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Hot flashes and cardiac vagal control: a link to cardiovascular risk?

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Abstract

Objective—The understanding of the physiology of hot flashes is incomplete. The autonomic nervous system has been hypothesized to play a role in hot flashes but has received limited empirical attention. Further, emerging research has linked hot flashes to cardiovascular risk. Reduced high frequency heart rate variability (HF-HRV), an index of vagal control of heart rate, has been associated with cardiovascular events. We hypothesized that decreases in HF-HRV would occur during hot flashes relative to periods preceding and following the hot flash.

Methods—Thirty peri- and postmenopausal women ages 40–60 reporting ≥ 4 hot flashes/day underwent laboratory hot flash provocation testing, with measurement of sternal skin conductance and electrocardiogram. Hot flashes were reported and identified from sternal skin conductance. HF-HRV was estimated using spectral analysis of the heart rate time series. The five minute interval during the hot flash was compared to two non-flash periods prior and following the hot flash via mixed effects models.

Results—HRV was significantly decreased during hot flashes relative to periods prior to ($b=0.18$, $SE=0.05$ $p=0.0001$) and after ($b=0.16$, $SE=0.05$, $p=0.002$) physiologically-measured hot flashes, controlling for age, race, education, task condition, menopausal status, task, hypertension status, diabetes status, physical activity, body mass index, smoking, and anxiety. Findings were unchanged considering self-reported hot flashes.

Conclusions—Significant decreases in cardiac vagal control occurred during hot flashes, which may help shed light on the physiology of hot flashes. The autonomic nervous system may deserve greater attention in understanding the mechanisms linking hot flashes to cardiovascular risk.

Keywords

hot flashes; hot flushes; vasomotor symptoms; heart rate variability; cardiac vagal control; menopause

Introduction

Most women experience hot flashes at some point during the menopausal transition.¹ Hot flashes are associated with reduced physical, emotional, and social quality of life,² as well as reported sleep problems³ and depressed mood during midlife.⁴ The understanding of the physiology of hot flashes is incomplete. Models indicate that hot flashes are dramatic heat

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dissipation events occurring due to the narrowed thermoneutral zone among women with hot flashes,⁵ likely secondary to the reproductive hormone changes of the menopausal transition.⁶ In addition, given the increase in heart rate, flushing, and sweating observed during hot flashes,⁷ involvement of the autonomic nervous system (ANS) has long been hypothesized.^{7–8} However, the predominant focus has been on the sympathetic branch of the ANS, rather than the parasympathetic branch, and has yielded inconclusive results.^{8–9}

There has been little examination of the parasympathetic branch in hot flashes. Although the increased heart rate previously observed to accompany hot flashes has often been assumed to be sympathetically mediated, manifest changes in heart rate may be the result of decreased parasympathetic influences (delivered to the heart via the vagus nerve), increased sympathetic cardiac control, or both. Thus, parasympathetic nervous system function, including cardiac vagal control, during hot flashes remains an open question.

Emerging research also suggests possible links between hot flashes and cardiovascular risk. In the Women's Health Initiative¹⁰ and the Heart and Estrogen Replacement Study (HERS),¹¹ it was the women reporting vasomotor symptoms who experienced the highest risk of incident coronary heart disease (CHD) with hormone use. In the Study of Women's Health Across the Nation (SWAN) Heart Study, women reporting hot flashes had greater evidence of subclinical cardiovascular disease (CVD) compared to women not reporting hot flashes.¹² A large body of literature has shown reductions in cardiac vagal control (as measured by indices such as high frequency heart rate variability; HF-HRV) to be prospectively associated with cardiovascular morbidity and mortality.^{13–16}

Therefore, an examination of cardiac vagal control during hot flashes may promote further understanding of the physiology of hot flashes. It may additionally help shed light on links between hot flashes and cardiovascular risk. We hypothesized that reductions in cardiac vagal control would be observed during physiologically-identified hot flashes as compared to control periods preceding and following hot flashes.

