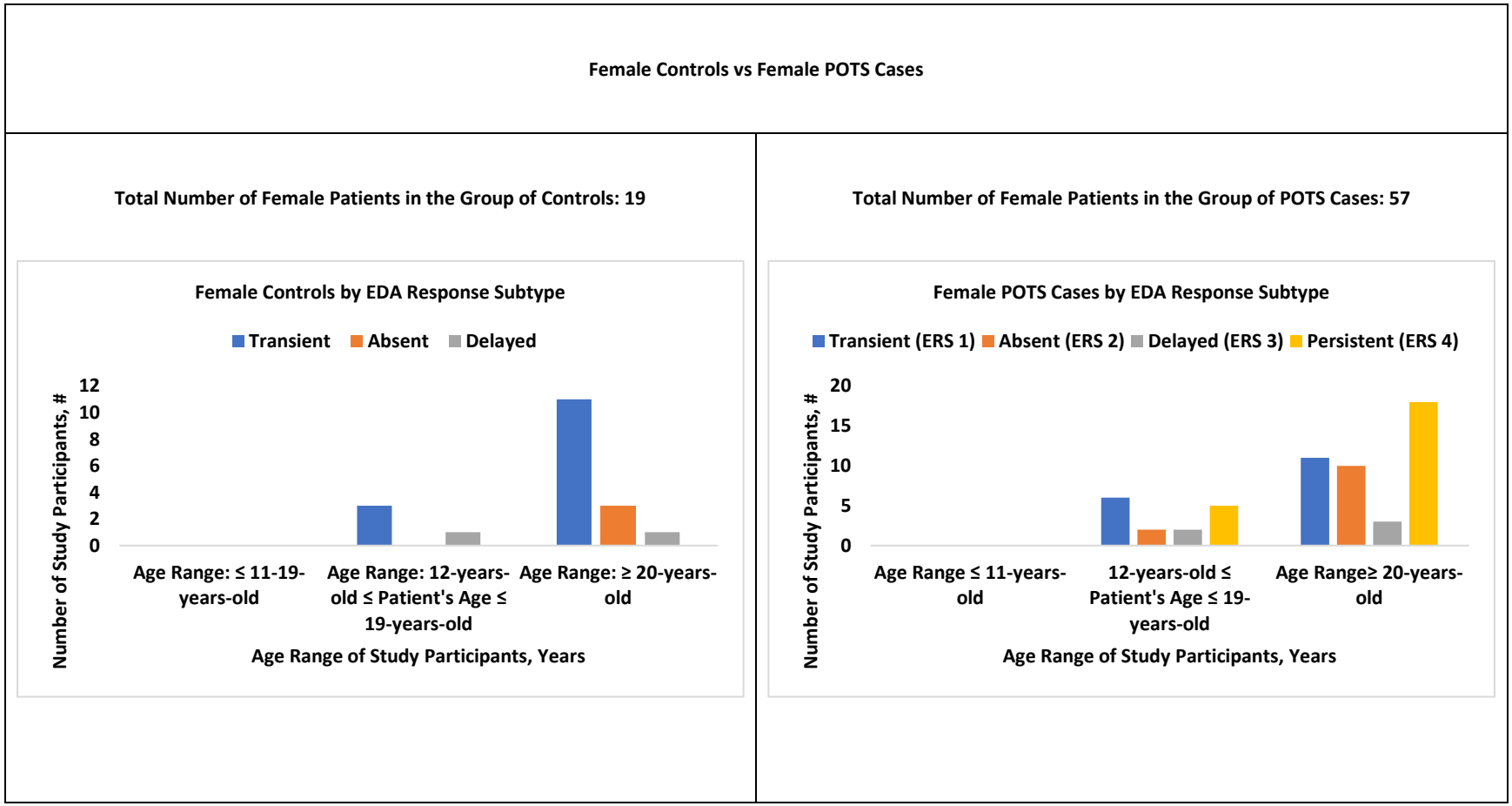
Distributions of the Entire Study Population vs the Age and Sex Matched Population Subset



Note. Abbreviations: Abbreviation: EDA, electrodermal activity; ERS, EDA response subtype.

Supplemental Figure 10

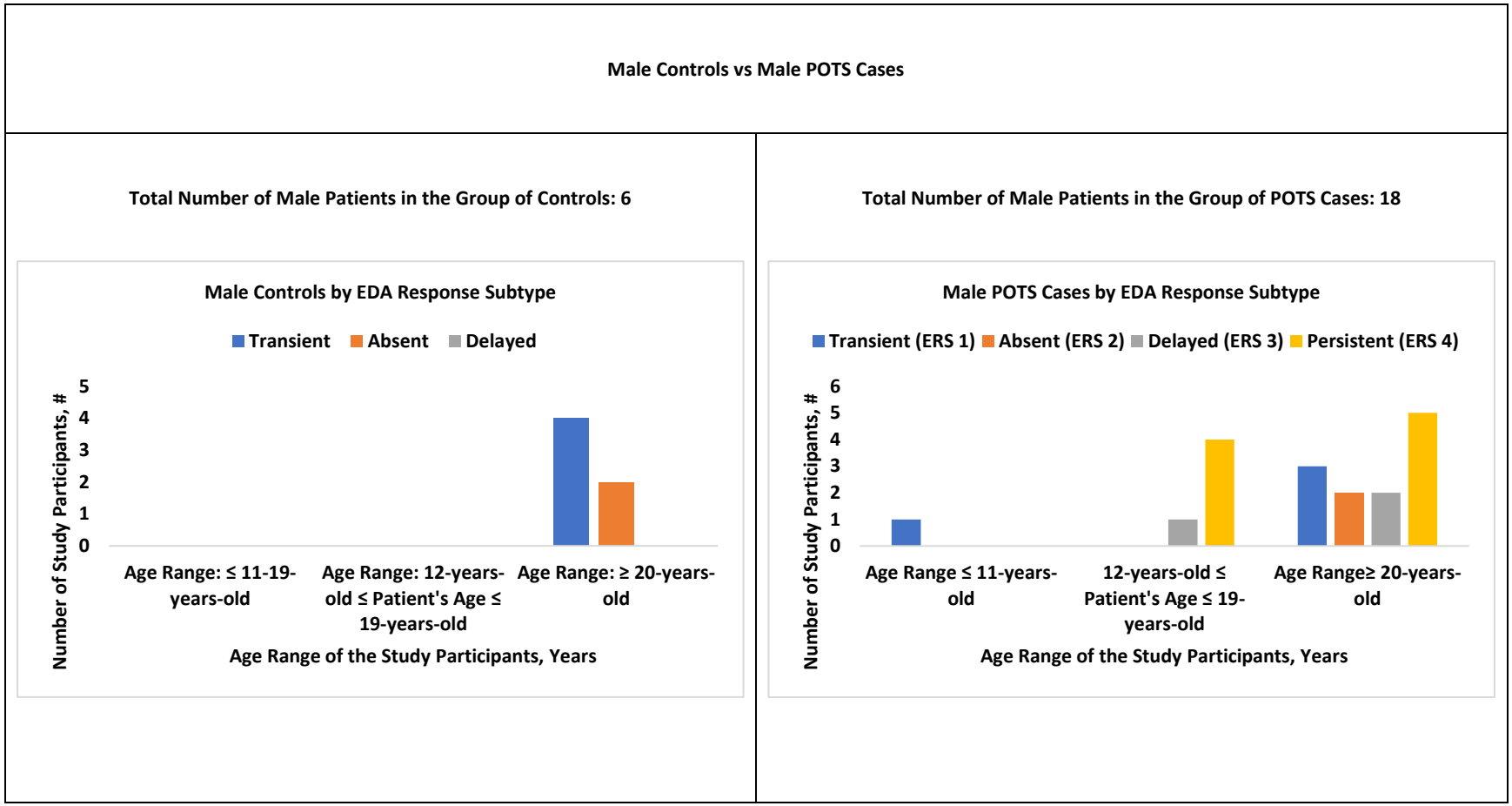
Distribution of POTS cases and controls by EDA Response Subtype and sex.



