Brief Report

Heart Failure–Specific Relationship Between Muscle Sympathetic Nerve Activity and Aortic Wave Reflection

PHILIP J. MILLAR, PhD, CATHERINE F. NOTARIUS, PhD, NOBUHIKO HARUKI, MD, PhD, AND JOHN S. FLORAS, MD, DPhil

Toronto, Canada

ABSTRACT

Background: Reflected arterial waves contribute to left ventricular (LV) afterload. Heart failure patients with reduced ejection fraction (HFrEF) are afterload sensitive and sympathetically activated. We tested the hypothesis that HFrEF patients exhibit a positive relationship between sympathetic vasoconstrictor discharge and aortic wave reflection.

Methods: Sixteen treated patients with HFrEF (61 ± 9 years of age, left ventricular ejection fraction 30 ± 7%, 3 women) and 16 similar-aged healthy control subjects (57 ± 7 years of age, 4 women) underwent noninvasive measurements of radial pulse waveforms (applanation tonometry) to calculate central blood pressures and aortic wave reflection characteristics: augmentation pressure (AP), augmentation index (AI_x), and AI_x corrected to a heart rate of 75 beats/min (AI_x@75). Muscle sympathetic nerve activity (MSNA) burst frequency was recorded from the fibular nerve (microneurography).

Results: HFrEF patients had higher AI_x (26 ± 9 vs 17 ± 15%; $P < .05$) and MSNA burst frequency (48 ± 7 vs 39 ± 11 bursts/min; $P < .05$) and lower central diastolic pressure than control subjects (64 ± 8 vs 70 ± 9 mm Hg; $P = 0.05$). There were no between-group differences in heart rate, other measures of blood pressure (brachial and central; $P > .05$), AP (11 ± 5 vs 7 ± 8 mm Hg; $P = 0.11$), or AI_x@75 (19 ± 9 vs 13 ± 11%,-$P = 0.14$). MSNA correlated positively with AP ($r = 0.50$; $P < .05$), AI_x ($r = 0.51$; $P < .05$), and AI_x@75 ($r = 0.54$; $P < .05$) in HFrEF patients but not in control subjects ($r = 0.002–0.18$; $P > 0.49$).

Conclusions: In patients with HFrEF, but not similarly aged healthy subjects, indices of aortic wave reflection correlate positively with MSNA. By increasing LV afterload, such neurovascular coupling could impair LV performance and worsen heart failure symptoms. Therapies that attenuate neurogenic vasoconstriction may benefit HFrEF patients by diminishing arterial wave reflection. (*J Cardiac Fail 2019;25:404–408*)

Key Words: Augmentation index, heart failure with reduced ejection fraction, muscle sympathetic nerve activity, wave reflection.

Age-related progression of arterial stiffness is accelerated by diabetes, hypertension, and heart failure.[1,2] A key consequence of increased arterial stiffening is augmented transmission speed. Earlier return of the reflected pulse wave during late systole and its merger with the expelled forward wave increases central aortic systolic and pulse pressure, 2 components of left ventricular afterload.[1] Importantly, the magnitude of wave reflection, quantified commonly as augmentation pressure (AP) or, relative to the aortic pulse pressure, as augmentation index (AI_x), can independently predict cardiovascular events and all-cause mortality.[3]

One mechanism thought to contribute to increased arterial stiffness and wave reflection is peripheral sympathetic activation.[4–7] In healthy young men and postmenopausal women, direct measures of muscle sympathetic nerve activity (MSNA) correlate independently with pulse-wave velocity,[4] a noninvasive reference measure of central arterial stiffness,[1] or with aortic wave reflection.[5–7] Unknown is whether AP or AI_x relate to MSNA in patients with heart

From the University Health Network and Mount Sinai Hospital Division of Cardiology, Department of Medicine, University of Toronto, Toronto, Ontario, Canada.

Manuscript received November 26, 2018; revised manuscript received February 26, 2019; revised manuscript accepted March 6, 2019.

