ORIGINAL RESEARCH

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Predictors of orthostatic intolerance in healthy young women

Abstract

Purpose: Orthostatic intolerance is more prevalent in women. The purpose of this investigation was to evaluate the physiological responses of orthostatic tolerant and intolerant females to progressive lower body negative pressure (LBNP) and to identify predictors of orthostatic tolerance.

Methods: Following baseline measurements, eleven healthy, moderately active women (mean age 24 ± 3 yr) underwent an orthostatic challenge involving four 12-minute stages of progressive LBNP at -15, -30, -45 and -60 mmHg. Traditional haemodynamic characteristics, as well as baroreceptor sensitivity, were analyzed across all stages.

Results: Five women became presyncopal during the test and were classified as low tolerant (LT) while the remaining six were classified as high tolerant (HT). LBNP by group (tolerance) interactions were significantly different for stroke volume ($P=0.008$) and the rate of decline (slope) of stroke volume ($P=0.03$). During the early stages of LBNP, the LT group displayed a higher stroke volume than the HT group (76.4 ± 8.6 vs. 60.0 ± 13.3 mL/beat; $P=0.02$) yet by the final stage, stroke volumes were similar (22.5 ± 11.9 vs. 22.7 ± 4.5 mL/beat, $P = 0.99$). Baroreceptor sensitivity, heart rate variability and blood pressure variability were not significantly different between the groups.

Conclusions: The results of this investigation suggest that orthostatic intolerance in women can be identified during the initial stages of an LBNP challenge, as evidenced by a more rapid decline in stroke volume.

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Acute orthostatic intolerance presents during a postural shift, in which blood volume is rapidly translocated away from the central and cerebral vasculature and into the periphery, resulting in decreased cardiac filling pressure, stroke volume and cardiac output [1,2]. Concurrently, compensation to maintain blood pressure occurs through sympathetic activation, increasing heart rate and vasoconstriction; however, when this response is inadequate, insufficient cerebral perfusion ensues and symptoms of presyncope develop [1,3]. Recently, stroke volume has been shown to be associated with cerebral perfusion, influencing average and pulsatile cerebral blood flow [4].

Individual differences exist in the response to orthostasis, with some individuals exhibiting marked reductions in blood pressure (i.e., hypotension) and/or presyncopal symptoms, while others are much more tolerant [5-7]. Independent of chronic orthostatic hypotension, resulting from cardiovascular abnormalities or autonomic nervous system dysfunction, the genesis of acute orthostatic intolerance has yet to be elucidated [8]. More prevalent in females [9-12], orthostatic intolerance is increased following bed rest [13,14], space flight [10,15], blood donation [16] and heat exposure [17]. The greater vulnerability of women to orthostatic intolerance in these situations warrants a characterization of differential responses to orthostasis in women.

The vast majority of research has identified predicting factors and hemodynamic responses to orthostatic intolerance in only men [5,6,18], or via a comparison of men and women [7,9,11,19]. Fu and colleagues [7] provided compelling evidence of gender differences in stroke volume regulation during orthostatic stress; however, in order to better understand the sequela leading to a presyncopal event in women, a sample comprised of only women would lend itself to fewer confounding factors. Only one study has compared the responses of orthostatic tolerant and intolerant women: Morikawa and colleagues [20] compared endurance-trained and untrained Asian women and eloquently reviewed the results of syncopal and non-syncopal women for each group. As previous work has shown in males [21], the endurance-trained women were more intolerant than the untrained women; however, these researchers did not focus on the results of the untrained syncopal group. It is unclear why these women were more intolerant than their untrained counterparts, and this warrants further study. In light of potential ethnic differences in hemodynamic stress responses [22] the exploration of this phenomenon in Caucasian women is also of interest. The primary purpose of this research was to distinguish the physiological responses of tolerant and intolerant, moderately physically active, young, Caucasian women under induced central hypovolemia. We

hypothesized that there would be greater reductions in stroke volume for intolerant women throughout a graded lower body negative pressure (LBNP) challenge. Further, we suspected that early changes in stroke volume would serve as the strongest predictor of orthostatic tolerance.