Note. Abbreviations: EDA, electrodermal activity; ERS, EDA response subtype

Supplemental Figure 11

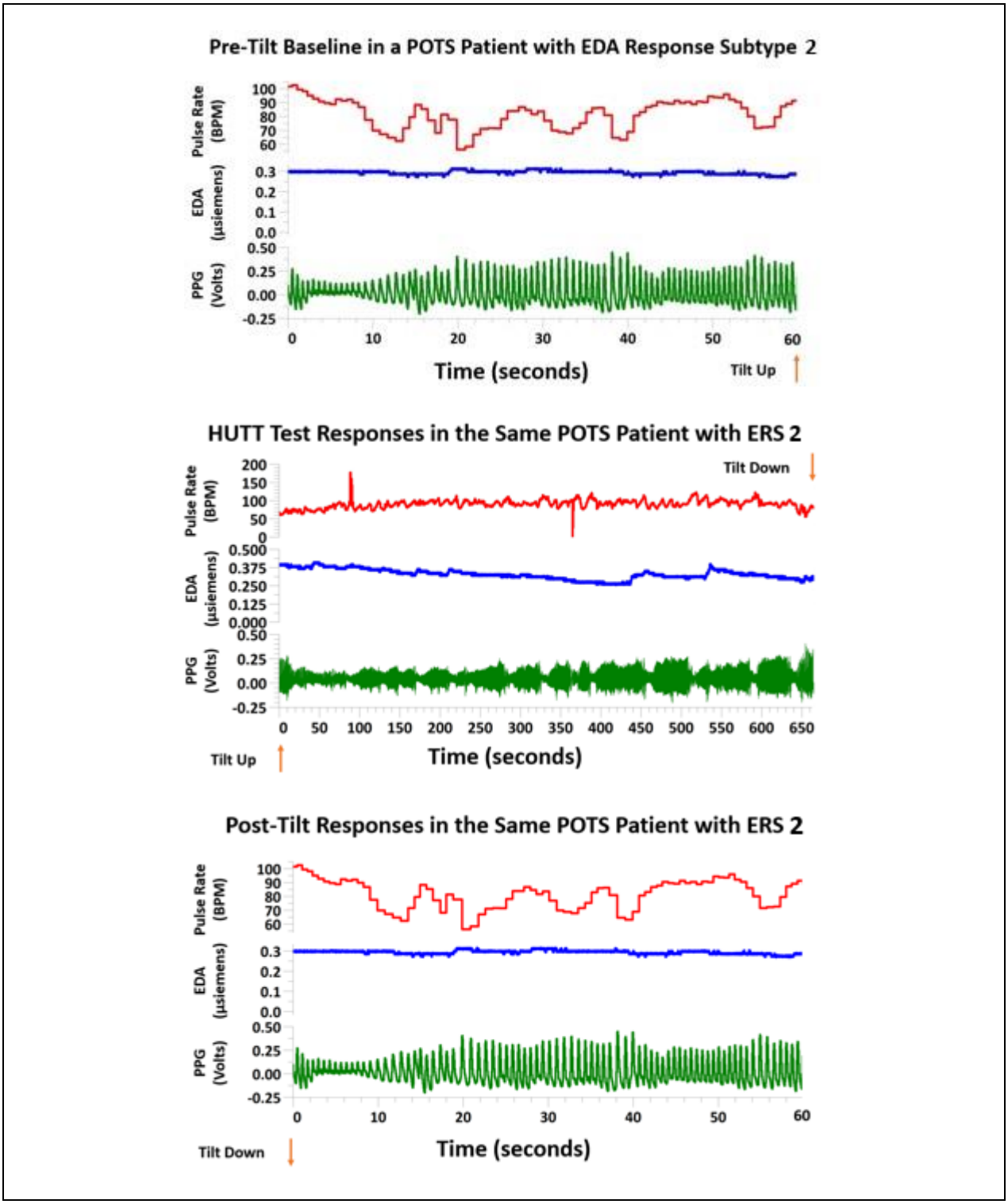
Distribution of POTS cases and controls by EDA Response Subtype and sex.



