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Is Heart Rate Variability Associated With Frequency and Bother of Vasomotor Symptoms Among Healthy Peri-Menopausal and Post-Menopausal Women?

Salene M.W. Jones, PhD^{1,*}, Katherine A. Guthrie, PhD², Andrea Z. LaCroix, PhD³, Barbara Sternfeld, PhD⁴, Carol A. Landis, PhD, RN⁵, Susan D. Reed, MD, MPH⁶, Andrea Dunn, PhD⁴, Bette Caan, DrPH⁴, Lee S. Cohen, MD⁷, Julie Hunt, PhD², and Katherine M. Newton, PhD¹

¹Group Health Research Institute, 1730 Minor Ave, Seattle, WA 98101

²Fred Hutchinson Cancer Research Center, Seattle, WA

³University of California San Diego, San Diego, CA

⁴Kaiser Permanente Division of Research, Oakland, CA

⁵School of Nursing, University of Washington, Seattle, WA

⁶Department of Obstetrics and Gynecology, University of Washington, Seattle, WA

⁷Massachusetts General Hospital, Harvard Medical School, Boston, MA

Abstract

Objective—Research has suggested that the autonomic nervous system (ANS) is involved in the experience of vasomotor symptoms (VMS) during menopause. We examined the relationship of VMS intensity and heart rate variability (HRV), a measure of ANS function.

Methods—Women (n=282) were recruited from 3 American states for a clinical trial of yoga, exercise and Omega-3 fatty acid supplements for vasomotor symptoms. To be eligible, women had to report at least 14 vasomotor symptoms per week, with some being moderate to severe. Sitting electrocardiograms were recorded for 15 minutes using Holter monitors at both baseline and 12 week follow-up. Time and frequency domain HRV measures were calculated. Women completed daily diary measures of VMS frequency and bother for 2 weeks at baseline and for 1 week at the follow-up assessment 12 weeks later. Multivariable linear regression was used to assess the relationship between VMS and baseline HRV measures and to compare change in HRV with change in VMS over the 12 weeks.

Results—Baseline HRV was not associated with either VMS frequency or bother at baseline. Change in HRV was not associated with change in VMS frequency or bother across the follow-up.

*Corresponding author: jones.s@ghc.org, 206-287-2108.

Conflict of Interest: Dr. LaCroix has been supported by Sanofi-Aventis for an unrelated project. Dr. Newton serves on the board of the North American Menopause Society. The remaining authors (Jones, Guthrie, Sternfeld, Landis, Reed, Dunn, Caan, Cohen, Hunt) do not have any conflicts of interest to report.

Ethical statement: This study complied with all ethical guidelines including the 1964 Declaration of Helsinki.

Interpretation—HRV was not associated with basal VMS frequency or either in perimenopausal and postmenopausal women experiencing high levels of VMS. Autonomic function may be associated with the onset or presence of VMS but not the number or either of these symptoms.

Keywords

Heart rate variability; vagal tone; hot flashes; parasympathetic nervous system; vasomotor symptoms

Background/Introduction

Autonomic nervous system (ANS) function may contribute to the development of vasomotor symptoms (VMS) in menopausal women. The neurotransmitter norepinephrine has been implicated in the physiology of VMS [1] and this neurotransmitter is released from the sympathetic nervous system (SNS) synapses [2], one of the two branches of the ANS. According to the model of neurovisceral integration, some measures of heart rate variability (HRV) reflect vagal control of the heart, and indicate parasympathetic nervous system (PSNS) [3] modulation. Both branches of the ANS contribute to HRV, which reflects the flexibility of the body to adapt to physiological and environmental changes and challenges [3]. Altered ANS function that may contribute to the physiology of VMS may be reflected in diminished HRV. Finding new ways to address VMS and to explore the underlying physiology of VMS were primary and secondary aims of the MsFLASH (Menopause Strategies: Finding Lasting Answers for Symptoms and Health) trials [4]. This paper reports on an analysis from the second MsFLASH trial in which we examined the association of HRV with the weekly average of VMS and investigated whether changes in HRV were related to changes in VMS over time after a 12-week intervention of yoga or exercise compared to usual activity.

Several studies have investigated the proximal relationship of HRV and VMS during hot flashes [5-7]. Two studies showed an increase in low frequency HRV, a measure of sympathetic function, during hot flashes [8, 9]. However, not all studies showed the relationship between low frequency HRV and onset of hot flashes [5, 7]. Several studies reported a decrease in high frequency HRV, a measure of parasympathetic function, right before and during hot flashes [5-7]. Overall, these studies suggest a role of the autonomic nervous system in the expression and occurrence of vasomotor symptoms, but this may be limited to HRV during hot flashes and not resting HRV.