Materials and Methods

Participants

Twelve healthy, normotensive, young women (mean age 24 ± 3 yr) participated in this study. All were moderately physically active and non-smokers. As endurance training has been shown to be a factor in orthostatic tolerance [21,23] and VO_2max is a poor predictor of orthostatic tolerance [21], women were recruited with similar physical activity levels (exercise 2x per week or fewer). The women participated in a variety of activities and recreational sports but were not involved in any formal endurance training.

Prior to the testing, participants were provided with an orientation to the protocol and instrumentation, and also completed a medical screening questionnaire after providing written informed consent. This research was approved by the University of British Columbia Clinical Ethics Review Board and adhered to the guidelines established by the declaration of Helsinki. Participants arrived to the lab having refrained from eating in the two hours prior to their scheduled testing. All participants abstained from vigorous exercise, caffeine or alcohol in the twelve hours prior to the LBNP protocol. Menstrual cycle was not controlled for as there is compelling evidence that phase of menstrual cycle does not influence orthostatic tolerance in healthy young women [24] and does not influence haemodynamic parameters during an orthostatic challenge in healthy individuals [25].

Experimental Protocol

The experimental protocol involved one day of testing in which measurements of stature and body mass preceded instrumentation, followed by a 72 minute progressive lower body negative pressure (LBNP) protocol. This technique has been used to simulate orthostasis in a variety of situations and populations as a means to study cardiovascular response to central hypovolemia and haemorrhage [26]. Ambient temperature in the laboratory was $21\text{-}22^\circ\text{C}$ and all testing took place in the same laboratory during the afternoon hours [27], within a one month time frame. Participants wore a neoprene skirt and were positioned supine in the pressure chamber, straddling a bicycle seat, and sealed below the waist at the iliac crest. Throughout the LBNP protocol, subjects were required to control their

respiratory frequency at a fixed rate of 12 breaths/min (0.20 Hz) by following a metronome tone.

After 12 minutes of baseline data collection at ambient barometric pressure, four 12-minute stages of progressive LBNP at -15, -30, -45 and -60 mmHg were applied. The negative pressure was terminated if any of the following symptoms were observed: 1) a sudden drop in heart rate or blood pressure, or a sustained drop in systolic blood pressure (SBP) below 90 mmHg, along with qualitative symptoms, and/or 2) at the participant request. Close monitoring of qualitative symptoms of nausea, excessive sweating, tunnel vision, light-headedness, and/or dizziness were also used to identify presyncope. A final recovery stage took place where ambient pressure was re-applied for the final 12 minutes of data collection after the last negative pressure stage.

Haemodynamic Measurements

All hemodynamic measurements were collected continuously throughout all stages of the LBNP protocol using an analog-to-digital converter (Powerlab/16SP ML 795; ADInstruments, Colorado Springs, CO) interfaced with a computer. Continuous heart rate was measured using electrocardiography (ECG; ML 132; ADInstruments) configured in the standard bipolar limb lead II. Beat-by-beat SBP and diastolic (DPB) blood pressure was measured noninvasively using a Finapres finger cuff blood pressure device (Ohmeda Inc, Englewood, CO). Blood pressure was also measured every 3 minutes using automated cuff occlusion (BMP-100 VSM Medtech, Coquitlam, BC) and used to verify readings obtained from the Finapres. Stroke volume was estimated using impedance cardiography (HIC-3000, Bio-Impedance Technology, Inc., Chapel Hill, NC), which has been validated for its use during LBNP, and strongly correlated with echocardiography [28].

Data Analysis

All data were analyzed by a single researcher. Mean arterial pressure (MAP) was calculated as $[(SBP-DBP)/3 + DBP]$ and pulse pressure (PP) was calculated as $SBP - DBP$. Slope was calculated for changes in stroke volume over each stage of LBNP for each participant using Microsoft Excel (Redmond, WA) where the absolute stroke volume was plotted against the stage of LBNP. Group means were then calculated from the individual slopes. Cardiac output (CO) was calculated by multiplying heart rate and stroke volume. Total peripheral resistance was calculated as MAP/CO .

