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Effects of Chronic Pelvic Pain on Heart Rate Variability in Women

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Abstract

Purpose: Interstitial cystitis/bladder pain syndrome and myofascial pelvic pain are frequently comorbid chronic pelvic pain disorders. Differences in bladder function between interstitial cystitis/bladder pain syndrome and myofascial pelvic pain suggest that efferent autonomic function may differentiate these syndromes. Heart rate variability, defined as the difference in duration of successive heartbeats, serves as an index of autonomic function by measuring its ability to modify heart rate in response to neurophysiological changes. High frequency heart rate variability was used as a reflection of more rapid vagally mediated (parasympathetic) changes.

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Low frequency heart rate variability signified slower fluctuations related to the baroreflex and sympathetic outflow.

Materials and Methods: Heart rate variability was derived by autoregressive frequency analysis of the continuous electrocardiogram recording of heart rate with the subject supine for 10 minutes, tilted 70 degrees with the head up for 30 minutes and supine again for 10 minutes. This institutional review board approved study included 105 female subjects, including 32 who were healthy, and 26 with interstitial cystitis/bladder pain syndrome, 12 with myofascial pelvic pain and 35 with interstitial cystitis/bladder pain syndrome plus myofascial pelvic pain.

Results: In all positions healthy controls had higher high frequency heart rate variability than women with interstitial cystitis/bladder pain syndrome and interstitial cystitis/bladder pain syndrome plus myofascial pelvic pain. Subjects with myofascial pelvic pain were similar to controls with greater high frequency heart rate variability at baseline (supine 1) and in upright positions than subjects with interstitial cystitis/bladder pain syndrome. Differences in low frequency heart rate variability were less evident while low-to-high frequency ratio differences appeared to be driven by the high frequency heart rate variability component.

Conclusions: Subjects with interstitial cystitis/bladder pain syndrome had diminished vagal activity and a shift toward sympathetic nervous system dominance. Overall these data support the hypothesis that changes in autonomic function occur in interstitial cystitis/bladder pain syndrome but not in myofascial pelvic pain. These changes may result from interstitial cystitis/bladder pain syndrome or contribute to its pathophysiology through abnormal self-regulatory function.

Keywords

urinary bladder; cystitis; interstitial; myofascial pain syndromes; heart rate; autonomic nervous system

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INTERSTITIAL cystitis/bladder pain syndrome is a common CPP disorder.[1] MPP is commonly comorbid with IC/BPS.[2] Little is known regarding ANS function in CPP, although we recently reported normal ANS structure in women with IC/BPS.[3] Beat-to-beat variation in HR, termed HRV, reflects ANS function, representing the relative sympathetic and parasympathetic contributions to HR control. HF-HRV assesses vagal parasympathetic function and mirrors the integrative system for adaptive self-regulation.[4]

Lutgendorf et al found higher baseline HR in subjects with IC/BPS, compatible with lower HF-HRV (not reported).[5] Additionally, HR and blood pressure increased more than expected during bladder hydrodistention in patients with IC/BPS.[6] Neither of these studies addressed the specificity of these autonomic changes for IC/BPS, particularly since reduced HF-HRV occurs in a variety of chronic pain conditions such as complex regional pain syndrome,[7] fibromyalgia,[8] chronic neck pain,[9] irritable bowel syndrome[10] and headache.[11] Therefore, HF-HRV might be a biomarker for pain related diseases.[12]

We hypothesized that unique ANS changes in IC/BPS absent from other CPP disorders underlie the bladder dysfunction that characterizes IC/BPS. The current study compared autonomic function between women with IC/BPS and those with MPP. Since women with IC/BPS report that stress commonly triggers IC/BPS flares,[13] we investigated whether

orthostatic stress might induce an abnormal HF-HRV response. These observations might reflect the underlying neural networks in CPP disorders and aid clinical evaluation with a noninvasive physiological marker. Thus, we expected to find that 1) healthy controls would exhibit higher HF-HRV than each pain group, 2) HF-HRV would be lowest in women with IC/BPS than in the other CPP groups and 3) women with IC/BPS would differ in their response to orthostatic stress.

