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Cardiac Autonomic Function and Hot Flashes Among Perimenopausal and Postmenopausal Women

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Abstract

Objective—Abnormalities in autonomic function are posited to play a pathophysiologic role in menopausal hot flashes. We examined relationships between resting cardiac autonomic activity and hot flashes in peri- and postmenopausal women.

Methods—Autonomic function was assessed at baseline and 12 weeks among peri- and postmenopausal women (n=121, mean age=53) in a randomized trial of slow-paced respiration for hot flashes. Pre-ejection period (PEP), a marker of sympathetic activation, was measured with impedance cardiography. Respiratory sinus arrhythmia (RSA), a marker of parasympathetic activation, was measured with electrocardiography. Participants self-reported hot flash frequency and severity in 7-day symptom diaries. Analysis of covariance models were used to relate autonomic function and hot flash frequency and severity at baseline, and to relate changes in autonomic function to changes in hot flash frequency and severity over 12 weeks, adjusting for age, body mass index, and intervention assignment.

Results—PEP was not associated with hot flash frequency or severity at baseline or over 12 weeks (P>.05 for all). In contrast, there was a trend toward greater frequency of moderate-to-severe hot flashes with higher RSA at baseline (β=.43, p=.06), and a positive association between change in RSA and change in frequency of moderate-to-severe hot flashes over 12 weeks (β= .63, p=.04).

Conclusion—Among peri- and postmenopausal women with hot flashes, variations in hot flash frequency and severity were not explained by variations in resting sympathetic activation. Greater parasympathetic activation was associated with more frequent moderate-to-severe hot flashes, which may reflect increased sensitivity to perceiving hot flashes.

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Keywords

Autonomic function; hot flashes; menopause

Introduction

Hot flashes are reported by an estimated 70–80% of women during the menopause transition,[1] often with a negative impact on quality of life. Despite their common occurrence among women in midlife, the pathophysiology of hot flashes is not clear. Hormonal changes play a role in the development of these symptoms, supported by the onset of hot flashes during the menopause and other periods of estrogen withdrawal, as well as the efficacy of estrogen administration in reducing or eliminating hot flashes.[2] However, hormonal changes alone do not explain the variability in hot flash frequency, severity, and bother reported by women during the menopause transition, nor the fact that hot flashes are not reported by all women undergoing either gradual or sudden estrogen withdrawal.[3]

The autonomic nervous system, which regulates visceral organ function and the fight-or-flight stress response, has been suggested to play a role in the pathophysiology of hot flashes.

Autonomic function is altered during hot flashes, supporting a temporal relationship that may relate to pathophysiology. Specifically, acute decreases in high frequency heart rate variability, related to parasympathetic tone,[4–6] and acute increases in very low frequency and low frequency heart rate variability, measures related to sympathetic activation,[7,8] have been observed during hot flash episodes.[4–6] In contrast, evidence linking resting autonomic function to hot flashes is mixed, with some studies reporting differences in cardiac markers of sympathetic or parasympathetic activation among women with and without hot flashes,[9] but others finding no relationship of autonomic function to hot flash frequency[10,11] or severity.[12] Overall, interpretability of this small literature is limited by varied definitions and measurement of both hot flashes and markers of autonomic function, and small and homogenous samples in some studies. As a result, the role of both sympathetic and parasympathetic activation in the pathophysiology of hot flashes remains unclear.

In the current study, we aimed to gain a deeper insight into relationships between resting cardiac autonomic function and the frequency and severity of hot flashes. To that end, we examined associations between resting cardiac autonomic function and hot flash frequency and severity among peri- and postmenopausal women enrolled in a randomized trial of slow paced respiration for hot flashes.