Baroreceptor sensitivity (BRS) was analyzed using specialized software (Nevrokard NKFP 8.7.0 and BRS 5.7.0, Nevro-

kard, Izola, Slovenia). After ectopic beats were isolated in the ECG, a clean 3-5 minute sample was analyzed for baroreceptor sensitivity. Estimates of BRS were obtained via calculation of the slope between changes in R-R interval (RRI) and changes in SBP (sequence method), and the alpha coefficient in the low frequency (LF) or high frequency (HF) bands (cross spectral method) [29].

For the sequence method, inclusion criteria were as follows: a RR interval variation of greater than 5 ms, blood pressure changes greater than 0.5 mmHg, minimum sequence duration of four beats, sequence correlation coefficient greater than 0.85, and a one beat delay between SBP and RR interval. For the spectral method, the software uses fast Fourier transformation to determine spectral density of blood pressure and RR interval. The spectral gain of oscillations were set to fixed signal bandwidths of low frequency (0.04 – 0.15 Hz, LF) and high frequency (0.15 – 0.45 Hz, HF) as per current recommendations [29]. Measures of heart rate variability and blood pressure variability were also analyzed via the software.

Statistical Analysis

For each haemodynamic variable, a mean value was calculated from the data obtained at 3, 6, 9, and 12 minutes of that stage, with the intention of demonstrating the overall physiological impact of the entire stage. It has been determined previously that most cardiovascular changes occur within 3-5 minutes after a change in chamber pressure [26]. For the BRS data, the final stage (-60) was not included in the statistical analysis as the minimum duration required for the software analysis was not attained prior to symptoms of presyncope in LT. Two-way repeated measures ANOVA were performed using SPSS 16.0 (SPSS Inc, Chicago, IL) to assess the group by LBNP stage interaction effects of all haemodynamic measures and the resting BRS comparisons were made using independent samples t-test. Homogeneity of the groups was assessed using Levene's Test for Equality of Variances. All values are expressed as means $\pm$ SD and statistical significance was set at $P < 0.05$.

Results

Participant Characteristics and Orthostatic Tolerance

Eleven of the twelve participants completed the study. One subject dropped out in the early stages of LBNP due to anxiety related to the negative pressure. Five of the remaining eleven women (45%) became presyncopal in the last stage of the LBNP protocol (low tolerance; LT). Upon test termination, all five women displayed a sudden drop in SBP to below 90 mmHg, followed seconds later with a verbal description of pre-

FIGURE 1. Mean haemodynamic responses for high (HT; ●) and low (LT; ○) tolerance groups with LBNP from baseline to -60 mmHg. SV = stroke volume; HR = heart rate; CO = cardiac output; * $P < 0.05$ where LT differed from HT in response to LBNP.

TABLE 1. Characteristics of high and low tolerant women.

	High Tolerance (HT)	Low Tolerance (LT)
Height, cm	164.8 ± 3.7	165.3 ± 5.9
Mass, kg	59.1 ± 6.1	58.4 ± 4.1
Age, yr	23.7 ± 3.8	24.2 ± 2.4
BMI, kg/m ²	23.7 ± 3.8	24.2 ± 2.4
BSA, m ²	1.65 ± .08	1.64 ± .07

Values are means ± SD ($P = ns$)

BMI = body mass index; BSA = body surface area

FIGURE 2. Individual relationships between SV and LBNP at baseline, -15, -30, -45 and -60 mmHg in HT ($n = 6$; ●) and LT ($n = 5$; ○). The means slopes for each group are shown. The linear equation for HT (—) is $y = -11.791x + 82.114$ ($r^2 = 0.997$) and for LT (—) is $y = -16.906x + 106.64$ ($r^2 = 0.981$); $P = 0.03$ for decay of SV.

FIGURE 3. Mean decreases in stroke volume from rest to -60 mmHg LBNP for HT (white bar) and LT (black bar); $P = 0.07$.

TABLE 2. Mean resting and maximal LBNP haemodynamics for high and low tolerant women.

