A Novel Noninvasive Device to Assess Sympathetic Nervous System Function in Patients With Heart Failure

Monica Parry ▼ Chantelle A. Nielson ▼ Fiona Muckle ▼ Sheila O'Keefe-McCarthy ▼ Rene van Lien ▼Jan H. Meijer

Background: Heart failure is a complex syndrome associated with sympathetic nervous system and renin–angiotensin–aldosterone system hyperactivity. Sympathoinhibition and downregulation of sympathetic activity using medications and exercise training improve outcomes in patients with heart failure. Impedance cardiography provides data on hemodynamic and autonomic function that may assist with safe medication, exercise monitoring, and titration.

Purpose: The purpose of this pilot study was to evaluate the sensitivity of the Vrije Universiteit Ambulatory Monitoring System (VU-AMS) version 5*fs* to detect hemodynamic and sympathetic nervous system changes associated with postural shift in persons with heart failure with reduced ejection fraction.

Methods: In this descriptive study, participants ($N = 28$) were recruited from an outpatient device clinic at a tertiary care hospital in Ontario, Canada. They completed a sit-to-stand posture protocol wearing an ambulatory blood pressure (ABP) and a noninvasive VU-AMS version 5*fs* impedance cardiography system.

Results: Most ($n = 18$, 64%) participants were eliminated from the final analyses in this sample because of difficulty in Q-onset and B-point identification in peculiar electrocardiogram and impedance cardiogram waveforms. The remaining participants ($n = 10$) had a mean age of 69 years ($SD = 10$ years) and responses to a sit-to-stand posture protocol that included a 5% increase in heart rate ($p = .001$), an 18% decrease in stroke volume ($p = .01$), and an 8% decrease in left ventricular ejection time ($p = .01$). Participants had an increased preejection period (11%, $p = .01$), a drop in cardiac output of 13% ($p = .02$), and a reduced mean arterial pressure of approximately 4% ($p = .09$) with standing.

Discussion: Although the VU-AMS version 5*fs* system detected anticipated hemodynamic and sympathetic nervous system changes to postural shift in participants ($n = 10$), the elimination of 64% ($n = 18$) of the sample because of scoring difficulties limits the use of this impedance cardiography device using standard scoring algorithms in persons with heart failure with reduced ejection fraction.

Key Words: electric impedance • heart failure • sympathetic nervous system

Nursing Research, September/October 2015, Vol 64, No 5, 351–360

Heart failure is the final common stage of many diseases of the heart; it is a major public health issue projected to affect one in five adults during their lifetime (Lloyd-Jones et al., 2010). Despite advances in management, heart failure carries substantial risk of morbidity and mortality. Heart failure is a complex syndrome associated with sympathetic nervous system and renin–angiotensin–aldosterone system hyperactivity, leading to accelerated heart rates, increased shortness of breath, fatigue, and edema (Kishi, 2012). In addition, heart failure negatively affects cognitive function and emotional well-being, leading to inadequate self-care, greater disability, and increased mortality (Zuccalà et al., 2003). These deficits are greater than expected with normal aging and make performing instrumental activities of daily living (e.g., remembering medications and scheduling appointments) more difficult.

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Supplemental digital content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal's Web site (www.nursingresearchonline.com).

DOI: 10.1097/NNR.0000000000000111

Cognitive Impairment and Sympathetic Nervous System Dysregulation

The etiology of cognitive impairment in heart failure is not fully understood but is thought in part to be because of reduced

cerebral perfusion and oxygenation because of reduced ejection fraction. Depression is also prevalent in persons with heart failure; up to 50% of persons with heart failure have clinically significant depression (Rutledge, Reis, Linke, Greenberg, & Mills, 2006). Neuroimmune factors link symptoms of depression to injury of the cardiovascular system and a poorer heart failure prognosis (Barton et al., 2007). Depression and heart failure are characterized by sympathetic nervous system dysregulation (Barton et al., 2007). Compensatory responses to low cardiac output states cause autonomic hyperactivity and neurohormonal activation that become pathologic over time, worsening the heart failure prognosis. Sympathetic nervous system dysregulation in heart failure causes greater psychological, stress-induced myocardial ischemia (Barton et al., 2007). Sympathetic nervous system dysregulation also exacerbates heart-failure-related autonomic dysfunction (Redwine et al., 2014). In fact, Redwine et al. (2014) found that psychological factors are associated with reduced β-blockade efficacy in patients with cardiovascular disease. This suggests that persons with heart failure and depression differentially respond to β-blockers because their β-adrenergic receptors are hyperresponsive to these agonists.

Management of Sympathetic Nervous System Dysregulation

Suppression of sympathoinhibitory cardiovascular reflexes (arterial and baroreceptors) and augmentation of sympathoexcitatory reflexes (arterial chemoreceptors) worsen the prognosis for persons with heart failure (Kishi, 2012). Various hormonal factors (angiotensin II, nitric oxide, atrial natriuretic peptide, prostaglandins, and aldosterone) modulate this sympathetic activity. Sympathoinhibition and downregulation of sympathetic activity using β-blockers, alpha2 blockers, angiotensin-converting enzyme inhibitors, angiotensin receptors blockers, and exercise improve heart failure outcomes (McKelvie, 2008). Exercise also improves cognitive function in persons with cardiovascular disease (Smith et al., 2010). However, the underlying mechanisms between frequency and intensity of exercise and the role of β-blockers to cognitive and sympathetic nervous system function have not been investigated.