Resting HRV, which represents a general, brief measure of parasympathetic function, can easily be measured in clinical settings, and less is known about how this measure relates to VMS. Of the three studies examining HRV and VMS, one study showed no association between basal HRV and presence or absence of VMS [10] while two studies reported lower basal HRV for women with vasomotor symptoms compared to women without symptoms [11, 12]. Overall, this body of research suggests that autonomic dysfunction, as indexed by HRV, is associated with the onset of VMS and that women with VMS show different autonomic function on resting measures of HRV.

The current study investigated peri- and postmenopausal women [13] to determine if the level of vasomotor symptoms, as indexed by frequency and bother, were related to resting HRV among women experiencing on average, 7.6 VMS per day [13]. Even though autonomic differences have been linked to onset and presence of vasomotor symptoms, whether autonomic changes could explain differences in symptom level is less clear. The current study was one of the largest studies to examine the relationship between VMS and HRV, but also one of the few studies to examine the relationship of symptom intensity, not just presence or absence of symptoms, and HRV.

Materials and Methods

Participants and Procedures

Women were recruited from three MsFLASH sites in Indianapolis, IN, Oakland, CA, and Seattle, WA, as part of the second MsFLASH trial. Trial details [14-16] and the overall design of the MsFLASH trials [4, 14] have been published elsewhere. Briefly, women in this 3×2 randomized controlled trial were randomized to yoga, exercise or control and were simultaneously randomized to omega-3 or placebo capsules. Eligibility criteria included age between 40 and 62 years, 14 or more vasomotor symptoms per week, in the menopausal transition or postmenopausal, and general good health (able to participate in exercise or yoga). Women also had to be able to read and speak English and be able to give informed consent. Exclusion criteria included body mass index (BMI) greater than 37 kg/m², unstable medical condition, hormone use in the past month, current use of the intervention strategies (yoga or meditation, exercise, omega-3 supplements) or major depressive episode in the past 3 months. Recruitment was by mass mailing to age-eligible women from purchased mailing lists and health plan enrollment databases. Women were screened for eligibility by phone and, if eligible, completed vasomotor symptom diaries twice daily for two weeks and then completed an in-person baseline visit that included the HRV measurement. Women were then randomized to the 12-week interventions and, following completion of the intervention, again completed vasomotor symptom diaries for one week and completed a second HRV measurement visit. For this particular analysis, women from the larger study (n=355) were excluded if they reported beta-blocker use or heart disease diagnoses (excluded n=11) or if heart rate was not measured, or covariate data was missing (n=62) at baseline, prior to receiving any intervention, for a final sample size of 282. All procedures were approved by the institutional review boards before the study began and met the standards set by the Helsinki Declaration of 1964.

Measures

Vasomotor Symptom Diaries—Women completed symptom diaries for two weeks before the HRV measurement at baseline and one week at the 12-week follow-up. In the morning after waking, women recorded the number of night sweats and rated the bother and level of the symptoms for that night. In the evening before going to bed, women recorded the number of hot flashes and rated the bother of the symptoms for that day. Women were asked to rate VMS bother on a four-point scale: 1 - not at all, 2 - a little, 3 - moderately, and 4 - a lot. Average daily vasomotor symptom (hot flash and night sweat) frequency and

bother were calculated by taking the mean across all 14 days at baseline and all 7 days at follow-up. Frequency and bother were examined separately.

Heart Rate Variability (HRV)—HRV was measured using electrocardiogram (ECG). Women came into the research clinics for assessments and Burdick Vision Holter monitors were placed. After prepping the skin, 5 electrodes were placed on the chest. Women sat for a 10-minute acclimation period before sitting quietly while breathing normally for 15 minutes of ECG data collection. Interbeat intervals were determined by a computer from the R to R spikes on phase plots from the ECGs by three raters with extensive experience in HRV measurement. Data were cleaned to remove ectopic beats and artifact. Raters were compared to each other in pairs on a subset of recordings. Correlations between the HRV values derived from two raters coding the same ECG recording indicated rater reliability for coding and cleaning the data was high ($r's > 0.97$).