Note. Abbreviations: EDA, electrodermal activity; ERS, EDA response subtype

Supplemental Figure 12

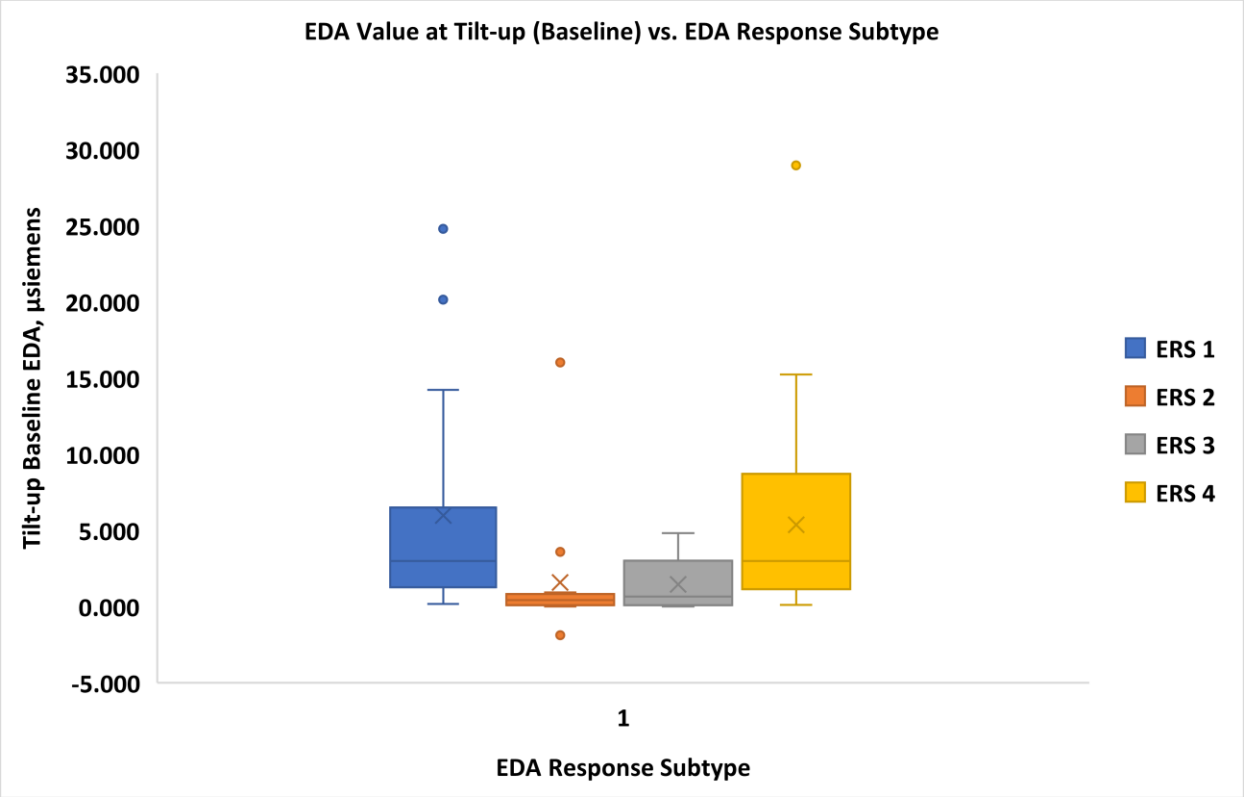
Representative tracings of FPV, EDA and PR before, during and after a HUTT in the same patient.



Note. Abbreviations: EDA, electrodermal activity; ERS, EDA response subtype; ERS 2 is an acronym for the Absent electrodermal activity response subtype; FPV, finger pulse volume; HR, heart rate; HUTT, head-up tilt-table test; POTS, postural orthostatic tachycardia syndrome; PPG, photoplethysmography.

Supplemental Figure 13

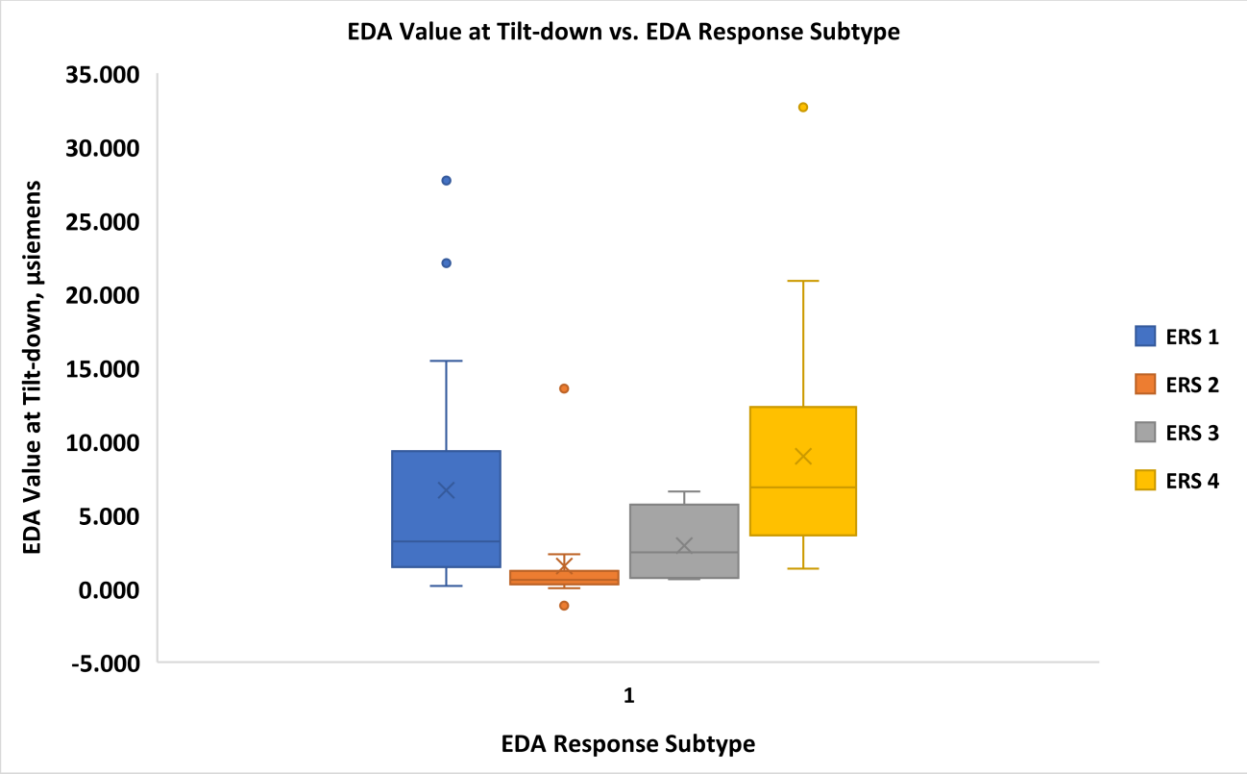
Skin Conductance Level at Tilt-up vs. Electrodermal Activity Response Subtype



Note. Abbreviations: EDA, electrodermal activity; ERS, electrodermal activity response subtype.