Measurement of Sympathetic Nervous System Dysregulation

Invasive measurement of sympathetic nervous system activity has included direct microneurographic recordings of action potentials of nerves innervating the skeletal muscle and skin, measurement of spillover norepinephrine, plasma and urinary catecholamines, and measurement of sweat and salivary gland activity (van Lien, 2014). Measurement of cardiac contractility, influenced primarily though β-adrenergic receptors, is currently the preferred noninvasive method to measure sympathetic nervous system activity (van Lien, 2014). Contractility is reflected in a more rapid incline to the ejection phase after the onset of ventricular depolarization—a time interval referred to as "the preejection period," measured using impedance cardiography. Ambulatory assessment of hemodynamic and sympathetic nervous system function using impedance cardiography has been used to measure cardiovascular reactivity in persons with a family history of cardiovascular disease (Wright, O'Donnell, Brydon, Wardle, & Steptoe, 2007) and hypertension (McFetridge-Durdle, Routledge, Parry, Dean, & Tucker, 2008). However, it has not been used clinically to assess sympathetic nervous system dysfunction in persons with heart failure with reduced ejection fraction (HFrEF), who are at high risk for cognitive and emotional decline, increased disability, and mortality.

The technique of electrical bioimpedance measures the effective resistance to current flow through the body, part of the body, or organs by applying a small alternating current. When applied to the thorax, variations in impedance are observed, synchronous to the pumping activity of the heart. From these variations in impedance, the impedance cardiography signal is obtained. Complementary to the electrocardiogram that records the electrical activity of the heart, the impedance cardiography signal reflects the hydrodynamic aspects of the cardiac cycle. These changes are generated by fluctuations in blood volume and flow velocity in the ascending aorta and aortic arch during systole and diastole. Beginning in the 1940s, the assessment of impedance was primarily used to measure cardiac output and stroke volume to monitor inflight physiology during aerospace applications. Over the past decades, refinements in impedance cardiography have led to the development of invasive diagnostic and prognostic tools in cardiovascular medicine (cardiac resynchronization therapy-pacemaker [CRT-P], and CRT-defibrillator [CRT-D] devices). Newer generation implanted CRT-P and CRT-D devices are used to treat advanced-symptom-class heart failure to improve fluid volume management and mechanical synchrony. This leads to better hemodynamics and systolic function (Horwich, Foster, De Marco, Tseng, & Saxon, 2004). In fact, some studies have shown that CRT devices improve ventricular filling (Abraham & Hayes, 2003) and reduce mean heart rates from baseline (M = 76, SD = 10) to 3 months of follow-up (M = 72, SD = 8; $p < .01$; Fantoni et al., 2005). Others have shown that CRT devices reduce sympathetic nervous system activity (Najem et al., 2006). After CRT, persons with HFrEF report significantly improved indices of systolic function. These improvements include a reduced QRS duration (milliseconds; M = 165, SD = 18) compared with baseline (M = 190, SD = 27; p = .005) and a reduced left ventricular electromechanical delay (milliseconds; M = 161, SD = 43) compared with baseline (M = 180, SD = 33; p = .03; Horwich et al., 2004). The noninvasive Vrije Universiteit Ambulatory Monitoring System (VU-AMS) version 5*fs* noninvasively measures indices of sympathetic function not currently measured using invasive CRT technologies. These include preejection period and left ventricular ejection time and can be used as measures of left ventricular performance (Table 1). The VU-AMS version 5*fs* allows recording of autonomic

TABLE 1. Impedance-Generated Hemodynamic and Sympathetic Nervous System Parameters and Definitions

Hemodynamic variable	Parameter	Definition
Left ventricular function	CO = cardiac output	Amount of blood ejected from the left ventricle in 1 minute
Preload	SV = stroke volume	Amount of blood ejected with each beat
Afterload	SVR = systemic vascular resistance	Amount of resistance that the heart must pump against
Contractility	d*Z*/d*t* = impedance changes over time	Reflects the force of ventricular contraction
	PEP = preejection period	Time from ventricular depolarization to ventricular ejection
	LVET = left ventricular ejection time	Period over which blood is ejected from the left ventricle

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and cardiovascular activity in research and in naturalistic settings and, therefore, may be a clinically suitable measure of sympathetic nervous system function in persons with HFrEF. When left ventricular failure occurs, the preejection period lengthens (reduced left ventricular pressure during ventricular contraction), and the left ventricular ejection time shortens. Reduced preload—obtained through diuretic therapy—results in decreased stroke volume and shortened left ventricular ejection time. Noninvasive assessment of preejection period and left ventricular ejection time could assist with the safe and accurate prescription and monitoring of pharmacological, psychological, and behavioral therapies for persons with depression and HFrEF.