Time domain and frequency domain measures were calculated from the interbeat intervals. The following time domain measures were used: standard deviation of the R-R (normal to normal) intervals (SDNN); root mean square of the successive differences (RMSSD) of the R-R intervals; and the ratio of SDNN and RMSSD (SDNN/RMSSD). The following frequency domain measures were calculated: normalized low frequency (LF, 0.04 to 0.15 hertz), normalized high frequency (HF, 0.15 to 0.40 hertz), and the low/high frequency ratio (LF/HF ratio). RMSSD and high frequency HRV measures indicate parasympathetic nervous system function [3]. Low frequency HRV and SDNN generally reflect sympathetic nervous system function with possibly some parasympathetic nervous system function [17]. The two ratios, LF/HF and SDNN/RMSSD, measure the balance of sympathetic and parasympathetic activity on the heart.

Covariates measured at baseline—As stress may affect both vasomotor symptoms and HRV [18], perceived stress was a covariate in the analyses. Stress was measured using the 10-item version of the Perceived Stress Scale (PSS) [19]. Surveys also asked about age, alcohol use (number of drinks per week), smoking (currently smoking or not) and the date of the last menstrual period to determine menopausal status. Women self-reported their last period as well as number of periods in the past year and whether they had an oophorectomy or hysterectomy. This was used in determining menopausal status. Height (electronic scale) and weight (stadiometer) measurements were used to calculate body mass index (BMI) as a continuous variable.

Statistical Analyses

Baseline Analyses—We used linear regression to evaluate the relationship of the two measures of vasomotor symptoms (frequency and bother) to the six measures of HRV (SDNN, RMSSD, SDNN/RMSSD, LF, HF and the LF/HF ratio). We also utilized dichotomous variables for SDNN, RMSSD, normalized low frequency and normalized high frequency using median splits. Vasomotor symptom frequency, SDNN and RMSSD were log-transformed as the data were not normally distributed. All analyses controlled for study site, menopausal status, smoking, alcohol consumption, body mass index (BMI, continuous), perceived stress and age. Vasomotor symptom frequency and bother were the outcomes

while HRV measures were the predictors. To control for Type I error, we used the Benjamini-Hochberg correction for multiple comparisons [20, 21]. As 16 women reported a diagnosis of diabetes, analyses were run a second time without women with diabetes.

Secondary Analyses—The secondary analysis compared change in HRV with change in vasomotor symptoms from baseline to 12-weeks. Change scores were calculated for each frequency domain HRV measure (LF, HF and LF/HF ratio) and vasomotor symptom measure. Vasomotor symptoms were modeled as a function of each HRV measure. Outcomes were vasomotor symptom frequency and bother. To examine change in HRV time and change in vasomotor symptoms, we compared the change score for each of the HRV frequency measures to the change scores in vasomotor symptoms using linear regression. This comparison was made for the total sample first, then for each intervention group (exercise, yoga, usual activity) separately. Analyses controlled for treatment group (total sample analysis only), menopausal status, age, smoking, alcohol use, race/ethnicity, perceived stress, study site and BMI. The Benjamini-Hochberg Type I error correction [20, 21] was also applied to these analyses. Analyses were run a second time excluding women with diabetes.

Power Analyses—The study had 83% power to detect a small effect size (change in R^2 0.03, HRV accounting for 3.0% of the variance in level of vasomotor symptoms) in the baseline analyses (two-tailed alpha of 0.05, sample size of 282). For the secondary, change over time analyses, the study had 82% power to detect a correlation of 0.19, a small effect size (about 3.5% of the variance) in the total sample (two-tailed alpha of 0.05, sample sizes of 230 and 228).

Results

Women reported an average of 7.6 VMS (hot flashes plus night sweats) per day (Table 1). Women were moderately bothered by their VMS (mean 1.96, SD 0.49, scale 0-3). The majority of women were non-smokers (90%) and consumed fewer than 7 alcoholic drinks weekly (43%) or did not consume alcohol (40%). The average BMI was in the overweight range (26.9 kg/m², SD 4.4) and the average age was 54.5 (SD 3.8). Most women were post-menopausal (82%).

VMS frequency over the preceding two weeks was not related to any continuous time domain measures of HRV (all p 's > 0.21) nor to any dichotomous time domain measures of HRV (all p 's > 0.17, see Table 2) at baseline. No continuous frequency domain measure of HRV was related to VMS frequency (all p 's > 0.28) although the median splits for normalized low and high frequency were significant before the type I error correction (both p =0.044). Results did not substantively change when women with diabetes were excluded except the results for the median splits of low and high frequency were no longer significant even before the Type I error correction (both p =0.078). HRV measures accounted for less than 1% of the variance in frequency beyond covariates.