Materials and Methods

Sample

Participants were drawn from the Menopausal Treatment Using Relaxation Exercises (MaTURE) trial, a parallel-group, single-blinded, randomized trial of slow-paced respiration versus music listening for treatment of hot flashes in peri- and postmenopausal women. Details of the eligibility criteria, recruitment procedures, and study design have previously

been reported.[13] Briefly, participants were recruited from the San Francisco Bay Area between January 2012 and December 2014. Inclusion requirements included age of 40–59 years, being peri- or postmenopausal, and reporting at least four hot flashes per day in a validated 7-day hot flash diary. Exclusion criteria included being pregnant or breastfeeding in the past year, and using medications with known effects on hot flashes in the previous 3 months. Given the central role of paced respiration in the treatment trial, women with chronic pulmonary disease or baseline respiratory rate less than 10 breaths per minute were also excluded. All participants provided informed consent before randomization, and all procedures were approved by the institutional review board of the University of California, San Francisco.

Interventions

Participants were randomly assigned to either the paced respiration or music-listening intervention by computer algorithm. Women randomized to the paced respiration group received brief in-person instructions from a research coordinator on using a commercially available, portable guided breathing device (ReSPERATE; Intercure, Ltd.) to practice slowing their resting breathing rate to less than 10 breaths per minute. Participants randomized to the music control group were instructed on using an identical-appearing device re-programmed to play relaxing music rather than to guide breathing. Participants in both groups were instructed to use their assigned device for a minimum of 15 minutes per day for 12 weeks. Although participants were aware of their assigned intervention, study staff responsible for abstracting and scoring outcome data (including data on autonomic function and hot flashes) were blinded to intervention assignment.

Measures

To provide data on resting cardiac autonomic function, participants underwent impedance cardiography and electrocardiography to obtain measures of pre-ejection period (PEP) and respiratory sinus arrhythmia (RSA). PEP, the time period from the start of cardiac ventricular depolarization to ejection of blood from the ventricles, is a measure of cardiac contractility that has been shown to provide a pure measure of cardiac sympathetic activity without vagal influence.[14] RSA, the degree to which heart rate accelerates and decelerates during the respiratory cycle, provides an indication of the amount of influence of the cardiac vagus nerve. It is an established marker of parasympathetic activity, based on autonomic blockade studies showing that heart rate variability in the high frequency range is influenced only by vagal, not sympathetic, influences on the heart.[14–16]

Measures of PEP and RSA were obtained during laboratory visits at baseline (prior to intervention assignment) and after 12 weeks. According to standard protocols, participants were outfitted with electrodes by trained study staff, and then asked to sit still, relax, and view a neutral nature documentary video for a 10-minute period while resting measurements were obtained. For impedance cardiography measurements, four tetrapolar electrode bands were attached to the neck and torso of each participant while in a seated position. A constant current of 4 mAmp was sent to the outer and inner bands, while resistance to the current was measured to estimate basal impedance and blood flow through the heart. Electrocardiography was obtained with two spot electrode sensors placed below the right

clavicle and below the left breast.[17] All signals were integrated and stored using a Biopac MP150 data acquisition system (Biopac Systems, Inc.). To minimize measurement error, participants were asked to refrain from drinking alcohol, smoking, or using any other form of tobacco for at least 24 hours before measurements were obtained.

Trained research assistants visually inspected all waveforms off-line and edited and scored the data in one-minute bins for each of the minutes of the experiment using Mindware software (HRV 3.0, IMP 3.0). Following standard procedures,[18] Mindware software (Mindware Technologies, Ltd) was used to calculate average PEP (in milliseconds) by examining the time between ventricular depolarization (assessed by electrocardiogram output) and the B point of the dZ/dt wave indicating the opening of the aortic valve (measured by impedance cardiography). RSA was estimated with an algorithm that uses a 4 Hz time series to interpolate the interbeat interval,[19] and a second order polynomial was applied to minimize non-stationary trends. A random twenty percent of the data were selected to be re-scored to determine reliability, which exceeded 95%.