Sympathetic Nervous System Response to Orthostatic Stress

Short-term cardiovascular regulation is often studied by imposing orthostatic stress challenges such as sit-to-stand procedures. Hemodynamic responses to these challenges are affected by the elapsed time after postural change, length of rest period before the postural change, aging, disease, and medications (Smith, Porth, & Erickson, 1994). Within 2–3 minutes in healthy young people, there is a 30%–35% increase in heart rate, 25% decrease in stroke volume, and 15%–20% drop in cardiac output (Smith et al., 1994; see Figure, Supplemental Digital Content 1, http://links.lww.com/NRES/A151). Systolic and diastolic blood pressures fall by less than 10 and 4 mmHg, respectively (Nardo et al., 1999). During active standing, blood normally pools in the lower extremities, reducing ventricular filling and subsequent cardiac output. The amount of blood dislocated to the lower extremities is dependent on lower body vascular compliance (venous capacity, vascular wall compliance, and tissue edema). Successful compensatory mechanisms involve neurohormones, arterial baroreceptors, and the skeletal muscle pump of the lower body. The skeletal muscle pump helps to maintain venous return and cardiac output. With aging, there is decreased arterial distensibility, decreased venous compliance, and decreased ventricular compliance. This results in a reduced heart rate, stroke volume, and blood pressure response to posture change (Smith et al., 1994). In persons with HFrEF and signs of volume overload, there is no significant venous pooling in the upright posture because of venous distension and peripheral fluid overload. Therefore, there is little decrease in right ventricular filling pressures (preload) and little change in stroke volume, cardiac output, or arterial blood pressure by the Frank–Starling mechanism. Normally, a drop in blood pressure would unload the baroreceptors in the carotid bodies and aortic arch (orthostatic hypotension), which would cause parasympathetic withdrawal and sympathetic activation through baroreflex-mediated autonomic regulation. In HFrEF, the baroreceptor and underlying sympathetic nervous system hyperactivity unloading are blunted, causing minimal changes in heart rate and systemic vascular resistance to standing (Cody, Franklin, Kluger, & Laragh, 1982; Figure 1).

Purpose

Before noninvasive impedance devices can be used in clinical settings, the accuracy in assessing sympathetic nervous system function in persons with HFrEF needs to be investigated. The purpose of this pilot study was to evaluate the sensitivity of the noninvasive VU-AMS version 5*fs* to detect hemodynamic and sympathetic nervous system changes associated with postural shift in persons with HFrEF who had either an internal cardiac defibrillator or a CRT-P or CRT-D device. It is hypothesized that the VU-AMS version 5*fs* device will be sensitive to detect sitting and standing changes in systolic time intervals. Specifically, it is anticipated that participants with internal cardiac defibrillators or CRT devices with HFrEF will have a decrease in preejection period (reflective of increased sympathetic nervous system activity) and decrease in left ventricular ejection time (reflective of an increased heart rate) with a postural change from sitting to standing. It is also hypothesized that the VU-AMS version 5*fs* device will detect anticipated reductions in stroke volume (<25%), cardiac output (<15%), systolic blood pressure (<10%), and diastolic blood

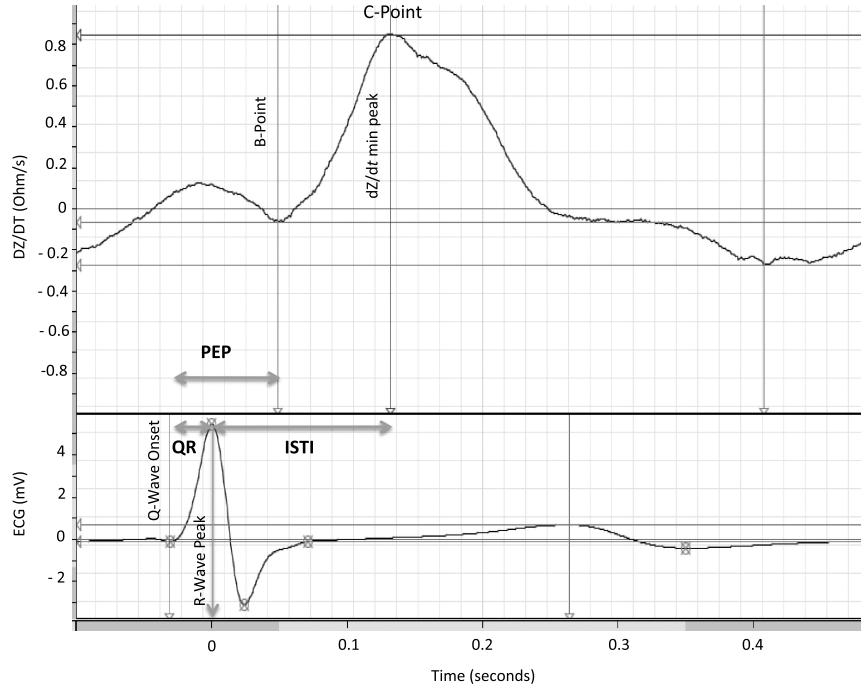

FIGURE 1. Impedance-generated hemodynamic (top) and electrocardiographic (ECG; bottom) waveforms.

pressure (<4%) during a sit-to-stand posture protocol in participants who exhibit no signs of volume overload.

METHODS

Participants

Participants were recruited from the outpatient device clinic at a tertiary care hospital in Southeastern Ontario, including men and women diagnosed with heart failure who were greater than 30 days postimplantation of either an internal cardiac defibrillator or CRT device. Participants in this study had a reduced ejection fraction and an intrinsic atrial rate; were able to read, write, and communicate in English and complete a sit-to-stand posture protocol; and could provide consent.