MATERIALS AND METHODS

Subjects

This institutional review board approved study at University Hospitals Case Medical Center, Cleveland, Ohio, was part of the ICEPAC study.[14] All subjects provided informed consent. The study population (accrual between February 2011 and September 2014) consisted of women 18 to 80 years old with and without CPP. IC/BPS was defined according to NIDDK (National Institute of Diabetes and Digestive and Kidney Diseases) criteria.[1] MPP was defined as 3 months or greater of CPP unrelated to bladder state with 2 or more of 5 pelvic floor tender points scoring 4 or greater of 10 on a numerical rating scale from 2 kg pressure. MPI[15] was used to provide an overall pain score and the 1990 fibromyalgia examination[16] was used to assess for fibromyalgia. Subjects stopped autonomically active medications 5 days prior to testing except 3 in the IC/BPS plus MPP group who continued diphenhydramine, amitriptyline or gabapentin plus citalopram.

The control group consisted of women on no medication with no history or manifestation (in the last 5 years) of any disorder commonly comorbid with IC/BPS. All women also met general study exclusions, including pregnancy; active intent or current breastfeeding; hematuria or infection on urinalysis; 3 urinary tract infections in the last 12 months; pelvic or bladder neoplasm; evidence of an unstable medical disorder affecting renal, hepatic, cardiovascular, respiratory or endocrine (HbA1c greater than 6.1) systems; uncontrolled psychiatric illness (untreated depression or psychosis); any central or peripheral nervous system disorder (diabetic neuropathy regardless of HbA1c level, Parkinson disease, Alzheimer disease, multiple sclerosis or stroke); consumption of 10 or more alcoholic beverages per week; or any major surgical intervention with general anesthesia in the 90 days prior to enrollment.

Tilt Table Testing

Testing consisted of 10 minutes with the subject supine at baseline, 30 minutes with a head up tilt at 70 degrees and 10 minutes of supine rest. Data analysis incorporated the last 5 minutes while supine before head up (supine 1), the first 2 consecutive 10-minute segments while upright (upright 1 and upright 2, respectively) and the first 5 minutes supine after reclining (supine 2). The Model 1 Nexfin® Monitor was used to record a continuous electrocardiogram, allowing us to examine not only differences in resting HRV (supine 1) but also differences in reactivity to a physical stressor (upright positions) and recovery from this stressor (supine 2).

Heart Rate Variability Analysis

In each position the time in milliseconds between successive heartbeats, called IBIs, were obtained from electrocardiogram recordings, written in a text file and analyzed using Kubios HRV 2.0[17] in accordance with published guidelines.[18] Artifacts in the R-to-R series were visually detected. We applied an artifact correction level that would differentiate and remove artifacts, differing abnormal IBIs from the mean IBI. Kubios provides time and frequency domain estimates of HRV. Time domain estimates are calculated based only on IBIs and associated variability while frequency domain estimates are derived via a power spectrum density analysis. In the current investigation the primary findings were virtually identical using either method as vagally mediated time and frequency domain estimates of HRV highly correlated (each r >0.920, data not shown).

The current investigation reports power spectrum density results, which allows for the examination of different components (sources) of variability. Specifically autoregressive estimates of HF (0.16 to 0.4 Hz) and LF (0.04 to 0.15 Hz) frequency power bands were obtained from this analysis. HF-HRV reflects vagal activity while LF-HRV in the supine position represents sympathetic baroreflex activity.[19] The LF/HF ratio was used as an index of sympathovagal balance. Time domain analyses can be used to derive vagally mediated HRV in addition to vagal and sympathetic nervous system influenced HRV, but not sympathetic baroreflex activity alone.