Hot flash frequency and severity were assessed at baseline and 12 weeks using a 7-day self-report diary, modeled after a diary that has been validated and administered in multiple prior clinical trials of interventions for menopause symptoms.[20] Participants were asked to record each hot flash they experienced and rate its severity as 1/mild: sensation of heat without sweating; 2/moderate: sensation of heat with sweating, able to continue activity; 3/severe: sensation of heat with sweating, causing cessation of activity, following the FDA guidelines for defining hot flash severity.[21] To promote accurate reporting, the diary was designed to be small and portable, so that participants could carry it with them during the day and keep it by their bedside at night.

Participants also completed structured-item questionnaires to assess age, race/ethnicity, relationship status, parity, history of hysterectomy and oophorectomy, educational status, smoking history, alcohol use, and past use of medications to treat hot flashes. Body mass index (BMI; kg/m^2) was calculated from height and weight measured by trained study staff during the baseline visit.

Statistical Analyses

Demographic and clinical characteristics of participants who provided cardiac autonomic data were examined using descriptive statistics, and logistic regression models were used to assess differences in participant characteristics between intervention groups at baseline. Treatment effect was evaluated using linear regression models of change in autonomic measures adjusting for baseline value, as well as age and BMI.

Multivariable models were then developed to assess relationships between cardiac autonomic markers (PEP and RSA) and hot flash measures in the combined participant sample. For assessment of hot flashes, analyses focused on two outcomes: 1) average frequency of any hot flashes, and 2) average frequency of hot flashes that were rated by the participant as being “moderate” or “severe”. ANCOVA models were used to simultaneously assess baseline associations between autonomic markers and hot flashes, and associations

between within-person changes in autonomic markers and within-person changes in hot flash outcomes over 12 weeks.

Outcomes were transformed due to evidence of non-normality detected in the distribution of outcomes in visual inspection of density plots. All models were adjusted for age and BMI given that past research has indicated that both of these variables are associated with both resting cardiac autonomic function and hot flashes.[22–24] Analyses were also adjusted for intervention assignment after confirmation that there were no significant interactions with intervention group. All statistical analyses were performed using SAS 9.4 (Cary, North Carolina).

Results

Baseline Participant Characteristics

Of the 123 participants randomized in the MaTURE trial, 121 contributed data on cardiac autonomic function at either baseline or 12 weeks and were included in baseline analyses. The sample was 58.7% white, with a mean age of 53.4 (SD 3.4). The majority of participants were naturally peri- or postmenopausal (32.7% and 54.5%, respectively). Over half were overweight or obese (mean BMI=26.5, SD 5.5) (table 1). After 12 weeks of follow-up, 89% (N=55) of women retained in the paced respiration group and 88% (N=52) retained in the music-listening group were confirmed to have completed at least 6 practice sessions per week (p=.98). In both groups, average practice time exceeded 15 minutes per day at 12 weeks (p=0.87).

Baseline and 12-Week Changes in Cardiac Autonomic Function

Complete data at baseline or 12 weeks was available for 118 women for PEP analyses, and 119 women for RSA analyses. There were no significant differences in resting autonomic measures (PEP, RSA) between the paced respiration and music control groups at baseline. No significant differences between groups in changes of autonomic measures from baseline to 12 weeks were observed. Additionally, no significant within-group changes in autonomic measures from baseline to 12 weeks were observed in either group (table 2).

Associations between Cardiac Autonomic Function and Hot Flashes

Complete data at baseline and 12 weeks was available for 74 women for PEP analyses, and 81women for RSA analyses. In ANCOVA models, no significant associations between PEP and hot flash measures were observed. There were also no significant associations between within-person change in PEP and within-person changes in hot flash outcomes from baseline to 12 weeks. In contrast, there was a trend toward higher RSA among participants with more frequent moderate-to-severe hot flashes at baseline. Additionally, within-person change in RSA was positively associated with within-person change frequency of moderate-to-severe hot flashes over 12 weeks, such that increased RSA was associated with more severe hot flashes over time (β= .63, p=.04) (Table 3).

