Title
Electrocardiographic Autonomic Nervous System Predictors of Outcomes in Acute Coronary Syndrome Patients

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Electrocardiographic Autonomic Nervous System Predictors
of
Outcomes in Acute Coronary Syndrome Patients

by

Patricia Rae Eileen Harris

DISSERTATION

Submitted in partial satisfaction of the requirements for the degree of

DOCTOR OF

PHILOSOPHY

in

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in the

GRADUATE DIVISION

of

the

Dedication

To my wonderful husband, Gary Alan Hanks,

With heartfelt appreciation for

sharing patience, caring,

inspiration and love

To my amazing son, Scott Samuel Harris,

With deep gratitude for being my guiding

light

To all of my family with thanks

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This dissertation is based on over ten years of work in intensive care nursing, five years of study in cardiovascular nursing, research methods, and biostatistics during my PhD program, and four years of research, specifically related to electrocardiographic autonomic nervous system measures, particularly heart rate variability and heart rate turbulence.

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From the depth of my soul, I would like to thank my dissertation committee members for their strong support, enlightening guidance, and valuable suggestions. To Dr. Barbara Drew, my graduate advisor and chair, I am especially grateful for the constant inspiration, trust, and employment. Working in the ECG Research Lab is a gift. I also owe my deepest gratitude to Dr. Phyllis Stein, my mentor in heart rate variability, for endless patience and encouragement. Spending time in Dr. Stein's Heart Rate Variability Laboratory at Washington University, St. Louis, Missouri has been an invaluable experience. My great appreciation also goes to Dr. Gordon Fung for sharing of expertise and time. Thank you all.

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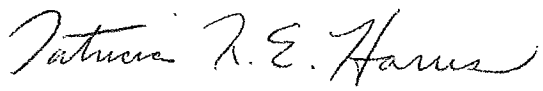

Patricia Rae Eileen Harris

May 10, 2012

Prelude

This dissertation contains four research papers. They are the product of my work as a nursing doctoral student at UCSF. Two papers are in review for publication. Paper 1 is a literature review, currently is in review with *Heart and Lung*. Paper 2, is in review with the *Annals of Noninvasive Electrocardiology*. The abstract for the 2nd paper was presented as an award-winning poster at the annual conference of The International Society for Computerized Electrocardiology in April 2010 (Albuquerque, New Mexico), and the abstract was published in Fall 2010. An abstract that served as the basis for the 3rd and 4th papers was presented at the annual conference of the European Society of Intensive Care Medicine in Barcelona, Spain in October 2010. That abstract was published in *Journal of Intensive Care Medicine* in 2010. The third paper serves as an adjunct study to the 4th, and the two papers have many similarities in content. Paper 4 is planned for submission to the *Journal for Cardiovascular Electrophysiology*. The co-authors who are listed in each paper provided guidance and assured the overall integrity of these studies, which are the foundation for this dissertation.

This dissertation does not represent a culminating moment in the research, but merely provides a glimpse through a great portal that leads to future avenues of inquiry.

Electrocardiographic Autonomic Nervous System Predictors of Outcomes in Acute Coronary Syndrome Patients

ABSTRACT

Autonomic nervous system (ANS) dysfunction has been associated with cardiac arrhythmias and death. The aim of this research was to determine whether electrocardiographic (ECG) measures of ANS function, heart rate variability (HRV) and heart rate turbulence (HRT), have prognostic value in patients with acute coronary syndrome (ACS). A secondary analysis was performed using 24-hour ECG recordings from patients enrolled in the IMMEDIATE AIM Trial, a prospective NIH-funded study conducted from 2002 - 2005. The ECG recordings were begun within minutes (median, 45 minutes) from patients' presentation to the UCSF Emergency Department with ACS symptoms. HRV and HRT were computed using research software (HRV Laboratory, St. Louis, MO). A total of 193 patients had recordings with sufficient data for analysis.

Multivariate analyses demonstrated that 5 HRV measurements were significantly associated with all-cause 1-year rehospitalization (p-values<.05). HRT was associated with cardiac-related 30-day and 1-year ED readmission and/or death. Patients with disrupted HRT markers had greater risk of adverse 30-day outcomes compared to patients with healthy markers (hazard ratio=3.6, p=.01), and greater risk of adverse 1-year outcomes (hazard ratio=3.2, p<.001). Comparison of HRT and routinely-measured TIMI risk scores showed similar sensitivity and specificity for 30-day (areas under the curve: HRT=0.647; TIMI=0.687) and 1-year outcomes (HRT=0.657; TIMI=0.605).

In conclusion, HRT provides a viable alternative to TIMI scores for risk assessment in patients with ACS. With appropriate software, HRT and HRV could be obtained from the ECG monitoring nurses routinely perform. Future studies are needed to determine whether ANS ECG markers identify patients who warrant closer follow-up.

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HRT = Heart Rate Turbulence
TIMI = Thrombolysis in Myocardial Infarction

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Chapter 1

Introduction

Introduction

Electrocardiographic Autonomic Nervous System Predictors of Outcomes in Acute Coronary Syndrome Patients

Patients who experience acute coronary syndrome (ACS) – umbrella term for myocardial infarction or unstable angina – are at high risk for repeat cardiac events and/or death. Recognition of those patients who may be at greatest risk for adverse outcomes is a fundamental responsibility of healthcare providers. Determining patients' risk can aid in planning appropriate preventative strategies. While accurate identification can be difficult, it needn't be left to chance. Numerous tools to assist in assessing patients' risk are available, including the Thrombolysis in Myocardial Infarction (TIMI), Global Registry of Acute Coronary Event (GRACE), and Platelet glycoprotein IIb/IIIa in Unstable angina: Receptor Suppression Using Integrilin (PURSUIT)[1] scoring systems. The American Heart Association and American College of Cardiology recommends their use.[2,3] However, many clinical and historical parameters are required to compute the scores, and no one system has been deemed vastly superior in comparison to the others. There is an ongoing need for improved risk stratification strategies.

The autonomic nervous system (ANS) plays a definitive role in cardiovascular function, and it's role in provoking life-threatening arrhythmias and sudden cardiac death is well documented[4,5]. Over the last half century, recognition of the clinical significance of electrocardiographic (ECG) ANS biomarkers has increased. A growing body of research has distinguished healthy versus abnormal ECG ANS patterns. Disrupted patterns have been associated with worse outcomes after myocardial infarction or episode of unstable angina. These ANS markers, which can offer a window into a patient's physiological ability to recover from disease, can be obtained through routine cardiac monitoring. Nurses are uniquely positioned to access this information that can be vital to a patient's well being. As professional caregivers who spend 24/7 at the hospitalized patients'

bedside, much insight about the patient's condition can be gained through the continuous patient monitoring. The discrete ANS markers that can be derived from ECG signals deserves the attention of healthcare providers.

The Ischemia Monitoring and Mapping in the Emergency Department In Appropriate Triage and Evaluation of Acute Ischemic Myocardium (IMMEDIATE AIM) database provided a unique opportunity to examine ECG ANS markers obtained very early in patients' evolving ACS. Twenty-four hour Holter recordings were started in the emergency department (ED) for 1,308 patients with cardiac symptoms. Of the patients who were admitted to the hospital, 303 received discharge diagnoses of myocardial infarction or unstable angina. My dissertation consists of a review of the literature and 3 studies that focus on ACS patients, using the IMMEDIATE AIM database as the foundation.

In reviewing the literature, I found an enormous amount of research that supports measuring ECG ANS measures in risk stratification of ACS patients, but there were no studies that examined measurements that were initiated in the ED within 45 minutes of patients' arrival. Given that patients are placed on a cardiac monitor as soon as they arrive with chest pain or other cardiac-related symptoms, obtaining the measurements early could be practical and cost-effective.

The literature also revealed that there are numerous parameters for measuring ECG ANS markers and no consensus on measurement method. I chose to focus upon two promising ECG ANS markers: heart rate variability and heart rate turbulence. The aims of my research were:

1) To determine the one-year prognostic value of heart rate variability, derived from 24-hour Holter ECG recordings, initiated in the ED, in patients who subsequently were diagnosed with ACS. Endpoints were all-cause rehospitalization and death.

2) To determine the 30-day and one-year prognostic value of heart rate turbulence, derived from 24-hour Holter ECG recordings, initiated in the ED, in patients subsequently diagnosed with unstable angina who had negative cardiac markers and no ST elevation (and therefore might be deemed low risk). Endpoints were cardiac-related in-hospital complications, cardiac rehospitalization, and/or cardiac death.
3) To determine the 30-day and one-year prognostic value of heart rate turbulence compared to the TIMI risk score, derived from 24-hour Holter ECG recordings, initiated in the ED, in patients subsequently diagnosed with unstable angina or non-ST elevation myocardial infarction. Endpoints were cardiac-related emergent return to the hospital and cardiac death.

My extensive review of the literature revealed that heart rate variability was associated with clinical depression, another risk factor for adverse outcomes, and a condition that nurses are trained to assess. Therefore, I focused my literature review on the conjunction of heart rate variability and clinical depression as related to patients recently diagnosed with ACS. The connection between mind and body comes into greater focus as one scrutinizes the vast array of investigative work. The review also serves as an introduction for readers who are not familiar with heart rate variability.

My sincere hope is that this dissertation, and the published articles that will arise from the papers, will serve the purpose of raising the level of awareness about ECG ANS predictors, and the phenomena of heart rate variability and heart rate turbulence.

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Chapter 2

Article 1 – Heart Rate Variability and Clinical Depression in Acute Coronary Syndrome Patients: A Critical Review of Recent Literature

Chapter 2

Heart Rate Variability and Clinical Depression in Acute Coronary Syndrome Patients: A Critical Review of Recent Literature

Short Title: HRV & Depression in ACS

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Abbreviations and Acronyms

For a list of heart rate variability variable abbreviations and definitions, please see Table 1.

ACC = American College of Cardiology
AHA = American Heart Association
ACS = acute coronary syndrome
BDI = Beck Depression Inventory
CCU = coronary care unit
DSM-IV = Diagnostic and Statistical Manual of Mental Disorders, fourth edition
ECG = electrocardiography
HRV = heart rate variability
log = natural logarithmic transformation
MDD = major depressive disorder
MI = myocardial infarction
UA = unstable angina

Key Words:

Acute Coronary Syndrome

Electrocardiogram

Depression

Heart Rate Variability

Outcomes

Abstract

Patients with acute coronary syndrome (ACS) are at risk for clinical depression and cardiac autonomic dysfunction. Both conditions can negatively impact the ability to recover from an acute physiological insult, such as unstable angina or acute myocardial infarction, increasing the risk for adverse cardiovascular events, even death. Heart rate variability (HRV) is based upon the ebb and flow of changes in the time intervals between heartbeats, and is a reflection of cardiac autonomic function. While these variations are not always visible to the naked eye, advances in bioengineering have allowed indirect capture of the phenomenon through electrocardiographic signals, providing a mathematical reflection of the patterns. The relevance of HRV in association with the experience of depression and outcomes of ACS has increasingly become the focus of healthcare researchers' attention. Seven recent studies offering evidence of the clinical significance of HRV and depression in ACS patients are reviewed.

Introduction

Relieving the burden of morbidity and mortality in cardiovascular disease is a vital, ongoing public health goal. While great progress has been made in managing acute coronary syndromes (ACS), the incidence of coronary events in the United States remains high. In 2009 (the most recent year with available data), almost 1.2 million hospitalizations in the United States were attributed to ACS, the umbrella term for myocardial infarction (MI) or unstable angina (UA).[1] Recognition and management of cardiovascular risk factors promotes tertiary prevention, potentially helping patients avoid repeated ACS episodes.

Alteration in autonomic nervous system function has been associated with significant risk of adverse outcomes for patients with cardiovascular disease.[2] Studies have linked the human autonomic response to threat – increased sympathetic and decreased parasympathetic activity – to higher risk of sudden cardiac death in the presence of MI.[3] UA patients also have an increased risk for death and other adverse events.[4] Heart rate variability (HRV) serves as a quantitative reflection of autonomic nervous system activity and as an assessment tool.[5]

HRV is based upon the concept of continuous variation in the spaces between sinus beats. A healthy human heart with an intact autonomic nervous system continuously adjusts to internal and external changes, so that a heart rate of 60 beats per minute does not mean that the heart beats precisely one time per second. Each interval varies slightly by milliseconds.[2,5]

The clinical significance of HRV in predicting outcomes of acute MI was recognized nearly 50 years ago. In 1965, Schneider and Costiloe presented evidence that MI patients had less sinus arrhythmia – a component of HRV associated with respirations – than healthy controls. Furthermore, the MI patients with the least amount of sinus arrhythmia were more likely to have a second MI within 2 years.[6] In 1978, Wolf

and colleagues reported that among patients admitted to a coronary care unit (CCU), those showing evidence of sinus arrhythmia upon admission tended to have less mortality and better prognosis.[7] A seminal 1987 study by Kleiger et al demonstrated that low HRV, measured with 24-hour Holter recorders 2 weeks after MI, was associated with all-cause mortality during 31 months of follow-up.[8] Since these early findings, research supporting the prognostic value of HRV measured after MI has expanded appreciably,[9] and includes ACS patients diagnosed with UA.[4] Albeit a distinct causal link between altered HRV and poor ACS outcomes has yet to be established. Inquiry is ongoing.[2]

Clinical depression also has been identified as a risk factor for further cardiac damage and death in ACS patients.[10-13] Notably, >30% of patients hospitalized for acute MI are reported to have mild to moderate depressive symptoms, and nearly 20% of MI patients experience major depression.[13] A physiological mechanism underlying the connection between depression and post-MI mortality, however, is not clear and there remains inconsistency in study results regarding the full extent of depression's role in adverse outcomes .[14,15]

The autonomic cardiac physiology behind HRV is known to have a complex interplay with psychosocial factors.[16] Understanding the association of HRV and depression as a means to improve the prognosis of ACS patients has become a focus of study.[17-24] The purpose of this review is to evaluate current research findings regarding HRV in conjunction with depression for assessment, risk stratification, and improvement in outcomes for ACS patients.

Heart Rate Variability Measurement

HRV is a noninvasive measurement that can be obtained from electrocardiographic (ECG) recordings, most commonly from 24-hour Holter monitoring. The measurements are derived from mathematical formulas and computed with the aid of software developed by bioengineers. HRV has been used primarily as a research tool

to assess autonomic function in physiological studies or examine the cardiac autonomic role in risk stratification across the continuum of health and disease. One limitation of HRV assessment is that sinus rhythm is required to make accurate measurements, so patients who have atrial fibrillation or a pacemaker are precluded from analysis.[5] Despite this constraint, the clinical benefits of HRV analysis have become more widely recognized in recent years. The American College of Cardiology (ACC) and American Heart Association (AHA) recommend education and skill in HRV assessment as a prerequisite to competence in ambulatory ECG interpretation.[25] ACC/AHA 2004 practice guidelines recommend considering use of HRV to assess risk of ventricular arrhythmias in management of patients recovering from ST-elevation MI (class IIb, usefulness is less well-established).[26]

HRV measurement methods typically fall into 3 categories: time domain, frequency domain, and nonlinear dynamics.[2,5,27] Several time and frequency domain measures are considered to correspond to each other mathematically.[5] HRV definitions are in Table 1.

Time domain HRV estimates variation in normal sinus R-to-R intervals over time, and quantifies the variation using descriptive statistics. For example, the standard deviation of all normal sinus R-to-R intervals over the length of a recording period is called SDNN.[2,5] There are 2 time domain categories: long-term, usually measured over 24-hours, potentially reflecting long cycles, such as circadian rhythm; and short-term, which can be measured in epochs of 5-10 minutes, possibly reflecting shorter cycles, such as respiration or baroreceptor activity.[5]

Frequency domain measures use spectral density analysis to estimate HRV. Frequency domain HRV is derived from mathematical algorithms, and examines the amount of underlying cyclic variation in intervals across time (known as variance or power) by the underlying frequency.[28] The spectrum is divided into 4 bands: high frequency (HF); low frequency (LF); very low frequency (VLF); and ultra low frequency

(ULF).[5,9,27] HF may synchronize with the respiratory cycle. LF has been associated with fluctuations in blood pressure along with changes in sympathetic and parasympathetic activity. VLF has been related to alterations in body temperature and sleep apnea-related heart rate changes. ULF has been associated with circadian rhythms.[29] These associations are hypothesized, not hard and fast categories.

The third category, nonlinear dynamic measures, takes into account the intricate interactions of physiological signals. They are computed based upon newer bioengineering developments, incorporating theories of complexity, chaos, and fractal characteristics.[29,30] These methods may capture information about underlying patterns of variability beyond what time and frequency domain measurements can offer.[2,29,30]

HRV variables appear to reflect an interchange between the parasympathetic and sympathetic autonomic branches. The underlying physiology is multifaceted. Associating specific HRV measures solely with one or the other autonomic branch is inaccurate.[2] For example, HF power often is ascribed to respiratory sinus arrhythmia, reflecting vagal involvement. While physiological study supports this relationship,[31] clinical research indicates that this is not true in all patients. Extremely high HF values may not necessarily reflect better parasympathetic control of heart rate, but other, more abnormal, phenomena.[32]

Search Strategies

We conducted a review of the literature using PubMed and Web of Science databases to identify key articles related to HRV measurement and depression in ACS patients. The search terms "heart rate variability" and "depression" were used in conjunction with "acute coronary syndrome," "myocardial infarction," or "unstable angina." To ensure the most current findings, the search was confined to articles <10 years old. With limiters in place, i.e. "human," "adult" and "English," we found 22 articles. The search was refined further to include only clinical studies of patients with recent

ACS diagnosis that used published standards for HRV time or frequency domain measures[5] or nonlinear dynamic measures supported by clinical research[33-35] with potential for clinical application.[30,36] Seven research studies, focusing upon HRV and depression in patients who had experienced ACS within the preceding 2 months, met inclusion criteria. An in-depth critique of each study's design and methodology was performed.

Review and Critique

The studies are organized into 2 broad groups, according to research objectives. The first group of 3 studies focuses upon substantiating the relationship between HRV and clinical depression in ACS patients.[18-20] The second group of 4 studies explores the nature of the relationships, linking HRV and depression with patient outcomes and/or other variables.[21-24] Studies for each group are presented chronologically. Study summaries are presented in Table 2.

Substantiating the Relationship between Heart Rate Variability and Depression.

Argentine researchers **Guinjoan et al** prospectively investigated the connection between depression and abnormal cardiac autonomic activity in 56 older patients who had had a recent ACS episode.[18] Older ACS patients, admitted to the CCU within the past 1-3 days, were recruited. Participants were interviewed and given depression scores based upon the Hamilton Depression Scale and criteria from the Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV). Patients were categorized into 2 groups: major depression or no depression.

For HRV analysis, morning ECG recordings of ~5-10 minutes (550 beats) were obtained with a device that detected R-waves and connected to a computer that analyzed the signals. Recordings were manually scanned. Ectopic beats were identified and interpolation was used to replace abnormal beats with normal R-to-R intervals. Several HRV time domain variables, reflecting short-term beat-to-beat variability (5),

were significant. In the frequency domain, HF power was significantly lower in depressed patients, and remained so in a multiple regression with clinical variables (p=.005). SDNN and total power (TP) also were measured, but not found to be significantly different between groups. The authors concluded that depression was related to decreased vagal cardiac activity in older ACS patients, noting that the sympathetic component could still be a factor and may have been dampened because the majority of patients were receiving beta-blocking medication.

This innovative study demonstrated that a relationship between HRV and depression exists. Measuring frequency domain measures over a short period under controlled conditions is appropriate and lends credence to the findings. However, there are limitations in this small study. SDNN or total power reflect long-term HRV and cannot be measured reliably over short periods of time.[5] The authors reported rMSNN, a nonstandard term, apparently equivalent to rMSSD (square root of the mean of the sum of squares of differences between adjacent normal R-to-R intervals).[5] The discrepancy in variable names fosters uncertainty.

A study by **Vigo et al** (19), including members of Guinjoan's research team (18), measured nonlinear dynamic variables in 52 depressed ACS patients. DSM-IV and the Hamilton Depression Scale criteria were used to diagnose major depression in older patients. Nonlinear dynamics measures were compared between depressed and nondepressed patients. ECG signals were obtained over 10 minutes in the same manner described by Guinjoan (18). Three HRV variables were measured. One was SD1, a measure derived from a scatter plot of R-to-R intervals, reflecting instantaneous beat-to-beat variation (34). The second was approximate entropy (ApEn), a measure of randomness or disorder within a system (29, 33). Higher ApEn values are associated with increased randomness in a system (19). The third measure was the short-term fractal-scaling exponent, known as $\alpha 1$ or DFA1, which is computed using detrended

fluctuation analysis, a method that takes into account changing conditions over time. Therefore, the measurement is useful in analysis of physiologic signals.[34,36,37]

SD1 and ApEn were lower, and DFA1 was higher, in depressed compared to nondepressed patients. The authors concluded that higher depression severity was related to reduced instantaneous beat-to-beat variability (SD1), increased randomness (ApEn), and increased fractal correlation properties (DFA1). Comparing Vigo's findings with results of others who examined nonlinear dynamics in relation to cardiovascular outcomes may provide helpful insight. Vigo's results contrast with those of Kop et al who used 24-hour ECG recordings to determine that DFA1 tended to be lower in older depressed adults; DFA1<1.0 was associated with higher risk of cardiovascular mortality over 15 years.[38] Mäkikallio et al examined the relationship between nonlinear dynamic indices and sudden cardiac death.[33] Low DFA1 predicted cardiac death in patients >65 years of age. Risk of dying was 2.5 times greater in patients with DFA1<1.0 compared to those with higher values. Mäkikallio found no significant difference in ApEn between patients with poor outcomes and those who were event-free. Stein et al also found that low DFA1 was associated with greater mortality risk in community dwelling adults ≥65 years.[35] The studies by Mäkikallio and Stein used 24-hour recordings to examine ≥10-year outcomes, however, and neither focused upon the relationship between HRV and depression.

Despite differences in findings, Vigo's work raises awareness of HRV nonlinear dynamics. According to Seely, physician and researcher of complex systems, ApEn, the entropy variable, reflects the Second Law of Thermodynamics, namely that entropy or randomness increases in a system over time.[29] Low ApEn measures, therefore, reflect reduced randomness and less complexity, or in other words, gridlock, mirroring a clogged system or a clotted vessel. However, the predictive value of ApEn in cardiac patients has not been established. Research by Tulppo et al showed that in healthy

subjects, DFA1 could be altered in opposite directions, depending upon type of exposure – cold face immersion (the measure decreased) or cold hand immersion (the measure increased). Tulppo concluded that DFA1 captures a dynamic interplay between sympathetic and parasympathetic activity.[37]

Strength of Vigo's study lies in its innovation. Measurement of 3 HRV variables enhances construct validity. On the other hand, inadequate explanation of the constructs and findings limits clinical applicability. The researchers characterized the 3 HRV variables as nonlinear; however, SD1 is a linear measurement.[34] Measurement of nonlinear variables over longer periods of time may be more reliable than short periods.[33,35] Furthermore, the study appears to be an extension of Guinjoan's work,[18] including a portion of the same sample, but this point was not clarified in the study's description, presenting a problem for verification of internal validity.

