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Altered Autonomic Reactivity During Lower Body Negative Pressure in End-Stage Renal Disease

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Abstract

Background: End stage renal disease (ESRD) is characterized by autonomic dysfunction. During orthostatic stress, sympathetic (SNS) activity increases and parasympathetic (PNS) activity decreases to maintain arterial blood pressure (BP). We hypothesized that ESRD patients have impaired ability to adjust cardiac SNS and PNS activity during orthostasis, which could contribute to increased blood pressure variability, orthostatic intolerance and falls.

Methods: We measured beat-to-beat BP and Electrocardiography at baseline and during increasing lower body negative pressure (LBNP) in 20 ESRD patients and 18 matched controls (CON). Heart rate variability was quantified as total power (TP) and standard deviation of the N-N interval, reflecting both SNS and PNS; high frequency (HF), root mean square of successive differences of neighboring N-N intervals (RMSSD), and percent of consecutive N-N intervals differing >50 milliseconds (pNN50), reflecting cardiac PNS activity; and low frequency (LF) and LF/HF, reflecting sympathovagal balance. BP variability was quantified as the standard deviation in systolic (SDSAP) and diastolic (SDDAP) BP.

Results: Baseline HF, RMSSD, and pNN50 were significantly lower in ESRD ($P < 0.05$). While CON had a significant decrease in HF ($P = 0.015$), RMSSD ($P = 0.003$), and pNN50 ($P = 0.005$) during LBNP, there was no change in heart rate variability in ESRD. There was no significant difference in BP response, but ESRD had a significantly blunted heart rate response during graded LBNP compared to controls ($P < 0.001$). There was no significant difference in SDSAP or SDDAP during LBNP between groups ($P > 0.05$).

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AUTHOR CONTRIBUTIONS

J.P. conceived of the research study and developed the protocols. K.Y., I.F., D.D., and J.P. performed the experiments. K.Y., I.F., and Y.L., analyzed the results. K.Y., I.F., and J.P. drafted the manuscript and figures. All authors discussed the results and edited the manuscript. All authors contributed to and approved final manuscript.

The authors have no financial or other conflicts of interest to disclose.

Conclusions: These data suggest that ESRD patients have impaired autonomic adjustments to orthostatic stress.

Keywords

Heart rate variability; Sympathetic activity; Parasympathetic activity; Autonomic function; Blood pressure variability; End-stage renal disease (ESRD)

INTRODUCTION

End stage renal disease (ESRD) is associated with increased risk of cardiovascular (CV) mortality. One factor contributing to increased CV risk in ESRD is autonomic imbalance,^{1,2} characterized by overactive sympathetic (SNS),^{1,3–5} depressed parasympathetic nervous system (PNS),^{6,7} and cardiac autonomic neuropathy leading to an increased risk for orthostatic intolerance and sudden cardiac death.^{1,8,9} In healthy humans, the autonomic nervous system makes moment-to-moment adjustments, via the cardiopulmonary and arterial baroreflexes, to maintain stable arterial BP both at rest^{6,10} and during orthostatic stress.¹¹ During orthostasis, SNS activity increases, while PNS activity decreases to maintain BP within a narrow range. A wider range, or an increase in blood pressure variability (BPV), is associated with autonomic imbalance and increased mortality risk.¹²

Cardiac autonomic neuropathy is a major clinical problem in ESRD that often leads to increased BPV, orthostasis and increased frequency of falls.^{3,13} One validated method to assess cardiac autonomic adjustments in response to orthostatic stress is with heart rate variability (HRV).¹⁴ While prior studies have shown that ESRD patients have decreased HRV, increased SNS and decreased PNS activity at rest,^{15,16} it is unknown whether ESRD patients have appropriate adjustments in cardiac autonomic tone in response to an orthostatic challenge. We hypothesized that ESRD patients have an impaired ability to further decrease PNS and increase SNS during orthostasis induced by graded lower body negative pressure (LBNP).

METHODS

Study Population

Thirty eight participants were enrolled: 20 with ESRD (on hemodialysis for ≥ 6 months) and 18 matched controls (CON). Exclusion criteria included: pregnancy, illicit drug use, hemoglobin <10 g/dL, symptomatic heart disease, history of atrial fibrillation, hospitalization within the prior 3 months, clonidine use or administration, resting BP >170/100 mmHg or <100/50 mmHg, a decrease in SBP to <90 mmHg during hemodialysis, and history of kidney transplant. This study was approved by the Emory University Institutional Review Board, and the Atlanta VA Medical Center Research and Development Committee.