Discussion

These findings from a large and diverse sample of peri- and postmenopausal women provide new evidence to evaluate relationships between autonomic function and hot flashes. Contrary to expectations, cardiac sympathetic activation as assessed by PEP was not significantly associated with hot flash frequency or severity at any timepoint. In contrast, there was a trend toward more frequency moderate-to-severe hot flashes among women with greater parasympathetic activation as reflected by RSA at baseline, and change in parasympathetic activation was positively associated with change in frequency of moderate-to-severe hot flashes over 12 weeks.

The theory that abnormal sympathetic autonomic function causes hot flashes[7,25] has driven research into treatment strategies that focus on reducing excess sympathetic tone. However, prior research on the relationship of sympathetic function and hot flash frequency or severity has yielded mixed results. Two previous studies have reported increases in sympathetic activation estimated by very low and low frequency heart rate variability during physiologically measured hot flash episodes,[7,8] suggesting that sympathetic activation occurs acutely during the brief experience of a hot flash. Other research has also reported greater basal sympathetic activation estimated by low frequency heart rate variability[10] or the ratio of low and high frequency heart rate variability[11] among women with hot flashes compared to those without hot flashes. Subsequently, an analysis of similar heart rate variability measurements in a recent, large, multicenter hot flash trial network found that these measures did not differentiate hot flash experience or intensity among women with hot flashes at baseline, nor were they correlated with changes in hot flashes in response to treatment.[12] Nevertheless, all of the above studies were limited by reliance on measures that are not pure markers of sympathetic activity.

Our study findings using resting PEP as a pure measure of cardiac sympathetic activation do not support the hypothesis that sympathetic activation is a major determinant of women's experience of hot flashes, given that PEP was unrelated to the frequency or severity of self-reported hot flashes. However, our research may have been limited by the fact that all women taking part in the MaTURE had frequent hot flashes per day at baseline, although some experienced resolution over the 12 week period. Even if differences in sympathetic activation do not contribute to variation in hot flash frequency or severity among women with a recent history of hot flashes, it is possible that they may contribute to differences in the onset or occurrence of hot flashes in women with hot flashes compared to those without hot flashes.

Abnormal parasympathetic function has also been implicated in the pathophysiology of hot flashes. Several previous studies have documented acute decreases in parasympathetic activity during physiologically measured and self-reported hot flash episodes, suggesting acute vagal withdrawal during hot flashes.[4–6] However, prior research has not found relationships between resting parasympathetic activity and hot flash frequency or severity among midlife women.[9,12] In the current study, there was evidence of an association between cardiac parasympathetic activation and frequency or severity of hot flashes at baseline and over 12 weeks. These findings are intriguing in that they suggest that resting

parasympathetic activation play a more important role in women's experience of hot flashes than has previously been suggested.

The relationship between parasympathetic activation and hot flashes observed in this study is at odds with other research indicating that decreased parasympathetic function tends to be a vulnerability factor for other adverse physical and mental health outcomes. It is known that lower levels of heart rate variability can impair the ability to adapt to stressors, for example, and are associated with more susceptibility to hypotension, sudden death, and mortality following myocardial infarction.[26] Moreover, low levels of RSA have been documented across a range of psychopathologies often associated with hot flashes, including anxiety[27,28] and depressive symptoms.[29] However, increased RSA levels are also known to be associated with greater interoceptive awareness, or increased sensitivity to bodily states.[30] A relationship between higher resting parasympathetic activation and more frequent self-reported hot flashes may therefore reflect greater sensitivity to detecting or perceiving hot flashes, resulting from greater interoception among these women. Future research may benefit from investigating how individual differences in interoception mediate the link between RSA levels and the subjective experience or reporting of hot flashes.

Of note, the device-guided paced respiration intervention used in this study did not produce significant changes in cardiac sympathetic or parasympathetic activation over 12 weeks, compared to the music-listening control intervention. While acute effects of paced respiration on cardiac autonomic function have been demonstrated in laboratory studies,[31,32] prior research has not yielded consistent evidence of a sustained effect of paced respiration interventions on cardiovascular autonomic function.[33] In the few randomized controlled trials with a similar design to the current study, equivalent autonomic markers were not assessed, and samples were comprised of men and women with hypertension and/or diabetes mellitus. It therefore remains unclear whether regular practice of paced respiration causes long-term changes in cardiac autonomic function, at least when practiced using this type of portable guided-breathing device.