Croatian researchers **Catipović-Veselica et al** performed a prospective study to examine the prevalence of minor and major depression in 297 hospitalized ACS patients in relation to HRV and clinical characteristics.[20] Patients underwent 24-hour ECG monitoring for HRV measurement and screening for major or minor depression prior to hospital discharge, an average of 14-18 days after admission. Physicians assessed presence of depressive disorders using DSM-IV criteria. HRV time variables were computed. Time domain HRV was significantly lower in depressed ACS patients compared to those without depression. Depression was more prevalent in patients with non-ST-elevation MI and UA than in those with ST-elevation MI ($p<.05$). Depressed patients tended to be women, were older, and often had comorbidities.

Catipović-Veselica's findings help bring to light characteristics associated with ACS patients' depression and altered HRV. The finding that depression was more prevalent among women than men, corresponds to results of other studies.[10,18,22,39] However, the finding that older patients were more depressed contradicts others.[10,39] While the large

sample size is a strength, univariate, as opposed to multivariate, statistical analysis is a limitation. Each variable was examined separately in relation to depression. The conclusions are based upon results that could change, if clinical and HRV variables were analyzed together.

Together, the 3 articles provide evidence substantiating the relationship between HRV and depression. However, methodologies were not uniform. Although each study used criteria from the DSM-IV to distinguish depression, the focus of the studies differed, examining only major depression,[18,19] or including mild to moderate depression in the analysis.[20] HRV measurement also was inconsistent, contributing to a continuing challenge for use of HRV in the clinical setting. There is need for a common language, meaningful to bioengineers and clinicians alike, to help advance validity and reliability of measurements. Clear communication about the import and applicability of findings is essential.

The different methodologies confound the ability to compare the findings. For example, Guinjoan used short 5-10 minute recordings and found significant associations between depression and short-term time domain HRV measures[18] while Catipović-Veselica examined 24-hour recordings and found significant associations between depression and long-term HRV measures.[20] Vigo sought to view short-term recordings in light of nonlinear dynamics.[19] The 3 studies – while all focused on the relationship between depression and HRV in ACS – may have captured different phenomena, or isolated portions of the same phenomenon. Nonetheless, the researchers' works are commendable, potentially contributing to better assessment tools that lead to innovative interventions for improving ACS outcomes.

Exploring the Relationships between Heart Rate Variability and Depression

Carney et al hypothesized that HRV mediates the effect of depression, and designed a study to identify this effect in post-MI patients.[21] The investigators proposed

that the effect of HRV would be to mediate the pathway between depression and time to death in ACS patients. The study was a secondary analysis of the Enhancing Recovery in Coronary Heart Disease (ENRICHD), a multicenter clinical trial. Consenting patients were screened 4 weeks after ACS hospitalization using the Beck Depression Inventory (BDI) and structured interviews. Cognitive impairment and severe illness were exclusion criteria. Patients were considered depressed if they met criteria for major or minor depression per the DSM-IV. Twenty-four-hour Holter monitors were used to obtain HRV. VLF was chosen for the HRV reference measure, and a risk score was derived from factors related to all-cause mortality, such as age, diabetes, and left ventricular ejection fraction, based upon the authors' previous research [17] Follow-up occurred after 6 and 30 months. All-cause mortality was the primary endpoint; 47 out of 678 patients died.

VLF power was significantly lower in depressed compared to nondepressed patients in univariate analysis. The relationship stayed significant after adjustment with the risk score. In analysis of proportional hazard across time, inclusion of VLF was found to alter the risk of mortality related to depression. Overall, the proportion of the hazard of depression related to mortality risk attributed to VLF was 27%. The researchers concluded that low HRV is a partial mediator on the effect of depression in MI patients' survival. This study built upon the authors' previous work in which autonomic dysfunction was proposed as a potential physiological mechanism linking depression with increased mortality after MI.[14,40,41] The sample size was large, drawn from 4 university-affiliated medical centers in the eastern United States. Procedures were clearly reported, and HRV measurement was standardized across the sites, supporting internal validity. While only one HRV variable was reported, an evidence-based rationale was provided. The sickest patients were excluded, so results could reflect a healthier population of acute MI patients, limiting generalizability.

Drago et al sought to determine if depressed ACS patients demonstrate cardiac

autonomic dysfunction, measured by HRV, and whether autonomic dysfunction was a mediating effect on depression in patients' 5-year prognosis.[22] Primary endpoints were recurrence of MI, need for revascularization, death, or a composite adverse event, including any of the 3. The investigators consecutively enrolled 100 acute MI patients at an Italian medical center. Psychiatric interviews and a self-administered BDI were used to screen for depression 7-14 days after admission. HRV was measured using 24-hour Holter monitors prior to hospital discharge. SDNN was computed. DSM-IV criteria were used to diagnosis patients major depressive disorder (MDD), or mild to moderate depression. SDNN was significantly lower at baseline in patients with major depression ($p<.01$) or mild to moderate depression ($p=.01$) compared to those who were not depressed. Over 5 years, 30 adverse events occurred, including 6 deaths. In univariate analyses, SDNN was associated with adverse events, but it was not an independent contributor in a multivariate regression. Depression was a significant contributor to all adverse outcomes in multivariate analysis with age and gender ($p=.04$). The authors concluded that depressed post-MI patients exhibited cardiac autonomic dysfunction, reflected by decreased SDNN.

The strength of this study lies in its consecutive, prospective enrollment of patients, long-term follow-up, and low attrition rate; 98 participants were followed until death or thorough 5 years. SDNN was appropriately obtained by means of 24-hour Holter recording. However, the small sample size and few deaths limit power to assess mortality as an outcome. A strong conclusion about the mediator role of autonomic dysfunction in mortality of depressed MI patients needs to be based upon a clear theoretical model, which this study lacked. Measurements at only one time point may limit evaluation of change. Measuring HRV and depression at multiple time points could yield more information regarding a mediating effect.

Glassman et al studied the influence of sertraline (selective serotonin reuptake

inhibitor; brand name: Zoloft) and mood improvement on HRV in ACS patients using data from the Sertraline Antidepressant Heart Attack Randomized Trial (SADHART), an international, multicenter clinical trial.[23] Patients with clinical risk factors, such as hemodynamic instability, severe heart failure, or suicide ideation, were excluded. Participants were provided with psychiatric screening. The Hamilton Depression Rating Scale was used to measure depression severity; patients diagnosed with MDD were recruited for continuing participation and then were randomly selected to receive either sertraline or a placebo. HRV was assessed 3 weeks after hospitalization (baseline) and at 16 weeks using 24-hour ECG recordings. Frequency domain measures, HF, LF, VLF, and ULF were obtained. Mood change was assessed with the Clinical Global Impressions score, a scale that measures disease severity and improvement attributed to treatment response.[42] Paired analyses of ECG recordings were performed for 258 patients.

Contrary to previous research showing recovery of HRV indices in the months following MI,[43] neither group showed an improvement in HRV after 16 weeks. ULF was significantly lower in the placebo group ($p<.05$) and LF was significantly lower in the sertraline group ($p<.05$). However, when the two groups were compared with each other, ULF power was significantly higher in the sertraline group because ULF was so low in the placebo group. Therefore, higher HRV was associated with administration of sertraline and better mood.

In addition, comparison of patients' moods, independent of treatment, showed that mood improvement was closely associated with higher LF power, but not statistically significant. Low LF in patients whose mood did not improve was the primary driver in this association. The investigators concluded that depression impairs HRV recovery after MI. The large sample size, spanning centers in North America, Europe, and Australia, supported external validity. HRV was analyzed at one core research laboratory, aiding

consistency in measurement.

Canadian researchers **Frasure-Smith et al** investigated connections between HRV, inflammation, and depression. Resting, morning measures of 3 HRV indices (SDNN, HF, and LF) and 2 inflammatory biomarkers (IL-6 and C-reactive protein) were examined in relation to the level of depressive symptoms in 682 post-ACS patients.[24] Data originally were collected for the Epidemiological Study of Acute Coronary Syndromes and Pathophysiology of Emotions (ESCAPE). Depressive symptoms were measured using the BDI, and patients were assessed for MDD in interviews with psychologists. HRV indices, measured in 20-minute ECG recordings, and inflammatory markers were obtained during follow-up visits 2 months after hospitalization.

Patients were categorized as depressed or nondepressed; 47 met criteria for MDD. Analysis of HRV and depressive symptoms did not reveal significant associations. However, SDNN, LF, and HF were significantly correlated with IL-6 in univariate analysis, and remained significant when adjusted with clinical factors (such as age, gender, and previous MI). All 3 HRV variables were significantly related to C-reactive protein in univariate analysis; only SDNN remained significant in the multivariate model ($p=.044$). Correlations between HRV and inflammatory markers, especially C-reactive protein, became stronger in association with greater depression. In patients with higher depression scores, HRV accounted for 4-5% of the variance in C-reactive protein in multivariate analysis. The authors concluded that HRV and inflammatory markers are elevated in association with post-MI patients' depression. This study built upon the investigators' previous work examining post-MI depression,[10] and the findings were consistent with other studies showing a relationship between inflammation and reduced HRV.[38,44,45] While long-term time domain indices, such as SDNN, ideally need to be measured using ≥18 hours of ECG data to assure accuracy,[5] the multivariate approach strengthened the analysis.

These 4 studies explored relationships, encouraging steps toward comprehending factors that underlie the relationship between HRV and depression in ACS. Three studies were secondary analyses of large clinical trials with many participants. While Drago's study was small in comparison, the data collection was prospective and consecutive. Carney and Drago came to disparate conclusions about the mediating effect of HRV (using different measures) on depression in mortality, indicating that additional research is warranted. Glassman's team found that a decline in cardiac autonomic functioning post-ACS might be tempered by an appropriate mood-enhancing intervention. The study by Frasure-Smith et al suggests the possibility of a mediating effect between HRV and inflammation in depressed ACS patients. These studies lay groundwork for increased insight into pathways that could assist in ACS patients' recovery.

Summary

The HRV and depression in ACS studies were either prospective and observational or retrospective analyses of clinical trials. Weight of evidence shows a significant relationship between HRV and depression in ACS patients with an impact on prognosis. However, the findings were not uniform. The differences likely reflect the dissimilarities in study design and methodology, representing a challenge for comparisons across studies. Sample sizes ranged widely from 52 to 682 participants.[19,24] Three studies analyzed data for ≤100 ACS patients, indicating low statistical power, potentially, leaving true differences undetected.[18,19,22] In addition, the corresponding physiology that HRV represents is not obvious, and no one approach to HRV measurement is considered to be ideal.[13] There are several methods for measuring depression as well. While all studies used interviews and DSM criteria, 3 studies included the BDI [21,22,24] and 3 others used the Hamilton Scale.[18,19,23] One study described only interviews to assess depression.[20] Results can vary widely depending upon

methodology.[12] In addition, cultural perceptions about depression could lead to differences in patients' reporting of symptoms. Nonetheless, the populations represented by these studies were drawn from all over the world. The research represents culturally diverse populations, demonstrates international collaboration, and provides inspiration for future investigation.

Key Points

- Evidence shows an association between HRV and depression in ACS patients, reflecting disruption of autonomic cardiac function.
- Worse outcomes are associated with decreased HRV and depression in post-ACS patients.
- HRV may act as a mediator between depression and mortality in ACS patients.
- HRV and inflammatory markers are elevated in association with depressive symptoms.
- Improved HRV and enhanced mood may be related.

Implications for Cardiovascular Clinicians

An essential component of tertiary prevention is improving outcomes for ACS patients. Early identification of the highest risk ACS patients, such as those with severely disrupted HRV and/or depression could help those who need the most recovery assistance.[46] Measuring HRV along with depressive symptoms during hospitalization could prove to be a useful risk assessment tools in conjunction with established guidelines. Future study aimed toward improving ACS care could investigate the cost-effectiveness of adding noninvasive HRV measurement to patients' plans of care. Examining interventions to improve ACS patients' HRV indices and depressive symptoms is a logical next step. Promising research toward this end is already underway, including evidence that practice of Tai Chi heightens mood,[47] improves HRV,[48] and enhances cardiovascular outcomes.[49]

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Table 1: Definitions of Frequently Used Heart Rate Variability (HRV) Measurements	
Variable Abbreviation	**HRV Definitions (unit of measurement)**
Time Domain Variables: Measured using descriptive statistics (5, 27)	
Long-Term Time Domain Measures:	
SDNN	Standard deviation of all normal R-to-R (NN) intervals over usually measured over ~24 hours (ms) [estimates global heart rate variability power; corresponds to total power]
SDANN	Standard deviation of the average normal R-to-R (NN) intervals in all 5-min segments usually measured over ~24 hours (ms) [corresponds to ULF]
SDNN index	Mean of the standard deviations of normal R-to-R (NN) intervals in all 5-minute segments over ~24 hours (ms} [corresponds to mean of 5-minute segments of total power]
Short-Term Time Domain Measures:	
rMSSD	Square root of the mean of squares of the differences between successive normal R-to-R (NN) intervals (ms); referred to as **rMSNN** in study by Guinjoan et al (17) [corresponds to HF]
pNN50*	Percentage of normal R-to-R intervals that are >50 ms different from previous normal R-to-R during recording time (%) [corresponds to HF]
Frequency Domain Variables: Measured using spectral analysis (5, 27)	
TP*	Total power, estimates global power, i.e. HF, LF, VLF, and ULF measured over ~24 hours (ms^2)
HF*	Average of 5-min segments of high frequency power for total recording time (ms^2); HF reference range = 0.15-0.4 Hz
LF*	Average of 5-min segments of low frequency power for total recording time (ms^2); LF reference range = 0.04-0.15 Hz
VLF*	Very low frequency power, averages of 5-minute segments measured over the total recording time (ms^2); VLF reference range =0.003-0.04 Hz
ULF*	Ultra low frequency power measured over ~24 hours (ms^2); ULF reference range ≤ 0.003 Hz
LF/HF*	Average of 5-min segments of normalized low/high frequency ratio: LF/(Total Power – VLF) x 100] divided by [HF/(Total Power – VLF) x 100]
Nonlinear Measures (9, 29, 33-36)	
ApEn	Approximate entropy: measure of randomness or disorder within a system; calculation of the logarithmic likelihood that patterns that are similar remain similar in the next incremental comparisons
DFA1	Detrended Fractal Analysis: Short-term fractal scaling exponent calculated over 3-11 beats, averaged over 1000 beats for 24 hours, also known as $\alpha 1$, reported as an exponent value)
SD12 **SD1, SD2**	**SD12**, SD1, and SD2 are derived from the Poincare plot (a scatter plot in which each R-R interval is plotted against the next R-R interval). SD12 is the ratio of the dispersion, or standard deviation, of the plot's perpendicular axis, indicating short-term, instantaneous beat-to-beat variance [known as **SD1**], versus the standard deviation of the plot's diagonal axis, indicating long-term, continuous variance [known as **SD2**] Note: While the SD1/SD2 ratio is a nonlinear measurement, SD1 and SD2 are linear measurements, when calculated alone. SD1 correlates precisely with rMSSD
* Natural log transformations are often performed for these variables, which usually are not normally distributed	
Note: Terms "variables," "measures," "measurements," and "indices" are often used interchangeably in referring to HRV.	

Table 2. Summary of Articles about Heart Rate Variability and Depression as related to Acute Coronary Syndrome

Author (date)	Sample	HRV Measurement	Design / Outcome Measure	Significant Results
Category 1: Substantiating the Relationship				
Guinjoan et al, 2004 (18)	n=56 ACS patients ≥60 years old, in CCU	Derived from 550 heartbeats: pNN50, SDNN, rMSSN, TP. HF, LF, LF/HF	• Cross-sectional. • Differences in HRV and depression scores between depressed and nondepressed patients ≤72 hours of admission	• n=19 depressed • pNN50 (p=.006), rMSNN (p=.009) and HF (p.024) lower in depressed patients compared to non-depressed patients
Vigo et al, 2004 (19)	n=52 ACS patients ≥60 years old, in CCU	Recorded over ~10 minutes: ApEn, DFA1, SD1	• Cross-sectional • Differences in nonlinear HRV measures in depressed patients ≤72 hours of ACS admission	• n=19 depressed • Depression associated with altered patterns of SD1 (p=.001), DFA1 (p=.023), and ApEn (p=.046)
Catipović-Veselica et al, 2007 (20)	n=297 ACS patients in CCU	Recorded over 24 hours: SDANN, SDNN, SDNN index	• Cross-sectional • Differences in HRV and clinical variables between those with and without depression at time of discharge	• n=79 major depression • n=87 minor depression • SDNN, SDANN, SDNN index lower (p<.05) in minor or major depression in univariate analyses
Category 2: Exploring the Relationships				
Carney et al, 2005 (21)	n=678 MI patients in CCU	Recorded over 24 hours: VLF (log)	• Longitudinal • Changes in HRV and depression associated with all-cause mortality, at 28 days, 6-months and 30 months after discharge	• n=311 depressed • Depression associated with decreased VLF and mortality after adjusting for potential confounders (p<.001)
Drago et al, 2007 (22)	n=100 consecutive acute MI patients in CCU	Recorded over 24 hours: SDNN	• Longitudinal • All-cause mortality starting 7-14 days after admission • Recurrent MI or require further revascularization ≤ 5 years	• n=15 major depression • n=35 mild-to-moderate depression • HRV lower in major (p<.01) and mild-to-moderate depression (p=.01)
Glassman et al, 2007 (23)	n=258 ACS patients with major depressive disorder	Recorded over 24 hours: HF, LF, VLF, ULF	• Longitudinal • Differences in HRV and depression between groups • Changes in HRV and depression between hospital baseline and 16-week follow-up	• n=258 depressed at follow-up • All HRV measures were low • ULF significantly higher in sertraline group compared to placebo group (p=.02) • LF higher with improved mood (p=.05)
Frasure-Smith et al, 2009 (24)	N=682 ACS patients with follow-up visit	Recorded over 30 minutes: Mean RR, SDNN, HF, LF	• Cross-sectional • Differences in HRV and 2 inflammatory markers (IL-6 and C-reactive protein) in relation to depression, measured 2 months after ACS episode	• n=191 depressed • SDNN, LF, and HF (all p<.001), inversely related to IL-6 and C-reactive protein (all p<.05) in univariate analyses. • Correlation between HRV and C-reactive protein stronger with severe depression (p<.05).

Abbreviations:

ACS = acute coronary syndrome
CCU = coronary care unit
HRV = heart rate variability
Log = natural logarithm transformation
MI = myocardial infarction
**** See Table 1 for heart rate variability (HRV) definitions***

Chapter 3

Article 2 – Heart Rate Variability Measured Early in Patients with Evolving Acute Coronary Syndrome Predicts One-Year Outcomes of Rehospitalization and Mortality

Chapter 3

Heart Rate Variability Measured Early in Patients with Evolving Acute Coronary Syndrome Predicts One-Year Outcomes of Rehospitalization and Mortality

Short Title: **Heart Rate Variability in ACS**

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Abstract

Objective: This study sought to examine the prognostic value of heart rate variability (HRV) measurement initiated immediately after emergency department (ED) presentation for patients with acute coronary syndrome (ACS).

Background: Altered HRV has been associated with adverse outcomes in heart disease, but value of HRV measured during the earliest phases of ACS related to risk of 1-year rehospitalization and death has not been established.

Methods: Twenty-four hour Holter recordings of 279 patients with ACS were started within 45 minutes of ED arrival; recordings with ≥18 hours sinus rhythm were selected for HRV analysis (N=193). Time domain, frequency domain, and nonlinear HRV were examined. Survival analysis was performed.

Results: During the 1-year follow-up, 94 patients were event-free; 82 readmitted; 17 died. HRV was altered in relation to outcomes. Predictors of rehospitalization included increased normalized high frequency power, decreased normalized low frequency power and decreased low/high frequency ratio. Normalized high frequency >42ms^2 predicted rehospitalization while controlling for clinical variables (hazard ratio [HR]=2.3, 95% confidence interval [CI]=1.4–3.8, p=.001). Variables significantly associated with death included natural logs of total power and ultra low frequency power (ULF_{log}). A model with ULF_{log}<8 milliseconds^2 (HR=3.8, 95% CI=1.5–10.1, p=.007) and troponin>.3 nanograms/milliliter (HR=4.0, 95% CI=1.3–12.1, p=.016) revealed that each contributed independently in predicting mortality. Nonlinear HRV variables were significant predictors of both outcomes.

Conclusions: HRV measured close to ACS onset may assist in risk stratification. HRV cutpoints may serve as useful prognostic indicators, providing additional incremental information to established assessment guidelines.

Key Words

Heart rate variability

Autonomic cardiac function

Acute coronary syndrome

Hospital readmittance

Mortality

Abbreviations and Acronyms **Note: See Table 1 for full definitions of HRV variables**
ACS = acute coronary syndrome CABG = coronary artery bypass graft CAD = coronary artery disease CI = confidence interval ECG = electrocardiography ED = emergency department HR = hazard ratio (ratio of incident rates; estimates relative risk) HRV = heart rate variability (HRV variables are defined in Table 1) $_{log}$ (subscript) = natural log transformation MI = myocardial infarction ml = milligrams ng = nanograms nu = normalized units

Introduction

Identification of patients at increased risk for rehospitalization or death within a year of presenting to the emergency department (ED) with acute coronary syndrome (ACS) can help guide ongoing therapy. Safe, cost-effective and readily available tools to aid risk assessment are needed. Heart rate variability (HRV) is a measure derived from noninvasive cardiac monitoring that reflects autonomic cardiac function (1-2) and may provide insight into patients' ability to recover from physiological insult, such as myocardial infarction (MI) or episode of unstable angina (UA). In a 1987 study by Kleiger and colleagues, the standard deviation of normal sinus R-to-R intervals (SDNN), measured using 24-hour Holter recordings, was associated with all-cause death in the post-MI population (3). Subsequent research has supported the association of decreased HRV and mortality in patients with cardiovascular disease (4-8). Less is known, however, about the prognostic value of HRV measurement initiated within the first hour of ED presentation during the earliest phases of ACS, particularly in association with risk of rehospitalization.