Measurements and Procedures

Blood Pressure and Electrocardiography (ECG)—Seated BP was measured in triplicate using an automated BP monitor (Omron, HEM-907XL, Omron Healthcare Co.

Ltd, Kyoto, Japan). Beat-to-beat arterial BP via finger photoplethysmography (NexFin, Edwards Life-Sciences/BMEYE B.V., Amsterdam, The Netherlands)¹⁷ and EKG were continuously monitored.

LBNP—An LBNP chamber was used to induce increasing doses of orthostatic stress. The chamber was sealed over the lower body, and a vacuum was used to apply negative pressure. Low dose LBNP, which isolates the cardiopulmonary baroreceptors, was categorized as 0 mmHg to −20 mmHg¹⁸ and high dose LBNP, which engages both cardiopulmonary and arterial baroreceptors, was categorized as −20 mmHg to −40 mmHg.

Direct Segmental Multifrequency Bioimpedance Analysis (DSM-BIA)—DSM-BIA using the Inbody S10 (Seoul, Korea) measures total and segmental body composition and is comparable to gold-standard methods such as dual energy X-ray absorptiometry (DEXA).^{19,20} A tetrapolar 8-point tactile electrode system was used to take direct segmental impedance measurements from the right arm, left arm, trunk, right leg, and left leg at 6 frequencies. Intracellular water (ICW) was estimated by high frequencies (250 kHz) and extracellular water (ECW) was estimated from low and high frequencies. ECW/ICW ratio was used to estimate extracellular volume status.²¹

Study Protocol—Participants were studied in the morning at the Emory University Human Physiology laboratory after abstaining from food, exercise, alcohol and caffeine for at least 12 hours. Studies were performed on a nondialysis day, after undergoing a normal, full dialysis session on the day prior to the study. Seated BP and HR were recorded in triplicate. DSM-BIA was performed to assess volume status. Study participants were fitted with electrodes for continuous ECG monitoring, and finger cuffs for continuous BP recording, and placed supine inside the LBNP chamber. Data were recorded for 10 minutes of baseline, followed by 18 minutes of LBNP, consisting of 3 minutes of consecutively increasing doses of negative pressure at −5, −10, −15, −20, −30, and −40 mm Hg. All data were recorded using a data acquisition system (PowerLab 16sp, ADInstruments, Sydney, Australia).

Data Analysis

HRV and BPV—Hemodynamic and ECG data were exported to the WinCPRS (Absolute Aliens, Turku, Finland) software program for analysis. HRV was quantified in the frequency domain using a fast-Fourier transformation over the measured time period, as total power (TP, 0.00–0.40 Hz), high frequency power (HF, 0.15–0.40 Hz), low frequency power (LF, 0.04–0.15 Hz), and low frequency to high frequency ratio (LF/HF). HRV was quantified in the time domain as the standard deviation in NN intervals (SDNN, ms), square root of the mean squared differences of successive NN intervals (RMSSD, ms), and percent of consecutive NN intervals that differed by more than 50 ms (pNN50).¹⁴ BP variability was quantified as the standard deviation in systolic (SDSAP) and diastolic (SDDAP) BP.¹²

Statistical Analysis—Linear mixed models in R²² (version 3.5.1, R Foundation for Statistical Computing, Vienna, Austria) were used to estimate within-group change of outcome, compare between-group differences at baseline and rate of change during LBNP.

We performed a partially adjusted model controlling for hypertension, and a fully adjusted model controlling for hypertension, diabetes, calcium channel blockers (CCB), angiotensin converting enzyme inhibitors (ACEI), angiotensin receptor blockers (ARB), and β -blockers. Subject-specific Gaussian random variables controlled for individual variability across different levels of doses. Statistical significance was evaluated by 2-tailed *t* test with a Satterthwaite approximation to degrees of freedom. Analyses were performed for both all-dose and high-dose LBNP (−20 to −40 mmHg).