Methods

Thirty-four African American and Caucasian women between the ages of 40 and 60 were recruited. Inclusion criteria included late perimenopausal (amenorrhea last 3–12 months) or postmenopausal (amenorrhea ≥ 12 months) status, reporting ≥ 4 hot flashes a day, and having a uterus and both ovaries. Women were excluded if having taken hormone therapy (oral or transdermal estrogen and/or progesterone), oral contraceptives, selective serotonin reuptake inhibitors or serotonin norepinephrine reuptake inhibitors, clonidine, methyl dopa, bellergeral, gabapentin, aromatase inhibitors, selective estrogen receptor modulators in the past 3 months, having taken isoflavone supplements or black cohosh in the past month, currently undergoing acupuncture for the treatment of hot flashes, reporting medical or psychiatric conditions associated with hot flash sensations (panic disorder, pheochromocytoma, leukemia, pancreatic tumor), or the inability to provide informed consent and follow study procedures. Of these 34 women, one woman was excluded due to equipment failure during the session, and three women were excluded due to no reported nor physiologically detected hot flashes during the laboratory session, for a final sample of 30 women.

Laboratory testing procedures took place in a $24 (\pm 1)^\circ\text{C}$ temperature-controlled room between the hours of 12:00 and 19:00, given the circadian rhythm of hot flashes with peak frequency occurring during the late afternoon hours.¹⁷ Participants underwent testing in a seated position and wore a light-weight cotton hospital "scrub" top and pants. Participants underwent four laboratory tasks: observation, mental stress, heating, and cold pressor. Heating has been previously shown to induce hot flashes among symptomatic women,^{9, 18}

and some suggestive evidence indicates that mental stressors may be associated with increased hot flash occurrence.¹⁹ Speech and cold pressor tasks have been shown to reliably provoke a stress response, including among postmenopausal women.²⁰ For the observation session, participants sat quietly for 30 minutes, during which time they read magazines or completed study self-report instruments. For the speech task, participants prepared (2 minutes) and delivered (3 minutes) a speech about an assigned topic while being observed by an experimenter, followed by a 5 minute rest period. For the heating task, a 22" × 14.5" electric heating pad maintained at a temperature of 42 (±1)°C was placed on the participant's torso for 30 minutes. For the cold pressor task, an ice pack was placed on the participant's forehead for up to 60 seconds. Skin conductance and ECG were measured continuously throughout testing.

Physiologic hot flashes were assessed via sternal skin conductance. Skin conductance was recorded from the sternum with a 0.5 V constant voltage circuit sampling from two silver/silver chloride electrodes (Vermed Inc, Bellows Falls, VT) at each site filled with 0.05 M KCL Unibase/glycol paste. Skin conductance was recorded via Grass polygraph (model 7D, skin conductance adaptor SCA1, Grass Technologies, Astro-Med Inc., West Warwick, RI) and digitized at 1 KHz by an analog to digital converter. Physiologic hot flashes were quantified from sternal skin conductance signals via previously-validated methods.²¹ A 5 minute reporting window was adopted, in which physiologically-defined hot flashes accompanied by a self report within 5 minutes were considered reported. A 10 minute lockout period was implemented, after the start of the flash, after which no hot flashes were coded. Participants subjectively reported hot flashes by pressing a time and date-stamped event marker and rating the severity of the hot flash (mild (1)-severe (4)).

Cardiac vagal control was measured by HF-HRV. Heart rate was measured by ECG via three silver/silver chloride electrodes (Kendall; Syracuse, NY) in a standard 3-lead configuration sampled at 1 KHz via Grass polygraph (model 7D, Grass Technologies, Astro-Med Inc., West Warwick, RI). ECG processing was conducted offline using custom software²² and consisted of R-spike detection with automated and manual artifact screening of the resulting inter-beat interval (IBI) event series. To derive estimates of HF-HRV, the IBI series was resampled at 4 Hz using linear interpolation and detrending and then subjected to autoregressive spectral analysis. Spectral density estimates within the high frequency band (.15 to .50 Hz) were then summed to yield HF-HRV. As is typically the case, HF-HRV values were highly skewed and therefore natural log transformed.

Height and weight were measured via a fixed stadiometer and a calibrated balance beam scale, respectively. Medication use, health status, menstrual history, parity, education, marital status, and smoking status were assessed by standard demographic and medical history questionnaires. Diabetes status was self-reported, doctor-diagnosed Type I or Type II diabetes or reported use of medication for the treatment of diabetes (n=4). CVD status/hypertension included 14 women who reported a history of hypertension or medications used to treat hypertension and one subject who reported a history of arrhythmia (who was included as she showed no evidence of arrhythmia during the laboratory procedures nor was she using any medication to treat arrhythmia). No other cardiovascular conditions were endorsed. Physical activity was assessed via the Paffenbarger scale.²³ Depressive symptoms were assessed via the Center for Epidemiologic Studies Depression Survey²⁴ and state (current anxiety symptoms) and trait (general propensity to experience anxiety) anxiety via the Spielberger State Trait Anxiety Inventory.²⁵ Only state anxiety was included in final models due to its high correlation with depressive symptoms ($r=0.80$, $p<0.0001$) and trait anxiety ($r=0.82$, $p<0.0001$), it being the affective variable with the strongest association with HF-HRV in the present study, and its prior documented robust associations with hot flashes. 1: 21 Task (heating, speech/cold pressor, vs. observation) was considered as a covariate in