To better approximate a normal distribution and meet the assumptions of linear analyses the natural log (ln) was applied to all HF-HRV and LF-HRV mean values. HF peak values were controlled for differences in respiratory rate among subjects.[20]

Statistical Analysis

IBM® SPSS® 19, Statistica 6.0 (Dell StatSoft, Tulsa, Oklahoma) and PRISM® 6.0 for Windows® were used to examine differences in HR, HF-HRV, HF peak and the LF/HF ratio across time between groups and with multiple 2-way (1 between factor and 1 within factor) ANOVAs. Within subject factors included physiological measures (ie HR, HF-HRV, LF-HRV, HF peak and LF/HF) during the tilt table test (supine and upright positions). Group assignment was used as the between subject factor. BMI and age were covariates in all analyses as they impact HRV.[21] Preplanned contrasts were applied to evaluate differences in HRV measures between groups.[22] All within and within-between interactions are reported with multivariate ANOVA tests (the Wilks λ and associated degrees of freedom.[23] Effect sizes (r) were used to examine the strength of between factor (group, time and group by time) associations and physiological assessments. Participants with missing data were excluded from analysis in case-wise fashion. To examine the confounding effects of overall pain intensity and the presence of fibromyalgia, which are both known to independently influence autonomic function, differences in the MPI pain scale across groups were examined using 1-way ANOVA and the frequency of occurrence of fibromyalgia (11 or greater of 18 tender points based on 1990 American College of Rheumatology criteria[16]) using the chi-square test. All tests were 2-tailed with significance set at $\alpha = 0.05$.

RESULTS

Subject demographics showed group differences in age ($F_{(3,109)}$ = 3.458, p = 0.019) and BMI ($F_{(3,109)}$ = 2.686, p = 0.050, see table). Respiration rate displayed no significant main effect of group ($F_{(3,99)}$ = 0.769, p = 0.51, r = 0.172), position (λ = 0.952, $F_{(3,97)}$ = 25.31, p = 0.19, r = 0.173) or group-position interaction (λ = 0.896, $F_{(9,236.22)}$ = 1.22, p = 0.285, r = 0.19).

HR analyses revealed a significant main effect of position (λ = 0.561, $F_{(3,97)}$ = 25.31, p <0.001, r = 0.173) and group ($F_{(3,99)}$ = 6.878, p <0.001, r = 0.172) but no significant interaction (λ = 0.939, $F_{(9,236.22)}$ = 0.676, p = 0.730, r = 0.19, part *A* of figure). Mean HR increased from supine 1 to upright positions and returned to baseline in supine 2 in all groups. Preplanned contrasts showed lower HR throughout each position in healthy control subjects compared to all subjects with CPP with no difference across groups.

HF-HRV analyses revealed a significant main effect of group ($F_{(3,97)}$ = 4.762, p = 0.01, r = 0.173) and position (λ = 0.824, $F_{(3,99)}$ = 6.73, p <0.001, r = 0.172) but no significant interaction (λ = 0.924, $F_{(9,231.35)}$ = 0.845, p = 0.575, r = 0.194, part *B* of figure). HF-HRV in all groups decreased from supine 1 to upright positions and returned to baseline in the supine 2 position. Preplanned contrasts revealed higher HF-HRV in healthy controls than in patients with IC/BPS ($F_{(1,97)}$ = 13.585, p <0.001) and IC/BPS plus MPP ($F_{(1,97)}$ = 5.56, p = 0.020) but not in those with MPP ($F_{(1,97)}$ = 0.972, p = 0.327) in all positions.

No significant main effect of group ($F_{(3,89)}$ = 0.905, p = 0.44, r = 0.181), position (λ = 0.978, $F_{(3,87)}$ = 0.66, p = 0.582, r = 0.183) or interaction (λ = 0.960, F(9,211.89) = 0.396, p = 0.94, r = 0.202) was found for LF-HRV (part *C* of figure).

The LF/HF ratio revealed a significant main effect of group ($F_{(3,97)}$ = 3.41, p = 0.021, r = 0.173) and position (λ = 0.813, $F_{(3,95)}$ = 7.29, p <0.001, r = 0.175) but no significant interaction (λ = 0.951, $F_{(9,231.35)}$ = 0.531, p = 0.851, r = 0.19, part *D* of figure). The LF/HF ratio for all groups increased from supine 1 to upright and returned to baseline in supine 2. Preplanned contrasts showed that healthy controls had a lower LF/HF ratio than patients with IC/BPS ($F_{(1,97)}$ = 7.977, p = 0.005) but not those with IC/BPS plus MPP ($F_{(1,97)}$ = 3.39, p = 0.10) or MPP ($F_{(1,97)}$ = 0.101, p = 0.75). Subjects in the MPP group had a lower LF/HF ratio in comparison to patients with IC/BPS ($F_{(1,97)}$ = 5.60, p = 0.020). These patterns remained at each phase except during supine 2 ($F_{(1,97)}$ = 0.258, p = 0.612).