RESULTS

Baseline Characteristics

Age, sex, race and body mass index were similar between ESRD ($n = 20$) and controls ($n = 18$). ESRD had a trend toward more diabetics ($P = 0.087$), and significantly more hypertensives ($P = 0.003$). There was a trend toward greater use of CCB ($P = 0.076$), ACEI and ARB ($P = 0.061$) and hydralazine ($P = 0.087$) in ESRD, although not statistically significant. There was no significant difference in diuretic use ($P = 0.335$), while ESRD had greater use of β -blockers ($P < 0.001$). Extracellular fluid volume calculated as ECW/ICW measured via bioimpedance was significantly higher in ESRD ($P = 0.027$). Baseline HR was significantly higher in ESRD compared to controls ($P = 0.024$); however, there were no significant differences in resting systolic, diastolic, or mean arterial pressure). Dialysis vintage ranged from 0.8 to 6.3 years, with a mean of 4.6 years. Hypertension was the etiology of ESRD in the majority of patients, and most had an arteriovenous fistula for dialysis access. Controls had normal renal function with a mean serum creatinine of 0.95 ± 0.04 mg/dL, (estimated glomerular filtration rate of $94 \text{ mL/min/1.73 m}^2$) (Table 1).

Resting HRV and BPV

In the partially adjusted model controlling for hypertension, baseline TP was significantly lower in ESRD compared to controls (dose*group, $P = 0.003$), suggesting decreased total HRV in ESRD. In the fully adjusted model controlling for hypertension, diabetes, CCB, ACEI/ARB, and β -blockers, baseline HF was significantly lower in ESRD compared to controls (dose*group, $P = 0.003$). Baseline SDNN (dose*group, $P = 0.001$) was significantly lower in ESRD in the partially adjusted model, while baseline RMSSD and pNN50 were significantly lower in ESRD in both the partially and fully adjusted models (dose*group, $P < 0.05$), suggesting reduced cardiac PNS activity. Baseline LF was significantly lower in the ESRD group in the partially adjusted model (dose*group, $P = 0.008$), suggesting altered sympathovagal balance. Baseline LF/HF was not significantly different between the groups. Similarly, there were no significant differences in resting measures of BPV quantified as SDSAP or SDDAP between the groups (Table 2).

BP and HR Response During Orthostatic Stress

All hemodynamic responses during LBNP were analyzed using both partially and fully adjusted models. *P* values were similar between the models, and only fully-adjusted values are given in the figures. There were no significant differences in SAP (Figure 1A) or DAP (Figure 1B) responses during LBNP between groups. However, there was a significant difference in the change in HR (Figure 1C) during LBNP (dose*group, $P = 0.029$). When

examining within-group changes in HR, ESRD ($P < 0.001$) and control ($P = 0.005$) groups both had a significant increase during LBNP, but this response was blunted in ESRD. These differences in HR response were more pronounced during high-dose LBNP (Figure 1C, dose*group, $P = 0.012$).

HRV and BPV Response During Orthostatic Stress

Total HRV—All HRV responses during LBNP were analyzed using both partially and fully adjusted models. TP is reflective of total HRV.¹⁴ There was no significant difference in the change in TP during LBNP between groups (Figure 2A, dose*group, $P = 0.286$).

Cardiac PNS Activity—SDNN, HF, RMSSD and pNN50 reflect cardiac parasympathetic activity.^{14, 23–25} There was no significant difference in the change in SDNN (Figure 2B) during LBNP between groups; however, within the control group, SDNN tended to decrease during high-dose LBNP ($P = 0.052$). There was no significant difference in the change in HF during LBNP between groups (Figure 2C). However, while HF did not change during LBNP in ESRD, HF significantly decreased in controls ($P = 0.015$). When isolating high-dose responses, there was a significant difference in HF response between groups (dose*group, $P = 0.022$). While the control group trended toward a decrease in HF ($P = 0.058$), there was no significant change in HF during high-dose LBNP within ESRD, suggesting blunted cardiac PNS withdrawal in ESRD. There was no significant difference in the change in RMSSD during LBNP between groups (Figure 2D). However, while RMSSD significantly decreased during LBNP within controls ($P = 0.003$), there was no significant change in RMSSD during LBNP within ESRD. When isolating high-dose responses, there was no significant difference in RMSSD responses between or within the groups. There was a significant difference in the change in pNN50 during LBNP between groups (Figure 2E, $P = 0.002$). While pNN50 significantly decreased during LBNP within the control group ($P = 0.005$), there was no significant change in pNN50 during LBNP within the ESRD group.