VMS bother was not significantly related to time domain measures of HRV (all p 's > 0.12) and was not significantly related to any frequency domain measures of HRV (all p 's > 0.58).

either as a continuous measure or using a median split for HRV. HRV measures accounted for less than 1% of the variance in VMS bother. Results did not substantively change when women with diabetes were excluded.

Secondary Analyses: Change Over Time

Change in HRV was not related to change in VMS frequency or bother, after controlling for covariates (Table 3). In the total sample, VMS frequency was not significantly related to the low/high frequency ratio, normalized low frequency HRV or normalized high frequency HRV ($p's > 0.17$). Change in VMS frequency was not significantly related to change in HRV from baseline to 12-weeks in any of the intervention groups when analyzed separately ($p's > 0.21$). Change in VMS bother was not related to change in any HRV measure in the total sample or any intervention group ($p's > 0.41$).

Discussion

We found no association between several time and frequency HRV measures and VMS frequency and bother in women currently having at least 2 VMS per day when examining these relationships in cross-sectional analyses of baseline MsFLASH trial data. We found change in HRV from baseline to 12 weeks across all groups was also unrelated to changes in intensity of VMS frequency or bother. HRV accounted for a miniscule amount of the variation in VMS frequency and bother. Combined with sufficient power to detect even small effects, this further suggests no relationship between VMS level and HRV.

Our findings seem contradictory to previous studies, however, important methodological differences must be considered as this provides direction for future research. First, previous studies included women who reported no VMS [11, 12] and showed decreased low frequency HRV [11] and a decreased low/high frequency ratio, a measure of the balance between the sympathetic and parasympathetic nervous systems [12], in women with vasomotor symptoms compared to women without symptoms. The current analysis was restricted to women with at least 2 VMS per day. HRV may be predictive of whether women experience VMS at all but not the frequency and bother of VMS among women who have them. Second, two studies showing a relationship between vasomotor symptoms and HRV [11, 12] used a retrospective rating scale and not a daily diary, as this study did, and the one previous study showing no association between basal HRV and vasomotor symptoms did use daily diaries [10]. It is possible that HRV is related to perception and memory of VMS but not to daily reported frequency or bother.

The ANS likely still has a role in the expression of VMS during menopause [5-7]. As stated earlier, HRV has been shown to change right before and during VMS [5-9]. Previous research has also suggested that HRV and autonomic function differ between women experiencing VMS and women not experiencing VMS [11, 12]. When combined with our results suggesting no relationship with level of VMS in symptomatic women, this body of research suggests that biological mechanisms, such as autonomic function, responsible for onset and presence of VMS may be different from those involved with VMS frequency and bother.

The limitations of this study should be considered. By design, the MsFLASH trials are limited to women currently experiencing VMS during menopause. Second, HRV was not measured during hot flashes or during any physical or emotional challenge such as orthostasis so results only apply to basal HRV. Whether women experienced VMS during recordings was also not documented. As implied by previous research, HRV may still change during the actual experience of hot flashes or may be related to presence or absence of vasomotor symptoms. We also did not measure 24-hour HRV, although both brief, resting HRV [11] and 24-hour HRV [9] were used in previous studies of VMS and HRV. A minimum of four minutes appeared to be sufficient for time and frequency HRV measures in a study that compared different lengths of time in measuring heart rate [22, 23].

The results of this study suggest that overall function of the SNS and PSNS as indexed by resting HRV is not associated with vasomotor symptoms level in peri- and post-menopausal women experiencing on average 7.6 mild to moderate VMS each day. Previous research has suggested HRV and the autonomic function HRV reflects as potential mechanisms in presence of VMS. This study suggests separate mechanisms may be associated with presence vs. level of VMS and future research should examine other possible mechanisms for level of vasomotor symptoms while continuing to investigate the role of the autonomic system in VMS presence. Future research should also examine whether HRV during physical and emotional challenges, particularly orthostatic challenge, are associated with the level of VMS.