	HT		LT	
	Rest	-60 mmHg	Rest	-60 mmHg
SBP (mmHg)	103.3 ± 7.7	100.2 ± 8.2	103.1 ± 6.4	102.2 ± 5.4
DBP (mmHg)	69.2 ± 6.7	71.3 ± 6.5 *	67.9 ± 2.0	72.8 ± 4.6 †
PP (mmHg)	34.1 ± 4.1	28.9 ± 5.1 *	35.2 ± 5.9	29.4 ± 7.1 *
MAP (mmHg)	80.5 ± 6.8	81.0 ± 6.7	79.6 ± 3.0	82.6 ± 3.6
TPR (units)	19.1 ± 4.2	49.7 ± 20.5 *	13.6 ± 3.4	35.9 ± 8.3 *
CO (L·min ⁻¹)	4.4 ± 0.9	1.9 ± 0.8 *	5.3 ± 1.0	2.2 ± 0.5 *
SV (ml) ‡	69.3 ± 14.9	22.5 ± 12.0 *	86.1 ± 15.8	22.6 ± 4.6 *
HR (bpm)	63.5 ± 6.4	89.3 ± 14.1 *	62.6 ± 13.3	97.2 ± 6.6 *
CI (L·min ⁻¹ ·m ²)	2.65 ± 0.50	1.14 ± 0.46	3.26 ± 0.69	1.35 ± 0.32

Values are means ± SD. SBP = systolic blood pressure; DBP = diastolic blood pressure; PP = pulse pressure; MAP = mean arterial pressure; TPR = total peripheral resistance; CO = cardiac output; SV = stroke volume; HR = heart rate; CI = cardiac index

*Significantly different from rest; $P < 0.01$

†Significantly different from rest; $P < 0.05$

‡Interaction effect (tolerance x LBNP); $P < 0.01$.

syncope symptoms. The remaining six women completed the protocol and were classified as high tolerance (HT). Participant characteristics for the two groups can be found in Table 1. There were no significant differences between the groups for height, body mass, age, body mass index or body surface area. Moreover, no significant relationships were found between any of these variables and orthostatic tolerance.

Haemodynamics

Significant interactions (group x LBNP) were shown for stroke volume ($P = 0.008$; Figure 1) and the rate of decline (slope) of stroke volume ($P = 0.03$; Figure 2). Absolute change in stroke volume approached statistical significance, with LT experienc-

ing greater mean reductions in stroke volume than HT ($P = 0.07$; Figure 3). Heart rate and cardiac output were significantly affected by increasing LBNP (Table 2; Figure 1). The difference between groups with respect to stroke volume was particularly prevalent during the early stages of LBNP where the LT group began at a higher stroke volume (76.4 ± 8.6 vs. 60.0 ± 13.3 ; $P = 0.02$) during the -15 mmHg stage, but had similar stroke volumes (22.5 ± 11.9 vs. 22.7 ± 4.5 mL/beat; $P = 0.99$) during the -60 mmHg stage. The difference in resting stroke volume between groups approached statistical significance ($P = 0.10$).

TABLE 3. Mean resting baroreceptor sensitivity measures for high and low tolerant women.

	HT	LT	<i>P</i>
BRS (ms/mmHg)	17.8 ± 13.2	12.2 ± 6.0	0.456
aLF (ms/mmHg)	13.0 ± 13.5	9.0 ± 2.9	0.508
aHF (ms/mmHg)	17.5 ± 14.1	13.6 ± 8.1	0.654
RRI LF (nu)	35.2 ± 14.0	27.7 ± 13.5	0.429
RRI HF (nu)	56.2 ± 17.0	43.0 ± 9.9	0.314
RRI LF/HF (nu)	0.92 ± 0.56	0.86 ± 0.47	0.862
SBP LF (nu)	51.4 ± 12.6	34.4 ± 10.0	0.055
SBP HF (nu)	32.3 ± 15.0	31.4 ± 12.1	0.919
SBP LF/HF (nu)	2.17 ± 1.28	1.52 ± 0.90	0.409

Values are means ± SD. RRI LF = low frequency of R-R interval; RRI HF = high frequency of RR interval; RRI LF/HF = LF/HF ratio of heart rate variability; SBP LF = low frequency of systolic blood pressure variability; SBP HF = high frequency of systolic blood pressure variability; SBP LF/HF = LF/HF ratio of blood pressure variability; BRS = baroreceptor sensitivity (sequence method); aLF = low frequency of baroreceptor sensitivity (spectral method); aHF = high frequency of baroreceptor sensitivity (spectral method)

FIGURE 4. Mean blood pressure and peripheral resistance responses for high (HT; ●) and low (LT; ○) tolerance groups with LBNP from baseline to -60 mmHg. SBP = systolic blood pressure; DBP = diastolic blood pressure; MAP = mean arterial pressure; TPR = total peripheral resistance; no group by LBNP differences.