Sympathovagal Balance—LF and LF/HF reflect SNS^{26,27} or sympathovagal interactions.^{28,29} There were no significant differences in the LF, or LF/HF responses during LBNP between groups (Figure 2F and Figure 2G).

BP Variability—In the partially and fully adjusted models, there were no significant differences in the change in SDSAP and SDDAP during LBNP between groups (Figure 3).

DISCUSSION

The major new findings of this study are that ESRD patients have significantly lower HRV at baseline and during LBNP, and blunted adjustments in HR and HRV in response to orthostatic stress induced via graded LBNP. These abnormalities in cardiac autonomic adjustments during LBNP suggest that ESRD patients have impaired ability to increase SNS and decrease PNS activity during orthostatic stress. Such autonomic imbalance may contribute to orthostasis, risk of falls and CV mortality in ESRD.

ESRD patients are at significantly increased risk of CV disease and sudden cardiac death. Prior studies have shown that both ESRD patients and those with chronic kidney disease not

yet on dialysis have chronic activation of the SNS^{1,3-5} and decreased PNS activity.^{6,7} Consistent with other studies,^{7,15,16} we observed that at baseline, ESRD patients have significantly lower resting HRV compared to controls. ESRD patients had significantly lower TP and SDNN (reflecting total HRV^{24,25,29}), SDNN < 30 ms (reflecting both decreased PNS and increased SNS outflow¹⁴), and pNN50 < 3% (reflecting impaired vagal activity¹⁴). To our knowledge, this is the first study reporting abnormal adjustments in HRV during orthostatic stress in ESRD. Orthostatic stress such as during volume removal with hemodialysis or upright posture, unloads volume-sensitive cardiopulmonary baroreceptors leading to a reflexive increase in SNS activity and a corresponding decrease in PNS activity in an effort to maintain stable arterial blood pressure.¹⁸ We observed a significant increase in HR and decrease in HF, RMSSD, and pNN50 during both low- and high-dose LBNP, and a trend toward a significant decrease in SDNN during high-dose LBNP within controls, indicative of increased SNS and decreased PNS activation to the heart during increasing orthostatic stress. In contrast, ESRD patients had a blunted increase in HR and no change in HRV measures in response to LBNP, suggesting a failure to adjust cardiac SNS and PNS activation in response to orthostatic stress. Such impairment in cardiac autonomic responses to orthostatic stress in ESRD could contribute to orthostatic intolerance, hemodynamic instability and increased risk of falls.

The autonomic nervous system plays a vital role in both long-term control of BP, as well as moment-to-moment adjustments to maintain hemodynamic stability in response to environmental factors such as orthostatic stress.³⁰ Cardiac autonomic neuropathy, a disorder characterized by impaired autonomic modulation of cardiac activity, is a major contributor to increased CV risk in ESRD⁹ and is observed in the majority of ESRD patients.^{15,31} Moreover, cardiac autonomic neuropathy is an independent predictor of CV mortality and sudden death in this patient population.³² Manifestations of cardiac autonomic neuropathy³³ include increased HR, lower HRV, exercise intolerance and orthostasis.³⁴ Our findings highlight that ESRD patients have impaired ability to increase cardiac SNS and decrease cardiac PNS activity assessed using HRV during orthostatic stress induced by LBNP. Such impairment could lead to orthostatic hypotension, the primary cause of 35% of all hospitalizations in the US,³⁵ increased blood pressure variability,^{13,36} greater risk of falls, and decreased quality of life in ESRD.

The mechanisms underlying cardiac autonomic dysregulation during LBNP in ESRD are not clear. One possibility is due to underlying diabetic neuropathy, since diabetes is the most common cause of ESRD in the US, and progression of diabetic nephropathy is closely linked to the onset and progression of neuropathic complications. However, nondiabetic ESRD patients also develop autonomic neuropathy over time, likely due to complications of uremia including retention of uremic toxins such as neurotoxic guanidines and beta-2 microglobulin,³⁷ and abnormalities of calcium-phosphorus metabolism leading to accelerated arterial calcification and impairment of baroreceptor nerve endings within the arterial wall.³⁸ Several studies^{3,6,10,39} although not all⁴⁰ have shown that ESRD patients have impaired arterial baroreflex sensitivity that could result in impaired modulation of SNS and PNS activity in response to changes in arterial BP.