Materials and Procedure

Before recruitment, ethics approval was obtained from the Health Sciences Research Ethics Boards at both Queen's University and University of Toronto, Canada, and conformed to the standards set by the latest revision of the Declaration of Helsinki. Before the study protocol could be implemented, a component of the protocol had to be tested and verified in participants who had internal cardiac defibrillator or CRT devices. The VU-AMS version 5*fs* used to measure the effective resistance to current flow through the body applies a small alternating current across the chest (50 kHz, 0.35 mA). The safety of generating this small current was tested in a controlled environment to ensure the settings of the internal cardiac defibrillator and CRT devices were not affected by this current.

In this descriptive study, eligible participants were mailed information about the study protocol and invited to participate at their next outpatient appointment to the Cardiac Rhythm and Device Clinic at the tertiary care center. Participants who agreed to an additional 30–45 minutes of clinic time to take part in the study protocol completed the informed consent procedure after clinic registration. Demographic characteristics were obtained from each participant, and health histories were obtained from the participant's health record.

Blood Pressure The primary investigator instrumented and performed all blood pressure measurements using the Spacelabs ABP system. All blood pressure measurements were taken using the participant's nondominant arm. The Spacelabs ABP cuff was placed around the upper arm at the level of the atrium according the Canadian Hypertension Education Program guidelines (Hackam et al., 2013). The Spacelabs Model 90207 ABP monitor has been validated and approved only for blood pressures at rest and in elderly persons standing and sitting (O'Brien, Waeber, Parati, Staessen, & Myers, 2001).

Impedance Cardiography The electrocardiogram and impedance cardiogram were collected using the seven-lead version of the VU-AMS version 5*fs* device, which is a minimally intrusive, small (32 × 65 × 120 mm) battery-powered device, weighing only 225 grams. Three indices of the VU-AMS version 5*fs* impedance cardiogram (dZ/dt, preejection period, and left ventricular ejection time) reflect sympathetic nervous system activity. The first derivative of the pulsatile change in transthoracic impedance (dZ/dt) reflects the momentary changes in aortic blood flow

during systole. The difference in amplitude of the d*Z*/d*t* waveform at its peak compared with the opening of the semilunar valves is the d*Z*/d*t* (min, C-point; Figure 1). It has been shown that this C-point coincides with the maximum diameter of the aortic arch (van Eijnatten, van Rijssel, Peters, Verdaasdonk, & Meijer, 2014). The preejection period is an index that links electrical and mechanical cardiac activity, and it is obtained by simultaneous recording of the electrocardiogram and impedance cardiogram. It is defined as the interval between the onset of ventricular depolarization (Q-wave onset in the electrocardiogram) and the opening of the semilunar valves (sharp upstroke in the d*Z*/d*t* or B-point in the impedance cardiogram). Much debate exists in the literature about preejection period scoring; when signal quality of the impedance cardiogram is compromised, reliable visual scoring of the B-point is difficult (van Lien, Schutte, Meijer, & de Geus, 2013). Three solutions have been proposed to improve preejection period scoring:

1. Score the more easily detected R-wave onset, and add a fixed value for Q-wave duration of 15 milliseconds (Berntson, Lozano, Chen, & Cacioppo, 2004).
2. Use the R-wave peak instead of the R-wave onset, and add a fixed value of 48 milliseconds (Brydon et al., 2008).
3. Assess the interval between the R-peak and the d*Z*/d*t* (min) peak or the initial systolic time interval (Meijer, Boesveldt, Elbertse, & Berendse, 2007).

The first two alternatives assume that the Q-wave duration and the R-wave peak are constant. There has been insufficient investigation to consider an estimated preejection period a valid alternative to actual preejection period, and none of these alternatives have been sufficiently verified in persons with HFrEF. Given this, standard practices were employed to measure actual preejection period in this study. All automatically detected Q-wave onset and B-points were visually inspected to ensure sufficient reliability. Scoring was also independently completed by two raters. Others have reliably used this method to measure systolic time intervals (preejection period and left ventricular ejection time) in persons with HFrEF (Reant et al., 2010). It was assumed that within-participant changes in preejection period reliably reflected changes in sympathetic drive to the left ventricle and that left ventricular ejection time signaled closure of the aortic valve. Two outer electrodes injected an alternating current to the thorax, and two inner electrodes measured the (periodical) time variations in impedance of the thorax *Z*(*t*). An average impedance *Z* was calculated from the voltage according to Ohm's law. Various other indices of hemodynamic and autonomic function were estimated using impedance cardiography, including heart rate, stroke volume, and cardiac output.

Procedure

Skin was prepared with alcohol before electrode application to ensure that electrode resistance was kept low. Seven disposable, prefilled Ag–AgCl spot electrodes were placed on the body (see Figure, Supplemental Digital Content 2, http://links.lww.com/NRES/A152). Three electrocardiogram electrodes were placed: (a) below the right collar bone 4 cm to the right of the sternum, (b) between the two lower right ribs, and (c) 4 cm under the left breast. Four impedance cardiogram electrodes were placed: (a) at the suprasternal notch; (b) on the xiphoid process; (c) on the spine, 3 cm above the suprasternal notch; and (d) on the spine, 3 cm below the xiphoid process. After visually establishing proper signal quality, the recording was started, and the participants were asked to rest and sit for 5 minutes. After 5 minutes of rest, hemodynamic and autonomic measures were collected for the sitting protocol. After data were collected, participants were asked to stand while adopting a comfortable posture. Within 2–3 minutes of standing, data were collected for all variables. Hemodynamic variables collected were heart rate and systolic and diastolic blood pressure. Autonomic reactivity was measured using the preejection period, left ventricular ejection time, stroke volume, and cardiac output. Systemic vascular resistance was calculated using the formula mean arterial pressure/cardiac output, where mean arterial pressure was calculated to be two thirds of diastolic blood pressure plus one third of systolic blood pressure (Klabunde, 2012). After electrocardiographic and impedance cardiography data were collected, participants were interviewed and examined for indicators of fluid volume overload. This interview/examination lasted approximately 10 minutes and was completed while patients were sitting comfortably at the end of their clinic visit.