Supplemental Figure 14

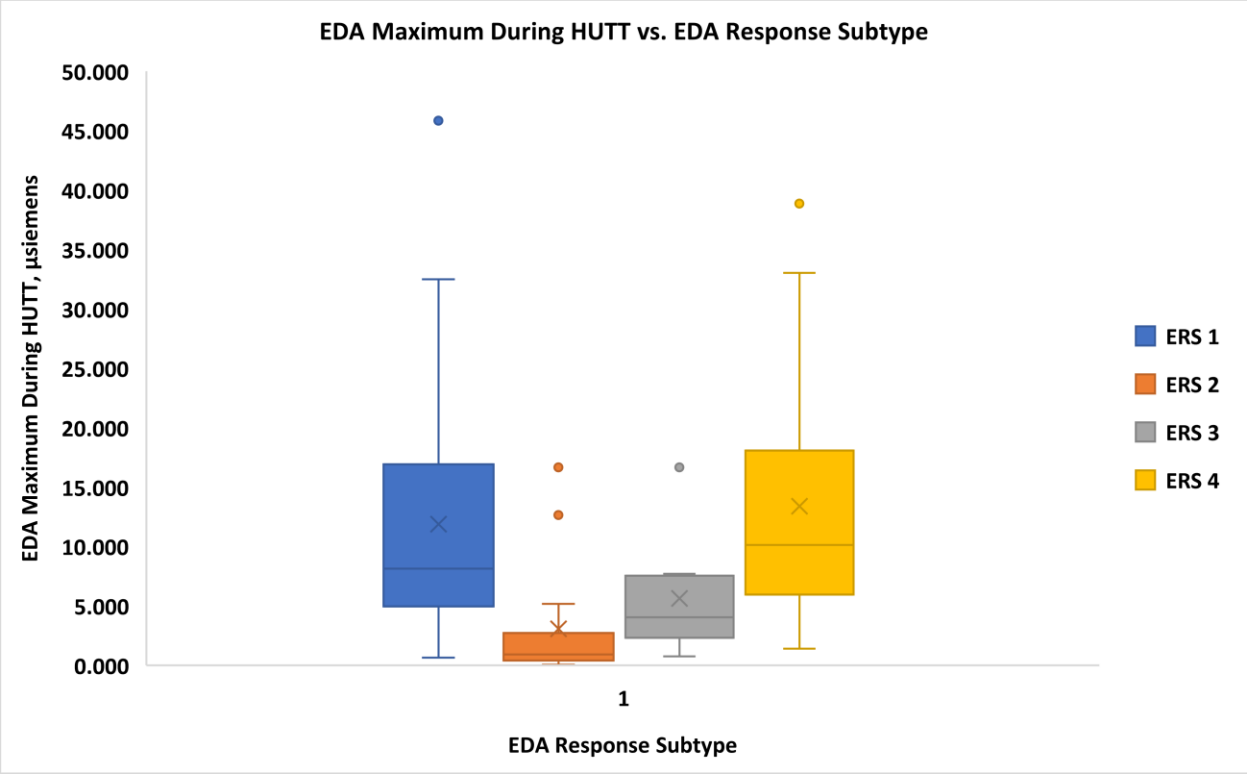
Skin Conductance Level at Tilt-down vs. Electrodermal Activity Response Subtype



Note. Abbreviations: EDA, electrodermal activity; ERS, electrodermal activity response subtype.

Supplemental Figure 15

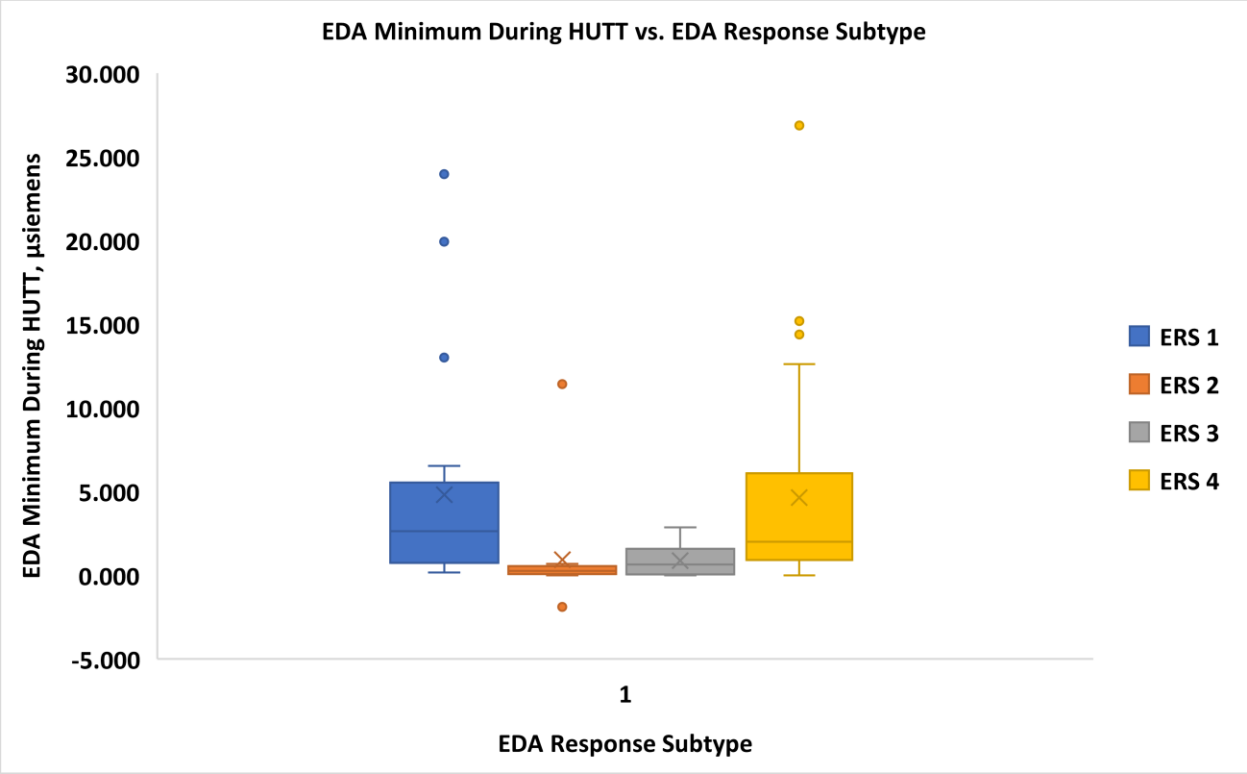
Maximum Skin Conductance Level During HUTT vs. Electrodermal Activity Response Subtype



Note. Abbreviations: EDA, electrodermal activity; ERS, electrodermal activity response subtype; HUTT, head up tilt-table test.