Reprint requests: John S. Floras, MD, DPhil, Suite 1614, 600 University Avenue, Toronto, Ontario, Canada, M5G 1X5. Tel: 416-586-8704; Fax: 416-586-8702. E-mail: john.floras@utoronto.ca

Funding: Heart and Stroke Foundation of Ontario (SPEC 6580). P.J.M. was supported by a Canadian Institutes of Health Research Postdoctoral Fellowship. J.S.F. was supported by the Canada Research Chair in Integrative Cardiovascular Biology.

See page 407 for disclosure information.

1071-9164/$ - see front matter

https://doi.org/10.1016/j.cardfail.2019.03.005

failure with reduced ejection fraction (HFrEF), a state characterized by elevated sympathetic activity,[8] increased arterial stiffness,[2] and a greater sensitivity to changes in afterload.[9]

The present investigation examined the relationships between aortic wave reflection and MSNA in patients with HFrEF and similarly aged healthy control subjects. We tested the hypothesis that HFrEF patients exhibit a positive relationship between resting MSNA and aortic wave reflection.

Methods

Participants

Sixteen patients with diagnosed and treated HFrEF and 16 healthy control subjects participated in this study. HFrEF patients were required to have a recent (<6 mo) measurement of left ventricular ejection fraction <40%. All were in sinus rhythm. Diabetes, renal disease, chronic obstructive pulmonary disease, and implanted cardiovascular device were exclusion criteria. Healthy control subjects were prospectively recruited and self-reported no history of cardiovascular disease. All participants were normotensive at rest. The study protocol was approved by the Research Ethics Boards of the University Healthy Network and Mount Sinai Hospital. All of the subjects provided informed written consents in advance.

Measurements

Central blood pressure and aortic wave reflection characteristics were assessed noninvasively with the use of a commercially device (Sphygmocor CVMS; Atcor Medical, Sydney, Australia). High-fidelity pressure waveforms were recorded with the use of a pen-like applanation tonometer placed over the right radial artery. The pulse waveform was calibrated to brachial blood pressure (Dinamap Pro 100; Critikon, Tampa, Florida), and a validated generalized transfer function applied to generate the aortic pressure waveform. Pulse wave analysis software was used to compute central blood pressures, AP, AI_x, and (to account for the inverse relationship between heart rate and AI_x) AI_x corrected to a heart rate of 75 beats/min (AI_x@75).[1] A minimum of 2 separate pulse-wave assessments were made in each subject, and only high-quality recordings were submitted to analysis.

Postganglionic multiunit MSNA was recorded from the left fibular nerve by percutaneously inserting a tungsten microelectrode (Frederick Haer, Brunswick, Maine) into a motor fascicle, as previously described.[10] The electrode was adjusted until spontaneous pulse-synchronous multifiber bursts of sympathetic activity were observed, increasing activity to a voluntary apnea and unresponsive to touch. Heart rate was acquired continuously from lead II of the electrocardiograph (ECG).

Experimental Protocol

All participants underwent cardiopulmonary stress testing to determine peak oxygen consumption.[11] On a separate visit, after 12−24-hour abstention from alcohol and caffeine, participants completed 10 minutes of seated rest followed by a 5-minute supine acclimatization period. Next, right brachial blood pressure measurements were taken each minute for 5 minutes; the final resting blood pressure was used to calibrate the pulse-wave assessment. After this, applanation tonometry of the right radial artery was completed and participants were instrumented to collect continuous measurements of resting heart rate and MSNA; a stable 7-minute epoch was recorded for analysis. All HFrEF medications were taken according to participants' usual schedule.

Data Acquisition

Continuously acquired data was digitized and stored in Labview (National Instruments, Austin, Texas) at either 1000 Hz (ECG) or 200 Hz (all other signals). An offline custom Labview program was used to analyze multiunit MSNA burst frequency (bursts/min).[10] Because the quantity of the vasoconstrictor, norepinephrine, released by sympathetic nerves over a unit of time is a direct function of firing frequency, MSNA was quantified as bursts/min.