Data Analysis

The VU-AMS version 5*fs* system averages, analyzes, and stores electrocardiographic and impedance cardiography data and has been validated in several studies (Goedhart, Kupper, Willemsen, Boomsma, & de Geus, 2006; Goedhart, van der Sluis, Houtveen, Willemsen, & de Geus, 2007). Electrocardiographic and impedance cardiography signals were imported into the VU-AMS data analysis and management software to score the interbeat intervals and preejection periods. Interbeat intervals—the intervals in milliseconds between two adjacent R waves—were obtained from the electrocardiogram by an online automated R-wave peak detector. Artefact preprocessing was performed on the interbeat interval data. All interbeat interval artifacts were accepted or overruled by visual inspection. Ensemble averaging of the impedance waveform over all beats in a 1-minute period was done by automated algorithms. Visual inspection of all automatically detected Q-wave onset (electrocardiogram) and B-point (impedance cardiogram) was done by the principal investigator. To reduce subjective bias, a second rater independently inspected all preejection period scores.

Data were entered and stored in Microsoft Access and verified through logic and range checks. The effects of postural change, from sit to stand, on hemodynamic and autonomic reactivity were computed and compared using the Statistical Package for the Social Sciences (Version 21). Pearson correlations were calculated in both sitting and standing positions.

Paired *t*-tests were used to compare the means and standard deviations of the sitting and standing cardiovascular measures taken with the ABP and the VU-AMS version 5*fs* systems for each of the posture protocols. For each index of cardiac function, the response to standing was computed as the difference between standing and sitting values, expressed as a percent change from the sitting values. Alpha was set at .05 for all analyses.

RESULTS

Sample

In this study, 23 men and five women completed a sitting-to-standing posture protocol wearing the Spacelabs ABP (Spacelabs, Model 90207; Spacelabs, Inc., Washington, DC) and the noninvasive VU-AMS version 5*fs* monitoring systems. Signal quality or difficult B-point determination led to the exclusion of a significant number of participants ($n = 18$). Some preprocessing artifacts were not deleted because of the nature of the interbeat interval data for persons with HFrEF. Results will be reported for the 10 participants who had adequate signal quality for data analyses.

Participants ranged in age from 53 to 83 years, with a mean age of 69 years ($SD = 10$ years). Eighty percent of the sample were male ($n = 8$), with a mean body mass index of 28 kg/m^2 ($SD = 5$ kg/m^2). Most (70%, $n = 7$) had Grade 3 or 4 left ventricular function and a mean ejection fraction of 31% ($SD = 9\%$), and 50% ($n = 5$) had slight limitation of physical activity (New York Heart Association Class II). Patient characteristics, symptoms, and comorbidities are summarized in Table 2.

Response to Standing

The Spacelabs ABP and VU-AMS version 5*fs* systems detected the expected directional hemodynamic and autonomic changes to standing: increased heart rate, decreased stroke volume, decreased cardiac output, decreased left ventricular ejection time, increased systemic vascular resistance, and increased preejection period. For example, when left ventricular failure occurs, the preejection period lengthens (reduced left ventricular pressure during ventricular contraction), and the left ventricular ejection time shortens. For each of the measures, the response to standing was computed. Heart rate increased by 5% ($p = .001$), stroke volume decreased by 18% ($p = .01$), and left ventricular ejection time decreased by approximately 8% ($p = .01$). Participants in this study had an increased preejection period (11%, $p = .01$), a drop in cardiac output of 13% ($p = .02$), and a reduced mean arterial pressure of approximately 4% ($p = .09$) upon standing. Percent changes in hemodynamic and autonomic variables for sitting and standing are depicted in Figures 2 and 3.

TABLE 2. Demographic Characteristics

Characteristic	*n*	(%)
Marital status (married)	10	(100)
Employment (full time)	2	(20)
Exertional dyspnea (yes)	6	(60)
Orthopnea (yes)	1	(10)
Dyspnea at rest (yes)	0	(0)
Nocturnal dyspnea (yes)	0	(0)
Leg edema (yes)	2	(20)
Hypertension (yes)	6	(60)
Diabetes (yes)	4	(40)
COPD (yes)	3	(30)
Arthritis (yes)	5	(50)
Depression (yes)	3	(30)
CVA (yes)	0	(0)
PVD (yes)	4	(40)

Note. $N = 10$. COPD = chronic obstructive pulmonary disease; CVA = cerebral vascular accident; PVD = peripheral vascular disease.