Supplemental Figure 16

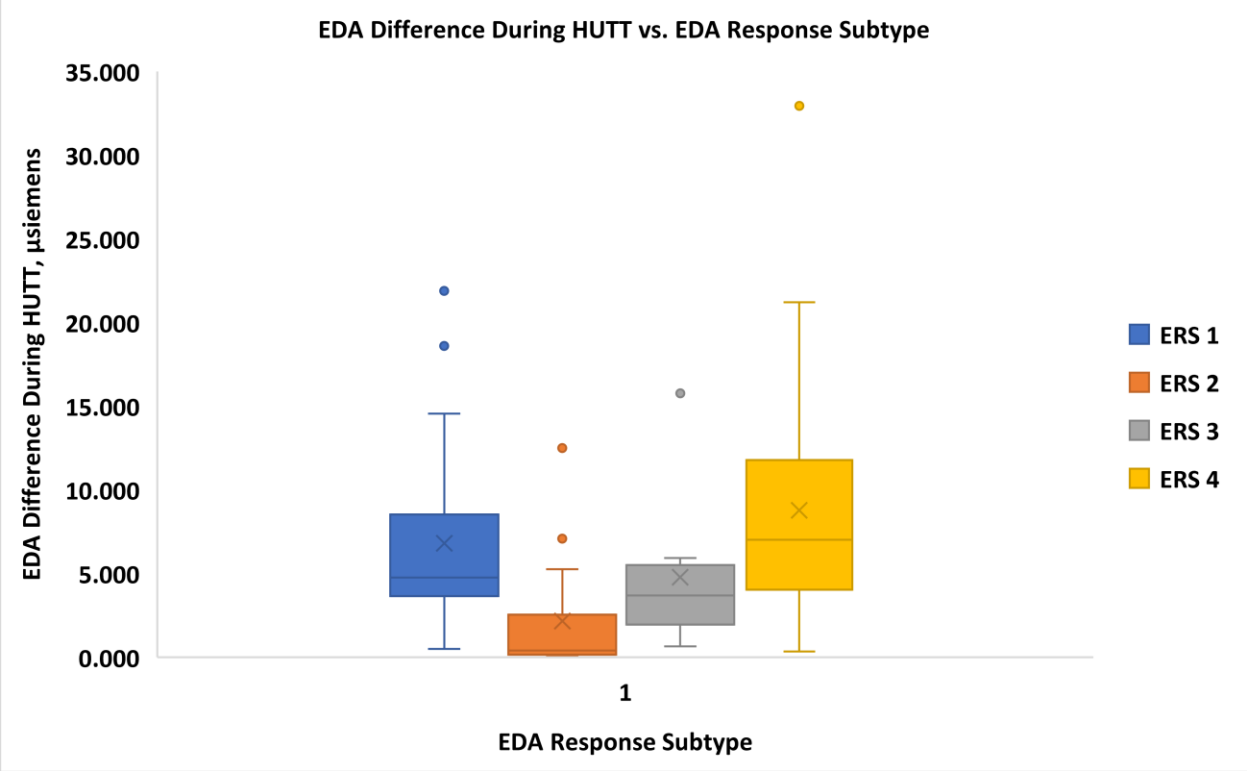
Minimum Skin Conductance Level During HUTT vs. Electrodermal Activity Response Subtype



Note. Abbreviations: EDA, electrodermal activity; ERS, electrodermal activity response subtype; HUTT, head up tilt-table test.

Supplemental Figure 17

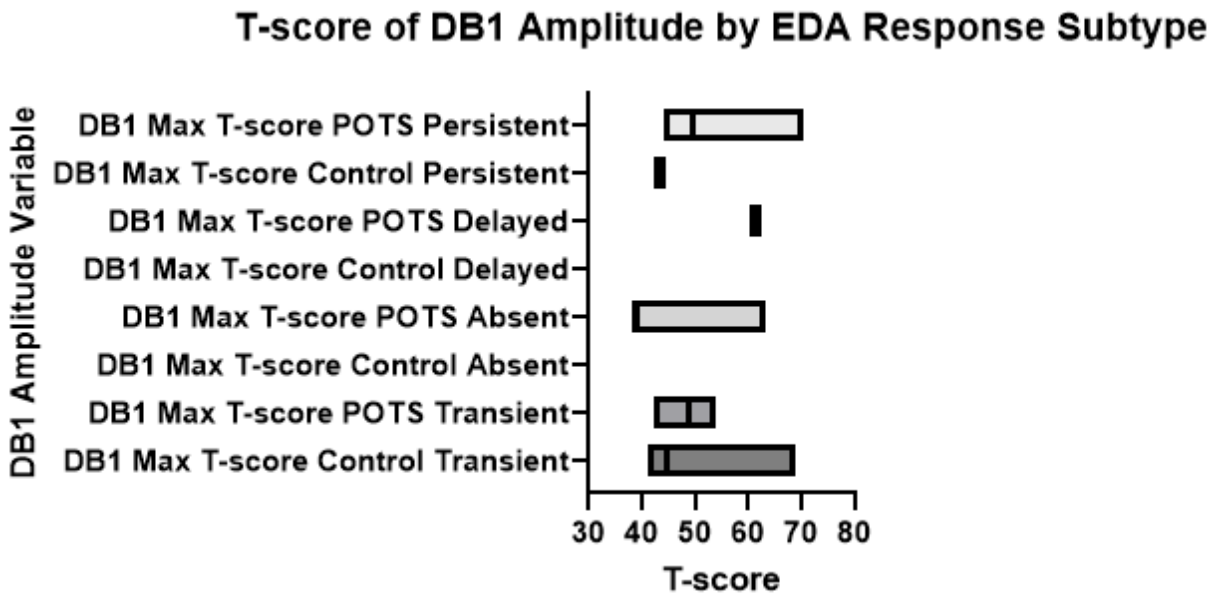
Peak-to-Peak Skin Conductance Level During HUTT vs. Electrodermal Activity Response Subtype



Note. Abbreviations: EDA, electrodermal activity; ERS, electrodermal activity response subtype; HUTT, head up tilt-table test.