Statistical Analysis

Between-group differences were evaluated with the use of independent t tests. The relationships between MSNA and AP, AI_x, and AI_x@75 were tested within each group with the use of Pearson correlation. Data were analyzed with the use of SigmaPlot (Systat Software, San Jose, California). All values were reported as mean ± SD; $P < 0.05$ was considered to be statistically significant.

Results

Baseline participant characteristics are presented in Table 1. There were no differences in age, height, weight, or body mass index between the groups. As expected, the HFrEF cohort displayed impaired left ventricular ejection fraction and reduced peak exercise capacity.

Table 2 presents the average hemodynamic, neural, and aortic wave reflection characteristics in the HFrEF and healthy control groups. Heart rate and all peripheral and central blood pressure values were similar ($P > 0.05$), with the exception of brachial and central diastolic blood pressures, which were lower in HFrEF (Both $P < 0.05$). AI_x was elevated in HFrEF ($P = 0.04$), but AP and AI_x@75 were not ($P = 0.11$ and $P = 0.14$, respectively). Patients with HFrEF demonstrated higher MSNA burst frequency ($P < 0.05$). In HFrEF patients, MSNA burst frequency correlated positively with AP ($r = 0.50$; $P < 0.05$), AI_x ($r = 0.51$; $P < 0.05$), and AI_x@75 ($r = 0.54$; $P < 0.05$; Fig. 1). No such relationships were detected in healthy control subjects ($r = 0.002-0.18$; $P > 0.49$).

Table 1. Baseline Characteristics

Characteristic	Control	HFrEF
Age (y)	55 ± 7	61 ± 9
Male	12	13
Weight (kg)	76 ± 16	79 ± 11
Height (cm)	174 ± 12	171 ± 11
BMI (kg/m^2)	25 ± 5	27 ± 4
Left ventricular ejection fraction (%)	–	31 ± 7
Peak VO_2 (mL·kg^{-1}·min^{-1})	32 ± 10	18 ± 8*
Percent predicted peak VO_2 (%)	114 ± 28	66 ± 26*
Etiology		
Ischemic	–	12
Dilated	–	4
Therapy		
β-Blockade	–	16
ACE inhibitor	–	10
Angiotensin receptor blocker	–	4
Calcium-channel blocker	–	1
Statin	1	15
Loop diuretic	–	6
Mineralocorticoid receptor antagonist	–	7

Values presented as mean ± SD or n. Data obtained from 16 healthy control subjects and 16 HFrEF patients. ACE, angiotensin-converting enzyme; BMI, body mass index; VO_2, oxygen consumption.
*$P \leq 0.01$ vs control.

Table 2. Hemodynamic, Neural, and Wave Reflection Characteristics

Characteristic	Control	HFrEF
Heart rate (beats/min)	68 ± 13	62 ± 9
Brachial pressure (mm Hg)		
Systolic	116 ± 20	116 ± 16
Diastolic	70 ± 9	64 ± 8*
Pulse	45 ± 12	52 ± 13
Central blood pressure (mm Hg)		
Systolic	105 ± 20	106 ± 14
Diastolic	71 ± 9	64 ± 8*
Pulse	35 ± 14	42 ± 9
MSNA burst frequency (bursts/min)	41 ± 9	48 ± 7*
AP (mm Hg)	7 ± 8	11 ± 5
AI_x (%)	17 ± 15	26 ± 9*
AI_x@75 (%)	13 ± 11	19 ± 9

Values presented as mean ± SD. Data obtained from 16 healthy control subjects and 16 HFrEF patients. AI_x, augmentation index; AI_x@75, augmentation index normalized for heart rate of 75 beats/min; AP, augmentation pressure; MSNA, muscle sympathetic nerve activity.
*$P \leq 0.05$ vs control.