The primary aims of this study were to answer the following questions in patients presenting to the ED with ACS:

1. Is HRV measured during the 24 hours after ED arrival predictive of 1-year all-cause:
    a. rehospitalization; or
    b. death?
2. Which HRV variables, if any, may serve as clinically useful tools to aid in risk stratification for ACS patients over the course of one follow-up year?

Methods

Research Design and Sample. A secondary analysis was performed of

electrocardiographic (ECG) data from the Ischemia Monitoring and Mapping in the Emergency Department In Appropriate Triage and Evaluation of Acute Ischemic Myocardium (IMMEDIATE AIM) study, a prospective clinical trial of patients who presented to the ED of a large urban hospital with symptoms of ACS (N=1308). We enrolled patients from 2002 to 2004. Each patient was followed for one year, and the study ended in 2005. Patients' verbal assent was obtained in the ED, and written consent was obtained from the patient or patient's surrogate after he or she stabilized. The University of California, San Francisco (UCSF) institutional review board approved the study.

Data Collection. Twenty-four hour Holter recorders (H-Scribe System, Mortara Instrument, Milwaukee, WI) were placed within minutes of ED arrival (median "door-to-Holter" time, 44 minutes). Sampling rate was 180 samples/second. Research nurses applied ECG leads, supervised monitoring, and downloaded data to the H-Scribe review station. Radiolucent electrodes and lead wires were used to aid uninterrupted monitoring. Patients' demographic and clinical information was gathered upon enrollment or extracted later via chart review.

Follow-up. Nurses followed patients for one year after their ED visit. Discharge diagnoses, determined in accordance with criteria of cardiovascular disease in the International Statistical Classification of Diseases and Related Health Problems, were identified from medical records. Data regarding patients' hospital readmissions and survival were collected via telephone calls, medical records, and the public access social security mortality database. One-year survival and rehospitalization information was obtained for all patients in the current analysis.

Inclusion Criteria. Recordings with no less than 18 hours of analyzable sinus rhythm, representing unique patients, admitted to the hospital for ST elevation MI or rule

out of MI (due to ST-elevation, ST-depression, inverted T-waves on initial 12-lead ECG, positive cardiac troponin, and/or persistent symptoms consistent with ischemic chest pain), and positively diagnosed with ACS by time of hospital discharge were selected (N=193). Figure 1 is a flowchart of the inclusion process.

Endpoints. Primary outcomes were all-cause rehospitalization or death between ED discharge and end of follow-up. Patients who returned to the hospital and subsequently died before year's end were assessed within analyses of the hardest endpoint. Rehospitalizations and/or deaths due to cardiac causes also were documented.

Demographic and Clinical Variables. Variables chosen for analysis included established risk factors (9) and potential confounders of outcomes. Age was examined both as a continuous variable and categorical variable, dichotomized at 65 years per the Thrombolysis in Myocardial Infarction risk score (9). MI and UA diagnoses were examined together, and then separately, in relation to HRV variables and outcomes.

Heart Rate Variability Analysis. ECG recordings were automatically scanned and manually edited using H-Scribe analysis software at the ECG Monitoring Research Laboratory, UCSF, School of Nursing. HRV research software validated by the Heart Rate Variability Laboratory, Washington University School of Medicine, St. Louis, Missouri, verified eligible recordings, and computed time domain, frequency domain, and nonlinear variables.

Time-domain measurements were computed using descriptive statistical methods. Fast Fourier transform spectral analysis evaluated HRV variables in the frequency domain.

To assess nonlinear HRV properties, two variables were selected, the short-term fractal-scaling exponent (DFA1) and the Poincaré ratio (SD12). DFA1 was computed

using detrended fluctuation analysis, a method that takes into account changing conditions over time and is applicable to analysis of physiologic signals (10-12). Poincaré plots are graphic representations of coordinates corresponding to consecutive normal R-R intervals, and were generated for each patient to visualize HRV organization and explore nonlinear HRV characteristics. The Poincaré ratio is the ratio of axes of an ellipse fitted to the plot (SD1=short axis/SD2=long axis, ratio=SD12), reflecting short-term, beat-to-beat variation compared to long-term, continuous variation (7,14-15).

HRV variables chosen for analysis were based upon published standards (1) and previous research (3-8,10-19). HRV definitions and additional details are in Table 1.

Statistical Analyses. Descriptive statistics assessed demographic and clinical variables. Variables without normal distribution were transformed using natural logs (7,19). Discharge diagnoses of UA or MI in relation to outcomes were examined using Chi Square.

Simple Cox regression survival analyses were performed for each HRV, demographic, and clinical variable to assess proportional hazard across time. Variables with $p<.10$ were included in multivariable analyses. HRV variables were retested in models with demographic and clinical risk factors ($alpha<.05$). Highly correlated variables ($r\geq.7$) were not tested within the same model.

To identify meaningful HRV cutpoints in relation to outcomes, receiver-operator curves were generated. High sensitivity and specificity provided a reference value for systematically assessing variables in relationship to each outcome by maximizing log likelihood in simple Cox regression analyses. In multivariate models, age and gender were retained as potentially relevant predictors and backward elimination further assisted in identifying the most significant prognostic contributors. Significant categorical HRV variables were examined and tested for interactions with covariates. Bootstrapping

(1000 samples, 95% confidence interval) was used to examine model stability (alpha<.05) (20). Harrell's Cumulative Index (C-statistic) was calculated to evaluate models' predictive ability. Analyses were performed using IBM statistical software (SPSS 19, Armonk, NY).

Results

Patient Characteristics and Outcomes. Median ECG recording time was 1439 minutes. Median follow-up for survivors was 369 days. Patient characteristics are in Table 2. Ninety-four patients (48.7%) had event-free outcomes. Eighty-two patients (42.5%) were readmitted for any cause; 67 had a cardiac diagnosis (82% of readmissions). Of the 15 patients who were readmitted for any cause, but not cardiac related, 9 had a comorbidity of diabetes. Seventeen patients (8.8%) died, 13 due to cardiac causes (76.5% of deaths).

Chi Square analysis revealed that all-cause death within one year was significantly more prevalent in patients diagnosed with MI as opposed to those with UA (p=.003; odds ratio 4.372, 95% CI 1.536-12.444). However, ACS diagnostic group was not a significant factor in prevalence of all-cause rehospitalization. Similarly, Chi Square analysis did not show cardiac death or cardiac rehospitalization to be significantly related to ACS diagnosis.

Significant univariable Cox Regression results for demographic and clinical variables are in Table 3.

Continuous HRV and 1-Year Rehospitalization. Simple Cox regression analyses demonstrated that decreased normalized low frequency (NLF), low/high frequency ratio (LF/HF), natural log of very low frequency (VLF_{log}), and DFA1 were significant predictors of all-cause rehospitalization, as were elevated normalized high frequency (NHF) and SD12 (Table 4). Simple Cox regression analyses also showed that

when hospitalization was limited to those who were admitted for cardiac causes (67 events, no deaths) decreased NLF (hazard ratio [HR]=.983, 95% confidence interval [CI]=.968-.997, p=.021), decreased natural log of the low-to-high frequency ratio (LF/HF_{log}) (HR=.688, 95% CI=.498-.950, p=.023), and increased NHF (HR=1.026, 95% CI=1.006-1.046, p=.012) remained significant predictors. Other HRV variables were not significantly different in relation to rehospitalization outcomes.

In Chi Square analyses of the 15 patients rehospitalized for a noncardiac reason, diabetes diagnosis was significantly related to hospital readmission (Pearson Chi Square, 14.614, p<.001).

NHF, NLF, LF/HF, DFA1, and SD12 continued to be significant predictors in conjunction with age, gender, living situation, diabetes, and history of coronary artery disease (CAD) in multivariable analysis. Predictive power ranged from 74% to 76% (Table 5). When patients diagnosed with UA were examined alone in the multivariate Cox Regression model, continuous NHF was a significant independent predictor of all-cause rehospitalization (p=.028).

Continuous HRV and 1-Year Mortality. In simple Cox Regression analyses, lower standard deviation of the average of normal R-to-R intervals in all 5-minute segments (SDANN), natural logs of total power (TP_{log}) and ultra low frequency power (ULF_{log}), and DFA1 were significantly associated with death. Higher SD12 also was significantly associated (Table 4). Other HRV variables were not significantly different in conjunction with survival. In examination of mortality with UA patients alone, HRV was not a significant predictor.

HRV Cutpoints and 1-Year Rehospitalization. A receiver operator curve showed that area under the curve (AUC) for NHF was .67 (p=.041) with higher values associated with rehospitalization. Systematic assessment of cutpoints using simple Cox regression

revealed the log likelihood was maximized at NHF=42 normalized units (nu) (HR=2.60, 95% CI=1.66-4.07, p<.001). Chi Square analysis showed that this cutpoint had sensitivity of 39%, specificity 88%; positive predictive value 74%; negative predictive value 63% (Chi Square=17.708, p<.001). Tested in the same manner, lower NLF was associated with rehospitalization, AUC=.67 (p=.040). NLF<50nu maximized the log likelihood (HR=1.975, 95% CI=1.28-3.05) of rehospitalization. Sensitivity was 70%; specificity 51%; positive predictive value 62%; negative predictive value 60% (Chi Square=8.398, p=.004). This method also identified LF/HF_{log} ratio, DFA1, and SD12 cutpoints; multivariate Cox regression analysis results are in Table 5.

HRV Cutpoints and 1-Year Mortality. HRV cutpoints associated with mortality were determined in similar fashion to those for rehospitalization. In simple Cox Regression models, low SDANN<53ms (HR=3.654, 95% CI=1.390-9.603, p=.009), TP_{log}<8.4ms^2 (HR=3.71, 95% CI=1.43-9.62, p=.007), ULF_{log}<8.0ms^2 (HR=3.70, 95% CI=1.39-9.60, p=.009), and high SD12>0.45 ratio (HR=3.358, 95% CI=1.296-.8.706, p=.013) were significant predictors of all-cause 1-year mortality.

Clinical Risk Model for 1-Year Rehospitalization. An interaction was found between NHF dichotomized at 42nu and diabetes (HR=2.667, 95% CI=1.08-6.62, p=.034). The consistency of the interaction remained significant when diabetes was tested using NHF as a continuous variable (p=.008). Combining NHF dichotomized at 42nu and diabetes created a variable with 4 categories. Cox regression analysis showed that patients with either NHF>42nu or diabetes were more likely to return to the hospital than patients without either of those conditions. Patients with both conditions were even more likely to return (Figure 2).

Similarly, patients with history of CAD and NLF<50nu were more likely to be rehospitalized than patients without either condition or with one condition alone (Figure 3).

Clinical Risk Model for 1-Year Mortality. Patients diagnosed with MI were at higher risk for mortality according to our Chi Square findings leading us to an examination of HRV in conjunction with cardiac troponin. In a Cox Regression model, ULF_{log}<8 ms^2 (HR=3.822, 95% CI=1.452-10.060, p=0.007) and peak troponin I >.3 nanograms/milliliter (ng/ml) (HR=3.956, 95% CI=1.288-12.144, p=0.016) were strong independent predictors of death (Model Chi-Square=14.625, p=0.001). Peak cardiac troponin of >.3 ng/ml was used as the cutpoint for analysis per the local laboratory standard definition of myocardial injury at the time of data collection.

In a second analysis, dichotomized ULF_{log}<8 ms^2 and peak troponin >.3 ng/ml were categorized into 4 groups (low to high risk) and served to examine the relationship of these variables with all-cause death (Figure 4). Fourteen out the 17 nonsurvivors, including 10 of 13 cardiac deaths, were identified by values of ULF_{log} <8ms^2 and/or troponin>0.3ng/ml. Presence of the two variables together proved to be a stronger predictor of death than either variable alone.

SDANN<53ms (HR 3.63, 95% CI 1.38-9.55, p=0.009) and cardiac troponin>0.3 ng/ml (HR=3.79, CI=1.24-11.64) (model Chi Square=14.197, p=0.020) provided another predictive model for all-cause mortality (model Chi Square, p=.001), as did TP_{log}<8.4ms^2 (HR=3.65, 95% CI=1.41-9.48, p=0.008) and troponin>0.3ng/ml (HR=3.54, 95% CI=1.23-11.53, p=0.021) (model Chi Square=14.559, p=0.001).

Cardiac Outcomes. Seventy-three rehospitalizations and 13 deaths were attributed to cardiac causes. Cox regression analyses revealed that NLF power (p=.006), NHF power (p-.004), LF/HF ratio (p=.006), and DFA1 (p=.031) were significantly associated with cardiac rehospitalization in univariate analysis. NHF power (p=.031) and LF/HF ratio (p=.047) remained significant in multivariate analyses with age, gender, comorbidity of diabetes, prior history of CAD, and living with significant other. These

relationships remained significant in bootstrap models.

Thirteen deaths within the first year were due to cardiac causes. When cardiac mortality alone was examined, low SDNN (HR=.764, 95% CI=.608-.958, p=.020), SDANN (HR=.712, 95% CI=.536-.946, p=.019), TP_{log} (HR=.298, 95% CI=.123-.718, p=.007), and ULF_{log} (HR=.323, 95% CI=.142-.735, p=.007) were significant predictors. Again, significant relationships were maintained in bootstrap models. Other HRV variables were not significantly different in conjunction with cardiac survival.

Poincaré Plots. Elevated Poincaré ratio, SD12, was a significant predictor of both rehospitalization and death; SD12>.45 was significant for both outcomes. Poincaré plots provided a visual representation of SD12 and HRV organization for each patient. To illustrate organizational differences, plots for three patients are depicted in Figure 5. Each row documents three 1-hour periods during the 24-hour recording time. SD12 for each hour is recorded to the left of each plot. Row A represents an unstable angina (UA) patient who has elevated NHF power and was rehospitalized. The plot is clustered high and to the right. Row B represents a patient diagnosed with non-ST elevation MI who died. The plot is clumped toward the lower left, suggestive of disease (12). Row C represents a patient diagnosed with UA who remained event-free. The plot shape is similar to that of a healthy person (12).

Discussion

Numerous studies have shown that altered HRV is associated with autonomic dysfunction and worse outcomes in patients with cardiac disease (3-8,13-18), and even linked to increased cardiovascular risk in older adults without previously recognized problems (11-2,19). The value of HRV in ACS prognosis has been demonstrated, and HRV is a class IIb recommendation for assessment of ventricular arrhythmias in patients with ST-elevation MI (21). However, it is not included in recommendations for non-ST-

elevation MI or unstable angina. We believe that that the innovation of our study lies in the very early initiation of ECG Holter recording – within the first hour of ED arrival – and demonstrating that HRV measured during the first 24 hours after ED presentation provides an excellent opportunity to obtain this vital information.

Additionally, HRV in relation to ACS patients without MI and their 1-year rehospitalization outcomes deserves further attention. In hospitalized UA patients, Huang et al found that transient ST depression and silent ischemia were associated with lower HRV. Patients who stabilized showed improvement in HRV after admission. SDNN<50ms was significantly associated with 4 deaths during the ensuing 11 months ($p<.0001$) (22). In addition, Carpeggiani et al measured HRV with Holter monitors started 48 ±14 hours after admission in myocardial infarction patients. The main endpoints were in-hospital complications, and low LF power was found to be a significant predictor (6). Lanza et al collected data from 1997 to 2001 using Holter recordings that were started within 24 hours of hospital admission in 543 unstable angina patients (23). Primary endpoints were in-hospital and 6-month deaths, and a secondary endpoint was nonfatal acute MI. The mean of the standard deviations of R-to-R intervals for all 5-minute segments in 24 hours (called the SDNN index) and LF power were significantly associated with in-hospital mortality in multivariate analysis. LF power and the LF/HF ratio were associated with 6-month mortality. HRV was not significantly associated with the nonfatal outcomes.

While evidence shows that HRV can be altered in UA patients, the changes in relation to 1-year outcomes need further investigation. To our knowledge, this is the first study to show that HRV measurements derived from 24-hour Holter recordings started within the first hour of ED presentation in patients with evolving ACS, including both UA and MI diagnoses, are associated with 1-year all-cause rehospitalization and mortality.

One-Year All-Cause Rehospitalization. Hospital readmittance after an ED visit with ACS diagnosis is common and contributes directly to the economic burden of healthcare. Johnston and colleagues studied insurance claims of 30,200 ACS patients between 2002 and 2007; even one cardiac rehospitalization within a year of ED presentation increased direct cost of care by nearly $10,000 (24). Identifying patients with increased risk of 1-year rehospitalization may assist in targeting appropriate care.

Approximately 43% of the ACS patients in our study were readmitted to the hospital for any cause and 38% for a cardiac reason within one year. These figures represent a higher proportion of rehospitalized patients than the 30% reported by Johnston et al. The high percentage of patients with diabetes (28%) may have contributed to this result. Of patients who were rehospitalized for a noncardiac reason, 60% had a comorbidity of diabetes.

While research has shown increased risks other than death in ischemic heart disease patients who have altered HRV, such as in-hospital complications (6), life-threatening arrhythmias (13), and ischemia after coronary artery bypass grafting (CABG) (14), less is known about the connection between HRV and rehospitalization of ACS patients. Our study revealed that increased NHF and SD12 along with decreased NLF, LF/HF ratio and DFA1 were significantly associated with rehospitalization for any cause within 1 year while controlling for demographic and clinical variables, i.e. age, gender, living with a significant other, CAD history, and diabetes comorbidity.

Erratic Rhythm and Rehospitalization. While research has established that HF power usually corresponds to the underlying parasympathetic modulation and respiratory sinus arrhythmia (25), recent findings suggest this may not always be the case (11,15,26). High NHF power in conjunction with low DFA1 in rehospitalized patients is consistent with the finding of erratic rhythm in relation to poorer outcomes, described

by Stein and colleagues. The presence of erratic rhythm may misleadingly elevate values of short-term HRV indices, such as high frequency power (15).

Cardiovascular Health Study (CHS) investigators examined autonomic predictors of cardiovascular death with 24-hour Holter monitoring in 1429 volunteers; 30% of the group had cardiovascular disease. In a subset of CHS recordings, low NLF, LF/HF ratio, and high NHF were associated with low DFA1 and a high degree of disorganized heart rate patterns, as seen in Poincaré plots. CHS investigators found that decreased DFA1 had a strong relationship to 12-year mortality (11). In a study of CABG patients, high SD12 on postoperative day 1 predicted myocardial ischemia on postoperative day 2 ($p<.01$) (14). Low DFA1 in conjunction with high SD12 may be present when heart rate patterns are irregular, and this beat-to-beat variability may not represent parasympathetic function (15,26). Our comparable HRV findings in ACS patients who were rehospitalized could indicate that a high degree erratic rhythm was present.

One-Year All-Cause Mortality. Our results indicated that abnormal HRV during the very early stages of ACS is prognostic of mortality. We found statistically significant associations with death and low SDANN, ULF_{log}, TP_{log}, and high SD12.

SDANN<53ms was associated significantly with all-cause death. Relative risk of death was almost 4 times higher for patients with measures below compared to those with measures above that cutpoint. In a study of cardiac resynchronization therapy's effectiveness for improving HRV in 113 heart failure patients, Fantoni et al found that SDANN was the first measure to increase after therapy. Lack of a positive change in SDANN helped identify those who were at increased risk for adverse events, including hospitalization and cardiovascular death (27). In addition, SDANN and ULF correspond to each other mathematically (1), and low ULF_{log} has been significantly associated with mortality in prior research (4).

In a two-year multicenter study (Autonomic Tone and Reflexes After Myocardial Infarction), HRV was examined in 1284 participants who had had an MI within the previous 28 days. SDNN<70 ms was significantly associated with higher mortality over 21-months compared to those with higher values (5). A meta-analysis by Buccelletti et al of 21 studies showed that in MI patients with SDNN<70ms, risk of death was four times higher over three years compared to those with higher SDNN (8). In our study, low SDNN was associated with cardiac death, and total power, which corresponds to SDNN (1), was significantly lower in all nonsurvivors. Patients with TP_{log}<8.4 ms^2 had relative risk of all-cause death nearly 4 times greater than those with higher values.

Our results were in accordance with CAST investigators who found high SD12 was associated with mortality over a year (p=.002) (7).

Identification of Clinically Relevant HRV Variables. Many factors contribute to the complexity of ACS outcomes as clinical practice guidelines for ACS management emphasize (9). We identified several HRV variables that, in conjunction with clinical factors, potentially could serve as useful tools in distinguishing groups of higher risk patients. Specifically, our analysis showed that NHF>42ms^2 and NLF<50ms^2, LF/HF<0.5, DFA1<0.95, and SD12>.45 predicted rehospitalization in a multivariable model including gender, age, living situation, CAD history, and diabetes.

Previous research has provided evidence that HRV can be altered in conjunction with diabetes (28) or heart disease (3-8,13-18). In particular, the presence of an interaction between NHF>42ms^2 and diabetes suggest that risk of adverse outcome with one of these predictors may vary depending upon presence of the other, and risk is highest when both conditions are present. Early assessment of HRV in ACS may provide additional information to determine rehospitalization risk in ACS patients who have diabetes or CAD history. Additionally, our finding that patients with diabetes made

up a large portion of patients readmitted to the hospital for noncardiac causes, may lend support to inclusion of all-cause outcomes in risk assessment.

Finally, we found that identification of abnormal HRV, such as ULF_{log} >8ms^2, TP_{log}<8.4ms^2, or SDANN<54ms, in conjunction with elevated troponin I might aid in assessing prognosis for MI patients. Filipovic et al demonstrated that elevated troponin postoperatively and decreased LF/HF ratio (<2) preoperatively were independent risk factors for 1-year mortality after noncardiac surgery in patients with a CAD history (29). While we found low LF/HF was associated with rehospitalization, our results support the premise that HRV variables serve as indicators of increased risk.

Poincaré Plots. Poincaré plots to aid in detecting low versus high risk patients potentially could serve as an adjunct tool (15,25). Huikuri and colleagues used Poincaré plots to distinguish abnormalities in post-MI patients with history of ventricular arrhythmia compared to a post-MI group without that history. After an episode of ventricular tachycardia (VT) induced via electrical stimulation, researchers noted the group in which VT was provoked displayed abnormal patterns in the hour prior to development of the arrhythmia (13). We found that Poincaré plots of patients who were rehospitalized or died varied from those who were event-free, and displayed patterns associated with poorer outcomes. The plots provided a visual reference, and an illustration may be useful (Figure 5).

Implications. HRV has become recognized as a reflection of cardiac autonomic modulation (2,30). Mechanisms behind the physiological interplay between the sympathetic and parasympathetic branches – along with the role of HRV patterns in prognostication of health and disease – warrant continuing investigation.

Practice standards recommend 24 hours of cardiac monitoring for ACS patients after ED presentation (29). Our Holter findings suggest that use of HRV measurements

to assist in identifying patients at highest risk for adverse events might be a practical addition to continuous ECG monitoring. Studies to examine cost effectiveness of HRV measurements incorporated into routine cardiac monitoring of hospitalized ACS patients could be a reasonable next step.