Blood Pressure, Vascular Resistance and Baroreceptor Sensitivity

The analyses revealed no significant interactions for orthostatic tolerance and SBP, DBP, PP, MAP or TPR. Stage of LBNP significantly affected DBP ($P=0.016$), PP ($P=0.002$) and TPR ($P<0.001$; Table 2). Total peripheral resistance was lower in LT compared with HT for all stages of LBNP (Figure 4); however, the difference was not statistically significant. Measures of heart rate variability, blood pressure variability and BRS were not significantly different between groups (Table 3).

Discussion

The major finding of this investigation is that orthostatic intolerance in women can be identified during a progressive LBNP challenge through a more rapid rate of decline in stroke volume. It was expected that LT individuals would display lower resting stroke volume, as previous work has suggested that the larger stroke volumes typical in male hearts may provide orthostatic advantage due to greater cardiac reserve [19]. Surprisingly, our groups had physiologically relevant differences in resting stroke volume (despite not reaching statistical significance) where LT displayed higher stroke volume than HT. Throughout the LBNP challenge, however, stroke volume de-

creased to a greater degree in LT, resulting in similar final stroke volume between groups. Our findings support previous research [6,18,20] where stroke volume was found to be related to orthostatic intolerance. Our work clearly shows that the rate at which stroke volume declines may be a major determinant of orthostatic intolerance rather than absolute stroke volume.

Cardiac Function and Orthostatic Tolerance

In this investigation, the LT group developed symptoms of presyncope despite larger initial stroke volume and similar cardiac output when compared with HT throughout the LBNP test. Previous research attributed gender differences in orthostatic tolerance to lower stroke volumes as a result of smaller overall heart size in women and subsequently less cardiac reserve during orthostasis [7]. In contrast, our work demonstrates that the rate of stroke volume decay is associated with orthostatic tolerance but not resting stroke volume. From a mechanistic perspective, more severe reductions in stroke volume during LBNP may inhibit the ability of systemic circulation to maintain pulse pressure, which is a primary determinant of cerebral blood flow pulsatility [30]. Cerebral blood flow pulsatility is thought to maintain cerebral perfusion during period of reduced mean cerebral blood flow, which is the final common

pathway during the development of syncope [31]. As such, it appears that the drastic reduction in stroke volume is associated with inhibited cerebral blood flow perfusion and the ensuing syncope [32].

A greater resting stroke volume, coupled with a higher incidence of orthostatic intolerance, is not unlike the physiological responses seen when comparing endurance-trained and untrained men [21] and women [20]. The relationship between aerobic training, ventricular compliance and orthostatic tolerance has been previously investigated and discussed. In summary, endurance-trained individuals have demonstrated a greater intolerance to an orthostatic stress [21,23]; likely the result of a more compliant ventricle [33]. The stress-strain relationship differs between normally active and endurance athletes, where athletes exhibit less ventricular stiffness and greater LV compliance, allowing for greater diastolic filling [21]. It is possible that the greater decline in SV displayed by the low tolerant women in our study was due to differences in ventricular compliance, as a more compliant ventricle during an orthostatic stress results in greater declines in SV for a given end-diastolic pressure [34]. By design, none of our participants was endurance trained. Baseline measures of blood pressure, heart rate and body mass index did not distinguish the groups as would normally be displayed in highly trained versus untrained individuals. In Morikawa's work investigating LBNP tolerance in moderately trained female runners to untrained women, there was a significant difference in resting heart rate [20]. Interestingly, the trained women who were more intolerant to LBNP had a VO_2max of $47.1 \text{ ml}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$; well below published endurance-trained norms, suggesting training volume is more important than aerobic capacity. For these reasons, we feel that controlling for training volume avoided a fitness effect in our study and speculate that genetic-based differences in ventricular function may be responsible [35].