Supplemental Figure 18

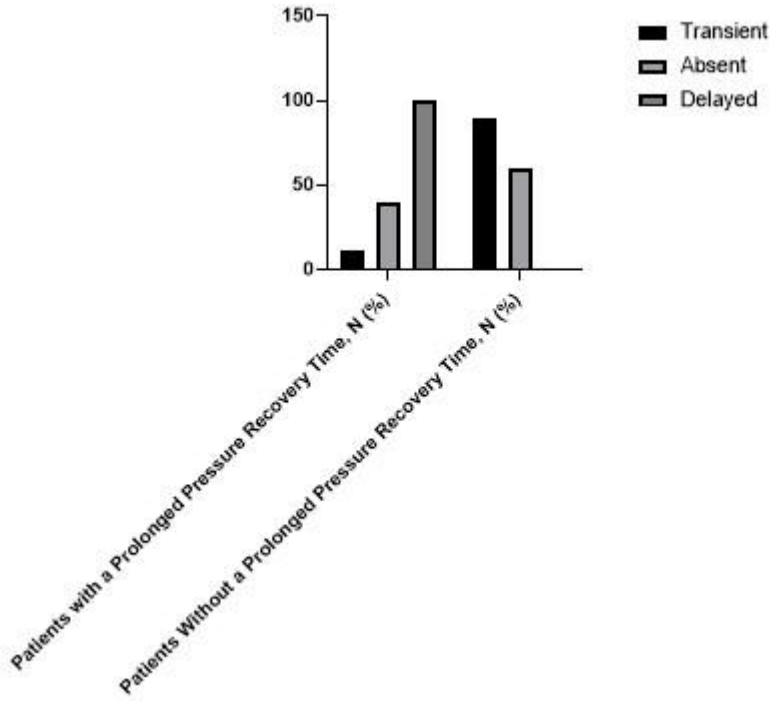
Median of the T-scores of the Raw Amplitudes of the First Deep Breathing Test Stratified by group and Electrodermal Activity Response Subtype



Note. Abbreviations: DB1, deep breathing test 1; EDA, electrodermal activity; POTS, postural orthostatic tachycardia syndrome.

Supplemental Figure 19

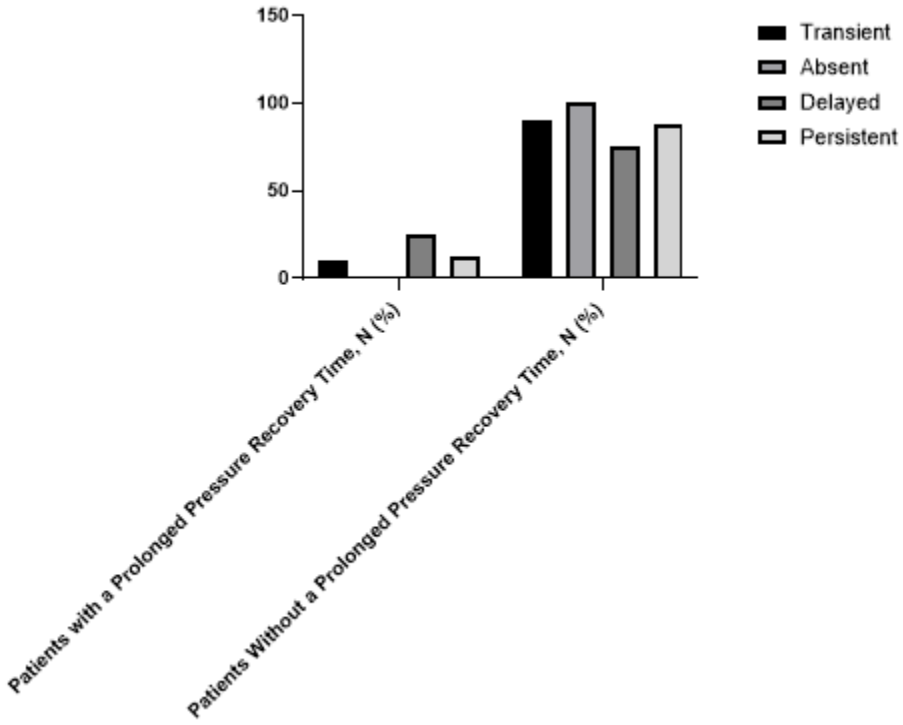
Presence in the Controls of a Prolonged Pressure Recovery Time (PRT) Based on Results from the Heart Rate Deep Breathing (HRDB) Tests Stratified by Electrodermal Activity Response Subtype (ERS)



Note. Abbreviations: EDA, electrodermal activity; ERS, EDA response subtype. Patients displaying the Delayed pattern of electrodermal response, i.e., those exhibiting EDA response subtype 3 (ERS 3), were in the greatest proportion (specifically 100% of them displayed ERS 3), compared with the other control patients (ERS 1 = 11.0%; and ERS 2 = 40.0%; $p<0.001$).

Supplemental Figure 20

Presence in the POTS Cases of a Prolonged Pressure Recovery Time (PRT) Based on Results from the Heart Rate Deep Breathing (HRDB) Tests Stratified by Electrodermal Activity Response Subtype (ERS)



Note. Abbreviations: EDA, electrodermal activity; ERS, EDA response subtype. Patients displaying the Delayed pattern of electrodermal response, i.e., those exhibiting EDA response subtype 3 (ERS 3), were in the greatest proportion (specifically 25% of them displayed ERS 3), compared with the other patients diagnosed with POTS (ERS 1 = 9.5%; ERS2 = 0.0% and ERS 4 = 11.5%; $p<0.001$).

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Appendix B

Supplemental Material B1

Copy of the IRB Determination Letter

University of California Los Angeles
10889 Wilshire Blvd, Suite 830
Los Angeles, CA 90095-1406

http://ora.research.ucla.edu/ohrpp
General Campus IRB: (310) 825-7122
Medical IRB: (310) 825-5344

APPROVAL NOTICE (No Continuing Review Required)
New Study

DATE:	5/25/2022
TO:	John Odeh , MSN, MBA, BSN, BS MEDICINE-CARDIOLOGY
FROM:	DANIEL CLEMENS, MD, PhD Chair, MIRB1
RE:	IRB#22-000769 Utility of Electrodermal Activity in Diagnosis of Postural Orthostatic Tachycardia Syndrome Version: Version 1.0 (May 4, 2022)

The UCLA Institutional Review Board (UCLA IRB) has approved the above-referenced study. UCLA's Federalwide Assurance (FWA) with Department of Health and Human Services is FWA00004642.