Limitations: This was a retrospective analysis of data collected between 2002 and 2004, and practice standards have changed during the ensuing years. Only 193 of 279 ACS patients had sufficient ECG recording time and analyzable signals, reflecting potential challenges in obtaining accurate data for assessment. High and low frequency power were measured in 5-minutes segments and averaged over the entire recording time. It was not possible to control for all potentially confounding factors. Conclusions about HRV in relation to mortality are tempered by low power.

Conclusions: Ten of the 12 HRV variables in our analysis served as indicators of 1-year all-cause rehospitalization or death. There are a variety of HRV measurement methods, and these could be complimentary (2). Our findings further suggest that there is not one primary HRV variable to indicate future vulnerability, but that abnormal HRV needs to be considered as an array, and viewed within the context of the patient's whole clinical profile. Time domain, frequency domain, and nonlinear HRV in conjunction with clinical indicators have potential for assisting in risk stratification of ACS patient subgroups, such as those with diabetes or prior CAD. HRV measured close to ACS symptom onset could provide additional useful information to assess ACS patients' risk of rehospitalization and/or death within one year of ED presentation.

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Table 1: Definitions of Heart Rate Variability Variables Computed for this Study	
Variable Abbreviation	**Definition (units)** **(All variables are computed over entire recording time of approximately 24 hours)**
Time Domain Variables (1,2)	
SDNN	Standard deviation of all normal R-to-R intervals (ms)
SDANN	Standard deviation of the average of normal R-to-R intervals in all 5-min segments (ms)
Frequency Domain Variables (1,2)	
TP_{log}*	Total power (ms^2}
HF_{log}*	Average of 5-min segments of high frequency power (ms^2}
LF_{log}*	Average of 5-min segments of low frequency power (ms^2}
VLF_{log}*	Very low frequency power, averages of 5-minute segments (ms^2}
ULF_{log}*	Ultra low frequency power (ms^2}
NHF**	Normalized 5-min intervals of high frequency power (nu)
NLF**	Normalized 5-min segments of low frequency power (nu)
LF/HF_{log}*	**Average of 5-min segments of normalized low/high frequency ratio (ratio)
Nonlinear Measures (6,8,10-12)	
DFA1	Detrended Fluctuation Analysis: Short-term fractal scaling exponent calculated over 3-11 beats, averaged over 1000 beats for 24 hours, also known as alpha 1 or α_1 (exponent value)
SD12	Poincaré Ratio: From Poincaré plot, ratio of the dispersion, or standard deviation, of perpendicular axis, indicating short-term, instantaneous beat-to-beat variance, versus the standard deviation of diagonal axis, indicating long-term, continuous variance, also known as SD1/SD2 ratio (ratio)
Reference Ranges for Frequency Domain Variables (1)	
High Frequency (HF=0.15-0.4 Hz) *Low Frequency (LF=0.04-0.15 Hz)*	*Very Low Frequency (VLF=0.003-0.04 Hz)* *Ultra Low Frequency (ULF≤0.003 Hz)*
* *Natural log transformations were performed for variables that were not normally distributed. Abbreviated subscript "log"*	
** *Normalized units (nu), appropriate for HF and LF only, represent relative value of each power component in proportion to total power without the VLF component* (12). High Frequency nu=100% x HF/(HF+LF). Low Frequency nu=100% x LF/(HF+LF) Normalized high and low frequency domain variables (NLF and NHF) were calculated to assess the proportional value contributed by high and low frequency power to total power without the very low frequency (VLF) and ultra low frequency (ULF) components (1). The low to high frequency ratio (LF/HF) offers similar information to the normalized variables.	
ms=milliseconds	

TABLE 2: DEMOGRAPHIC AND CLINICAL CHARACTERISTICS IN RELATION TO 1-YEAR OUTCOMES

Variable	# All ACS Patients n (% of total N)	All-Cause Outcomes		Event-Free
		Rehospitalized	Died	
N	193	82	17	94
Mean age in years	65±13	66±12	71±17	64±12
Male Gender, n	110 (57%)	40	9	61
Race, n:				
American Indian/Alaska Native	14 (7%)	5	2	7
Black/African American	33 (17%)	23	1	9
Asian & Pacific Islander	54 (28%)	23	3	28
White/Caucasian	92 (48%)	31	11	50
ACS Discharge Diagnosis, n:				
Unstable Angina	130 (67%)	61	6	63
Non-STEMI	43 (22%)	15	7	21
STEMI	20 (10%)	6	4	10
History or Comorbidity, n:				
Diabetes	53 (28%)	32	6	15
Hypertension	144 (75%)	68	12	64
Hypercholesterolemia	130 (67%)	62	11	57
Prior History of Coronary Artery Disease	124 (64%)	61	11	52
Clinical Factors:				
Mean±SD peak troponin I, nanograms/deciliter	10.6±17.9	9.6±17.2	20.5±22.8	9.6±17.1
Mean±SD maximum ST elevation, microvolts [a]	126±110	117±105	203±191	119±90
Mean±SD maximum ST depression, microvolts [a]	-54±80	-47±77	-101±100	-51±76
Chest pain on arrival to emergency department, n	181 (94%)	76	14	91
Enlarged cardiac silhouette on x-ray, n	38 (20%)	22	5	11
Social Factors, n:				
Nonsmoker	156 (81%)	66	12	78
Lives with significant other	142 (74%)	52	12	78
Therapies, n:				
Beta blocker	171 (89%)	73	15	83
Early reperfusion [b]	13 (7%)	2	3	8
Events during Course of Hospitalization, n:				
Percutaneous coronary intervention (not early)	62 (32%)	27	4	31
CABG during course of hospitalization [c]	14 (7%)	5	1	8
Complication during hospitalization [d]	23 (12%)	9	1	13
In-hospital death after emergency department	6 (3%)	0	6	0

Legend for Table 2

[a] Mean maximum ST elevation or depression as measured on initial ED 12-lead electrocardiogram

[b] Early reperfusion refers to thrombolytic or percutaneous coronary intervention within 90 minutes of emergency department (ED) presentation

[c] Coronary artery bypass graft (CABG)

[d] Complications during hospitalization other than death: cardiac arrest; cardiogenic shock; severe heart failure; extension of myocardial infarction; new myocardial infarction; transfer from admission unit due to acute instability

Percentages are rounded to nearest whole number.

Table 3: SIGNIFICANT DEMOGRAPHIC OR CLINICAL VARIABLES AND ONE-YEAR OUTCOMES
Simple Cox Regression Results (<0.10)

Clinical Variable	Adverse All-Cause 1-Year Outcomes	
	Rehospitalization	Died
	Hazard Ratio (95% CI) p-value	Hazard Ratio (95% CI) p-value
Total N	N=176 (no deaths) n with event = 82	N= 193 n with event = 17
Potential Risk Factors		
Age	1.494 (.968-2.308) p=.070[a]	1.405 (.952-2.074) p=.087[b]
Female gender	1.506 (.977-2.323) p=.064	ns
Race: African American	**1.967 (1.213-3.191) p=.006**	.ns
Myocardial infarction	ns	**3.937 (1.456-10.648) p=.007**
Diabetes comorbidity	**2.204 (1.412-3.439) p<.001**	ns
History of coronary artery disease	**1.918 (1.167-3.151) p=.010**	ns
Increased peak troponin (nanograms/milliliter)	ns	**1.290 (1.043-1.594) p=.019**[c]
Increased maximum ST elevation (natural log)	.ns	**1.663 (1.055-2.619) p=.028**
Decreased maximum ST depression*	ns	**1.037 (1.006-1.070) p=.018**
Enlarged cardiac silhouette	**1.764 (1.081-2.878) p=.023**	ns
Early reperfusion	.ns	3.202 (.919-11.151) p=.068
Potential Protective Factors		
Chest pain reported in emergency department	ns	.303 (.087-1.054) P=.060
Living with significant other	**.445 (.283-.699) p<.001**	ns

[a] Hazard ratio is based upon age dichotomized at 65 years per thrombolysis in myocardial infarction (TIMI) risk score (19)

[b] Hazard ratio is based upon ascending age per decade

[c] Hazard ratio is based on nanograms/milliliter ascending in increments of 10 units

ns: not statistically significant
CI: confidence interval
VPC: ventricular premature contractions

Bold identifies significant p-values <0.05

Table 4: SIGNIFICANT CONTINUOUS HRV VARIABLES AND ONE-YEAR OUTCOMES
Univariate Cox Regression Results (<0.10)

Variable Please see Table I for heart rate variability variable definitions	Rehospitalization **Hazard Ratio (95% CI) p-value**	Died **Hazard Ratio (95% CI) p-value**
Total N	N=176 (no deaths) n with event=82	N=193 n with event=17
Heart Rate Variability Variables		
Standard deviation of all normal R-to-R intervals (SDNN}*	.ns	1.176 (.983-1.406) p=.075
Standard deviation of the average of normal R-to-R intervals in all 5-min segments (SDANN)*	ns	**1.253 (1.001-1.567)** **p=.049**
Total Power (natural log)	ns	**2.257 (1.065-4.785)** **p=.034**
Very Low Frequency (natural log)	**1.321 (1.661-1.049)** **p=.018**	.ns
Ultra Low frequency (natural log)	ns	**2.183 (4.425-1.076)** **p=.030**
Normalized Low Frequency*	**1.299 (1.135-1.488)** **p<.001**	.ns
Normalized High Frequency*	**1.434 (1.200-1.713)** **p<.001**	ns
LF/HF ratio (natural log)	**1.706 (1.274-2.283)** **p=.001**	ns
Decreased short-term fractal scaling exponent (DFA1)	**3.257 (1.575-6.711)** **P=.001**	3.968 (.805-19.609) p=.090
Poincaré ratio (SD12)	**4.902 (1.485-16.179)** **p=.009**	**14.378 (1.340-154.221)** **p=.028**
Additional ECG Monitoring Variables		
Mean heart rate*	ns	**1.606 (1.106-2.331)** **p=.013**
Number of VPC over 24 hours (natural log)	**1.320 (1.320-1.500)** **p<.001**	ns

"Decreased" indicates that lower values are associated with increased risk
"Increased" indicates that higher values are associated with increased risk
ns: Not Significant
CI: Confidence Interval
VPC: ventricular premature contractions

Bold signifies significant p-values <0.05)

*Hazard ratio reported as change in increments of 10 units

Table 5: Heart Rate Variability, Clinical Variables & All Cause One-Year Rehospitalization
Continuous & dichotomized heart rate variability and 5 clinical variables
Multivariate Cox Regression and C-Statistic

Clinical variables in models:
Older age, female gender, living with significant other, history of coronary artery disease, diabetes

Variable	Hazard Ratio	95% Confidence interval	p-value	C-Statistic
Normalized Low Frequency* **(lower values linked with higher risk)**	1.253	1.091-1.471	.006	.758
Normalized Low Frequency <50ms^2	*1.721*	*1.071-2.764*	*.025*	*.746*
Normalized High Frequency* **(higher values linked with higher risk)**	1.370	1.121-1.675	.002	.762
Normalized High Frequency >42ms^2	*2.299*	*1.399-3.774*	*.001*	*.765*
Low/High Frequency Ratio **(lower values linked with higher risk)**	1.597	1.134-2.232	.006	.755
Low/High Frequency Ratio <0.5	*1.787*	*1.101-2.902*	*.019*	*7.45*
Short-term fractal scaling exponent (DFA1) **(lower values linked with higher risk)**	3.175	1.321-7.634	.010	.757
Short-term fractal scaling exponent (DFA1) <0.95	*1.776*	*1.096-2.878*	*.020*	*.749*
Poincaré Ratio (SD12) **(higher values linked with higher risk)**	5.408	1.304-22.427	.020	.752
Poincaré Ratio (SD12) >0.45	*1.816*	*1.077-3.060*	*.025*	*.741*

* Reported in increments of 10 units

Italics indicate dichotomized variables

ms=milliseconds

Figure 1: Flow Chart for Inclusion in Analysis of Heart Rate Variability in Acute Coronary Syndrome Study

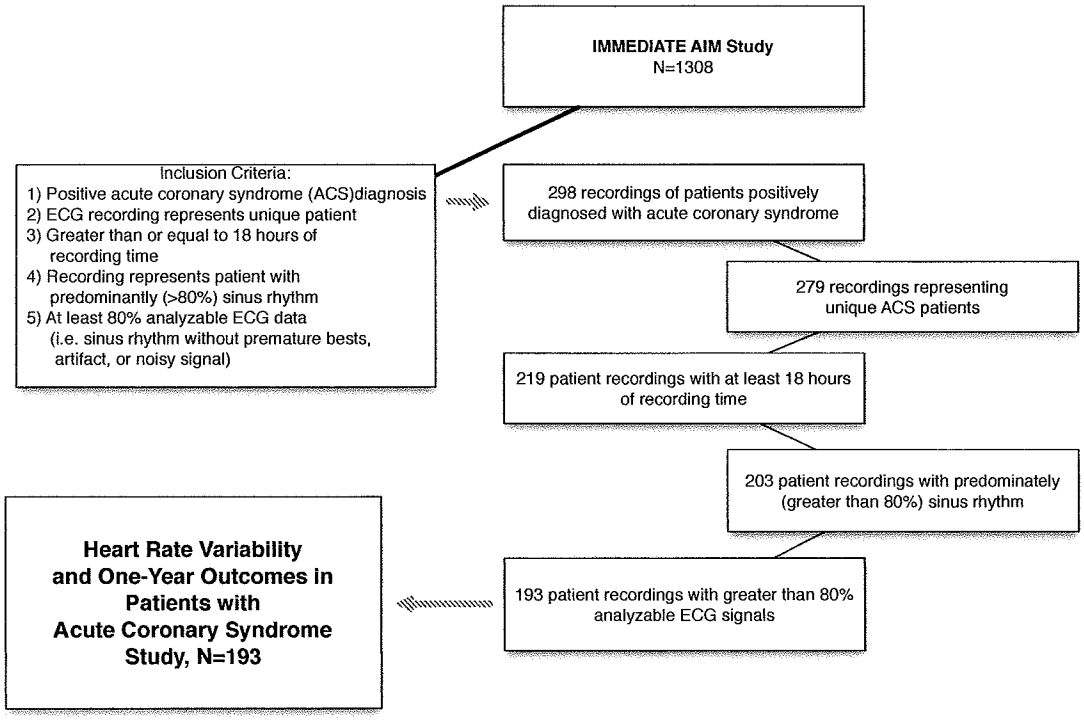
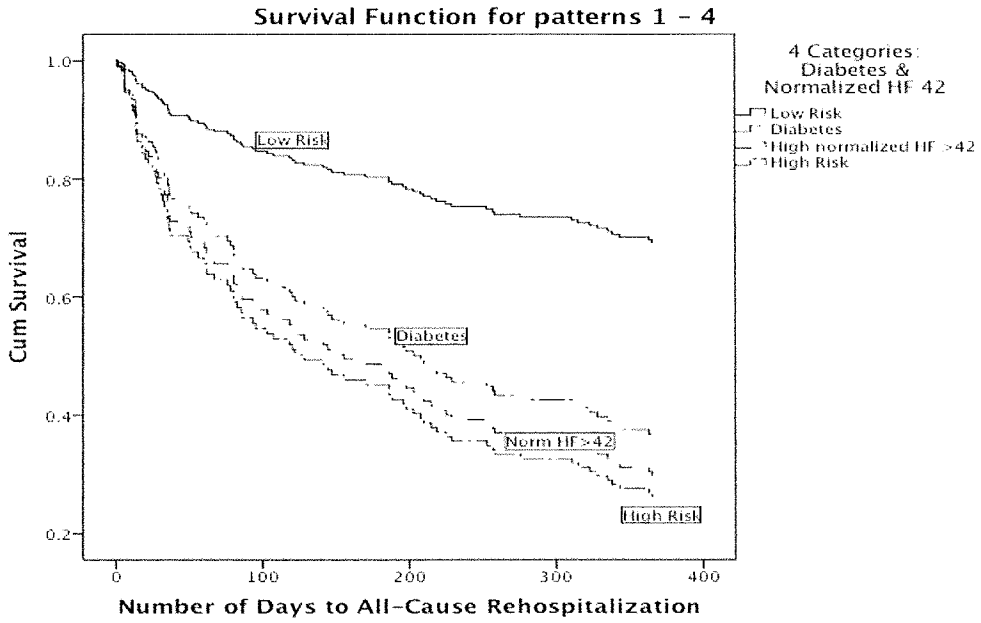


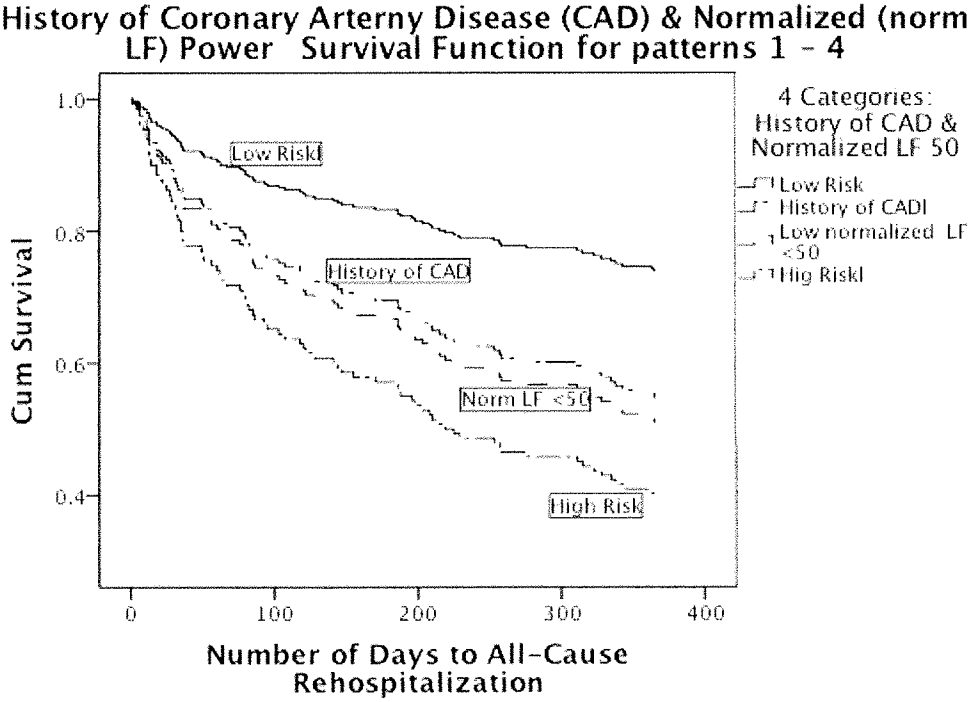
Figure 2. Normalized High Frequency power & Diabetes related to One-Year All-Cause Rehospitalization



Low Risk = No diabetes + normalized high frequency power <=42 ms (squared)
High Risk = Diabetes + nomralized high frequency power >42 ms (squared)
Normalized HF (Norm HF) 42 = Normalized High Frequency dichtomoized at 42 ms (squared)

Diabetes & Normalized High Frequency					
Variables in the Equation Note: Low Risk is compared to other categories	**N=176 (82 events, no deaths)**				
				95% Confidence Interval	
	Wald	p-value	Hazard Ratio	Lower	Upper
Low Risk n=103	26.00	<.001			
Low Risk: Diabetes n=30	12.14	<.001	2.766	1.561	4.901
Low Risk: NHF ≤42ms^2 n=24	15.39	<.001	3.294	1.816	5.976
Low Risk: High Risk n=19	16.67	<.001	3.638	1.957	6.762
Low Risk = No diabetes history & normalized high frequency power (NHF) ≤42 ms^2 High Risk = Both history of diabetes & NHF≤42ms^2					
Model Chi Square=26.77 (p-value<.001)					

Figure 3. Normalized Low Frequency and Coronary Artery Disease History Related to One-Year All-Cause Rehospitalization

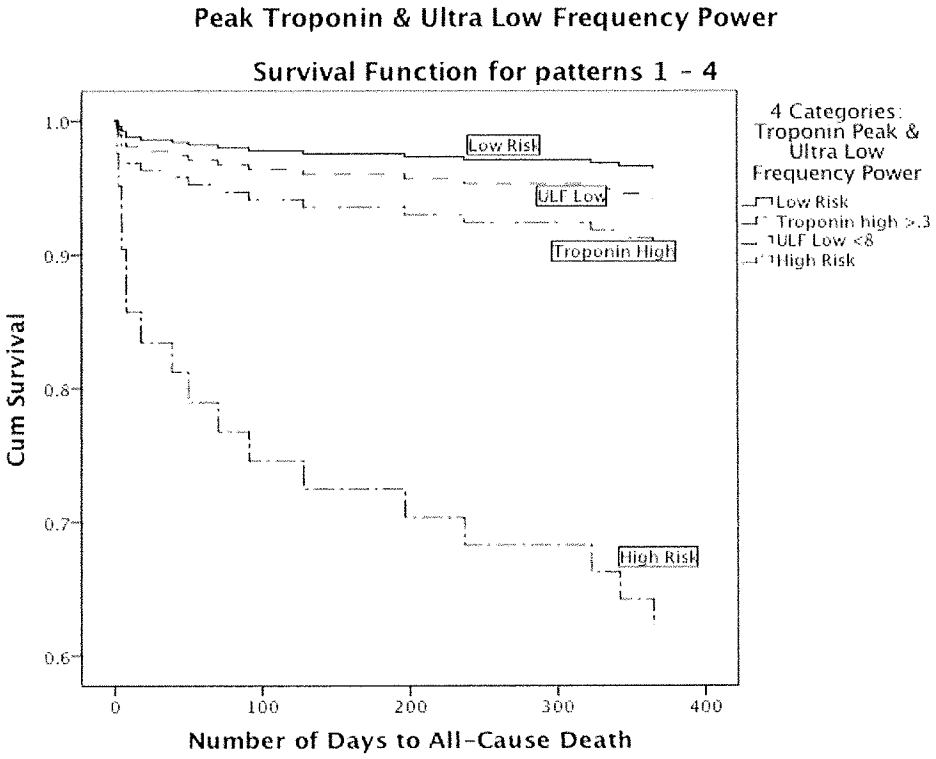


Low Risk = No CAD history + normalized low frequency power >=50 ms (squared)

High Risk = CAD history + normalized low frequency power <50 ms (squared)