Baroreceptor Sensitivity

No significant differences were found between groups with respect to baroreflex function. Previous work has shown individuals with poor orthostatic tolerance to have significantly reduced cardiovagal BRS (aLF) compared with those with normal orthostatic tolerance [36]. While the work of Gulli and colleagues included patients with previous episodes of posturally related syncope, reductions in aLF were also demonstrated in a distinct group of healthy controls (a group more comparable to the women in our study). There are some possible explanations that may explain the discrepancies between these findings and our results. Firstly, as the baseline blood pressures differed between groups in Gulli's work, this may have exagger-

ated systolic blood pressure oscillations occurring in the frequency range, thereby increasing aLF. Secondly, their cohort was of a large age range (22-60 years) possibly implicating age as a factor. Thus, our data in healthy young individuals does not support the role of a reduced baroreflex function as an indicator of orthostatic intolerance.

Predictors of Orthostatic Intolerance

While various mechanisms have been proposed to influence orthostatic tolerance, it is of value to physiologists and clinicians to have simple, non-invasive techniques to predict a given individual's tolerance to orthostatic stress. In the literature, various potential indicators of orthostatic intolerance have been suggested, including low frequency oscillations of R-R interval [37], early stage heart rate [38], stroke volume [21], TPR and MSNA [6] and pulse pressure [39], as well as early stage stroke volume and cardiac output [18].

In our research, as well as several other investigations, heart rate was not found to be a predictor of orthostatic tolerance [6,39,40]. Of the variables measures in this study, only stroke volume distinguished between tolerance groups among the women. Lower resting or early LBNP stroke volumes has also identified orthostatic intolerant in endurance athletes [20,21] healthy young men [6,18], and healthy young men and women [19]. In our study, however, resting stroke volume in isolation did not differentiate tolerance to LBNP. Instead, the rate of stroke volume reduction distinguished the groups. Future work assessing the changes in cerebral blood flow dynamics, matched to stroke volume decay, would further support this mechanism. Notably, while our work helps confirm strong role of cardiac filling in orthostatic tolerance, the use of stroke volume as a predictor has its challenges.

Limitations

In this, study we chose not to measure VO_2max . Previous work has shown maximum aerobic capacity to be a poor predictor of LBNP tolerance [4,21,41] and may only be a factor when investigating orthostatic intolerance in athletes with a VO_2max above $60\text{-}65 \text{ ml}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ [42,43]. Also, Hernandez *et al.* [44] showed an effect of aerobic fitness on LBNP response but not tolerance. Following this, we felt it was more important to recruit based on physical activity level (i.e., moderately active but not endurance trained) [45].

Another consideration in this work is the use of impedance cardiography for the assessment of stroke volume, as opposed to echocardiography commonly performed in our laboratory. The ideal left lateral decubitus body position for quality

acquisition of transthoracic echocardiography while in the LBNP chamber is not without challenges, particularly considering the duration of the protocol and controlling respiration rate in our participants. Impedance cardiography has been shown to be strongly correlated with echocardiography during LBNP [28] and has been shown to be reliable in resting subjects, providing good estimates of temporal changes in stroke volume [46].

Another potential limitation is our smaller sample size. Unlike many clinical investigations where patient data may be compiled and analyzed, the strict recruitment of participants matched for gender, age, fitness and health status, provided a challenge in obtaining a larger sample; however, our results are within the values reported in the literature and we were adequately powered to assess our hypothesis. Finally while we did not measure blood volume, known to affect arterial pressure during orthostatic stress [33], all participants indicated normal hydration practices in the days leading up to the testing, and the women were similar in body size.

Conclusion

The results of this investigation illustrate that orthostatic intolerance can be identified during the initial stages of LBNP through a more rapid rate of decline in stroke volume. Low and high tolerant females are similar in their responses to those seen in endurance-trained versus non-endurance trained individuals. While change in stroke volume differed between tolerance groups, the ability to utilize this measure as a predictor remains impractical.

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