Volume overload may also contribute to impaired autonomic adjustment to orthostatic stress. ESRD patients become progressively volume-overloaded with volume-mediated hypertension during the interdialytic period,⁴¹ and fluid overload has been associated with alterations in autonomic regulation in ESRD.⁴² In the current study, the ESRD group had significantly higher ECW/ICW ratio compared to controls, consistent with increased extracellular volume expansion. The decrease in venous return to the heart induced via LBNP may not have reached a threshold for the baroreceptors to sense a change in volume and depolarize.⁴² This is consistent with our finding that despite a lack of change in cardiac SNS and PNS activity during orthostatic stress, there were no exaggerated reductions in BP during LBNP in ESRD. Lastly, given that ESRD patients have chronically low PNS and high SNS^{1,2,43} at baseline, they may not have had further capacity to increase SNS or decrease PNS in response to orthostasis.

Surprisingly, we did not observe abnormal BP or BPV response in ESRD patients. Studies have shown that patients with higher SDSAPs and patients with SDSAPs greater than 15 mmHg are at significantly greater risk of CV mortality than patients with SDSAPs equal to or below this value. Although the ESRD group had significantly lower HRV, there were no differences in BPV at rest or during LBNP between the ESRD and control groups. Lack of difference in BPV may be due to differential antihypertensive medication treatment in the groups. A significantly greater proportion of the ESRD group was treated with β -blockers compared to controls, and there was a trend toward greater use of dihydropyridine calcium channel blockers, ACE-inhibitors and ARBs. There are mixed findings on the effects of β -blockers on BPV⁴⁴; some report an increase in BPV with β -blockers⁴⁵ while others report no effect on BPV.⁴⁴ Prior reports suggest that dihydropyridine calcium channel blockers,^{46,47} diuretics,⁴⁴ and long-term treatment with ARBs may reduce BPV.^{48,49} However, BPV remained not significantly different between groups in the fully-adjusted model that controlled for the classes of BP medications.

We acknowledge several limitations of this study. First, the study population was predominantly comprised of African-American males; therefore, the results may not be generalizable to women and other racial groups. Second, ESRD patients were studied on an interdialytic day; therefore, it is unclear if the results may be different if they were tested just after dialysis when they are more euvoletic. Third, there were a greater proportion of ESRD patients on β -blockers, and a trend toward greater use of ACEI, ARBs and CCBs. β -blockers,⁴⁵ ACEI and ARB have been shown to increase total HRV and HF⁵⁰; however, despite a greater proportion of ESRD patients treated with these agents, HRV measures remained significantly lower in ESRD patients. Further, after controlling for hypertension and medication usage, the results remained significant. Finally, the study may have been underpowered to detect differences in other HRV measures such as SDNN responses that showed a trend towards a difference between groups, but did not reach statistical significance.

In conclusion, this study showed that ESRD patients have significantly lower HRV at baseline, and lack of HRV adjustments during orthostatic stress. Impaired ability to modulate cardiac SNS and PNS tone during orthostatic stress may increase risk of

orthostatic intolerance, falls, and sudden death. Future studies should investigate mechanisms and therapeutic options targeting autonomic dysfunction in ESRD.

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FIGURE 1.

Blood pressure response during orthostatic stress. A, Systolic (SAP); B, diastolic (DAP); and C, heart rate response during low dose and high dose graded lower body negative pressure (LBNP) in end-stage renal disease (ESRD) and controls. * $P < 0.05$ for significant within group change. $^{\dagger}P$ value < 0.05 for significant between group difference during low and high dose LBNP. $^{\ddagger}P < 0.05$ for significant between group difference during high dose LBNP only.

FIGURE 2.

Heart rate variability response during orthostatic stress. A, Total power; B, standard deviation of the N-N interval (SDNN); C, high frequency (HF); D, root mean square of successive differences of neighboring N-N intervals (RMSSD); e, percent of consecutive N-N intervals that differ by more than 50 milliseconds (pNN50) during graded lower body negative pressure (LBNP) in end-stage renal disease (ESRD) and controls. * $P < 0.05$ for significant within group change. † P value < 0.05 for significant between group difference

during low and high dose LBNP. $^{\ddagger}P < 0.05$ for significant between group difference during high dose LBNP only.

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FIGURE 3.