History of Coronary Artery Disease (CAD) & Normalized Low Frequency					
Variables in the Equation	**N=176 (82 events, no deaths)**				
Note: Low risk is compared to other categories	Wald	p-value	Hazard Ratio	95% Confidence Interval	
				Lower	Upper
Low Risk n=44	13.21	.004			
Low Risk: CAD History n=62	3.97	.046	1.990	1.011	3.915
Low Risk: norm LF >50 n=19	3.56	.058	2.311	.973	5.490
Low Risk: High Risk n=51	12.58	<.001	3.318	1.710	6.436
Low Risk = No history of coronary artery disease & normalized high frequency power (norm LF) >=50 ms^2 High Risk = Both history of coronary artery disease & normalized low frequency power (norm LF) <=50 ms^2					
Model Chi Square=14.26 (p-value=.003)					

FIGURE 4. Ultra Low Frequency & Troponin Related to One-Year All-Cause Death

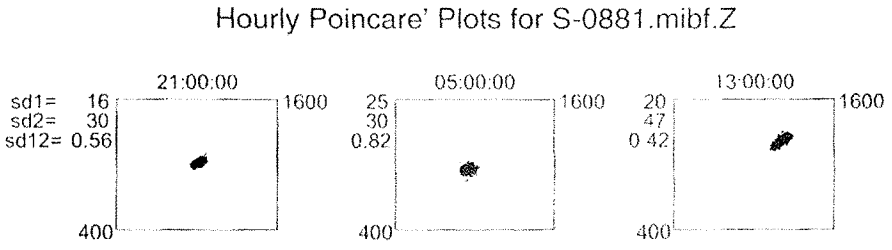


Low Risk = Troponin Peak <=0.3 + ultra low frequency power (natural log) >8.0
High Risk = Troponin Peak >0.3 + ultra low frequency power (natural log) <=8.0
ULF = ULtra Low Frequency Power (natural log)

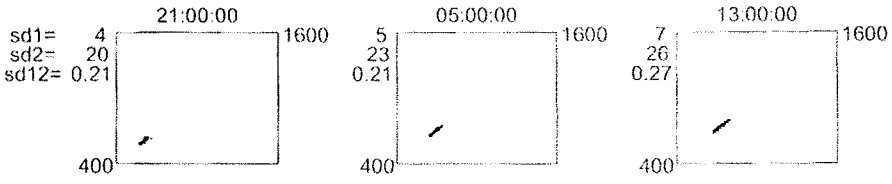
Troponin & Ultra Low Frequency Power					
Variables in the Equation Note: Low risk is compared to other categories	**N=193 (17 events)**				
	Wald	p-value	Hazard Ratio	95% Confidence Interval	
				Lower	Upper
Low Risk (n=85)	15.87	.001			
Low Risk: Troponin Peak >.3 (n=75)	*2.04*	*.153*	*2.680*	*.693*	*10.362*
Low Risk: ULF natural log < 8.0 (n=17)	0.18	.669	1.638	.170	15.743
Low Risk: High Risk (n=16)	13.10	>.001	12.971	3.237	51.976
Low Risk = Troponin <=.3 and ultra low frequency (ULF) natural log >=8.0 High Risk = Troponin >.3 and ultra low frequency (ULF) natural log <8.0					
Model Chi Square=22.640 (p-value<.001)					

FIGURE 5. THREE PATIENTS' OUTCOMES: POINCARÉ PLOTS

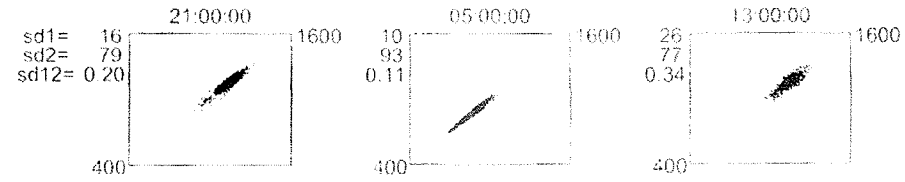
One-hour Poincaré Plots, 9-10:00 PM, 5-6:00 AM, 1-2:00 PM in Three Patients.



A. Unstable angina, NHF=59.83nu, NLF=23.59nu, DFA1=0.4772, $ULFI_{og}$=9.03ms^2; rehospitalized



B. Non-ST Elevation MI; NHF=26.64nu, NLF=49.08nu, DFA1=0.7437; ULF_{log}=7.57ms^2; died in 5 days



C. Unstable angina, NHF=32.61nu, LF=57.93nu, DFA1=1.140; ULF_{log}=9.55ms^2; event-free

X-axis=$RR_{(n)}$ interval duration (ms)
Y-axis=$RR_{(n)+1)}$ interval duration (ms)
X and Y axes each represent 400-1600 ms

SD1=Dispersion (standard deviation) perpendicular to axis of line of identity: Beat-to-beat instantaneous variance in RR intervals

SD2=Dispersion (standard deviation) along the line-of-identity axis (approximately lower left to upper right): Long-term continuous variance in RR intervals

SD12=SD1/SD2 Ratio

DFA1=Detrended fractal analysis, short-term fractal scaling exponent
NHF=high frequency power
NLF=low frequency power
ULF_{log}=natural log transformation of ultra low frequency power

MI=myocardial infarction
nu=normalized units

Chapter 4

Article 3 – Prognostic Value of Heart Rate Turbulence for Assessment of Short- and Long-Term Risk in Unstable Angina Patients

Chapter 4

Prognostic Value of Heart Rate Turbulence for Assessment of Short- and Long-Term Risk in Unstable Angina Patients

Short Title: **Heart Rate Turbulence in Unstable Angina**

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Abstract

Purpose: We sought to examine the value of assessing heart rate turbulence (HRT), derived from electrocardiographic recordings initiated in the emergency department (ED), in unstable angina (UA) patients.

Methods: Twenty-four hour Holter recordings were started ~45 minutes after ED arrival in patients with acute coronary syndrome symptoms. Patients subsequently diagnosed with UA whose recordings showed ≥18 hours of sinus rhythm were chosen for analysis. Turbulence onset and turbulence slope were computed. Endpoint was a composite of in-hospital complications, rehospitalization, or death.

Results: In multivariable analyses, UA patients (n=102) with turbulence onset ≥-0.0100% and turbulence slope ≤2.8 ms/R-R interval were more likely to experience adverse 30-day (hazard ratio 6.892, confidence interval 1.805–26.317, p=.005) and 1-year (hazard ratio 3.920, confidence interval 1.941–7.877, p<.001) cardiac outcomes than patients with higher values.

Conclusions: HRT measurement, initiated in the ED, may provide additional, incremental value to established risk assessment standards for UA patients.

Abbreviations and Acronyms
ACS = acute coronary syndrome
CABG = coronary artery bypass graft
CAD = coronary artery disease
CI = confidence interval
ECG = electrocardiography
ED = emergency department
HR = hazard ratio (ratio of incident rates; estimates relative risk)
HRT = heart rate turbulence
HRV = heart rate variability
MI = myocardial infarction
ms = milliseconds
PCI = percutaneous coronary intervention
TO = turbulence onset
TS = turbulence slope
UA = unstable angina
VPC = ventricular premature contraction

Key Words:

Acute coronary syndrome

Cardiac autonomic modulation

Heart rate turbulence

Outcomes

Prognosis

Unstable Angina

Introduction

Over recent decades, extraordinary improvements in timely care for patients with acute coronary syndrome (ACS) have resulted in better patient outcomes (1). Within the last 10 years, cardiovascular deaths have declined (2). Important developments, such as well-designed prehospital electrocardiographic systems, have enhanced ischemia detection (3). Prompt cardiac catheterization and revascularization procedures have saved myocardium (1). However, even with these positive developments, cardiovascular disease remains among the top causes of death in the United States (2) and worldwide (4). Ideally, primary prevention measures, such as education in smoking cessation, healthy diet, and exercise, would eliminate the need for secondary or tertiary prevention. The reality, however, is that prevention of repeated acute coronary events remains an essential healthcare concern.

As many as 30% of patients hospitalized for ACS are readmitted within one year resulting in increased health care cost and lost productivity (5). Patients who arrive in the ED with ACS symptoms and transient electrocardiographic changes consistent with ischemia, but whose cardiac serum markers remain negative, and consequently are diagnosed with unstable angina, remain at high risk for a range of cardiac complications from recurrent angina to life-threatening myocardial infarction. While only a "small percentage" of coronary heart disease deaths are attributed to angina pectoris (p. e70) (1), risk for unstable angina patients tends to be highest within the year after hospitalization (6). Standards for management of non-ST elevation myocardial infarction (MI) and unstable angina are similar. Nevertheless, recognition of unstable patients who may be at highest risk for repeated events is a prudent approach for planning appropriate follow-up care. Cardiac risk scores help achieve this end (1). However, additional, potentially useful, assessment information can be provided with data derived from efficient use of noninvasive, continuous electrocardiographic (ECG) monitoring

during hospitalization.

Heart rate turbulence (HRT) refers to fluctuations in the cardiac cycle in response to a ventricular premature contraction (VPC). Schmidt et al recognized the clinical significance of heart rate turbulence (HRT) for prediction of mortality after acute MI in1999 (7). The investigators observed a pattern of brief acceleration and immediately followed by a more gradual deceleration of heart rate after a VPC in ECG data obtained from Holter recordings. These small interval changes are in the range of milliseconds (ms) and can be visualized with the aid of signal averaging (8-10).

The phenomenon was named HRT, and the two phases of oscillation, acceleration followed by deceleration, were measured with parameters termed turbulence onset (TO) and turbulence slope (TS). The two HRT parameters examine the period encompassing at least two sinus RR intervals prior to a ventricular beat, the VPC itself, a compensatory pause, and the following 15 sinus intervals (11-15). Several investigators have proposed mechanisms to explain TO and TS (7-15). Subsequent study findings have supported the hypotheses:

- TO, which characterizes the initial heart rate acceleration after a ventricular premature contraction (VPCs), has been correlated with baroreflex sensitivity and associated with immediate vagal withdrawal in response to a drop in arterial blood pressure after the VPC. Sympathetic enhancement to raise blood pressure is initiated, but with slower response than the parasympathetic system (10,11)
- TS characterizes the subsequent deceleration of heart rate, and is more complex, reflecting vagal and sympathetic system interaction. The slow sympathetic response (compared to that of the vagal system) to drop in blood pressure increases the blood pressure gradually, which indirectly sets the conditions necessary for slowing of the heart rate (10,11).

To calculate TO and/or TS, at least 5 VPCs during a 24-hour Holter recording are required with measurements averaged (15).

Schmidt et al found that post myocardial infarction (MI) patients with values of turbulence onset and slope deemed to be abnormal were 3.2 times more likely to die during 21 months of follow-up (7). Subsequent research has supported their findings in MI patients (16-19). In 2006, Lanza et al showed that patients whose TO and TS appeared to be disrupted were at high risk for cardiac mortality within 6 months of admission for an episode of acute unstable angina (20).

The overall objective of our study was to determine the prognostic value of HRT, measurement initiated early upon a symptomatic patient's entry into the emergency department (ED), for identifying risk of adverse events. ECG Holter recordings of patients admitted to the hospital to rule out MI, whose serial serum cardiac enzymes remained negative, and subsequently received a discharge diagnosis of unstable angina, were examined.

The primary aim of this study was to answer the following 2-part question for patients presenting to the ED with ACS symptoms who have negative cardiac troponin and subsequently are diagnosed with unstable angina:

- Is HRT measured during the 24 hours after ED arrival prognostic of

  1) 30-day, and/or

  2) 1-year

adverse cardiac events after transferring out of the ED, including in-hospital complications, rehospitalization, and death?

A secondary aim was to answer the following question in the same patient group:

- Is HRT measured during the 24 hours after patient presentation to the ED with ACS symptoms associated with 1-year all-cause adverse events?

Methods

Research Design and Sample. A retrospective analysis was performed of ECG data from the Ischemia Monitoring and Mapping in the Emergency Department In Appropriate Triage and Evaluation of Acute Ischemic Myocardium (IMMEDIATE AIM) study, a prospective clinical trial of patients who presented to the ED of a large urban hospital with symptoms of ACS (N=1308 recordings; 1153 unique patients). Study design and data collection have been described elsewhere (21).

Ethical Considerations. The University of California, San Francisco (UCSF) institutional review board approved the study. Verbal assent was obtained at time of recruitment, and written consent was obtained from the patient after stabilization or from the patient's surrogate.

Data Collection. We assured placement of 24-hour Holter recorders (H-Scribe System, Mortara Instrument, Milwaukee, WI) as soon as possible after ED arrival (median door-to-Holter time for all participants was 45 minutes). The sampling rate was 180 samples/second. Trained research nurses applied the ECG leads, supervised monitoring, and downloaded data to the H-Scribe review station. Radiolucent electrodes and lead wires were used to aid uninterrupted monitoring during procedures, such as cardiac catheterization. Patients' demographic and clinical information was gathered upon enrollment or extracted later via chart review.

Follow-up. We followed patients for one year after their ED visit. Data regarding patients' hospital readmissions and survival was collected via telephone calls, medical records, and the public access social security mortality database. One-year survival and rehospitalization information was obtained for all patients in the current analysis.

Inclusion Criteria. Recordings that represented individuals whose peak serum cardiac troponin during hospitalization was ≤0.3 nanogram/milliliter (ng/ml), according to the local laboratory cutoff for myocardial injury, and who were positively diagnosed with unstable angina prior to discharge were included. Unstable angina was defined according to Diagnosis Related Group for angina pectoris, intermediate coronary syndrome, i.e. evidence of coronary occlusion without myocardial infarction. We distinguished between patients with new-onset angina and those who were experiencing reoccurring or worsening of angina symptoms. Recordings with at least 18-hours of normal sinus beats, after automatically scanning and manually editing, were included in this analysis.

Endpoints. The primary endpoints comprised a composite of adverse cardiac outcomes within 30 days and 1 year of transfer out of the ED, including cardiac-related in-hospital complications, cardiac rehospitalization, and/or cardiac death. Patients with more than one adverse outcome (i.e. patients who experienced an in-hospital complication and who were later readmitted or died) were included in the analysis one time only. Cardiac rehospitalization may have been due to reoccurring ACS and/or heart failure. Death was considered to be due to a cardiac cause, if sudden cardiac death, acute myocardial infarction or heart failure was reported. The secondary outcome was a composite of all-cause rehospitalization and/or death between ED discharge and end of the follow-up year.

Demographic and Clinical Variables. Variables chosen for analysis included established risk factors, such as those identified by the Thrombolytic in Myocardial Infarction (TIMI) risk stratification score, including age, gender, history of coronary artery disease, and other clinical and demographic factors potentially related to outcomes (1).

Electrocardiographic Monitoring Variables. Variables derived from Holter

monitoring, such mean heart rate and number of ventricular premature contractions (VPC) over the recording time were calculated. We also cataloged new evidence of ST segment elevation or depression, and/or t-wave changes.

ECG recordings were automatically scanned and manually edited using H-Scribe analysis software at the ECG Monitoring Research Laboratory, UCSF, School of Nursing. ECG research software, validated by the Heart Rate Variability Laboratory, Washington University School of Medicine, St. Louis, Missouri, verified eligible recordings, and computed HRT along with heart rate variability (HRV). HRV time domain, frequency domain, and nonlinear variables were chosen, according to published guidelines or previous studies (22, 23). HRV and HRT both have potential for providing relevant and complimentary information of autonomic cardiac modulation (14, 23).

Heart Rate Turbulence Analysis. To obtain HRT variables, R-R intervals were exported as text files and transformed via a dedicated MatLab program (Mathworks, Natick, Massachusetts) for compatibility with the research software. TO and TS were derived from recordings with sinus R-R intervals that has at least 5 VPCs during the recording time. Isolated VPC were used to arrive at values for TO and TS, as described by Bauer et al (15).

Turbulence onset (TO), indicator of early sinus acceleration after a VPC, was calculated by measuring the differences between 2 sinus beats following a compensatory pause (RR_1 and RR_2) and the 2 sinus beats immediately prior to the VPC (RR_{-1} and RR_{-2}), using the formula: $\{[(RR_1 + RR_2) - (RR_{-1} + RR_{-2})]/(RR_{-1} + RR_{-2}) \times 100\}$, expressed as a percentage (8, 15, 21).

Turbulence slope (TS), indicator of late sinus deceleration after a VPC, was measured as the maximum positive slope of all slopes in a series of regression lines derived from 5 consecutive sinus beats within the first 15 sinus beats after the VPC. TS

is expressed in milliseconds (ms) per RR interval (15).

Statistical Analyses. Descriptive statistics were used to examine demographic and clinical variables. To assess proportional hazard across time, univariate Cox regression survival analyses were performed for each demographic, clinical, and ECG Holter variable. Dichotomous HRT variables were created using cut-points for normal values according to published clinical standards, i.e TO<0.0% and TS>2.5 ms/RR interval (15).

Risk categories also were created. Low risk was "normal" HRT; medium risk was designated if a patient's recording showed 1 "abnormal" HRT variable; and high risk was designated if a patient's ECG recording showed 2 abnormal HRT variables (15). Receiver-operator curves also were generated for TS and TO to identify reference values with high sensitivity and/or specificity for systematically assessing variables in relationship to each outcome by maximizing log likelihood in univariate Cox Regression analyses.

HRT variables were retested within multivariate regression models with each HRV and other ECG variables, and/or demographic and clinical variables that were significantly associated with outcomes (p-values <0.10) per univariate analysis. HRV variables that were not normally distributed were transformed to natural algorithms. Backward elimination was methodically employed to identify the most significant predictors within multivariable models. In addition, age, as a known risk factor (1), and potential confounder, was chosen a priori for inclusion in multivariable models related to 1-year outcomes. Alpha was set at <.05. Variables that were highly correlated with each other (r >.700) were not tested within the same model.

Bootstrapping (1000 samples, 95% confidence interval) was used to examine model stability (alpha<.05). Harrell's Cumulative Index (C-statistic) was calculated to

evaluate models' predictive ability. Analyses were performed using International Business Machines statistical software (SPSS 19, IBM, Armonk, NY).

Results

Patient Characteristics. Of unique patients diagnosed with unstable angina, 130 had recordings with ≥18 hours of analyzable sinus rhythm, and 102 of those recordings represented patients with negative serial cardiac troponin. For this subgroup of IMMEDIATE AIM patients, the median ECG Holter recording time was 1439 minutes; median time between symptom onset and Holter placement was 4 hours; median door-to-Holter time was 47 minutes; median follow-up period for survivors was 369 days. A majority of patients had a previous history of coronary artery disease (n=78, 76.5%), including 55 who had had a prior MI (54%); 47 had had a previous percutaneous coronary intervention (PCI) (46%); 30 who had had a coronary artery bypass graft (CABG) (29%). Eight-six (84%) patients had one or more cardiac catheterizations. See Table 1 for patient characteristics.

Within 30 days of ED discharge, 87 patients had event-free outcomes; 15 (15%) experienced adverse cardiac events. Two patients experienced in-hospital complications, i.e. hemodynamic instability that required transfer to a higher level of care. Both survived and were not readmitted. Eleven patients reported readmission due to a cardiac diagnosis (11%). Two patients died due to a documented cardiac cause. There were no reported noncardiac events.

After the first 30-day period, an additional 30 patients (29%) were readmitted with a cardiac diagnosis; 2 more people died due to a cardiac-related cause bring the total number of deaths within one year to 4 (4%). Another 6 people were admitted to the hospital with a primary diagnosis that was other than cardiac; however, notably, all reentered the hospital with a recent history of acute coronary syndrome; 5 of 6 were

diabetic. Over the course of the follow-up year, 49 patients remained event-free.

Clinical and Demographic Variables related to Outcomes. In univariate Cox regression analyses, demographic and clinical variables that were related to 30-day adverse outcomes with $p<.10$, also were related to 1-year adverse cardiac and all-cause outcomes. These variables were: type of angina (new or reoccurring); evidence of left main coronary artery disease as determined by cardiac catheterization prior to or during the hospitalization; and living without a significant other. In addition, other variables related to 1-year cardiac and all-cause outcomes were: comorbidity of diabetes; hypertension; prior history of coronary artery disease; left ventricular hypertrophy per evidence on admitting ECG; and a presenting symptom of nausea and/or vomiting. Left bundle branch block was associated with 1-year cardiac outcomes only. Age, gender, and race were not significantly related to outcomes. Univariate regression analysis results for demographic and clinical with p-values, and hazard ratios for significant variables, are outlined in Table 2.

Electrocardiographic Holter Monitoring Variables. In univariate analyses, VPCs at a rate >10 per hour were associated with adverse 1-year cardiac and all-cause outcomes, as was new incidence of ST depression. We also examined new incidents of ST-elevation or t-wave inversion and episodes of ventricular tachycardia with 3 or more beats in relation to outcomes; the results were not significant in our sample and are not shown. All HRV variables, except the percentage of normal R-R intervals >50 ms different from the previous normal R-R interval (pNN50), were significantly associated with one or more of the outcomes. See Table 3.

For the 80 patients with computable HRT values, mean TO was -.0045 (±.028, standard error =.0031) and mean TS was 6.658 (±6.294, standard error =.7037). Receiver operator curves showed that TO was significantly associated with 1-year

outcomes (area under the curve =.641 ,p=.030) and TS was significantly associated with 30-day outcomes (area under the curve =.672, p=.039) in patients who had >5 PVCs during the recording time (n=80). At the traditional cut-point values, turbulence onset and/or turbulence slope also were associated with all three outcomes in univariate analyses. The traditional risk categorical variables of low, medium, and high, also were related to 30-day and 1-year outcomes (with the 22 patients with <5 VPCs included in the low risk group).

Heart Rate Turbulence Categorical Risk Score. Patients with unstable angina may have different acceptable HRT parameters than patients with MI (20). A systematic search for cut-points showed a strong statistical relationship with outcomes could be found at TO=0.0100% and TS=2.8ms/RR interval (Table 3).

TO and TS with the new cut-points demonstrated relevance as significant predictors of outcomes in multivariable analyses. The low, medium, and high risk categorical variables were revised with the cut-off values and verified the strong association with each outcome (see Figures 1 and 2 for the revised Turbulence Risk Score categories in relation to 30-day and 1-year cardiac outcomes). Similar to the HRT risk categories established by Bauer et al (15), we determined optimal HRT categories in the study group of unstable angina patients, thus:

- Low Risk = No risk factors: TO< -0.0100% and TS>2.8 ms/RR interval (n=55, 54%);

  22 patients with less than 5 VPCs in the recording were included in this group (15, 19)
- Medium Risk = 1 risk factor: TO> -0.0100% or TS<2.8 ms/RR interval (n=25, 24.5%)

- High Risk = 2 risk factors: TO> -0.0100% and TS<2.8 ms/RR interval (n=22, 21.5%).