all models, with speech and cold pressor conditions combined into a stress category due to small cell sizes and use of these two manipulations as laboratory stressors. All study procedures were approved by the University of Pittsburgh Institutional Review Board and all participants provided written informed consent.

Relations between average HF-HRV values and participant characteristics were estimated using Pearson and point biserial correlations. Pre-flash, flash, and post-flash time periods were identified by comparing HF-HRV during the minute at which the physiological onset of the hot flash occurred (i.e., minute zero) to each of the preceding 10 minutes and following 10 minutes within a single mixed effects regression. Using $p=0.10$ for the purposes of data reduction, this model yielded three distinct periods: 1) a pre-flash period, ranging from 10 min to 2 min prior to flash onset, in which all but one of the minutes were statistically greater than minute zero; 2) a flash period, ranging from 1 min prior to 4 min following onset, in which none of the minutes differed from minute zero; and 3) a post-flash period, ranging from 5 min to 10 min following onset, in which each of the minutes were greater than minute zero. These pre- and post-flash periods were next entered into subsequent models as within-subject factors, with the during-flash time segment considered the referent.

Relations between flash intervals and HF-HRV values were estimated with linear mixed effects models, with random intercepts for flashes nested within subjects and maximum likelihood estimation. Within-group correlation structure was modeled as a first order continuous autoregressive, nested within flashes and subjects. Base models included the covariate task. Expanded models additionally included age, race/ethnicity, menopausal status, education, cardiovascular conditions, diabetes status, BMI, smoking status, physical activity, and state anxiety. Covariates were selected based upon prior documented associations with HF-HRV and/or hot flashes as well as univariate associations with HF-HRV at $p<0.10$ in the present study, with cardiovascular condition and diabetes status forced into expanded models. All continuous predictors were grand mean centered. Physiologic flashes and onset times were used for all primary models; subjective flashes and times were considered in secondary models. Interactions between flash time segment (pre, during, post) and task, state anxiety, menopausal status, and ethnicity were also tested via the likelihood ratio test, given prior evidence of the importance of these variables in the reporting and physiologic occurrence of hot flashes.^{1, 21}

Results

Participants were on average 53 years old, postmenopausal, and overweight (Table 1). Factors associated with lower average HF-HRV levels were higher age ($r=-0.22$, $p=0.048$), African American race ($r=-0.25$, $p=0.02$), smoking ($r=-0.26$, $p=0.02$), anxiety ($r=-0.40$, $p=0.0002$), diabetes status ($r=-0.28$, $p=0.009$), postmenopausal status ($r=-0.49$, $p<0.001$), and a marginally higher BMI ($r=-0.19$, $p=0.08$). Across the women, 53 hot flashes were physiologically detected, 49 of which were reported. Fifteen self-reported hot flashes were not physiologically detected. Most physiologic hot flashes occurred during observation/rest ($N=22$, 41%), with an additional 17 (32%) flashes occurring during heating and 8 (15%) during stress.

Examination of hot flashes in relation to HF-HRV indicated that hot flashes were associated with significant reductions in HF-HRV as compared to periods before and following hot flashes (Table 2, Figure 1). Further analysis of minute-by-minute changes in HF-HRV prior to, during, and after physiologic hot flashes revealed an abrupt decrease in HF-HRV in the minute prior to the onset of the hot flash that was sustained for several minutes (Figure 2).

Several additional analyses were conducted. First, subjective hot flash reports were examined in relation to HF-HRV changes. Findings were consistent with physiologic hot flash results, although slightly weaker (relative to flash interval, models adjusted for task; pre-flash: b (SE)=0.12 (0.05), $p=0.007$, post-flash: b (SE)=0.11 (0.05), $p=0.03$). In addition, physiologic hot flash models were repeated with examination of interactions by menopausal status, race, anxiety, and task. The only interaction observed was a significant interaction between the pre-flash period and anxiety (b (SE)= -0.02 (0.006), $p=0.008$), with the HF-HRV reduction during the hot flash relative to the pre-flash period less pronounced among more anxious women. These differences were largely driven by a lower baseline HF-HRV among more anxious women.