Correlational Analysis

There were significant positive correlations between systemic vascular resistance and preejection period in both sitting ($r = .73$, $p < .05$) and standing ($r = .73$, $p < .05$) positions and a significant negative correlation between cardiac output and preejection period in both sitting ($r = -.73$, $p < .05$) and standing ($r = -.77$, $p < .05$) positions. Heart rate was negatively correlated to stroke volume while sitting ($r = -.78$, $p < .05$), but this was lost when participants stood ($r = -.49$, $p = ns$). There were no significant expected correlations between heart rate and left ventricular time when sitting ($r = -.04$, $p = ns$) or standing ($r = .11$, $p = ns$), between heart rate and cardiac output when sitting ($r = -.15$, $p = ns$) or standing ($r = .22$, $p = ns$), between heart rate and preejection period when sitting ($r = -.22$, $p = ns$) or standing ($r = -.55$, $p = ns$), or between preejection period and left ventricular ejection time when sitting ($r = .07$, $p = ns$) or standing ($r = -.06$, $p = ns$; Table 3).

DISCUSSION

Physiology of Hemodynamic and Sympathetic Nervous System Responses

Reliability of ambulatory preejection period scoring is very sensitive to the selection of the correct landmarks in the electrocardiogram (Q-onset) and in the impedance cardiogram (B-point). Detection of the Q-onset and the B-point in this sample of participants with reduced ejection fraction heart failure required laborious visual inspection. This tedious manual inspection can threaten the validity of results during data interpretation (van Lien, 2014) and can limit its use in the clinical setting. Eighteen participants were eliminated from the final analyses in this sample because of difficulty in Q-onset and B-point identification in peculiar electrocardiogram and impedance cardiogram waveforms. Although the Spacelabs ABP and VU-AMS version 5*fs* systems detected anticipated hemodynamic and sympathetic nervous system changes to postural shift in persons with HFrEF ($n = 10$), the elimination of 64% ($n = 18$) of the sample because of scoring difficulties limits use of this noninvasive device using standard scoring algorithms.

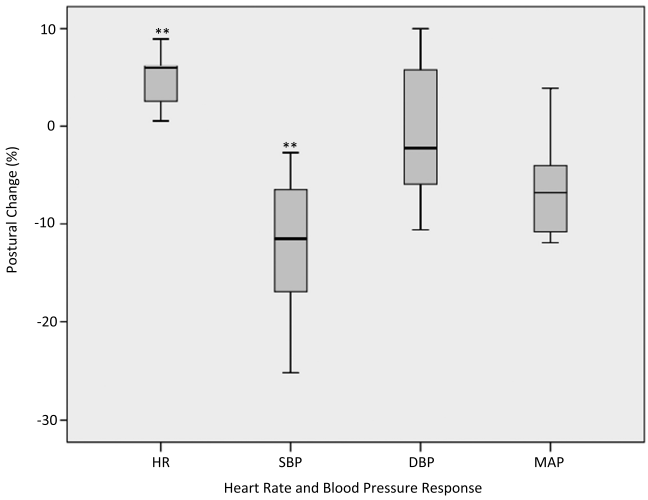

FIGURE 2. Heart rate and blood pressure response to standing in participants with HFrEF, expressed as percent change from sitting values. HR = heart rate; SBP = systolic blood pressure; DBP = diastolic blood pressure; MAP = mean arterial pressure. $^{**}p < .01$.

From the impedance cardiogram, various systolic time intervals were computed, including the preejection period and the left ventricular ejection time. Participants in this study had a mild increase in heart rate with standing—which was less than that seen in healthy volunteers—and in populations with hypertension and chemical sensitivities (McFetridge-Durdle et al., 2008, 2009; Sherwood, McFetridge, & Hutcheson, 1998). This blunted response to standing likely reflects current heart failure treatments that attempt to modulate heart failure sympathoexcitation using β-blockers and CRT devices. The blunted increase in heart rate observed in participants was accompanied by a parallel fall in stroke volume, left ventricular ejection

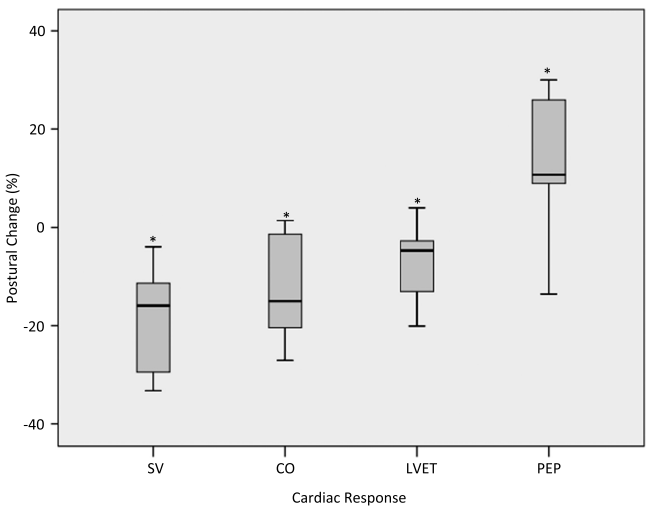

FIGURE 3. Cardiac response to standing in participants with HFrEF, expressed as percent change from sitting values. SV = stroke volume; CO = cardiac output; LVET = left ventricular ejection time; PEP = preejection period. $^{*}p < .05$.