Heart Rate Turbulence Prediction Models for 30-Day and 1-Year Outcomes. Since there were 15 cardiac events (and no noncardiac events) for 30-day outcomes, only 2 predictors could reasonably be included in the model. Each candidate variable was tested in conjunction with HRT. TS, dichotomized at 2.8ms/RR interval, and the revised turbulence risk score were the strongest predictors of 30-day outcomes. Evidence of ≥50% occlusion in the left main coronary artery consistently proved to be another strong predictor. Eight of the 10 patients with >50% occlusion of the left main artery had previously had a CABG and one had had a PCI. These 10 patients also had hypertension.

A small, but significant, correlation was found between turbulence onset and >50% occlusion of the left main artery (r=.278, p=.016). VPCs per hour also were correlated with the HRT risk scores (r=.267, p=.007) with smaller correlations related to TO (r=.250, p=.011) and TS (r=.200, p=.044). These relationships did not meet our criteria to exclude the variables from being tested within the same multivariable model.

Along with the HRT variables and evidence of ≥50% occlusion in the left main coronary artery, diabetes, and living without a significant other remained significant in regression models of 1-year cardiac and/or all-cause outcomes. Diabetes was not a significant factor in cardiac rehospitalizations. However diabetic patients returned in higher proportion when all hospitalizations were considered. Of the 34 patients with diabetes, 25 (73% of diabetic patients) were readmitted to the hospital for any cause within one year as opposed to 28 of 68 patients without diabetes (41%) who returned.

Seventy-four patients reported living with a significant other, which was a significant predictor for staying out of the hospital. Twenty-eight (38%) returned to the hospital within one year for a cardiac cause whereas 19 of the 28 (68%) patients who

reported living without a significant other returned. Age was dichotomized at 70 years according to prior research (20) and because it showed promise as an optimal cut-point, however it was not a significant independent predictor. Age also was stratified per decade and dichotomized at 65 years, per the Thrombolysis in Myocardial Infarction risk score (1), and was not significantly associated with outcomes. Patients who were 50 to 60 years of age returned to the hospital in the greatest proportion; 12 of 21 (57%) returned for a cardiac cause within the year. Of the 4 nonsurvivors, all were younger than 70 years, 2 were diabetic, 2 did not live with a significant other, and 1 had evidence of >50% occlusion of the left main artery. This finding is in contrast to the well-recognized risk of older age in relation to death (1, 5).

Among other clinical variables, type of angina, hypertension, history of coronary artery disease, left ventricular hypertrophy, left bundle branch block, and nausea or vomiting symptoms did not remain significant in multivariable models. Electrocardiographic variables, new ST depression and >10 VPCs per hour, also did not remain significant. None of the HRV variables were found to be significant in multivariable analysis with HRT in the model. Select dichotomized HRV variables were tested, such as DFA1 1.0 exponent value found to be a significant predictor of cardiovascular mortality in conjunction with HRT in an older community-dwelling population (24), and remained not significant. While not significant in multivariate analysis with HRT, normalized high frequency <28 normalized units power correctly identified the 4 patients who died; 29±3 normalized units is a published normal standard (23). In comparison, the HRT risk score correctly identified, as high risk, 3 of the patients who died, but 1 nonsurvivor was in the low risk group.

In summary, HRT remained the most significant predictor when adjusted with clinical cardiac risk factors (1), ECG indictors (3, 21), HRV (23, 24), and in relation to revascularization procedures, i.e. PCI and CABG. In predictive regression models, which

included age>70 years, diabetes, left main coronary occlusion >50%, and presence of social support (living with or without a significant other), turbulence risk scores with TO dichotomized at -0.0100% and TS dichotomized at 2.8ms/RR interval consistently remained significant indicators of 1-year outcomes. The multivariable models remained significant with bootstrapping.

Discussion

Our findings provide further evidence of the prognostic power of HRT in predicting cardiovascular outcomes. This is the first study to our knowledge to examine HRT calculated from Holter recordings started within the first hour after presentation to the ED in patients with symptoms of acute coronary syndrome (or unstable angina). Furthermore, increased risk of an adverse outcome associated with positive peak cardiac troponin was controlled by including only patients with negative biomarkers during their hospitalization. While nearly all of the ACS patients in our study were vulnerable, further identification of those with highest risk of rehospitalization or death is a reasonable approach. In multivariable survival analyses, HRT consistently was the most significant predictor of 30-day and 1-year outcomes in our study.

Since Schmidt et al showed that absence of HRT was a significant predictor of total morality in 100 patients with coronary heart disease (7), numerous studies have expanded those findings to aid in physiological understanding (9, 10) and clinical application (16-20, 23, 24). However, optimal timing for clinical assessment of HRT has not been established (25). In the study by Schmidt et al, HRT was measured during a stable period from 2 weeks up to 3 months after patients experienced an MI (7). To investigate the relationship between HRT and heart rate and test this association in acute MI survivors, Bauer et al examined HRT in patients 2-3 weeks after MI (9). Huikuri

et al (18) measured HRT at two time periods after MI in 2 patient groups, early (defined after 5 to 21 days in the first cohort, and 2 to 4 weeks in the second) and late (at 6 weeks in the first cohort, and 10-14 weeks in the second). The investigators found that HRT improved over time, and that both time periods for measurement were prognostic of ventricular arrhythmias, fatal or near-fatal arrhythmic events. In the study of unstable angina patients by Lanza et al, 24-hour Holter recordings were started within 24 hours of hospital admission. (20). While optimal timing of HRT assessment of unstable angina patients was not an aim in our study, we did establish that HRT measured from 24-hour recordings started early after ED arrival was associated with outcomes up to a year after the patient's visit.

In our study, we found that the optimal cut-points for significant association with outcomes were different from the HRT standard values for predicting mortality after MI (15). Our findings suggest that the HRT parameters, most useful for risk stratification, may need adjustment according to patient characteristics, diagnoses, and outcomes. This conclusion is similar to that reached by Stein et al (23) and Lanza et al (20), both of whom suggested that normal and abnormal HRT values may vary according to the population. Stein et al examined HRT in adults ≥65 years of age who lived within the community. Approximately 70% did not have prevalent coronary vascular disease. Stein et al found a cutoff of TS<3 ms/RR interval was abnormal. The cutoff value for TO remained the same at >0.0%. Lanza et al reported that mortality was higher in unstable angina patients with TO >-1.52% and TS <4.9 ms/RR interval. The authors suggested that the adjusted cut-off values would be more predictive of mortality in unstable angina patients. In the patients we studied, we found that TO >0.0100% and TS <2.8 ms/RR interval was significantly predictive of adverse outcomes compared to the traditional values of TO >0.0 and TS<2.5 ms/RR interval. The values we found most useful were

much closer to the standard parameters reported by Bauer et al. However, our patients arguably were sicker (54% with previous MI and 33% with diabetes) compared to patients studied by Lanza (42% with previous MI and 20% with diabetes) or Stein (30% with clinical cardiovascular disease and 15% with diabetes), which may partially account for the different findings. A high to low range for normal TO and TS values may be realistic.

In multivariate analysis, we found that >50% occlusion of the left main artery remained a significant predictor of adverse outcomes, especially in models with TS. In addition, we found the small correlation between TO and >50% occlusion of the left main artery. This finding is not surprising since compromised vessels are known to affect HRT (7,9). Healthy HRT responsiveness requires an intact interaction between vagal and sympathetic systems (8, 10, 11). Cygankiewicz et al followed 146 patients who underwent a CABG procedure for ≥1 year (as 8 out of 10 patients with >50% left main artery occlusion did in our study), and also found that abnormal TS was a significant predictor of cardiac death in patients. However, TO was not prognostic (24). Lanza et al found a moderate association between HRT and the inflammatory serum marker, C-reactive protein (20), suggestive that inflammation associated with plaque could play a role in disrupting HRT responsiveness.

Diabetes is a known risk factor for cardiovascular mortality after MI (1). Miwa et al reported that HRT can predict cardiac mortality in diabetic and nondiabetic post-MI patients (19). While diabetes was not associated with adverse cardiac outcomes in our study, we found that diabetes was a significant predictor of all-cause outcomes.

The value of social support also was underscored in our study, which also is known to be an important factor in recovery and rehabilitation (1). Living without a significant other was highly significant in multivariate analyses in relation to 1-year

adverse outcomes, both cardiac and all-cause..

A high percentage of patients in our study were readmitted to the hospital for cardiac reasons (44%) compared to the literature in which 30% is cited (5). However, more than 3 of 4 had a previous diagnosis of CAD, and 1 out of 3 had a comorbidity of diabetes, reflecting an ill group of people with advanced disease and/or comorbidities, possibly contributing to the relatively high percentage of adverse outcomes. In any event, hospital readmittance after an ED visit, in which ACS is diagnosed, is common and contributes directly to the economic burden of healthcare. Johnston and colleagues reported that even one cardiac rehospitalization within a year of ED presentation with ACS increased direct care cost by nearly $10,000 (5). To be sure, rehospitalization in itself is not a reflection of quality of care. A structured, decision-making approach has been found to be safe and cost-effective, and is recommended (1). An additional risk-assessment tool, such as HRT, could be a practical choice to help healthcare providers identify patients with increased risk of 30-day or 1-year adverse cardiac events, especially when patients' cardiac biomarkers are negative and guidance less definitive.

Implications. Our findings suggest that evaluation of HRT to assist in identifying patients at highest risk for adverse events could be a practical addition to continuous ECG monitoring. HRT is an independent predictor of cardiovascular events in unstable angina patients with negative serum troponin. HRT can be computed from 24-hour Holter monitors. The value of continuous 24-hours ECG monitoring for ACS patients is well recognized and recommended (1, 3, 21). Measurement of HRT, incorporated into the routine cardiac monitoring of hospitalized ACS patients, could be a reasonable next step toward reducing costs and saving lives. Future research could include a cost-benefit analysis.

Limitations: This was a retrospective analysis of data collected between 2002 and

2004. Practice standards for ACS management have been updated in the intervening time. The study was small and was hampered by ECG artifact and insufficient ECG recording, reflecting potential challenges to accurate assessment. In addition, HRT requires sinus beats to compute, so patients with atrial fibrillation could not be included. When possible, we verified the reason for rehospitalization, but not all medical records were available.

Conclusions: Measurement of HRT upon ED arrival in patients with ACS symptoms reasonably could provide additional useful information to assess risk of cardiac rehospitalization and/or death within one year of ED presentation in patients who have negative serial cardiac biomarkers and are diagnosed with unstable angina.

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Table 1: Demographic and Clinical Characteristics of Unstable Angina Patients in Relation to Primary (cardiac) and Secondary (all-cause) Outcomes

Variable *Percentages are rounded to nearest half percent.*	Total Unstable Angina Patients	Adverse Outcomes			1-year Event-Free
		30-day Cardiac	1-year Cardiac *Including 30-day cardiac events*	1-year All-Cause *Including all cardiac events*	
N (number of unique patients)	102	15	47	53	49
Mean age in years	65±13	64±8.9	65±12	65±11	64±13
Male gender, n *(% of total N)*	55 (54%)	8	23	26	29
Race, n *(% of total N)*:					
American Indian/Alaska Native	4 (4%)	1	2	2	2
Black/African American	22 (21.5%)	2	15	16	6
Asian & Pacific Islander	25 (23.5%)	4	10	13	12
White/Caucasian	51 (50%)	8	20	22	29
Type of Angina, n *(% of total N)*					
New onset	42 (41%)	2	16	17	25
Recurrent or worsening symptoms	60 (59%)	13	31	36	24
Prior history or comorbidity, n *(% of total N)*:					
Diabetes	34 (33%)	7	20	25	9
Hypertension	81 (79.5%)	12	43	47	34
Hypercholesterolemia	74 (72.5%)	12	36	41	33
Coronary artery disease [a]	78 (76.5%)	13	40	45	33
Family history of coronary artery disease	56 (55%)	10	25	28	28
Clinical factors assessed upon arrival:					
Mean±SD body mass index	27.9±7	26.1±6	27.2±6	27.4±7	28.5±7
Mean±SD maximum ST elevation, microvolts [b]	105.3±66	117.8±71	04.5±67	109.6±71	100.8±52
Mean±SD maximum ST depression, microvolts [b]	-33.0±36	-34.8±35	-35.4±40	-36.2±40	-29.6±30
T-Wave inversion [b], n *(% of total N)*	24 (23.5%)	4	12	14	10
Left ventricular hypertrophy [b], n *(% of total N)*	15 (15%)	2	10	11	4
Left bundle branch block [b], n *(% of total N)*	2 (2%)	1	2	2	0
Enlarged cardiac silhouette on admission x-ray, n *(% of total N)*	18 (17.5%)	1	10	11	7
Symptoms (patients may have had one or more):					
Chest pain on arrival, n *(% of total N)*	97 (95%)	4	43	14	48
Shortness of breath, n *(% of total N)*	62 (61%)	10	30	33	29
Nausea and/or vomiting, n *(% of total N)*	35 (34%)	6	21	23	12
Artery occlusion >50% based upon cardiac catheterization, n *(% of total N)*:					
Left main artery	10 (10%)	4	8	8	2
Left anterior descending artery	82 (80%)	14	40	45	37
Left circumflex artery	44 (43%)	8	24	27	17
Right coronary artery	55 (54%)	11	30	33	22
Social factors, n *(% of total N)*:					
Current smoker	17 (17%)	4	11	11	6
Lives with significant other	28 (27.5%)	7	28	20	8
Therapies during hospitalization, n *(% of total N)*:					
Beta blocker	89 (87%)	13	42	46	43
Percutaneous coronary intervention (PCI)	23 (22.5%)	6	13	14	9
Coronary artery bypass graft (CABG)	6 (6%)	2	2	3	3

Legend for Table 1

[a] Prior coronary artery disease diagnosis (including prior myocardial infarction, PCI and/or CABG)

[b] Evidence on initial ED 12-lead electrocardiogram

SD = standard deviation

Table 2: Demographic or Clinical Variables and Short- and Long-Term Outcomes Univariate Cox Regression Results

Variable Total N=102	Adverse Outcomes (In-hospital complications, rehospitalization, death)		
	30-Day Cardiac Outcomes	1-Year Cardiac Outcomes	1 Year All-Cause
	Hazard Ratio (95% CI) *p-value*	Hazard Ratio (95% CI) p-value	Hazard Ratio (95% CI) p-value
# of patients with outcome	15	47	53
Age >70 years	*.155 = ns*	*.341 = ns*	*.380 = ns*
Gender	*.978 = ns*	*.505 = ns*	*.485 = ns*
Race	*.404 = ns*	.137 =ns	*.141 = ns*
Type of Angina: New or Recurrent	**5.16 (1.16-22.89)** ***.031***	**1.74 (0.95-3.19)** ***0.72***	**1.92 (1.08-3.42)** ***.027***
Body mass index	*.304 = ns*	*.362 = ns*	*.448 = ns*
Diabetes	*.260 = ns*	**1.73 (0.97-3.09)** ***.064***	**2.10 (1.22-3.61)** ***.007***
Hypertension	*.958 = ns*	**3.13 (1.12-8.73** ***.029***	**2.31 (0.99-5.41)** ***.053***
Hypercholesterolemia	*.471 = ns*	*.281 = ns*	*ns = .201*
Family history of coronary artery disease	*.996 = ns*	*.987 = ns*	*.333 = ns*
History of coronary artery disease	*.303 = ns*	**2.19 (0.98-4.90)** ***.056***	**2.18 (1.03-4.63)** ***.042***
Enlarged cardiac silhouette on admission X-ray	.257 = ns	*.757 = ns*	*.815 = ns*
Maximum ST elevation ≥0.1 millivolts (mV)	.753 = ns	*.883 = ns*	*.864 =ns*
Maximum ST depression ≥ -0.05 millivolts (mV)	*.802 = ns*	*.682 = ns*	*.554 =ns*
T-wave inversion	*.746 = ns*	*.650 = ns*	*.525 = ns*
Left ventricular hypertrophy	*.873 = ns*	***1.87 (.93-3.76)*** ***.081***	**1.84 (.94-3.58)** ***.074***
Left Bundle Branch Block	*.140 = ns*	**3.61 9.87-14.99)** ***.077***	*.101 = ns*
Shortness of Breath	*.610 = ns*	*.516 = ns*	*.639 = ns*
Nausea or vomiting	*.650 = ns*	**1.74 (.98-3.09)** ***.061***	1.67 (.97-2.87) ***,067***
Left Main Artery >50% occlusion per current or previous catheterization	**3.55 (1.13-11.16)** ***.030***	**2.74 (1.28-5.88)** ***.010***	**2.41 (1.13-5.12)** ***.023***
Other coronary artery* with >50% occlusion per current or previous catheterization	*≥.663 = ns*	*≥.247 = ns*	*≥.268 = ns*
Current Smoker	*.210 = ns*	*.104 = ns*	*.227 = ns*
Chest pain reported in emergency department	*.744 = ns*	*.151 =ns*	*.223 = ns*
Received beta blocker	*.935 = ns*	*.588 = ns*	*.960 = ns*
Percutaneous coronary intervention	*.108 = ns*	*.178 = ns*	*.221 = ns*
Coronary artery bypass graft	*.121 = ns*	*.950 = ns*	*.679 = ns*
Living without significant other	**2.45 (0.89-6.77)** ***.083***	**2.52 (1.40-4.53)** ***.002***	**2.29 (1.31-4.00)** ***.004***

Table 2 Legend

CI: confidence interval
* "other coronary artery" refers to left anterior descending, left circumflex or right coronary artery; each was tested individually and lowest p-value reported.

ns: not significant
Hazard ratio and confidence interval reported for p-value ≤0.10 only
Bold identifies p-values <.10

Table 3: Electrocardiographic 24-hour Holter Variables and Short- and Long-Term Outcomes Univariate Cox Regression Results

Variable Total N=102	Adverse Outcomes (In-hospital complications, rehospitalization, death)		
	30-Day Cardiac Outcomes	1-Year Cardiac Outcomes	1 Year All-Cause
	Hazard Ratio (95% CI) *p-value*	Hazard Ratio (95% CI) p-value	Hazard Ratio (95% CI) p-value
# of patients with outcome	15	47	53
Mean heart rate	*.668 = ns*	*.655 = ns*	*.651 = ns*
Ventricular premature contractions <10 per hour	2.37 (.86-6.54) *.095*	1.98 (1.1-2.3.57) *.023*	*2.111 (1.216-3.665)* *.008*
New ST event (depression >.1 millivolts)	*.384 = ns*	1.240 (.985-1.562) *.068*	*1.238 (.989-1.549)* *.062*
SDNN: Standard Deviation of all normal R-R intervals (ms)	.98 (.96-.99) *.008*	.990 (.981-.999) *.034*	*.989 (.981-.998)* *.014*
SDANN: Standard deviation of the average of normal R-to-R intervals in all 5-min segments (ms)	.97 (.953-.996) *.021*	.988 (.977-.998) *.024*	*.987 (.977-.997)* *.010*
SDNN index: Average of 5-min standard deviations of normal R-R intervals (ms)	.96 (.930-.995) *.023*	*.165 = ns*	*.988 (.974-1.002)* *.089*
rMSSD: Root mean square of successive differences of normal R-R intervals (ms)	.96 (,92-1.0) *.060*	*.653 = ns*	*.655 = ns*
pNN50: Percentage of normal R-R intervals >50 milliseconds different from previous normal R-R interval	*.101 = ns*	*.538 = ns*	*.428 = ns*
TP: Total power (ms^2)	.42 (.25-.72) *.002*	.62 (.41-.93) *.022*	.589 (.399-.869) *.008*
HF: Average of 5-min segments of high frequency power (ms^2)	.45 (.25-.81) *.007*	*.296 = ns*	*.235 = ns*
LF: Average of 5-min segments of low frequency power (ms^2)	.42 (.25-.74) *.002*	.71(.52-.99) *.043*	.697 (.513-.949) *.022*
VLF: Very low frequency power, averages of 5-minute segments (ms^2)	.53 (.33-.831) *.006*	.71 (.52-97) *.029*	.670 (.503-.894) *.007*
ULF: Ultra low frequency power (ms^2)	.44 (.22-.89) *.021*	.65 (.44-.94) *.024*	.622 (.437-.886) *.008*
NHF: Normalized 5-min intervals of high frequency power (nu)	*.652 = ns*	1.021 (.996-1.046) *.098*	1.024 (1.000-1.048) *.048*
LHF: Normalized 5-min segments of low frequency power (nu)	*.410 = ns*	.98 (.960-1.001) *.065*	.979 (.960-.999) *.038*
DFA1: Short-term fractal scaling exponent (exponent value)	*.321 = ns*	.33 (.099-1.096) *.070*	.29 (.094-.906) *.033*
SD12: Poincaré Ratio	*.902 = ns*	*.202 = ns*	6.47 (.812-51.55) *.078*
Turbulence Onset >0.0% (traditional normal cut-point)	*.351 = ns*	1.785 (.996-3.200) *.052*	*1.742 (1.004-2.025)* *.048*
Turbulence Onset >.0100%	3.732 (1.188-11.722) *.024*	2.491 (1.381-4.492) *.002*	2.199 (1.271-3.804) *.005*
Turbulence Slope <2.5 ms/R-R interval (traditional normal cut-point)	2.47 (1.26-9.57) *.016*	2.52 (1.37-4.62) *.003*	2.33 (1.31-4.16) *.004*
Turbulence Slope <2.8 ms/R-R interval	5.58 (1.98-15.69) *.001*	2.97 (1.64-5.37) *<.001*	2.71 (1.54-4.76) *.001*
Heart Rate Turbulence score with traditional cut-points Overall model for 3 risk categories: Low, Medium, High	1.75 (.90-3.41) *.098*	1.56 (.107-2.9) *.021*	1.51 (1.05-2.16) *.025*

Table 3 Legend

CI: confidence interval VPC: ventricular premature contractions ns: not significant	Hazard ratio and confidence interval only reported for p-value ≤0.10 Bold identifies p-values <.10