Discussion

In this initial investigation, reductions in HF-HRV, an index of cardiac vagal control, were observed during physiologically-assessed hot flashes as compared to the minutes preceding and following hot flashes. In fact, a progressive decline in HF-HRV was observed in the minute preceding that was sustained for several minutes after the onset of the hot flash. Associations between hot flashes and HF-HRV were robust to adjustment for multiple demographic, behavioral, and biologic risk factors.

The physiology of hot flashes is incompletely understood. Current models cite hot flashes as dramatic thermoregulatory events occurring in the context of the altered thermoregulatory functioning observed among symptomatic peri- and postmenopausal women.⁵ These thermoregulatory changes may be due in part to the changing hormonal milieu of the menopausal transition.⁶ In addition, given the increase in heart rate, flushing, and sweating observed during hot flashes,⁷ involvement of the ANS has long been hypothesized. Despite central adrenergic involvement,²⁶ as well as some evidence for increased circulating epinephrine during hot flashes,²⁷ evidence has not consistently supported a role for peripheral sympathetic involvement in hot flashes.⁸ The present study indicated acute reductions in HF-HRV during hot flashes as compared to periods preceding and following hot flashes. These findings suggest a role of the parasympathetic branch of the ANS in hot flashes.

The present findings are also notable given the emerging findings linking hot flashes to cardiovascular risk. In the WHI10 and HERS,¹¹ it was the women with hot flashes at study baseline in the hormone arm who were at greatest risk for incident CHD (in the case of WHI, the older women with hot flashes). Further, in the SWAN Heart Study, we found that women with hot flashes showed greater evidence of subclinical CVD relative to women with hot flashes, controlling for cardiovascular risk factors as well as serum estradiol concentrations.¹² A sizable literature prospectively links lower tonic HF-HRV to elevated cardiovascular risk across multiple populations.^{13–15} Although less well-established, emerging evidence also links phasic changes in cardiac vagal control to CVD risk. Decreases in HF-HRV may precede ambulatory ischemic events among men with coronary artery disease,²⁸ and phasic decreases in cardiac vagal control has been associated with coronary artery and aortic calcification among postmenopausal women.¹⁶ The present results may suggest cardiac vagal control for further consideration in understanding the links between hot flashes and cardiovascular risk.

Several other factors were associated with HF-HRV. In multivariable models controlling for age, postmenopausal women had lower HF-HRV than the perimenopausal women. Although prior findings are not entirely consistent,²⁹ low endogenous estradiol states, such as after oophorectomy³⁰ and postmenopausally,³¹ have been associated with reduced cardiac vagal control, which exogenous estrogen administration³² may restore. Reproductive

hormones were not measured in this initial investigation, and therefore their role cannot be determined here. While differences in hormones such as estradiol are likely involved in differences in HF-HRV between peri- and postmenopausal women, they are unlikely to have driven the reductions in HF-HRV during hot flashes, as estradiol does not change during the occurrence of hot flashes.²⁷

More anxious women had lower HF-HRV than their less anxious counterparts. Thus, these women had attenuated decreases associated with hot flashes. Previous research has shown consistent links between anxiety and reduced HF-HRV.³³ Moreover, anxiety is one of the most consistent and robust factors associated with hot flashes in prospective epidemiologic investigations¹ and clinical investigations.²¹ Therefore, reduced vagal tone may play an important role in relations between anxiety and hot flashes.

Several additional findings deserve mention. First, the primary study findings pertained to physiologically-assessed hot flashes. The physiologic assessment of hot flashes is recommended to avoid the influence of mood, memory, and other psychological factors involved in hot flash reporting,³⁴ and in this study has the particular advantage of providing precise information regarding the timing of occurrence of the hot flash. Physiologically-measured and subjectively-reported hot flashes were largely concordant here. Accordingly, findings for the subjectively-reported hot flashes were largely consistent with primary results, although slightly attenuated relative to physiologic hot flash models, suggesting that HF-HRV changes related to hot flashes are unlikely to be due solely due to the subjective experience of hot flashes.