TABLE 3. Hemodynamic and Autonomic Variables While Sitting and Standing: Correlations

Variable	1	2	3	4	5	6	7	8
1. HR	1.00	.50	.54	.15	−.55	.11	.22	−.49
2. SBP	.22	1.00	.77**	.71*	.18	.19	−.60	−.71*
3. DBP	.60	.65*	1.00	.78*	.27	−.14	−.61	−.82**
4. SVR	.35	.63	.88**	1.00	.73*	−.12	−.91**	−.93**
5. PEP	−.22	.41	.55	.73*	1.00	.06	−.77**	−.61
6. LVET	−.04	.21	.07	.18	.07	1.00	.04	.27
7. CO	−.15	−.58	−.85**	−.96**	−.73*	−.18	1.00	.85**
8. SV	−.78*	−.57	−.90**	−.85**	−.56	.14	.80**	1.00

Note. Sitting, below diagonal; standing, above diagonal. CO = cardiac output; DBP = diastolic blood pressure; HR = heart rate; LVET = left ventricular ejection time; PEP = preejection period; SBP = systolic blood pressure; SV = stroke volume; SVR = systemic vascular resistance. $^{*}p < .05$. $^{**}p < .01$.

time, and subsequently, mean arterial pressure. The principal determinants of left ventricular ejection time are heart rate and stroke volume, with the duration of left ventricular ejection time usually strongly and inversely related to changes in heart rate. In this study of persons with HFrEF, left ventricular ejection time was not correlated to heart rate possibly because of β-blocker treatment and CRT technology. The preejection period assesses cardiac contractility, a reflection of sympathetic nervous system activity. The preejection period is inversely related to sympathetic nervous system activity, such that increases in preejection period reflect decreases in sympathetic nervous system activity. Participants in this study had a lower preejection period than that reported in healthy volunteers and in populations with chemical sensitivities (McFetridge-Durdle et al., 2009; Sherwood et al., 1998; Willemsen, De Geus, Klaver, van Doornen, & Carroll, 1996). Participants also had a significant increase in preejection period to standing; the percent change from sitting was higher than that reported in healthy volunteers and in populations with hypertension and chemical sensitivities (Table 4). These reduced inotropic cardiac responses to standing may be related to increased afterload (systemic vascular resistance and systolic blood pressure), arterial–ventricular load mismatching, physical deconditioning, and/or impaired sympathetic nervous system regulation (β-adrenergic desensitization).

Cardiac contractility can decrease independently from sympathetic effects when the stretch of the cardiac muscle fibers fails to increase stroke volume through the Frank–Starling mechanism (van Lien, 2014). In a normal heart, contractility increases as muscle length increases. However, in persons with HFrEF, contractility decreases as muscle length increases. There were significant reductions in stroke volume and cardiac output to standing, and participants did not appear to be able to translate the inotropic stimulation from sitting to standing into improved myocardial fiber shortening.

There are similarities between the abnormalities associated with reduced ejection fraction and those seen in physical deconditioning. Prolonged inactivity and reduced ejection

TABLE 4. Systolic Time Intervals (Sitting and Standing) in Participants With a Reduced Ejection Fraction Compared With Values Reported in the Literature for Healthy Participants and Participants With Chronic Disease

		Sitting		Standing		
Interval	**Participants**	***M***	***(SD)***	***M***	***(SD)***	**% change**
HR (bmp)	Reduced ejection fraction[a]	68	(14)	71	(15)	5**
	Healthy volunteers[b]	64	(8)	80	(11)	26*
	Healthy volunteers[c]	NR	NR	NR	NR	NR
	Chemical sensitivities[d]	74	(10)	82	(12)	11**
	Hypertension[e]	63	(14)	70	(15)	12*
PEP (ms)	Reduced ejection fraction[a]	113	(21)	127	(32)	11*
	Healthy volunteers[b]	127	(9)	135	(10)	7*
	Healthy volunteers[c]	134	(14)	143	(10)	7*
	Chemical sensitivities[d]	125	(19)	125	(22)	0
	Hypertension[e]	119	(19)	122	(25)	3
LVET (ms)	Reduced ejection fraction[a]	318	(50)	292	(42)	–8*
	Healthy volunteers[b]	284	(17)	243	(18)	–15**
	Healthy volunteers[c]	280	(41)	258	(36)	–8*
	Chemical sensitivities[d]	292	(39)	260	(40)	–11**
	Hypertension[e]	326	(53)	292	(46)	–10**

Note. bpm = beats per minute; HR = heart rate; LVET = left ventricular ejection period; ms = milliseconds; NR = not reported; PEP = preejection period. [a]Current study. [b]Sherwood et al., 1998; N = 11, mean age = 25 years. [c]Willemsen et al., 1996; N = 25, mean age = 27 years. [d]McFetridge-Durdle et al., 2009; N = 17, mean age = 47 years. [e]McFetridge-Durdle et al., 2008; N = 17, mean age = 61 years. *$p < .05$. **$p < .01$.