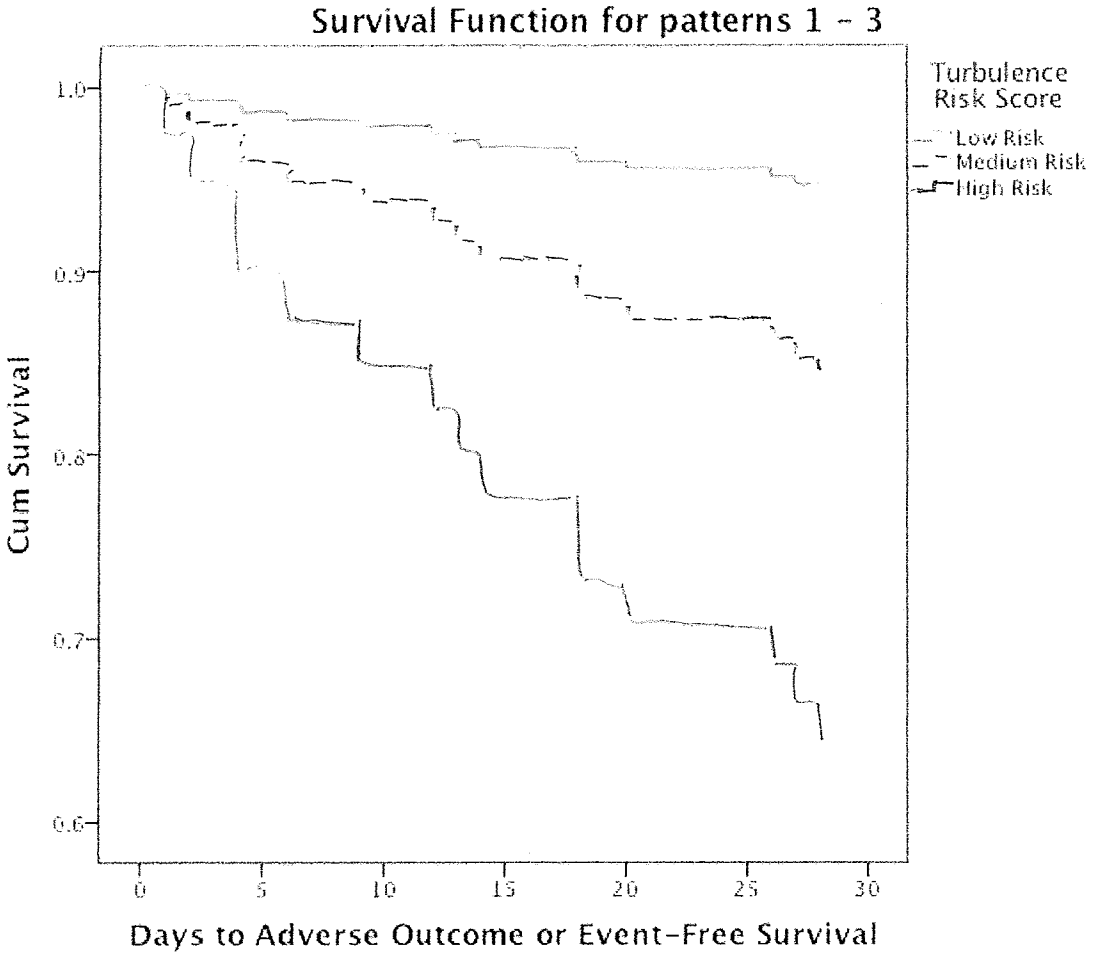
Table 4: Heart Rate Turbulence and Clinical Variables in Unstable Angina Patients
Comparison of Cox Regression Models for 30-Day and 1-Year Outcomes

	Variables in the Model			Full Model	
	Hazard Ratio	95% Confidence interval	p-value	Chi Square (p-value)	C-Statistic
30-Day Cardiac Outcomes (15 events)					
Model 1. Turbulence Onset (TO ≥ -0.0100%)	3.121	.949 – 10.264	.061	8.924 (.012)	.708
50% occlusion of left main coronary artery*	2.346	.713 – 7.721	.160		
Model 2. Turbulence Slope (TS ≤ 2.8ms/R-R interval)	5.712	2.029 – 16.079	.001	19.079 (<.001)	.767
50% occlusion of left main coronary artery*	3.737	1.186 –11.773	.024		
Model 3. Turbulence Risk Score revised - 3 risk categories:					
Low (TO<-0.0100% and TS>2.8ms/R-R)	---	Reference value	.010	16.684 (.001)	.769
Medium (TO≥0.0100% or TS≤2.8ms/R-R)	.2.164	.451 – 10.393	.335		
High (TO≥-0.0100% and TS≤2.8ms/R-R)	6.892	1.805 – 26.317	.005		
50% occlusion of left main coronary artery*	2.949	.883 – 9.847	.079		
1-Year Cardiac Outcomes (47 events)					
Model 1. Turbulence Onset (TO ≥ -0.0100%)	2.691	1/437 – 5.040	.002	30.875 (<.001)	.797
50% occlusion of left main coronary artery*	.925	.925 – 4.612	.077		
Living without significant other	1.663	1.663 – 5.596	<.001		
Diabetes	1.582	,870 – 2.876	.133		
Age>70 years	.568	.289 – 1.117	.101		
Model 2. Turbulence Slope (TS ≤ 2.8ms/R-R interval)	3.183	1.739 – 5.827	<.001	35.625 (<.001)	.790
50% occlusion of left main coronary artery*	3.536	1.555 – 8.041	.003		
Living without significant other	2.624	1.432 – 4810	.002		
Diabetes	1.638	.891 – 3.011	.112		
Age>70 years	1.633	.839 – 3.178	.149		
Model 3. Turbulence Risk Score revised - 3 risk categories:					
Low (TO<-0.0100% and TS>2.8ms/R-R)	---	Reference Value	.001	36.158 (<.001)	.812
Medium (TO≥0.0100% or TS≤2.8ms/R-R)	2.247	1.017 – 4.963	.045		
High (TO≥-0.0100% and TS≤2.8ms/R-R)	3.920	1.941 – 7.877	<.001		
50% occlusion of left main coronary artery*	2.474	1.062 - 5.761	.036		
Living without significant other	2.905	1.581 – 5.339	.001		
Diabetes	1.623	.874 – 3.014	.125		
Age>70 years	1.760	.889 – 3.482	.105		
1-Year All-Cause Outcomes (53 events)					
Model 1. Turbulence Onset (TO ≥ -0.0100%)	2.302	1.289 – 4.113	.005	29.483 (<.001)	.806
50% occlusion of left main coronary artery*	1.786	.812 – 3.928	.150		
Living without significant other	2.776	1.557 – 4.950	.001		
Diabetes	1.955	1.123 – 3.404	.018		
Age>70 years	1.572	.842 – 2.933	.156		
Model 2. Turbulence Slope (TS ≤ 2.8ms/R-R interval)	2.827	1.591 – 5.023	<.001	34.551 (<.001)	.785
50% occlusion of left main coronary artery*	2.733	1.226 – 6.092	.014		
Living without significant other	2.411	1.357 – 4.283	.003		
Diabetes	2.050	1.169 – 3.597	.012		
Age>70 years	1.482	.799 -2.749	.212		
Model 3. Turbulence Risk Score revised - 3 risk categories:					
Low (TO<-0.0100% and TS>2.8ms/R-R)	---	Reference value	.002	34.429 (<.001)	.810
Medium (TO≥0.0100% or TS≤2.8ms/R-R)	1.843	.891 -3.812	.099		
High (TO≥-0.0100% and TS≤2.8ms/R-R)	3.316	1.726 – 6.371	<.001		
50% occlusion of left main coronary artery*	2.122	9.35 – 4.815	.072		
Living without significant other	2.659	1.491 – 4.740	.001		
Diabetes	2.038	1.148 – 3.618	.015		
Age>70 years	1.547	.824 – 2.905	.175		

Table 4 Legend

* 50% occlusion of left main artery per present or past cardiac catheterization
ms=milliseconds

Figure 1. Turbulence Risk Score and 30-Day Cardiac Outcomes



Categories:

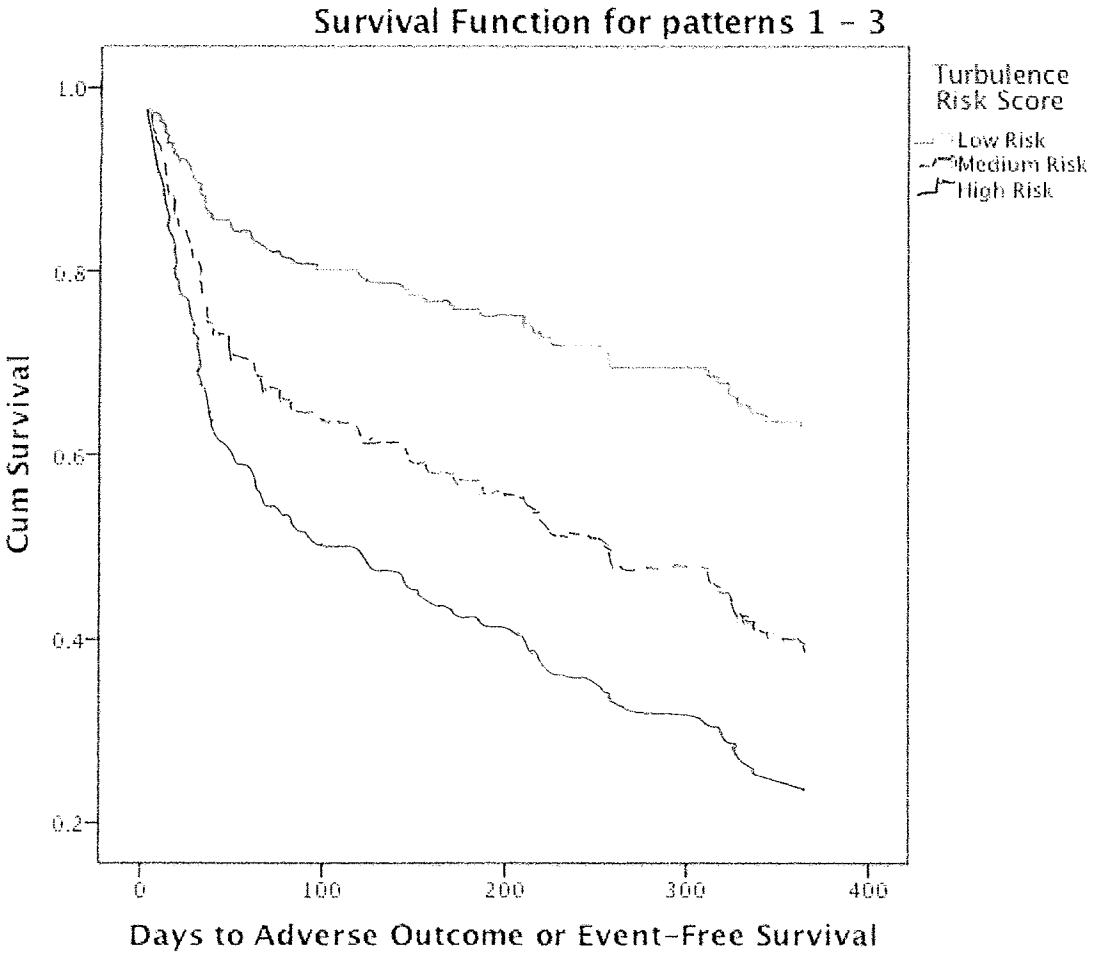
Low Risk = turbulence onset < -0.0100% and turbulence slope >2.8 ms/RR interval or fewer than 5 premature contractions in Holter recording (n=55)

Medium Risk = either turbulence onset > -0.0100% or turbulence slope <2.8 ms/RR interval (n=25)

High Risk = both turbulence onset > -0.0100% and turbulence slope <2.8 ms/RR interval (n=22)

	Wald Statistic	p-value	Hazard ratio	95% Confidence Interval
Low Risk	9.518	.009	Reference value	
Medium Risk	2.037	.154	2.975	0.666-13.293
High Risk	9.067	.003	7.690	2.038-29.010
Omnibus Test of Model Coefficients: Chi Square = 12.400; p-value = .002				

Figure 2. Turbulence Risk Score and 1-Year Cardiac Outcomes



Categories:

Low Risk = turbulence onset < -0.0100% and turbulence slope >2.8 ms/RR interval or fewer than 5 ventricular premature contractions in Holter recording (n=55)

Medium Risk = either turbulence onset >0 -.0100% or turbulence slope <2.8 ms/RR interval (n=25)

High Risk = both turbulence onset > -0.0100% and turbulence slope <2.8 ms/RR interval (n=22)

	Wald Statistic	p-value	Hazard ratio	95% Confidence Interval
Low Risk	12.285	.002	Reference value	
Medium Risk	4.580	.012	2.053	1.062-3.966
High Risk	11.880	.001	3.136	1.637-6.006
Omnibus Test of Model Coefficients: Chi Square = 13.356; p-value = .001				

Chapter 5

Article 4 – Prognostic Value of Heart Rate Turbulence for Risk Assessment in Unstable Angina and Non-ST Elevation Myocardial Infarction Patients

Chapter 5

Prognostic Value of Heart Rate Turbulence for Risk Assessment in Unstable Angina and Non-ST Elevation Myocardial Infarction Patients

Short Title: Heart Rate Turbulence in Non-STEMI/Unstable Angina

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Abstract

Purpose: We sought to examine the prognostic value heart rate turbulence (HRT), derived from electrocardiographic recordings initiated in the emergency department (ED) in non-ST elevation myocardial infarction (NSTEMI) and unstable angina (UA) patients.

Methods: Twenty-four hour Holter recordings were started ~45 minutes after ED arrival in patients with cardiac symptoms. Patients subsequently diagnosed with NSTEMI or UA who had recordings with ≥18 hours of sinus rhythm and sufficient data to compute Thrombolysis In Myocardial Infarction (TIMI) risk scores were chosen for analysis (N=166). Endpoints were emergent cardiac ED reentry and/or death at 30 days and 1 year.

Results: In Cox Regression models, HRT and TIMI risk scores together were significant predictors of 30-day (Model Chi Square=13.200, p=.001, C-statistic=.725) and 1-year (Model Chi Square=31.160, p<.001, C-statistic=.695) endpoints, outperforming either measure alone.

Conclusions: HRT measurement, initiated in the ED, may provide additional, incremental value to TIMI risk assessment scores for NSTEMI and UA patients.

Abbreviations and Acronyms
ACS = acute coronary syndrome
CABG = coronary artery bypass graft
CAD = coronary artery disease
CI = confidence interval
ECG = electrocardiography
ED = emergency department
HR = hazard ratio (ratio of incident rates; estimates relative risk)
HRT = heart rate turbulence
HRV = heart rate variability
MI = myocardial infarction
ms = milliseconds
PCI = percutaneous coronary intervention
TIMI = Thrombolysis in Myocardial Infarction (risk score)
TO = turbulence onset
TS = turbulence slope
UA = unstable angina
VPC = ventricular premature contraction

Key Words:

Acute coronary syndrome

Electrocardiographic monitoring

Heart rate turbulence

Non-ST elevation myocardial infarction

Outcomes

Prognosis

Unstable angina

Introduction

Patients who present to a hospital emergency department (ED) with ischemic discomfort that is subsequently diagnosed as unstable angina (UA) or non-ST elevation myocardial infarction (NSTEMI) are a heterogeneous group in terms of risk for death or nonfatal cardiac events. The most recent guidelines for the management of patients with UA or NSTEMI (1) recommend the use of risk stratification tools such as the Thrombolysis In Myocardial Infarction (TIMI) risk score (2) to assess the patient's likelihood of future adverse cardiac events.

Antman et al developed the TIMI risk score (2) composed of 7 (1-point) risk indicators rated on presentation to the ED. The composite end points (all-cause mortality, new or recurrent MI, or severe recurrent ischemia prompting urgent revascularization within 14 days) increase as the TIMI risk score increases. Additional research has demonstrated the accuracy of the TIMI risk score in predicting 30-day (3,4) and 1-year (5) outcomes, including myocardial infarction (MI) or cardiovascular death, in ED patients with cardiac symptoms who do not have ST elevation on the electrocardiogram.

Because all patients who present to the ED with symptoms suggestive of acute coronary syndrome (ACS) receive continuous electrocardiographic (ECG) monitoring as part of their routine care, we sought to determine if the ECG measure, heart rate turbulence (HRT), could be used to provide prognostic information. HRT refers to fluctuations in the cardiac cycle in response to a ventricular premature complex (VPC) (6). The two phases of oscillation, acceleration followed by deceleration, are measured with parameters termed turbulence onset (TO) and turbulence slope (TS). The two HRT parameters examine the period encompassing at least two sinus RR intervals prior to a ventricular beat, the VPC itself, the ensuing compensatory pause, and the subsequent

15 sinus intervals. To calculate TO and/or TS, at least 5 VPCs during a 24-hour ECG recording are required (7).

Abnormal HRT in healed myocardial infarction – measured 2 to 3 weeks after the index event - has been shown to identify individuals who are 3.2 times more likely to die during 21 months of follow-up (8). HRT also has been examined in recordings started immediately after an MI patient's admission to a hospital's coronary care unit, and abnormal measures have been associated with higher risk of mortality up to 360 days (9). In UA patients, abnormal HRT measured within 24 hours of admission has been shown to confer an increased risk for cardiovascular mortality over the ensuing 6 months (10). What remains unknown is whether abnormal HRT measured at the earliest possible phase of ACS care when a patient is initially attached to a cardiac monitor in the ED would have prognostic value. If HRT has prognostic value during the earliest phase of care, future cardiac monitor algorithms could be designed to measure this parameter to augment the traditional TIMI risk tools, potentially, providing a basis for therapeutic decision-making.

The opportunity to investigate HRT during the earliest phase of care was available to us from our Ischemia Monitoring and Mapping in the Emergency Department In Appropriate Triage and Evaluation of Acute Ischemic Myocardium (IMMEDIATE AIM) study, a prospective clinical trial of 1308 patients presenting to our institution's ED with symptoms of ACS funded by NIH (RO1HL69753). Twenty-four hour 12-lead ECG recordings were started in the ED for 1308 patients with a median door to ECG start time of 45 minutes (median time from symptom onset was 4 hours). Thus, the aim of our analysis was to determine whether abnormal HRT, measured in the initial 24 hours after ED presentation, in patients with ACS symptoms but no ST elevation, would provide prognostic information equal to or above and beyond the TIMI risk score for short-term

(30-day) or long-term (1-year) outcomes, identified as the composite end-point of cardiac-related ED readmission, cardiac rehospitalization, and/or cardiac death.

Methods

Sample and Data Collection. Of 1308 ED patient visits for symptoms of ACS, there were 1153 unique patients enrolled from 2002 to 2004. Verbal assent was obtained at time of recruitment, and written consent was obtained from the patient or surrogate after stabilization. We placed 24-hour Holter recorders (H-Scribe System, Mortara Instrument, Milwaukee, WI) as soon as possible after patients arrived in the ED. Trained research nurses applied the ECG leads, supervised monitoring, and downloaded data to the H-Scribe review station. Radiolucent electrodes and lead wires were used to aid uninterrupted monitoring during procedures, such as cardiac catheterization. The University of California, San Francisco (UCSF) institutional review board approved the study. Study design and data collection have been detailed elsewhere (11).

Patients' demographic and clinical information was gathered upon enrollment or extracted later via chart review.

Follow-up. We followed patients for one year after their initial ED visit and hospitalization. Data regarding patients' ED or hospital readmissions and survival was collected via telephone calls, medical records, and the public access social security mortality database. One-year survival and rehospitalization information was obtained for all patients in the current analysis.

Inclusion Criteria. ECG recordings with at least 18 hours of normal sinus beats, which represented individuals admitted to the hospital for rule out myocardial infarction (MI) and who received a discharge diagnosis of unstable angina or NSTEMI, were included in the analysis. NSTEMI was identified by ST-segment depression or T-wave

inversion, positive serum troponin biomarker, the absence of ST-segment elevation, and chest pain or equivalent angina symptoms (1). Unstable angina was defined according to Diagnosis Related Group for angina pectoris, intermediate coronary syndrome, i.e. evidence of coronary occlusion without myocardial infarction. Recordings were automatically scanned, manually edited and annotated.

Patients without enough clinical data to compute a TIMI score were excluded from the final analysis.

Endpoints. The primary endpoint comprised a composite of cardiac-related events within 30 days and 1 year of ED discharge, including return to the ED with cardiac symptoms and subsequent cardiac diagnosis, cardiac rehospitalization and/or cardiac death. Treatment in the emergency room with a cardiac diagnosis (whether followed by transfer to hospital cardiac care or not) was considered an emergent reentry. Pre-scheduled cardiac procedures were not included in the analysis. Patients with more than one event (specifically, patients who were readmitted and later died) were included in the analysis one time only. Return to the ED or rehospitalization was considered cardiac, if the patient was diagnosed with a reoccurring ACS episode and/or heart failure. Death was considered to be due to a cardiac cause, if sudden cardiac death, acute myocardial infarction or heart failure was reported in the hospital record or in patient follow-up data.

Demographic and Clinical Variables. Demographic information was collected, including gender, race, comorbidities, and coronary artery disease (CAD) history. The 7 parameters required to calculate a TIMI risk score were obtained from the patient's ED record, cardiac catheterization report, and/or discharge summary, including:

1) Age (≥65 years)

2) Number of CAD risk factors (≥3)

3) Known coronary artery stenosis >50%

4) Aspirin use within the previous 7 days

5) Angina episodes within the prior 24 hours

6) ST changes >0.5 millimeters

7) Positive cardiac marker.

Each risk parameter was assigned 1 point, and risk increases with ascending values. For this analysis, TIMI risk scores were divided into 6 categories; patients with 0-1 risk factor were grouped together into one low risk category, and patients with scores of 6-7 were placed into the highest risk category, in accordance with the literature (2). Categories 2 through 5 remained the same. If extent of coronary disease was unknown, the default position was to count the parameter as "0". If aspirin was listed as a routine medication, the default position was to count the parameter as "1" (unless there was mention in the patient's chart that the medication had not been taken); if there was no mention of aspirin in the chart, the parameter was counted as "0". Beyond these default decisions, if data for computing the TIMI score was missing, the score was not computed and the participant was not included in the analysis.

Electrocardiographic Monitoring Variables. Variables derived from 24-hour Holter monitoring, such as mean heart rate and number of ventricular premature contractions (VPC), were calculated, in addition, to HRT. The ECG sampling rate was 180 samples/second.

ECG recordings were automatically scanned and manually edited using H-Scribe analysis software at the ECG Monitoring Research Laboratory, UCSF, School of Nursing. ECG research software, validated by the Heart Rate Variability Laboratory, Washington University School of Medicine, St. Louis, Missouri, verified eligible recordings, and computed HRT.

Heart Rate Turbulence Analysis. To obtain HRT variables, R-R intervals were exported as text files and transformed via a dedicated MatLab program (Mathworks, Natick, Massachusetts) for compatibility with the research software. TO and TS were derived from recordings with sinus rhythm and ≥25 VPCs during the recording time in accordance with previous research (8). Isolated VPC were used to arrive at values for TO and TS, as described by Bauer et al (7).

Turbulence onset (TO), indicator of early sinus acceleration after a VPC, was calculated by measuring the differences between 2 sinus beats following a compensatory pause (RR_1 and RR_2) and the 2 sinus beats immediately prior to the VPC (RR_{-1} and RR_{-2}), using the formula: $\{[(RR_1 + RR_2) - (RR_{-1} + RR_{-2})]/(RR_{-1} + RR_{-2}) \times 100\}$, expressed as a percentage (7,8,9).