Pain severity derived from the MPI was lowest for healthy control subjects at a mean ± SD of 0.1 ± 0.2. This was significantly different from that in all CPP groups (p <0.001). Mean values in the IC/BPS and MPP groups (3.3 ± 1.3 and 3.4 ± 1.4, respectively) were not different from each other and the mean value in the IC/BPS plus MPP group (4.3 ± 1.2) was significantly greater than that in the IC/BPS group (p = 0.005). Fibromyalgia criteria were met by none of the healthy control group by definition but by 5 of 26 subjects with IC/BPS (19%), 6 of 12 (50%) with MPP and 16 of 35 (46%) with IC/BPS plus MPP (different from IC/BPS, p <0.05). Thus, since pain magnitude and fibromyalgia prevalence were lowest in the IC/BPS group, the HRV abnormalities identified cannot be due to these factors.

DISCUSSION

To our knowledge this is the first HRV study assessing the response to a physiological stressor (tilt table) in women with IC/BPS. There are 4 major findings. 1) Women with IC/BPS demonstrate reduced parasympathetic activity compared to women without IC/BPS, ie healthy control subjects and women with isolated MPP. 2) The withdrawal of vagal activity results in an elevated LF/HF ratio in subjects with IC/BPS. 3) Despite these differences the parallel contour of the curves across groups suggests similar changes from supine to upright positions regardless of diagnosis (see figure). This indicates a constant underlying physiological response, in agreement with our prior findings of an intact ANS structure in subjects with IC/BPS.[3] 4) More severe pain or comorbid fibromyalgia, which are both known to influence HRV, do not account for these findings since they were least prevalent in the IC/BPS group, in which HRV differences were greatest.

These findings support our fundamental hypothesis of an aberrant autonomic response to stress in women with IC/BPS that is not solely due to the presence of CPP since this response does not occur in subjects with MPP alone. These results also emphasize the importance of disentangling comorbid CPP phenotypes such as MPP and IC/BPS when assessing deeper physiological characteristics. HF-HRV findings in women with combined IC/BPS plus MPP generally paralleled those in subjects with IC/BPS rather than those in subjects with MPP.

A reduced sympathetic surge (associated with a lesser decrease in HF-HRV) with upright posture has been reported in males with CPP.[24] In both supine positions the LF/HF ratio was higher in subjects with IC/BPS compared to healthy controls, suggesting a shift toward sympathetic dominance at rest in these individuals that was likely mediated by decreased HF-HRV. Interestingly these findings were not as clear in subjects with IC/BPS plus MPP, suggesting that MPP may have a protective effect on autonomic function or IC/BPS may be deleterious to normal autonomic function. Future studies using additional measures of sympathetic activity (eg hemodynamic measures) in combination with parasympathetic activity will be necessary to investigate these alternatives.

An optimally functioning ANS is critical for the stress response. Resting HF-HRV provides a psychophysiological index of self-regulation (eg emotional regulation) in addition to health. Thayer and Lane proposed HF-HRV as an indicator of the capacity for cognitive and affective regulation with low HF-HRV reflecting reduced ability to psychologically modulate physiological responses.[4] Since CPP has been associated with psychological distress manifested by depression, anxiety, somatic preoccupation and posttraumatic stress disorder,[25,26] HF-HRV may provide an objective measure of the capacity to generate appropriate emotional coping responses. Individual differences in HF-HRV may thus reflect variations in pain sensitivity and coping ability. As such, HF-HRV may provide an important tool for understanding the psychophysiological complexities of pelvic pain in women and it suggests that IC/BPS may inhibit self-regulatory resources much more than MPP. If true, we would expect a worse outcome for subjects with IC/BPS than those with MPP.