Discussion

The objective of this study was to determine if the elevated sympathetic outflow directed toward skeletal muscle (MSNA) in patients with HFrEF is associated with greater aortic wave reflection. We report (1) higher measures of AI_x in our cohort of treated HFrEF patients and (2) positive relationships between measures of aortic wave reflection and MSNA in HFrEF patients but not in healthy control subjects. These results are consistent with the concept that peripheral sympathetic activation can augment left ventricular afterload by increasing wave reflection.

Previous comparisons of aortic wave reflection characteristics in HFrEF patients and control subjects have yielded inconsistent findings, likely because of between-study differences in heart failure etiology, severity, and medical management. For example, aortic wave reflection has been reported to be both lower[12] and higher[13] in HFrEF compared with control subjects. In the present series, HFrEF patients had higher AI_x than similar-age healthy control subjects, with values similar to those reported previously.[9]

The focus of the present study was on whether increased sympathetic outflow to skeletal muscle resistance vessels is a determinant of aortic wave reflection in HFrEF. Prior work has reported positive associations between MSNA and measures of wave reflection in healthy young men[6] and post-menopausal women.[5,7] However, muscle sympathetic activation emerges as HFrEF progresses, and in those with advanced HFrEF every cardiac cycle can be accompanied by a sympathetic burst and concomitant norepinephrine discharge.[8] The positive relationships between MSNA burst frequency and AP, AI_x, and AI_x@75, suggest a novel mechanism by which increased peripheral sympathetic activity can adversely affect left ventricular-vascular coupling in HFrEF and accelerate disease progression.

In contrast, there was no relationship between MSNA and wave reflection in the healthy middle-aged, primarily male, control group. In previous experiments we identified a positive correlation between MSNA and forearm vascular resistance in healthy middle-aged men with low, but not with high, exercise capacity.[11] It is conceivable that preserved or augmented endothelium-mediated dilation in well trained individuals, compared with sedentary or HFrEF subjects, attenuates neurovascular coupling. If so, such potent intercession may contribute to the dissociation, in the healthy cohort as a whole, of the magnitude of arterial wave reflection from MSNA. Of note, the present data were acquired from a small number of Caucasian volunteers and may not pertain to other groups, such as African Americans, who exhibit both increased sympathetic vascular transduction and higher rates of hypertension.[14]

AI_x has been identified as a promising therapeutic target in HFrEF. Borlaug et al[9] reported small randomized trial data indicating that AI_x-guided drug therapy achieved a greater improvement in peak oxygen consumption than contemporary medical care. The present findings raise the possibility that by reducing aortic wave reflection, pharmacologic or nonpharmacologic interventions that attenuate central sympathetic outflow or neurovascular transduction would also improve ventricular-arterial coupling and lower cardiac afterload in HFrEF patients. For example, atorvastatin, a lipophilic statin, can lower both MSNA[15] and AI_x[16] in HFrEF patients, and renal denervation can lower MSNA and AI_x in drug-resistant hypertensive patients.[17] Aerobic exercise training has also been shown in HFrEF to lower MSNA[18] and in coronary artery disease to lower AI_x.[19] Although such data do not establish a causal link, there is accumulating support for the hypothesis that attenuation of muscle sympathetic outflow would reduce arterial wave reflection in HFrEF.