This study has limitations that warrant mention. First, while hot flashes were assessed using detailed symptom diaries, this study did not include physiological measures of hot flash-related vasodilation or sweating to provide additional insight into the biological underpinnings of hot flashes and autonomic function. Exploration of the relationship between both physiologic and self-reported measures of hot flash experience and basal parasympathetic function may be warranted in future research. Second, frequent daily hot flashes were required for eligibility, and relationships between autonomic function and hot flashes may differ for less symptomatic women. As there was no control arm in this study, we cannot determine how relationships between autonomic function and hot flashes may differ over time in the absence of an active intervention. Additionally, participants had to be willing and able to commit to the behavioral study interventions over 12 weeks and to abstain from using other clinical treatments for hot flashes. Overall, generalizability of these findings may be limited due to these requirements. Further, significant mean associations were not seen in all analytic models, and findings may have been spurious in the context of multiple comparisons.

Despite these limitations, this study had considerable strengths. Multiple measures of autonomic function were measured in a rigorously controlled setting. Retention rates were high throughout the observed period. Hot flashes were assessed by self-report diaries over seven days, which offers more reliability and limited retrospective recall bias than retrospective recall at one point in time. Further, multiple important aspects of hot flash experience, including frequency and severity, were assessed at each time point. The participant sample was also ethnically diverse and representative of women from across the menopause transition.

Conclusions

In this large sample of peri- and postmenopausal women enrolled in a behavioral paced respiration intervention trial for hot flashes, resting cardiac sympathetic activation was not associated with greater hot flash frequency or severity. In contrast, cardiac parasympathetic activation was associated with greater overall hot flash frequency and severity. These findings point to potentially more complex relationships between basal cardiac autonomic function and hot flashes than has previously been proposed, such as the possibility that increased resting parasympathetic tone may be associated with greater interoception affecting women's perception of hot flashes.

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Table 1

Baseline characteristics of participants included in cardiac autonomic function analyses (n=121)

	Paced respiration (N=62)	Music listening (N=59)	Total Sample (N=121)	p-value
Age in years (mean, SD)	53.1 (3.4)	53.7 (3.4)	53.4 (3.4)	0.29
Race (number, %)				
White	38 (61.3)	33 (55.9)	71 (58.7)	0.55
Black/African-American	13 (21.0)	16 (27.1)	29 (24.0)	0.43
Latina/Hispanic	2 (3.2)	4 (6.8)	6 (5.0)	0.37
Asian/Asian-American	12 (19.4)	8 (13.6)	20 (16.5)	0.39
Other/unspecified	5 (8.1)	5 (8.5)	10 (8.3)	0.94
Education (number, %)				
College+ graduate	56 (90.3)	54 (91.5)	110 (90.9)	0.82
Relationship status (number, %)				
Married or in a significant relationship	42 (67.7)	29 (49.2)	71 (58.7)	0.04
Single/widowed/divorced	20 (32.3)	30 (50.8)	50 (41.3)	
Parity				
Live births (mean, SD)	1.31 (1.3)	1.31 (1.6)	1.31 (1.4)	0.63
Medication Use (number, %)				
Beta-blocker	8 (6.8)	7 (6.3)	15 (6.6)	0.86
Sympathomimetic	2 (1.7)	3 (2.7)	5 (2.2)	0.62
Anti-cholinergic	14 (12.0)	18 (16.1)	32 (14.0)	0.37
Nicotinic antagonist	2 (1.7)	0 (0)	2 (0.9)	0.17
Menopausal history (number, %)				
Hysterectomy	6 (9.7)	7 (11.9)	13 (10.7)	0.70
Bilateral oophorectomy	1 (1.6)	2 (3.4)	3 (2.5)	0.53
Naturally postmenopausal[a]	26 (48.1)	34 (60.7)	60 (54.5)	0.19
Perimenopausal[b]	21 (38.9)	15 (26.8)	36 (32.7)	0.18
Past use of hot flash treatments (number, %)				
Hormones (Estrogen)	7 (11.3)	7 (11.9)	14 (11.6)	0.92
Gabapentin	0 (0.0)	2 (3.4)	2 (1.7)	0.14
Alternative Therapies	13 (21.0)	19 (32.2)	32 (26.4)	0.16
Body Mass Index (number, %)				
< 25 kg/m2	25 (40.3)	29 (49.2)	54 (44.6)	0.44
25 to <30 kg/m2	21 (33.9)	14 (23.7)	35 (28.9)	
>= 30 kg/m2	16 (25.8)	16 (27.1)	32 (26.4)	
Vital signs (mean, SD)				
Systolic blood pressure (mmHg)	122.31 (19.7)	118.85 (14.2)	120.62 (17.2)	0.35
Diastolic blood pressure(mmHg)	77.23 (10.9)	76.37 (11.9)	76.81 (11.3)	0.57
Heart rate (bpm)	70.42 (10.4)	67.97 (11.5)	69.22 (11.0)	0.13
Respiratory rate (breaths/pm)	13.60 (2.5)	13.97 (3.2)	13.78 (2.8)	0.66