Several limitations deserve mention. First, this study represents an initial investigation, the first to investigate links between cardiac vagal control and hot flashes, and included a relatively small sample of women. Results should be replicated in a larger sample of women. However, it is notable that this was primarily a within-woman analysis in which the flash was the unit of analysis, rather than the woman, and therefore fewer subjects are required to test study hypotheses. Second, respiration was not measured here, and should be measured in future investigations. Although large increases in respiration could confound findings, changes in respiration within normal bounds should not.³⁵ Aside from the public speaking task, in which changes in respiration may have played a role in the HF-HRV changes during this task, women sat quietly throughout testing, and dramatic increases in respiration are generally not observed with hot flashes.⁹ Third, the full array of cardiovascular risk factors was not assessed here, and the sample included diabetic and hypertensive women. However, these risk factors were largely unrelated to hot flashes and were controlled in main analyses. Importantly, the analysis was primarily a within-woman analysis of acute changes in HF-HRV during the flash. Therefore, between-woman differences in risk factors, age, or other characteristics could not explain the study findings.

The study had several strengths. Hot flashes were physiologically recorded as well as subjectively recorded, allowing for greater precision in the timing and occurrence of hot flashes. This investigation was a highly-controlled laboratory investigation with continuous ECG and sternal skin conductance measurement, allowing close examination of minute-by-minute HRV changes free of many other extraneous influences characteristic of ambulatory settings.

Conclusions

This is the first study to examine cardiac vagal control during hot flashes. Findings indicated acute reductions in HF-HRV during hot flashes. These findings further shed light on the physiology of hot flashes, suggesting a role for the ANS, and particularly for vagal control

in hot flashes. These findings may also suggest another possible mechanism in considering links between hot flashes and cardiovascular risk.

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Figure 1.
High frequency heart rate variability (HF-HRV) during a hot flash relative to pre- and post-flash intervals.
Adjusted for task
* $p < 0.05$ as compared to flash period

Figure 2.
Minute-by-minute heart rate variability (HF-HRV) power in relation to hot flash occurrence.
* $p < 0.05$ as compared to time 0

Table 1

Subject characteristics

N	30
Age (M, SD)	52.5 (5.3)
Race/ethnicity (n, %)	
Caucasian	15 (50)
African American	15 (50)
Education	
Less than college	9 (30)
College or higher	21 (70)
Menopausal status (n, %)	
Perimenopausal	12 (40)
Postmenopausal	18 (60)
BMI (M, SD)	28.3 (6.2)
Smoking status (n, %)	
Yes	21 (70)
No	9 (30)
State anxiety (M, SD)	29.3 (7.2)
Physical Activity Score (M, SD)	1946.6 (3621.5)
Reported hot flashes (median, interquartile range)	1 (1)
Physiologically detected hot flashes (median, interquartile range)	2 (2)
Intensity rating (M, SD)	1.8 (1.0)

Table 2

HF-HRV changes associated with hot flashes

	HF-HRV			
	Model 1		Model 2	
	B (SE)	p	B (SE)	p
Flash interval				
Pre-flash	0.18 (0.05)	0.0001	0.18 (0.05)	0.0001
Post-flash	0.16 (0.05)	0.002	0.16 (0.05)	0.002
Flash (referent)	--	--	--	--
Task				
Heat	0.07 (0.08)	0.37	0.08 (0.08)	0.29
Stress	0.20 (0.10)	0.05	0.24 (0.10)	0.02
Observation/Rest (referent)	--	--	--	--
Age	--	--	-0.05 (0.03)	0.09
Race/ethnicity				
African American	--	--	0.40 (0.30)	0.20
Caucasian (referent)			--	--
Education	--	--		
Less than college (referent)			--	--
College or higher			-0.26 (0.30)	0.39
BMI	--	--	-0.01 (0.03)	0.63
Physical activity	--	--	0.15 (0.08)	0.08
Menopausal status	--	--		
Perimenopausal (referent)			--	--
Postmenopausal			-0.99 (0.26)	0.001
Smoking status	--	--	-0.14 (0.38)	0.71
Anxiety	--	--	-0.07 (0.02)	0.005
Diabetes status	--	--	-0.16 (0.40)	0.67
Hypertension/CVD status [†]	--	--	0.04 (0.25)	0.87

[†] Hypertension (N=14), arrhythmia (N=1)

Note: Models include covariates as listed