Blood pressure variability during orthostatic stress. A, Standard deviation in systolic blood pressure (SDSAP); and B, standard deviation in diastolic blood pressure (SDDAP), during graded lower body negative pressure (LBNP) in end-stage renal disease (ESRD) and controls.

TABLE 1.

Baseline characteristics.

Characteristic	Control <i>n</i> = 18	ESRD <i>n</i> = 20	<i>P</i> Value
Age, years	47 ± 2	46 ± 2	0.766
Sex, male/female	7/11	10/10	0.492
Race, black/white	16 to 2	18 to 2	0.911
BMI, kg/m ²	30.6 ± 1.4	29.2 ± 1.2	0.495
Diabetes, yes/no	0/18	3 /17	0.087
Coronary artery disease, yes/no	0/18	1/20	0.336
Hypertension, yes/no	8/10	18/2	0.003 [*]
Types of antihypertensive medication, <i>n</i> (%)			
Calcium channel blockers	4 (22)	10 (50)	0.076
ACEI/ARB	3 (17)	9 (45)	0.061
Beta-blockers	2 (11)	15 (75)	<0.001 [*]
Diuretic	5 (28)	3 (15)	0.335
Hydralazine	0 (0)	3 (15)	0.087
ECW/ICW	0.607 ± 0.009	0.639 ± 0.009	0.027 [*]
Baseline hemodynamics			
Heart rate, bpm	68 ± 3	76 ± 2	0.024 [*]
SAP, mmHg	130 ± 4	136 ± 8	0.502
DAP, mmHg	78 ± 3	77 ± 3	0.866
MAP, mmHg	99 ± 4	101 ± 5	0.698
Dialysis characteristics			
Dialysis vintage, years		4.6 ± 0.79	
Etiology of ESRD, <i>n</i> (%)			
Hypertension		14 (70%)	
Diabetes		2 (10%)	
Lupus		3 (15%)	
Not specified		1 (5%)	
Hemodialysis access, <i>n</i> (%)			

Characteristic	Control <i>n</i> = 18	ESRD <i>n</i> = 20	<i>P</i> Value
AV fistula		12 (60%)	
AV graft		7 (35%)	
Catheter		1 (5%)	

Values are mean ± SE.

Abbreviations: ACEI, angiotensin converting enzyme inhibitors; ARB, angiotensin receptor blocker; BMI, body mass index; DAP, diastolic arterial blood pressure; ECW/ICW, extracellular water/intracellular water; ESRD, end-stage renal disease; MAP, mean arterial pressure; SAP, systolic arterial blood pressure.

* *P* value < 0.05.

TABLE 2.

Resting heart rate variability and blood pressure variability.

Characteristic	Control <i>n</i> = 18	ESRD <i>n</i> = 20	<i>P</i> Value (Partial)	<i>P</i> Value (Full)
Baseline HRV				
TP, ms ²	2433 ± 479	653 ± 233	0.003 *	0.270
HF, ms	356 ± 77	205 ± 106	0.255	0.003 *
LF, ms ²	720 ± 172	183 ± 63	0.008 *	0.093
LF/HF	255 ± 47	233 ± 49	0.750	0.172
NN Interval, ms	904 ± 33	797 ± 22	0.011 *	<0.001 *
SDNN, ms	48.3 ± 4.7	25.1 ± 4.6	0.001 *	0.131
RMSSD, ms	36.3 ± 4.1	21.3 ± 6.1	0.048 *	<0.001 *
pNN50, %	14.1 ± 3.3	3.0 ± 1.6	0.006 *	<0.001 *
Baseline BPV				
SDSAP, mmHg	4.6 ± 0.4	3.8 ± 0.4	0.157	0.751
SDDAP, mmHg	3.0 ± 0.2	2.3 ± 0.3	0.054	0.855

Values are mean ± SE.

Abbreviations: HF, high frequency; LF, low frequency; SDNN, standard deviation in NN interval; pNN50, proportion of NN >50ms; SDSAP, standard deviation in systolic blood pressure; SDDAP, standard deviation in diastolic blood pressure SDPP, standard deviation in pulse pressure; SDMAP, standard deviation in mean arterial pressure; TP, total power.

Partially adjusted *P* values controlled for hypertension. Fully adjusted *P* values controlled for hypertension, diabetes, calcium channel blockers, angiotensin converting enzyme inhibitors/angiotensin receptor blockers (ACEI/ARB), and beta-blockers.

* *P* value < 0.05.