Turbulence slope (TS), indicator of late sinus deceleration after a VPC, was measured as the maximum positive slope of all slopes in a series of regression lines derived from 5 consecutive sinus beats within the first 15 sinus beats after the VPC. TS is expressed in milliseconds (ms) per RR interval (7,8,9).

Dichotomous HRT variables were created using cut-points for normal values according to published clinical standards, i.e. TO<0.0% and TS>2.5 ms/RR interval. Risk categories were established according to published measurement standards (7):

- Low risk = "normal" HRT variables (TO<0.0% and TS>2.5 ms/RR interval)
- Medium risk = 1 "abnormal" HRT variable (TO≥0.0% or TS≤2.5 ms/RR interval)
- High risk = 2 abnormal HRT variables (TO≥0.0% and TS≤2.5 ms/RR interval).

Statistical Analyses. Descriptive statistics were used to examine demographic and clinical variables. To assess proportional hazard across time, univariate Cox regression survival analyses were performed for each outcome using the TIMI or HRT risk scores. Harrell's Cumulative Index (the C-statistic, a measure of concordance) was

calculated to evaluate models' predictive ability (12).

HRT and TIMI variables and risk scores were retested within multivariate regression models in relation to outcomes. Alpha was set at <.05. C-statistics were generated again to reassess the models' predictive ability.

Bootstrapping (1000 samples, 95% confidence interval) was used to examine model stability (alpha<.05) (13). Analyses were performed using International Business Machines statistical software (SPSS 19, IBM, Armonk, NY).

Results

Patient Characteristics. Out of 1153 unique patient recordings, we determined that 256 represented patients diagnosed with unstable angina or unstable angina; 173 recordings had ≥18 hours of analyzable sinus rhythm. Seven patients were missing parameters, beyond the default positions, required to compute the TIMI score. Complete ECG, clinical, and follow-up data was available for a total of 166 patients. For this subgroup of IMMEDIATE AIM patients, the median ECG Holter recording time was 1439 minutes; median time between symptom onset and Holter placement was 4 hours and 15 minutes; and median door-to-Holter time was 46 minutes. The median length of hospital stay was 3 days with a range of 1-26 days; 41 patients (25%) stayed in the hospital 1 day. The median follow-up period for survivors was 368 days.

A majority of patients had prior history of coronary artery disease (n=115, 69%). Among these patients, 76 had had a previous MI (54%); 64 had had a previous percutaneous coronary intervention (PCI) (39%) and 37 had had a coronary artery bypass graft (CABG) (22%). One hundred eleven patients had had one or more cardiac catheterizations (67%). See Table 1 for additional patient characteristics.

Outcomes. Within 30 days of ED discharge, 140 (84%) patients had event-free outcomes; 26 (16%) experienced adverse cardiac events. Twenty-one patients returned

to the ED with cardiac symptoms and received a cardiac-related diagnosis; 16 were readmitted to the hospital. Five people died within the first 30 days.

After the first 30-day period, an additional 59 patients (36%) returned to the ED and received a cardiac diagnosis; 44 of those were readmitted to the hospital. Four more people died due to a cardiac-related cause bringing the total number of deaths within one year to 9 (5%). Over the course of the follow-up year, 77 (47%) patients remained event-free. See Table 2 for patient outcomes.

TIMI and Heart Rate Turbulence Risk Scores. TIMI and HRT risk scores were computed for each patient. The numbers of patients within each category are in listed Table 3 (TIMI) and Table 4 (HRT).

Twenty-seven patients had too few VPCs to calculate TO or TS. To examine the usefulness of the turbulence measures individually, TO dichotomized at 0% and TS dichotomized at 2.5 ms/RR interval were tested in a univariate Cox regression model, and both were significant predictors of 1-year outcomes in patients for whom the scores could be computed (TO, hazard ratio = 2.100, 95% Confidence Interval [CI} 1.340-3.292, p=.001; TS, hazard ratio = 2.302, 95% CI 1.459-3.632, p<.001; n=139; 79 events). TS was a significant predictor of 30-day outcomes (TS, hazard ratio 2.704, 95% C! 1214-6020, p=.015), but TO was not.

To compute turbulence risk scores, the 27 patients without TO or TS measurements due to too few VPCs were placed in the low risk group in accordance with standards (7). Results of the TIMI and HRT risk scores in relation to 30-day and 1-year outcomes examined in univariate Cox regression models are reported in Table 5. Multivariate models with both TIMI and HRT risk scores together in relation to 30-day and 1-year outcomes are presented in Table 6.

The TIMI risk score categories were divided into 3 groups for visual comparison to

the 3 categories in the HRT risk score. Since categories 0-3 were closely aligned, category 4 was medium risk, and 5-6 showed highest risk in our sample, the divisions were created accordingly. A Cox Regression model examining the 1-year outcomes is in Figure 1 (model statistics are: Chi Square 31.263, p<.001, C statistic = .687; HRT risk score hazard ratio = 1.870, 95% CI 1.428-2.448; TIMI risk score hazard ratio = 1.535, 95% CI 1.176-2.003, p=.002).

The HRT risk score, again including all 166 patients, then was examined in a multivariate Cox regression model with the TIMI score parameters included as 7 separate variables. In relation to 30-day outcomes, the overall model was significant (Chi Square = 18.037, p=.021), and the turbulence risk score was the most significant independent predictor in the model (hazard ratio = 1.843, 95%CI 1.107-3.069, p=.019). The only other variable the remained a significant predictor was 2 severe episodes of angina within the prior 24-hours (hazard ratio = .3.18, 95%CI .105-.958, p=.042). In relation to 1-year outcomes, the turbulence risk score was again the most significant predictor (hazard ratio = 1.908, 95%CI 1.433-2.542, p<.001). More than one severe episode of angina within the previous 24 hours (hazard ratio - .588 95% CI .350-.986) and use of aspirin within the previous 7 days (hazard ratio = .578 96% CI .343-.975, p=.040) also were significant independent predictors. Examining the TIMI parameters separately in a multivariate model improved the C-statistic marginally to .735 in relation to 30-day outcomes, and .724 in relation to 1-year outcomes.

Discussion

Our findings offer evidence that HRT measured early in the ED has accuracy, approximately equivalent to the TIMI risk score, in predicting 30 day and 1 year outcomes. Since Schmidt et al showed that absence of HRT was a significant predictor of total mortality in 100 patients with coronary heart disease (6), numerous studies have

expanded those findings to aid in physiological understanding (14-17) and clinical application (8-10,18-21). However, optimal timing for clinical assessment of HRT has not been established (7). In the study by Schmidt et al, HRT was measured during a stable period from 2 weeks up to 3 months after patients experienced an MI (6). To investigate the relationship between HRT and heart rate and test this association in acute MI survivors, Bauer et al examined HRT in patients 2-3 weeks after MI (8). Huikuri et al (20) measured HRT at two time periods after MI in 2 patient groups, early (defined after 5 to 21 days in the first cohort, and 2 to 4 weeks in the second) and late (at 6 weeks in the first cohort, and 10-14 weeks in the second). The investigators found that HRT improved over time, and that both time periods for measurement were prognostic of ventricular arrhythmias, fatal or near-fatal arrhythmic events. Sade et al (9) measured HRT immediately after admission to the coronary care unit, within 6 hours of symptom onset, in MI patients. In the study of unstable angina patients by Lanza et al, 24-hour Holter recordings were started within 24 hours of hospital admission. (10). Both Sade and Lanza found HRT to be highly prognostic of adverse outcomes, including death 6 months to one year after an ACS episode. While optimal timing of HRT assessment was not an aim in our study, we did establish that HRT measured from 24-hour recordings started early after ED arrival was associated with outcomes up to a year after the patient's visit.

A high percentage of patients in our study were readmitted to the hospital for cardiac reasons (48%) over the course of one year compared to the literature in which 30% is cited (22). However, more than 2 of 3 had a previous diagnosis of CAD, and over 1 in 4 had a comorbidity of diabetes, reflecting an ill group of people with advanced disease and/or comorbidities, possibly contributing to the relatively high percentage of adverse outcomes. In any event, hospital readmittance after an ED visit, in which ACS is

diagnosed, is common and contributes directly to the economic burden of healthcare. Johnson and colleagues reported that even one cardiac rehospitalization within a year of ED presentation with ACS increased direct care cost by nearly $10,000 (22). To be sure, return to the ED and rehospitalization in itself is not a reflection of quality of care. A structured, decision-making approach has been found to be safe and cost-effective, and is recommended (1). An additional risk-assessment tool, such as HRT, could be a practical choice to help healthcare providers identify non-STEMI and UA patients with increased risk of 30-day or 1-year adverse cardiac events.

The C-statistic indicates the ability of a statistical model to predict an outcome, and can be used for multivariable models, providing information similar to the area under the curve for univariate models. A C-statistic value of .5 would indicate that the model has a 50% chance of predicting an accurate outcome, or, in other words, provide no additional information. The C-statistic scores in our TIMI and HRT risk score univariate models, in relation to both outcomes range from 60.5% (TIMI risk score as a predictor of 1-year outcomes) to 68.7% (TIMI risk score as a predictor of 30-day outcomes). The HRT risk score provides an accurate estimate in 64.7% of patients' 30-day outcomes and 65.7% for 1-year outcomes. In a multivariate model, the TIMI and HRT risk scores, together, increase predictive ability to 72.5% for 30-day outcomes, and 69.5% for 1-year outcomes. Figure 1 provides a visual comparison. While this increase is only incremental, the results do indicate that the predictive ability of the HRT risk score is similar to that of the TIMI risk score. In cases for which TIMI parameters may be unknown or their acquisition delayed, the HRT risk score may provide a meaningful alternative, particularly, since this parameter can be obtained within the first 24-hours through routine ECG monitoring. This is the first study to our knowledge to examine HRT calculated from ECG recordings started within the first hour of presentation to the ED in

patients who arrive with symptoms of acute coronary syndrome, and are subsequently diagnosed with unstable angina or non-ST elevation MI.

Implications. Our findings suggest that evaluation of HRT to assist in identifying ACS patients at high risk for adverse cardiac events over the course of 30 days or 1 year could be a practical addition to continuous ECG monitoring. HRT has been shown to be an independent predictor of cardiovascular events in ACS patients without ST elevation with predictive ability similar to the TIMI risk score. Information about each parameter needed to compute the TIMI score may not always be immediately available. The HRT is a noninvasive measurement that can be derived from routine ECG monitoring and does not require multiple parameters to obtain. HRT may provide a reasonable adjunct and/or alternative means for risk stratification of ACS patients from the time they enter the ED with cardiac symptoms.

HRT can be computed from 24-hour ECG monitoring. Continuous 24-hours ECG monitoring for ACS patients is recommended (1), and cardiac patients are monitored from the time they enter the ED. With many patients staying in the hospital for 1 day (25% in our sample), the importance of gaining as much prognostic information as possible in a limited amount of time cannot be over emphasized. Measurement of HRT, incorporated into the routine cardiac monitoring of hospitalized ACS patients, is a reasonable next step toward reducing costs and saving lives. Future research could confirm the value of early measurement of HRT from the time the ACS patients enter the ED with an aim toward development of computer algorithms to add to bedside monitoring and aid in risk assessment.

Limitations: This was a retrospective analysis of data collected between 2002 and 2004. Practice standards for ACS management have been updated in the intervening time. The study was small and was hampered by ECG artifact and insufficient ECG

recording time, reflecting potential challenges to accurate assessment. In addition, HRT requires sinus beats to compute, so patients with atrial fibrillation could not be included. Our decision to include aspirin when possible, we confirmed the reason for rehospitalization and death, but not all medical records were available.

Conclusions: Measurement of HRT upon ED arrival in patients with cardiac symptoms could provide additional useful information to assess risk of emergent cardiac readmission and/or cardiac death within 30 days or one year in patients who have non-ST elevation ACS.

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Table 1: Characteristics of Unstable Angina/Non-ST elevation Myocardial Infarction Patients

Variable *Percentages refer to % of total N and are rounded to nearest half percent.*	Total number of patients N=166	Number of patients with Cardiac-related Events		Number of patients Event-Free N=77
		30-day N=26	1-year (including 30-day outcomes) N=89	
Mean age in years	65 ± 13	65 ± 12	66 ± 13	65 ± 12
Male	91 (55%)	13	44	47
Race				
African American	31 (19%)	4	24	7
Asian	44 (27%)	9	20	24
Caucasian	79 (48%)	12	36	43
American Native/Pacific Islander	12 (7%)	1	9	3
Latino ethnicity, n (% of total N)	15 (9%)	2	12	3
ACS Diagnoses				
Unstable angina	126 (64.7%)	21	72	54
Non ST-elevation myocardial infarction	40 (24.6%)	5	17	23
History or Comorbidity				
Coronary artery disease prior history	115 (69%)	19	70	45
Family history of coronary artery disease	88 (53%)	12	41	47
Diabetes	44 (27%)	12	30	14
Hypertension	128 (77%)	18	73	55
Hypercholesterolemia	113 (68%)	16	64	49
Current smoker	30 (18%)	3	17	13
In-hospital Therapy				
Beta blocker	147 (89%)	23	78	69
Percutaneous coronary intervention (PCI)	52 (31%)	10	27	25
Coronary artery bypass graft (CABG)	12 (7%)	3	6	6
24-hour Electrocardiographic Data				
Mean heart rate, beats per minute	65±11	68±13	65±11	65±10
Mean number of VPCs per hour (median)	20±38 (4)	28±40 (12)	24±35 (7)	15±40 (3)
Mean turbulence onset (n=139), %	-0.0053±,0264	-0.0±.0241	-0006±.0286	-.0129±.0212
Mean turbulence slope (n=139), ms/RR interval	6.411±4.684	3.4716±3.640	5.673±5.738	7.354±5.984

ms = milliseconds
VPC = ventricular premature contraction

Table 2. Patients' Cardiovascular Outcome	
30-day cardiovascular outcomes	
• Returned to Emergency Department (16 patients were admitted to the hospital from the ED)	21 (13%)
• Died	5 (3%)
• TOTAL 30-DAY CARDIOVASCULAR OUTCOMES	26 (16%)
1-year cardiovascular outcomes (including 30 day outcomes)	
• Returned to Emergency Department (60 patients were admitted to the hospital from the ED)	80 (48%)
• Died	9 (5%)
• TOTAL 1-YEAR CARDIOVASCULAR OUTCOMES	89 (54%)

Table 3. TIMI Risk Scores: Frequency of patients within each category

TIMI Category	Number of patients in category	Percent of Total N (N=166)
0-1 lowest risk	9	5.4
2 low risk	17	10.2
3 medium low risk	60	36.1
4 medium risk	49	29.5
5 medium high risk	28	16.9
6-7 high risk	3	1.8
TOTALS	**166**	**100.0**

Table 4. HRT Risk Scores: Frequency of patients within each category

HRT Category	Score Parameters	Number of patients in category	Percent of Total N (N=166)
low risk	TO< -0% and TS>2.5 ms/RR interval or too few VPCs to calculate	101	60.8%
medium risk	TO> -0% or TS<2.5 ms/RR interval	43	25.9%
high risk	TO> -0% and TS<2.5 ms/RR interval	22	13.3%
TOTALS		**166**	**100.0**

TO = turbulence onset; TS = turbulence slope
TS = turbulence slope
VPC = ventricular premature contractions

Table 5. Comparison of Heart Rate Turbulence & TIMI Risk Scores in Univariate Cox Regression (N=166)

30-Day Outcomes				
Risk Score Measure	**Model Chi Square**	**Model *p*-value**	**Hazard Ratio (95% CI)**	**C-Statistic**
HRT Risk	7.923	0.005	1.911 (1.198-3.048)	.647
TIMI Risk	6.702	0.010	1.613 (1.121-2.320)	.687
1-Year Outcomes				
Risk Score Measure	**Model Chi Square**	**Variable *p*-value**	**Hazard Ratio (95% CI)**	**C-Statistic**
HRT Risk	22.553	<0.001	1.851 (1.42-2.41)	.657
TIMI Risk	9.905	0.002	1.371 (1.13-1.67)	.605

Table 6. Heart Rate Turbulence & TIMI Risk Scores in Multivariate Cox Regression (N=166)

A. Single Model with HRT & TIMI Risk Scores: 30-Day Adverse Outcomes (26 events)

Model Chi Square (model *p*-value) = 13.200 (.001)

Model C-Statistic = .725

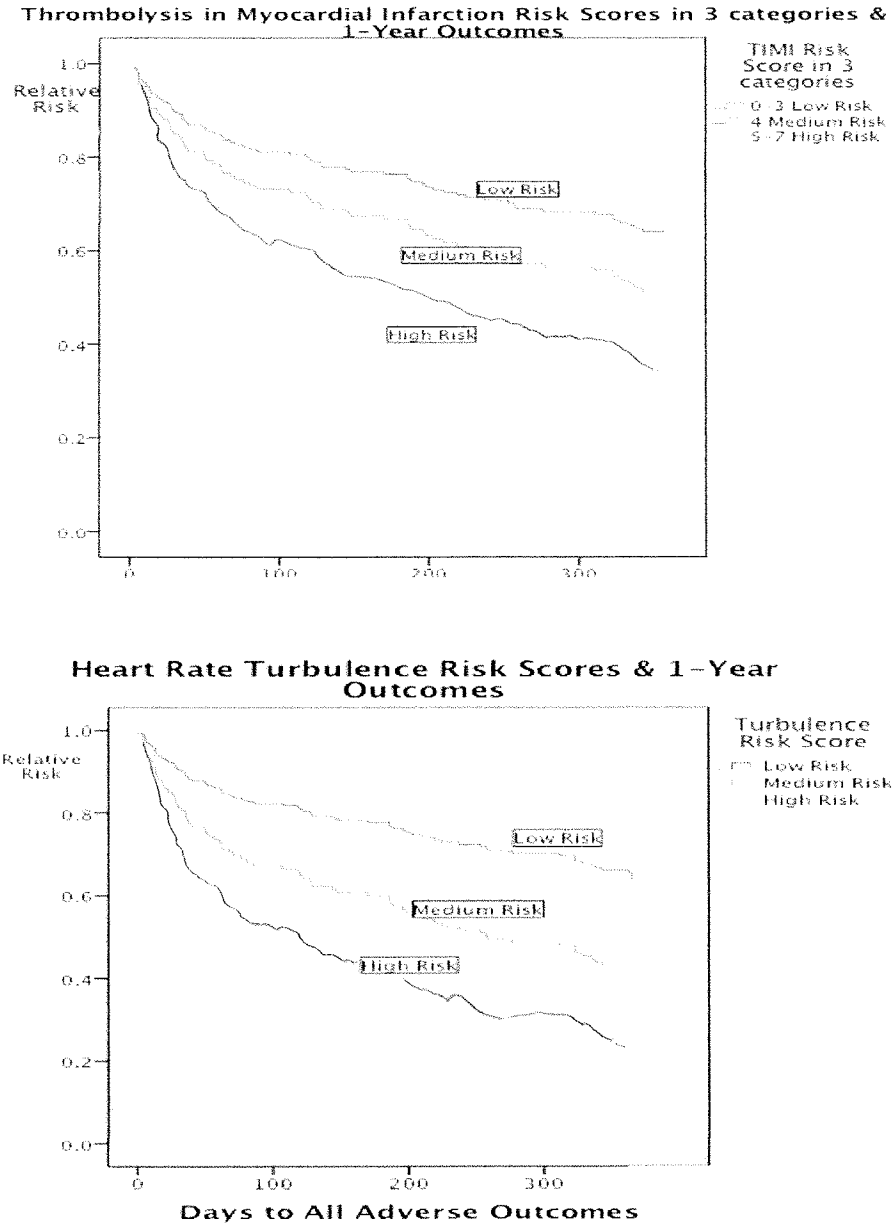
Risk Score Measure	Wald Statistic	Variable *p*-value	Hazard Ratio (95% CI)
HRT Risk	7.572	0.013	1.818 (1.33-2.915)
TIMI Risk	3.352	0.018	1.570 (1.080-2.283)

B. Single Model with HRT & TIMI Risk Scores: 1-Year Adverse Outcomes (89 events)

Model Chi Square (model *p*-value) = 31.089 (<.001)
Model C-Statistic = .695

Risk Score Measure	Wald Statistic	Variable *p*-value	Hazard Ratio (95% CI)
HRT Risk	20.776	<0.001	1.860 (1.424-2.428)
TIMI Risk	9.667	0.002	1.383 (1.127-1.696)

Figure 1. Comparison of Thrombolysis In Myocardial Infarction (TIMI) and Heart Rate Turbulence (HRT) Risk Scores in 1-Year ACS Outcomes of Emergent Cardiac readmission or Cardiac Death.



Patients start with a relative risk of 1.0 (in other words, 100% of the patients are alive) at emergency department discharge (upper right hand corner). Relative risk is equivalent to the percentage of patients correctly predicted to experience an adverse outcome, i.e. emergent cardiac readmission or death, over the course of one year.

Chapter 6

Conclusion

Conclusion

Electrocardiographic Autonomic Nervous System Predictors of Outcomes in Acute Coronary Syndrome Patients

In conclusion, the electrocardiographic (ECG) autonomic nervous system (ANS) predictors did demonstrate predictive value in outcomes of acute coronary syndrome (ACS) patients. Heart rate variability (HRV) or heart rate turbulence (HRT) can add incremental value to existing risk stratification assessments. HRV was a significant predictor of one-year ACS outcomes, including all cause rehospitalization and all-cause death, in multivariate analysis. Similarly, HRT was a significant predictor of outcomes. In comparison to the Thrombolysis in Myocardial Infarction (TIMI) score, HRT faired equally well. HRT may be a reasonable alternative to the TIMI score, if all the clinical parameters required for computation, are not available. HRT or HRV can be obtained from the routine monitoring that patients undergo. Large prospective studies are needed to verify these findings. Future directions may include cost assessment and work with bioengineers to develop algorithms that include these parameters. Risk stratification is an important component in the continuum of patient care. Potential tools that can assist in this effort could be readily available. Incorporation of ECG ANS markers into risk stratification may be a useful addition.

Additional Reading List

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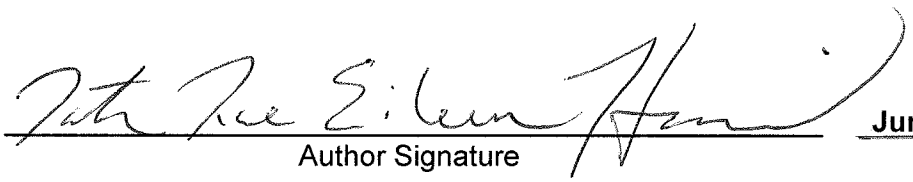

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