Submission and Review Information

Type of Review	Expedited Review

Approval Date	5/25/2022
Expiration Date of the Study	N/A

Regulatory Determinations

-- **Expedited Review Category(ies)** - The UCLA IRB determined that the research meets the requirements for expedited review per 45 CFR 46.110 category 5.

-- **HIPAA General Waiver** - The UCLA IRB waived the requirement for HIPAA Research Authorization for the research.

-- **Waiver of Informed Consent** - The UCLA IRB waived the requirement for informed consent under 45 CFR 46.116 for the entire study.

The UCLA IRB has determined that continuing review of the research for this protocol is not required. The Principal Investigator is required to complete Annual PI Assurances within the webIRB submission system in order to confirm that the research remains active. Study amendments and post approval reports are still required.

Important Note: Approval by the Institutional Review Board does not, in and of itself, constitute approval for the implementation of this research. Other UCLA clearances and approvals or other external agency or collaborating institutional approvals may be required before study activities are initiated. Research undertaken in conjunction with outside entities, such as drug or device companies, are typically contractual in nature and require an agreement between the University and the entity.

General Conditions of Approval
As indicated in the PI Assurances as part of the IRB requirements for approval, the PI has ultimate responsibility for the conduct of the study, the ethical performance of the project, the protection of the rights and welfare of human subjects, and strict adherence to any stipulations imposed by the IRB.

The PI and study team will comply with all UCLA policies and procedures, as well as with all applicable Federal, State, and local laws regarding the protection of human subjects in research, including, but not limited to, the following:

- Ensuring that the personnel performing the project are qualified, appropriately trained, and will adhere to the provisions of the approved protocol,
- Implementing no changes in the approved protocol or consent process or documents without prior IRB approval (except in an emergency, if necessary to safeguard the well-being of human subjects and then notifying the IRB as soon as possible afterwards),

- Obtaining the legally effective informed consent from human subjects of their legally responsible representative, and using only the currently approved consent process and stamped consent documents, as appropriate, with human subjects,
- Reporting serious or unexpected adverse events as well as protocol violations or other incidents related to the protocol to the IRB according to the OHRPP reporting requirements.
- Assuring that adequate resources to protect research participants (i.e., personnel, funding, time, equipment and space) are in place before implementing the research project, and that the research will stop if adequate resources become unavailable.
- Arranging for a co-investigator to assume direct responsibility of the study if the PI will be unavailable to direct this research personally, for example, when on sabbatical leave or vacation or other absences. Either this person is named as co-investigator in this application, or advising IRB via webIRB in advance of such arrangements.

Appendix C

Supplemental Material C1

A Copy of the IRB Approval Letter for Amendment Request 1

University of California Los Angeles
10889 Wilshire Blvd, Suite 830
Los Angeles, CA 90095-1406

http://ora.research.ucla.edu/ohrpp
General Campus IRB: (310) 825-7122
Medical IRB: (310) 825-5344

APPROVAL NOTICE (No Continuing Review Required)

DATE:	7/8/2022
TO:	John Odeh , MSN, MBA, BSN, BS MEDICINE-CARDIOLOGY
FROM:	DANIEL CLEMENS, MD, PhD Chair, MIRB1
RE:	IRB#22-000769-AM-00001 Addition of Key Personnel (Other Personnel) Utility of Electrodermal Activity in Diagnosis of Postural Orthostatic Tachycardia Syndrome Version: Version 1.0 (May 4, 2022)

The UCLA Institutional Review Board (UCLA IRB) has approved the above-referenced study. UCLA's Federalwide Assurance (FWA) with Department of Health and Human Services is FWA00004642.

Submission and Review Information

Type of Submission	Amendment
Type of Review	IRB Review: Expedited
Approval Date	7/8/2022
Expiration Date of the Study	N/A

Regulatory Determinations

-- **Expedited Review Category(ies)** - The UCLA IRB determined that the research meets the requirements for expedited review per 45 CFR 46.110 category 5.

-- **HIPAA General Waiver** - The UCLA IRB waived the requirement for HIPAA Research Authorization for the research.

-- **Waiver of Informed Consent** - The UCLA IRB waived the requirement for informed consent under 45 CFR 46.116 for the entire study.

The UCLA IRB has determined that continuing review of the research for this protocol is not required. The Principal Investigator is required to complete Annual PI Assurances within the webIRB submission system in order to confirm that the research remains active. Study amendments and post approval reports are still required.

Important Note: Approval by the Institutional Review Board does not, in and of itself, constitute approval for the implementation of this research. Other UCLA clearances and approvals or other external agency or collaborating institutional approvals may be required before study activities are initiated. Research undertaken in conjunction with outside entities, such as drug or device companies, are typically contractual in nature and require an agreement between the University and the entity.

General Conditions of Approval

As indicated in the PI Assurances as part of the IRB requirements for approval, the PI has ultimate responsibility for the conduct of the study, the ethical performance of the project, the protection of the rights and welfare of human subjects, and strict adherence to any stipulations imposed by the IRB.

The PI and study team will comply with all UCLA policies and procedures, as well as with all applicable Federal, State, and local laws regarding the protection of human subjects in research, including, but not limited to, the following:

- Ensuring that the personnel performing the project are qualified, appropriately trained, and will adhere to the provisions of the approved protocol,
- Implementing no changes in the approved protocol or consent process or documents without prior IRB approval (except in an emergency, if necessary to safeguard the well-being of human subjects and then notifying the IRB as soon as possible afterwards),
- Obtaining the legally effective informed consent from human subjects of their legally responsible representative, and using only the currently approved consent process and stamped consent documents, as appropriate, with human subjects,
- Reporting serious or unexpected adverse events as well as protocol violations or other incidents related to the protocol to the IRB according to the OHRPP reporting requirements.

- Assuring that adequate resources to protect research participants (i.e., personnel, funding, time, equipment and space) are in place before implementing the research project, and that the research will stop if adequate resources become unavailable.
- Arranging for a co-investigator to assume direct responsibility of the study if the PI will be unavailable to direct this research personally, for example, when on sabbatical leave or vacation or other absences. Either this person is named as co-investigator in this application, or advising IRB via webIRB in advance of such arrangements.