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Table 1

Study population characteristics (n=282). BMI=Body mass index, SSRI=selective serotonin reuptake inhibitor, SNRI=serotonin norepinephrine reuptake inhibitor, HRV=heart rate variability, SDNN=standard deviation of the N-N interval, RMSSD=root mean square successive difference, Ln=natural log

	Mean (SD) or Percent (n)
Age	54.51 (3.76)
Race/Ethnicity	
Caucasian	64.5% (182)
African American	26.2% (74)
Other	9.2% (26)
Education	
High school diploma or less	4.3% (15)
Some college or technical school	31.6% (89)
Bachelor's degree or above	63.1% (178)
Employment status	
Full time	61.3% (173)
Part time	13.8% (39)
Retired or not employed	16.3% (46)
Other (disabled, etc.)	8.2% (23)
Married or living with partner	66.0% (186)
Smoking Status	
Never	65.6% (185)
Past	24.1% (68)
Current	9.9% (28)
Alcohol use	
0 drinks	40.4% (114)
1-6 drinks per week	42.6% (120)
7 or more drinks per week	17.0% (48)
Average BMI	26.92 (4.39)
Menopausal status	
Postmenopausal	81.6% (230)
Perimenopausal	18.4% (52)
Hysterectomy	17.7% (50)
Bilateral oophorectomy	8.9% (25)
Medications	
Anti-depressants (SSRI, SNRI)	12.0% (34)
Anti-hypertension	13.5% (38)
HRV	
Mean RR interval	852.38 (115.33)
Ln SDNN	3.42 (.41)
Ln RMSSD	3.09 (.49)
SDNN/RMSSD	1.80 (.47)

	Mean (SD) or Percent (n)
Absolute low frequency	452.21 (615.00)
Normalized low frequency	62.91 (17.34)
Absolute high frequency	264.60 (371.97)
Normalized high frequency	37.09 (17.34)
Low/high ratio	2.55 (2.50)
Vasomotor symptoms	
Frequency, #/day	7.62 (3.81)
Bother	1.96 (.49)

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Table 2

Relationship of baseline HRV and vasomotor symptom frequency and bother (n=282). Linear regression analyses adjusted for age, menopausal status, smoking status, alcohol use, race/ethnicity, perceived stress and BMI. No results were significant following Type I error correction. The natural log was used for SDNN, RMSSD and vasomotor symptom frequency. HRV=heart rate variability, SDNN=standard deviation of the N-N interval, RMSSD=root mean square successive difference, LF=low frequency, HF=high frequency, Ln=natural log.

HRV measure	Regression Coefficient	Standard Error	p-value
Outcome: Ln Vasomotor symptom frequency			
Ln SDNN	-0.088	0.062	0.90
Median split SDNN	0.069	0.051	0.18
Ln RMSSD	-0.038	0.054	0.49
Median split RMSSD	-0.067	0.053	0.20
SDNN/RMSSD	0.070	0.056	0.21
LF normalized	0.002	0.002	0.29
Median split LF	0.104	0.051	0.04
HF normalized	-0.002	0.002	0.29
Median split HF	-0.104	0.051	0.04
Ln LF/HF	0.029	0.031	0.35
Outcome: Vasomotor symptom bother			
Ln SDNN	-0.111	0.072	0.13
Median split SDNN	-0.001	0.060	0.98
Ln RMSSD	-0.088	0.063	0.16
Median split RMSSD	-0.042	0.061	0.50
SDNN/RMSSD	0.047	0.065	0.47
LF normalized	0.001	0.002	0.58
Median split LF	0.074	0.060	0.22
HF normalized	-0.001	0.002	0.58
Median split HF	-0.074	0.060	0.22
Ln LF/HF	0.009	0.036	0.79

Table 3

Adjusted correlations of change in HRV measures with change in VMS. Analyses (linear regression) controlled for age, menopausal status, smoking status, alcohol use, race/ethnicity, perceived stress, clinical site and BMI. The analysis for the total sample also controlled for intervention group. All VMS measures are the average over the two weeks (at baseline) or one week (at 12-week follow-up). No correlations were statistically significant before or following Type I error correction. VMS=vasomotor symptoms, LF=low frequency, HF=high frequency, HRV=heart rate variability.

	Yoga			Exercise			Usual Activity			Total
	Freq. n=68	Bother n=66	Bother n=73	Freq. n=73	Bother n=87	Freq. n=89	Bother n=230	Bother n=226		
LF	0.100	0.012	0.053	0.100	0.076	0.132	0.020	0.035		
HF	-0.100	-0.012	-0.053	-0.100	-0.076	-0.132	-0.020	-0.035		
Ln LF/HF	0.115	0.021	0.058	0.064	0.079	0.127	0.019	0.031		