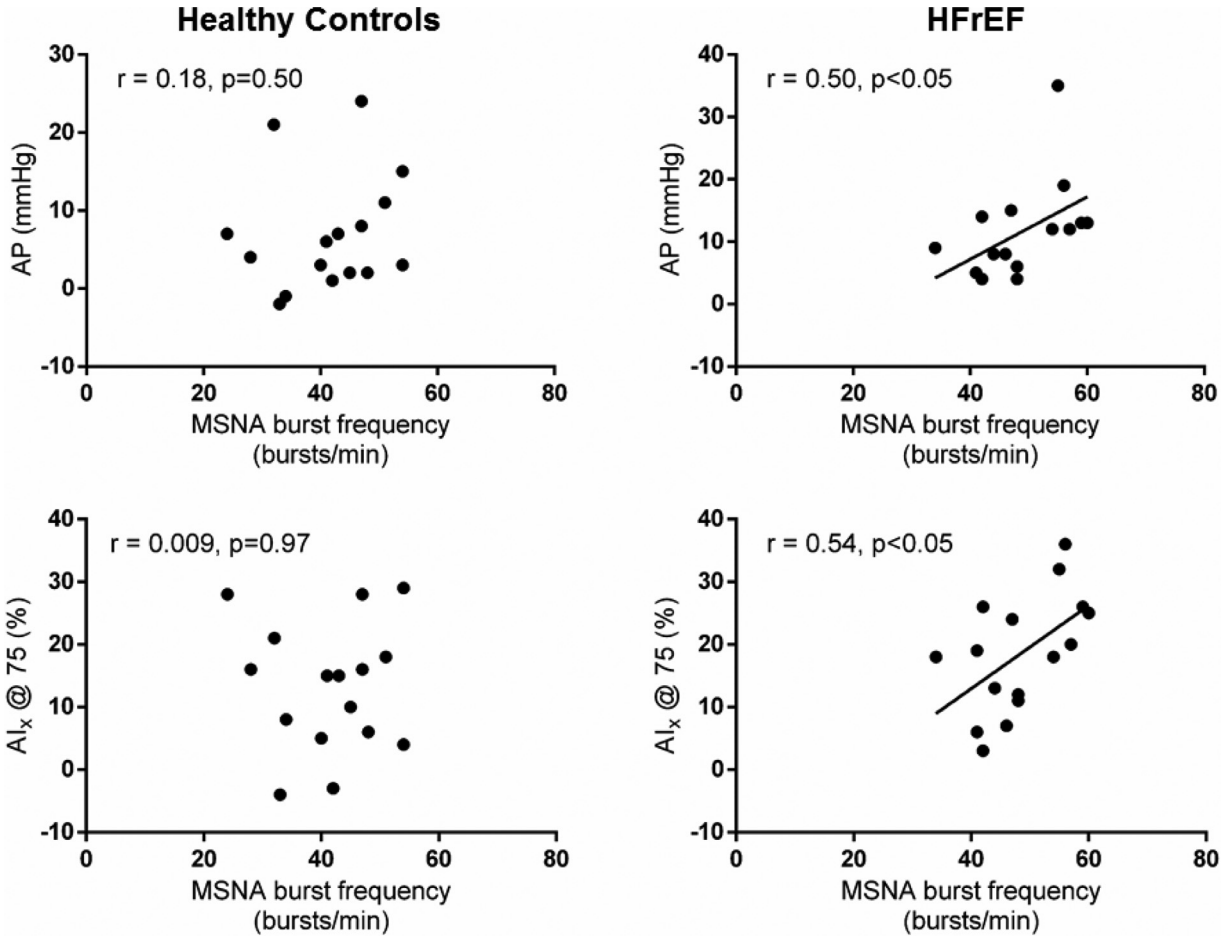

Fig. 1. Relationships between muscle sympathetic nerve activity (MSNA) and augmentation pressure (AP) and augmentation index normalized for heart rate (AI_x@75) in healthy control subjects (left) and patients with heart failure with reduced ejection fraction (HRrEF; right).

Conclusion

We demonstrate for the first time in patients with HFrEF that peripheral muscle sympathetic activity relates positively to the contribution of wave reflection to central aortic pressure. This finding adds to the known mechanisms by which sympathetic excitation can contribute to symptoms and augmented disease progression of patients with HFrEF.

Disclosures

None.