Appendix D

Supplemental Material D1

A Copy of the IRB Approval Notice for Amendment Request 1

Activity Details (Amendment Completed - Approved) Indicates an Amendment has been completed. This is automatically added by the Amendment sub process.

Author:	ANNIE HILO (OFC OF HUMAN RESEARCH PROTECTION PROGRAM)
Logged For (Study):	EDA in Investigations of POTS and Prevalence of POTS in Persons Screened for Dysautonomia at UCLA
Activity Date:	7/8/2022 4:12 PM

Property Changes | Documents | Notifications

Property	Old Value	New Value
activityType		_Protocol_Amendment Completed
Study		IRB#22-000769
author		ANNIE HILO
name		Amendment Completed - Approved
Amendment		IRB#22-000769-AM-00001
Motion		Approved
Amendment.status	Awaiting Action	Approved
Amendment.dateEnteredState	7/8/2022 4:10 PM	7/8/2022 4:12 PM
Amendment.Meeting Time		N/A
Amendment.activities		Added elements: • 8DA5B0EA1B53588
Amendment.activities{8DA5B0EA1B53588}.name		Sent Letter/Notice To PI: *Approved* (Expedited)
Amendment.Modified Study.Approval Letter	fromString.html	fromString.html

Appendix E

Supplemental Material E1

A Copy of the IRB Approval Letter for Amendment Request 2

University of California Los Angeles
10889 Wilshire Blvd, Suite 830
Los Angeles, CA 90095-1406

http://ora.research.ucla.edu/ohrpp
General Campus IRB: (310) 825-7122
Medical IRB: (310) 825-5344

APPROVAL NOTICE (No Continuing Review Required)

DATE:	7/27/2022
TO:	John Odeh , MSN, MBA, BSN, BS MEDICINE-CARDIOLOGY
FROM:	DANIEL CLEMENS, MD, PhD Chair, MIRB1
RE:	IRB#22-000769-AM-00002 Addition of Aims and Change in Titles Exploratory Study of the Utility of Electrodermal Activity (EDA) in Investigations of the Assessment, Diagnosis, Diagnostic Tests, Mechanisms, Medication Impacts, Prognosis, and Symptoms of Postural Orthostatic Tachycardia Syndrome (POTS), and Prevalence of POTS in Persons Tested for Dysautonomia at UCLA, Between January 1, 2017, to December 31, 2021. Version: Version 1.0 (May 4, 2022)

The UCLA Institutional Review Board (UCLA IRB) has approved the above-referenced study. UCLA's Federalwide Assurance (FWA) with Department of Health and Human Services is FWA00004642.

Submission and Review Information

Type of Submission	Amendment
Type of Review	Expedited
Approval Date	7/27/2022
Expiration Date of the Study	N/A

Regulatory Determinations

-- **Expedited Review Category(ies)** - The UCLA IRB determined that the research meets the requirements for expedited review per 45 CFR 46.110 category 5.

-- **HIPAA General Waiver** - The UCLA IRB waived the requirement for HIPAA Research Authorization for the research.

-- **Waiver of Informed Consent** - The UCLA IRB waived the requirement for informed consent under 45 CFR 46.116 for the entire study.

The UCLA IRB has determined that continuing review of the research for this protocol is not required. The Principal Investigator is required to complete Annual PI Assurances within the webIRB submission system in order to confirm that the research remains active. Study amendments and post approval reports are still required.

Important Note: Approval by the Institutional Review Board does not, in and of itself, constitute approval for the implementation of this research. Other UCLA clearances and approvals or other external agency or collaborating institutional approvals may be required before study activities are initiated. Research undertaken in conjunction with outside entities, such as drug or device companies, are typically contractual in nature and require an agreement between the University and the entity.

General Conditions of Approval

As indicated in the PI Assurances as part of the IRB requirements for approval, the PI has ultimate responsibility for the conduct of the study, the ethical performance of the project, the protection of the rights and welfare of human subjects, and strict adherence to any stipulations imposed by the IRB.

The PI and study team will comply with all UCLA policies and procedures, as well as with all applicable Federal, State, and local laws regarding the protection of human subjects in research, including, but not limited to, the following:

- Ensuring that the personnel performing the project are qualified, appropriately trained, and will adhere to the provisions of the approved protocol,
- Implementing no changes in the approved protocol or consent process or documents without prior IRB approval (except in an emergency, if necessary to safeguard the well-being of human subjects and then notifying the IRB as soon as possible afterwards),

- Obtaining the legally effective informed consent from human subjects of their legally responsible representative, and using only the currently approved consent process and stamped consent documents, as appropriate, with human subjects,
- Reporting serious or unexpected adverse events as well as protocol violations or other incidents related to the protocol to the IRB according to the OHRPP reporting requirements.
- Assuring that adequate resources to protect research participants (i.e., personnel, funding, time, equipment and space) are in place before implementing the research project, and that the research will stop if adequate resources become unavailable.
- Arranging for a co-investigator to assume direct responsibility of the study if the PI will be unavailable to direct this research personally, for example, when on sabbatical leave or vacation or other absences. Either this person is named as co-investigator in this application, or advising IRB via webIRB in advance of such arrangements.

Appendix F

Supplemental Material F1

A Copy of the IRB Approval Notice for Amendment Request 2

Activity Details (Amendment Completed - Approved) Indicates an Amendment has been completed. This is automatically added by the Amendment sub process.

Author:	ANNIE HILO (OFC OF HUMAN RESEARCH PROTECTION PROGRAM)
Logged For (Study):	EDA in Investigations of POTS and Prevalence of POTS in Persons Screened for Dysautonomia at UCLA
Activity Date:	7/27/2022 11:24 AM

Property Changes | Documents | Notifications

Property	Old Value	New Value
activityType		_Protocol_Amendment Completed
Study		IRB#22-000769
author		ANNIE HILO
name		Amendment Completed - Approved
Amendment		IRB#22-000769-AM-00002
Motion		Approved
Amendment.status	Awaiting Action	Approved
Amendment.dateEnteredState	7/27/2022 11:21 AM	7/27/2022 11:24 AM
Amendment.Meeting Time		N/A
Amendment.activities		Added elements: • 8DA6B803FF50712
Amendment.activities{8DA6B803FF50712}.name		Sent Letter/Notice To PI: *Approved* (Response Review)
Amendment.Modified Study.Approval Letter	fromString.html	fromString.html