	Paced respiration (N=62)	Music listening (N=59)	Total Sample (N=121)	p-value
Health behaviors (number, %)				
Current cigarette smoker	4 (6.6)	8 (13.8)	12 (10.1)	0.19
Alcohol use on ≥ 5 day/week	8 (12.9)	6 (10.2)	14 (11.6)	0.64
Cardiac autonomic measures (mean, SD)				
PEP (ms) during movie	121.7 (13.7)	121.7 (13.4)	121.3 (13.5)	0.86
RSA (ms^2) during movie	5.56 (1.2)	5.20 (1.3)	5.38 (1.3)	0.23

[a] All women without a history of hysterectomy or bilateral oophorectomy who report no menstrual period for 1 year were considered naturally postmenopausal.

[b] Women without a history of hysterectomy or bilateral oophorectomy who report a menstrual period within the past year were considered perimenopausal.

Table 2

Mean change in cardiac autonomic function markers from baseline to 12 weeks, by intervention assignment

	Paced Respiration		Music Listening		Between-Group Difference	
	Mean change (95% CI)	**p-value**	**Mean change (95% CI)**	**p-value**	**Mean change (95% CI)**	**p-value**
Pre-ejection period (ms) (n=118)	−1.08 (−4.18−2.02)	.49	−0.76 (−3.79−2.27)	.62	−0.32 (−4.69−4.05)	.89
Respiratory sinus arrhythmia (ms^2) (n=119)	0.14 (−0.12−0.39)	.30	−0.02 (−0.28−0.24)	.89	0.15 (−0.22−0.52)	.41

All models adjusted by baseline autonomic function, age, and body mass index.

Table 3

Adjusted associations between cardiac autonomic measures and hot flash outcomes among all participants

Baseline Levels				
	Frequency of any hot flashes		**Frequency of moderate-to-severe hot flashes**	
	Coefficient	*p-value*	*Coefficient*	*p-value*
Pre-ejection period (ms)	−.01	.69	−.01	.86
Respiratory sinus arrhythmia (ms^2)	.34	.21	.43	.06
12-Week Change				
	Frequency of any hot flashes		**Frequency of moderate-to-severe hot flashes**	
	Coefficient	*p-value*	*Coefficient*	*p-value*
Pre-ejection period (ms)	−.00	.99	.00	.76
Respiratory sinus arrhythmia (ms^2)	.26	.44	.63	.04

ANCOVA with between-person associations at baseline and within-person changes in autonomic markers and hot flashes from baseline to 12 weeks. All models adjusted by intervention assignment, age, and BMI. The number of participants included was 74 and 81 for the PEP and RSA models respectively.