This study reflects the limitations and strengths of the parent ICEPAC trial. The MPP-only group was quite small. Findings in patients in this group were most similar to those in healthy controls and highlighted the phenotypic contrast with IC/BPS. A second limitation was the cross-sectional data assessment. Therefore, we cannot determine whether findings represent a consequence, an association or a predisposing factor for IC/BPS. Several scenarios could explain the current findings depending on which of these relationships exist. If the abnormalities occurred as a consequence of IC/BPS, overall autonomic outflow might have decreased to attempt to reduce bladder stimulation. On the other hand, if decreased autonomic outflow predisposes to the development of IC/BPS, one might consider whether the vagal anti-inflammatory pathway[27] or the failure of some other protective process modulated by the ANS leads to the development of the symptomology seen in patients with IC/BPS. Future trials that longitudinally track women with CPP as they recover will be necessary to determine whether and when these autonomic changes return toward normal.

It is unclear why subjects with IC/BPS had lower vagal activity, which was not seen in those with MPP. Fibromyalgia, a chronic pain condition reported to be frequently comorbid with other chronic pain conditions including IC/BPS,[28] is associated with sympathetic nervous system predominance. Importantly findings in our subjects were most likely not due to comorbid fibromyalgia or to higher pain severity as fibromyalgia was least prevalent in subjects with IC/BPS and pain magnitude was the lowest of all CPP groups.

Although many studies have addressed HRV in various forms of chronic pain, ICEPAC extends current concepts through some unique strengths. These strength are 1) assessment of autonomic structure[3] and function, 2) application of a consistent physiological stimulus, orthostatic stress, in contrast with other studies, which provided no stimulus at all or a psychological stimulus with its greater intrinsic variability across subjects, 3) phenotypic differentiation between 2 types of CPP and 4) detailed assessment of medical and psychological comorbidities such as fibromyalgia, excluding some confounding explanations.

CONCLUSIONS

Women with IC/BPS had lower vagal activity (indexed by HF-HRV) at baseline and during orthostatic stress compared with healthy controls and subjects with MPP as well as a shift toward sympathetic dominance (indexed by the LF/HF ratio), supporting the hypothesis of aberrant autonomic responsiveness. Furthermore, to our knowledge this is the first study to show disease related differences in HRV among individuals with IC/BPS, MPP and IC/BPS with comorbid MPP, which were clearly not due to pain severity or to comorbid fibromyalgia. Assessment of HRV may be a valuable tool to differentiate the original end organ insult or dysfunction, such as the bladder for IC/BPS or the pelvic floor muscles for MPP. Future studies will ascertain whether HRV can also have a role as a biomarker to predict or assess treatment responses.

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Abbreviations and Acronyms

ANS	autonomic nervous system
BMI	body mass index
CPP	chronic pelvic pain
HF	high frequency
HR	heart rate
HRV	HR variability
IBI	interbeat interval
IC/BPS	interstitial cystitis/bladder pain syndrome
ICEPAC	Interstitial Cystitis: Elucidation of Psychophysiologic and Autonomic Characteristics
LF	low frequency
MPI	Multidimensional Pain Inventory
MPP	myofascial pelvic pain