fraction are both associated with exercise intolerance, sympathetic hyperactivation, reduced heart rate variability, reduced peak oxygen consumption (VO_2), wasted skeletal muscle, and depleted skeletal muscle oxidative enzymes. Prolonged inactivity is common in persons with HFrEF—compounding deconditioning of the skeletal muscle and cardiovascular system—and abnormalities of autonomic control. Research conducted over the past 2 decades suggests that regular exercise training is effective and safe for persons with heart failure (McKelvie, 2008). However, more research is needed to determine the optimal intensity, duration, and frequency of training to maximize the clinical benefit and to clearly delineate which subgroups of patients might benefit the most (i.e., HFrEF and depression or heart failure with preserved ejection fraction and depression). Studies are also urgently needed to identify mechanisms for the cognitive deficits in heart failure and test innovative interventions to prevent cognitive loss and depression. The preejection period is a good choice for ambulatory monitoring of sympathetic nervous system activity, and impedance cardiography measurements using noninvasive spot electrodes are very well tolerated by patients. A noninvasive device would be useful in future exercise training trials as an alternative or adjunct to measuring sympathovagal activity using RR variability, autoregressive power spectral analysis, plasma norepinephrine levels, and muscle sympathetic nerve activity. However, determination of systolic time intervals using standard scoring algorithms needs to be evaluated in persons with HFrEF.

Limitations

In this study, signal quality—or difficult B-point determination—led to the exclusion of a significant number of participants. The initial systolic time interval may be a better alternative to measuring preejection period in persons with HFrEF because the beginning and end markers of this interval are substantially more pronounced and can be detected in an automatic way. The initial systolic time interval is the interval between the R-wave peak on the electrocardiogram and the dZ/dt (min) peak (C-point) on the impedance cardiogram (Figure 2). Changes in cardiac contractility may be reflected not only in the time it takes the left ventricle to build up adequate force to open the aortic valve (B-point) but also in the time it takes to reach peak ventricular ejection (dZ/dt-min), thus extending the preejection period (ventricular depolarization plus isovolumetric contraction) with the rapid part of the ejection phase (van Lien, 2014). The initial systolic time interval—interpreted as the time delay between the electrical and mechanical activities of the heart—has been gauged in healthy subjects by comparing this interval with markers of the cardiac cycle obtained by echocardiography (van Eijnatten et al., 2014). In this study, the investigators chose to use standard methods to measure actual preejection period, with two independent raters visually inspecting and scoring all automatically detected Q-wave onset and B-points to ensure sufficient reliability. Future research should compare estimated preejection periods using the fixed values of 15 milliseconds for Q-wave duration (Berntson et al., 2004) and 48 milliseconds for R-wave duration (Brydon et al., 2008) with actual preejection period values in persons with heart failure. Given that the information between preejection period and initial systolic time interval strongly overlap empirically and theoretically, initial systolic time interval itself might be a better marker of sympathetic nervous system activity in persons with HFrEF. Clearly, before considering fixed values or initial systolic time interval as alternative indicators of sympathetic responses, further validation is required.

In addition, because this was a pilot study, we did not employ the use of a comparison or control group of age-matched individuals. Aging reduces arterial distensibility, venous compliance, ventricular compliance, and stroke volume, and there is a reduced heart rate and blood pressure response to sympathetic stimulation. The purpose of this study was to evaluate the sensitivity of the noninvasive VU-AMS version 5*fs* device to detect hemodynamic and sympathetic nervous system changes associated with postural shift in persons with HFrEF who had either an internal cardiac defibrillator or a CRT device. Although we eliminated 18 participants from the final analyses because of scoring difficulties, we learned that alternative scoring methods are necessary if this noninvasive device is to be used in clinical or natural settings with this population. Future studies should include a comparison group of age-matched individuals and control for other cointerventions (CRT-P and CRT-D) and sympathetic stimuli that may influence study outcomes (e.g., caffeine, alcohol, or nicotine intake; depression). Once

scoring mechanisms are sorted, further research using larger sample sizes would improve the generalizability of the results.

Conclusion

The findings from this study have implications for more research. Heart failure and physical deconditioning are characterized by progressive fatigue, dyspnea, and depression, and depression in this population is associated with an increased risk of mortality. Many exercise studies in heart failure were conducted in an era before widespread use of β-blockers. Randomized controlled trials are needed to verify the cardiac adaptations to exercise training in persons with depression and heart failure, who are now routinely prescribed with β-blockers. Noninvasive devices have not been used to examine the hemodynamic and sympathetic nervous system responses to exercise training in persons with heart failure or depression in clinical settings. Noninvasive impedance technologies offer portability and the option of tailoring pharmacological, psychological, and behavioral therapies for these complex patients. Tailoring therapies may also be useful in other populations with chronic disease—who also have impairments in autonomic function—such as persons with diabetes and cardiac autonomic neuropathies. However, before these technologies can be used in persons with HFrEF and integrated into clinical practice settings, methods for reliable preejection period scoring need to be determined.

Accepted for publication June 16, 2015.

The authors would like to acknowledge that Parry and Nielson assumed the lead roles for the preparation of this manuscript. All content was reviewed by the contributing authors (Muckle, O'Keefe-McCarthy, Meijer, and van Lien). Parry and van Lien visually inspected all electrocardiogram and impedance cardiogram waveforms before data analyses were completed. Funding to conduct this research was obtained from the Bertha Rosenstadt Small Research Grant Program at the Lawrence S. Bloomberg Faculty of Nursing and the Connaught New Researcher Award at the University of Toronto.

Parry, Nielson, Muckle, O'Keefe-McCarthy, and Meijer declare no conflicts of interest. van Lien completed his PhD studies at VU University and was paid for his VU-AMS version5*fs* ICG research.

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