References

1. Laurent S, Cockcroft J, van Bortel L, Boutouyrie P, Giannattasio C, Hayoz D. European Network for Noninvasive Investigation of Large Arteries. Expert consensus document on arterial stiffness: methodological issues and clinical applications. Eur Heart J 2006;27:2588–605.
2. Marti CN, Gheorghiade M, Kalogeropoulos AP, Georgiopoulou VV, Quyyumi AA, Butler J. Endothelial dysfunction, arterial stiffness, and heart failure. J Am Coll Cardiol 2012; 60:1455–69.
3. Vlachopoulos C, Aznaouridis K, O'Rourke MF, Safar ME, Baou K, Stefanadis C. Prediction of cardiovascular events and all-cause mortality with central haemodynamics: a systematic review and meta-analysis. Eur Heart J 2010;31:1865–71.
4. Swierblewska E, Hering D, Kara T, Kunicka K, Kruszewski P, Bieniaszewski L, et al. An independent relationship between muscle sympathetic nerve activity and pulse wave velocity in normal humans. J Hypertens 2010;28:979–84.
5. Hart EC, Charkoudian N, Joyner MJ, Barnes JN, Curry TB, Casey DP. Relationship between sympathetic nerve activity and aortic wave reflection characteristics in postmenopausal women. Menopause 2013;20:967–72.
6. Casey DP, Curry TB, Joyner MJ, Charkoudian N, Hart EC. Relationship between muscle sympathetic nerve activity and aortic wave reflection characteristics in young men and women. Hypertension 2011;57:421–7.
7. Harvey RE, Barnes JN, Hart ECJ, Nicholson WT, Joyner MJ, Casey DP. Influence of sympathetic nerve activity on aortic hemodynamics and pulse wave velocity in women. Am J Physiol Heart Circ Physiol 2017;312:H340–6.
8. Floras JS. Sympathetic nervous system activation in human heart failure: clinical implications of an updated model. J Am Coll Cardiol 2009;54:375–85.
9. Borlaug BA, Olson TP, Abdelmoneim SS, Abdelmoneim Mohamed S, Melenovsky V, Sorrell VL, et al. A randomized pilot study of aortic waveform guided therapy in chronic heart failure. J Am Heart Assoc 2014;3:e000745.
10. Millar PJ, Murai H, Floras JS. Paradoxical muscle sympathetic reflex activation in human heart failure. Circulation 2015;131:459–68.

11. Notarius CF, Murai H, Morris BL, Floras JS. Effect of fitness on reflex sympathetic neurovascular transduction in middle-age men. Med Sci Sports Exerc 2012;44:232–7.
12. Weber T, Auer J, Lamm G, O'Rourke MF, Eber B. Arterial stiffness, central blood pressures, and wave reflections in cardiomyopathy-implications for risk stratification. J Card Fail 2007;13:353–9.
13. Curtis SL, Zambanini A, Mayet J, McG Thom SA, Foale R, Parker KH, Hughes AD. Reduced systolic wave generation and increased peripheral wave reflection in chronic heart failure. Am J Physiol Heart Circ Physiol 2007;293:H557–62.
14. Vranish JR, Holwerda SW, Young BE, Credeur DP, Patik JC, Barbosa TC, et al. Exaggerated vasoconstriction to spontaneous bursts of muscle sympathetic nerve activity in healthy young black men. Hypertension 2018;71:192–8.
15. Millar PJ, Floras JS. Statins and the autonomic nervous system. Clin Sci 2014;126:401–15.
16. Tousoulis D, Oikonomou E, Siasos G, Chrysohoou C, Zaromitidou M, Kioufis S, et al. Dose-dependent effects of short term atorvastatin treatment on arterial wall properties and on indices of left ventricular remodeling in ischemic heart failure. Atherosclerosis 2013;227:367–72.
17. Hering D, Lambert EA, Marusic P, Ika-Sari C, Walton AS, Krum H, et al. Renal nerve ablation reduces augmentation index in patients with resistant hypertension. J Hypertens 2013;31:1893–900.
18. Roveda F, Middlekauff HR, Rondon MU, Reis SF, Souza M, Nastari L, et al. The effects of exercise training on sympathetic neural activation in advanced heart failure: a randomized controlled trial. J Am Coll Cardiol 2003;42:854–60.
19. Edwards DG, Schofield RS, Magyari PM, Nichols WW, Braith RW. Effect of exercise training on central aortic pressure wave reflection in coronary artery disease. Am J Hypertens 2004;17:540–3.