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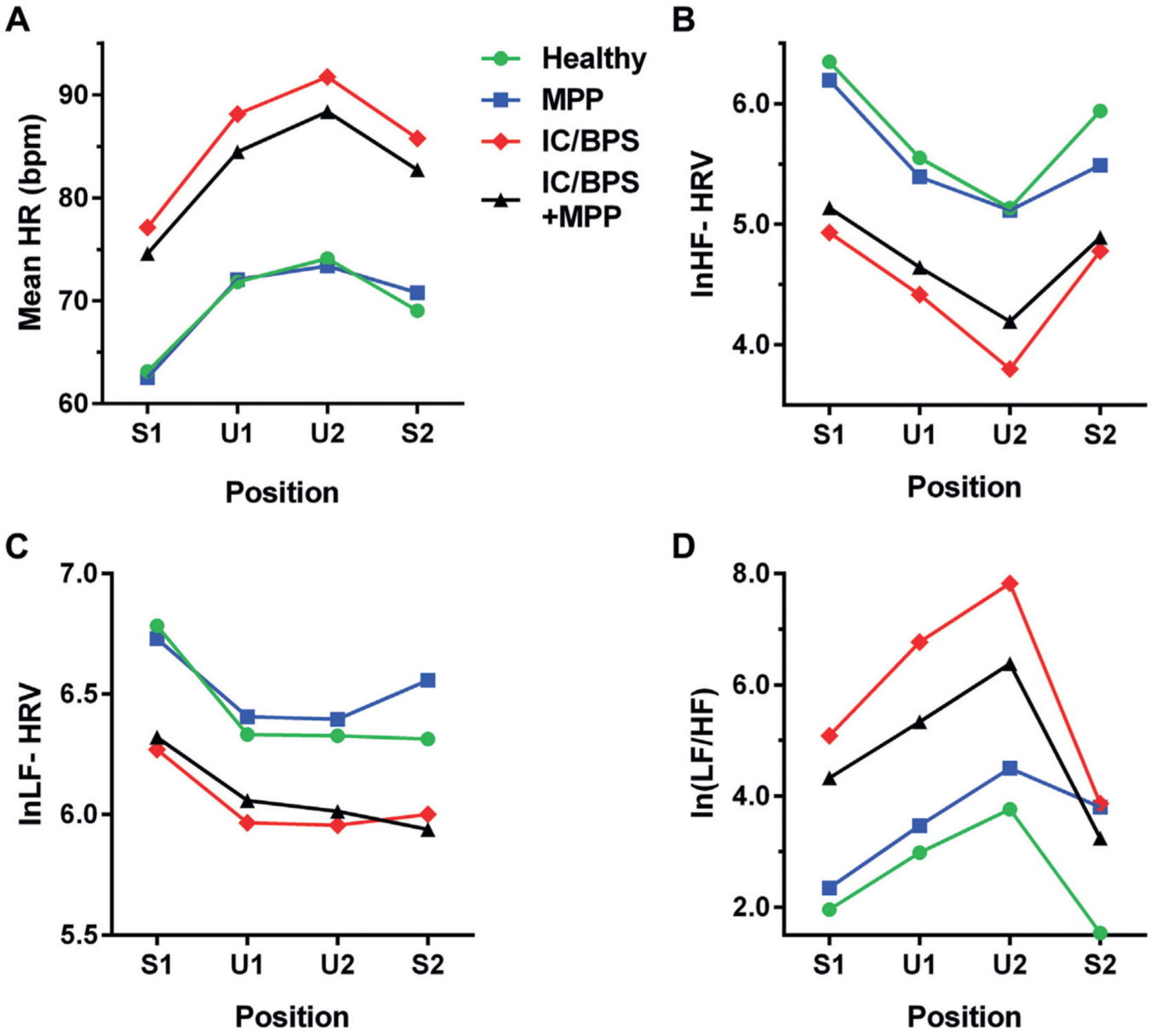

Mean age and BMI adjusted values of HRV and related measures at each tilt table position. *A*, HR in beats per minute (*bpm*). Estimates represent average HR in all positions, including supine 1 (*S1*), upright 1 (*U1*), upright 2 (*U2*) and supine 2 (*S2*). *B*, lnHF-HRV with higher values reflecting greater vagal activity. *C*, LF-HRV values with higher values reflecting higher baroreflex. *D*, LF/HF ratio, which measures sympathovagal balance. Higher values reflect shift toward sympathetic dominance.

Demographic features of each group

Group	No. Pts	Mean ± SD Age	Mean ± SD BMI (kg/m^2)	Mean ± SD HF Peak (Hz)
Healthy control	32	38.4 ± 15.2	26.5 ± 8.2	0.28 ± 0.04
MPP	12	33.4 ± 9.6	32.2 ± 7.3	0.28 ± 0.03
IC/BPS	26	46.8 ± 14.2	27.0 ± 6.4	0.28 ± 0.03
IC/BPS + MPP	35	38.7 ± 12.9	30.4 ± 7.8	0.27 ± 0.04
p Value	—	0.02	Not significant	Not significant