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Changes in heart rate variability during vasomotor symptoms among midlife women

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Abstract

Objective: Most midlife women report vasomotor symptoms (VMS), yet their physiology remains poorly understood. This study tested whether acute decreases in cardiac vagal control would occur with VMS in a large sample of women monitored during wake and sleep.

Methods: Two hundred and fifteen nonsmoking women aged 40 to 60 years with evidence of VMS were included. Women were free of a history of clinical cardiovascular disease or arrhythmia; or use of insulin, beta blockers, calcium channel blockers, or medications impacting VMS. Women underwent 24 hours of ambulatory monitoring for physiological (sternal skin conductance) and self-report (electronic diary) measurement of VMS; heart rate variability (electrocardiogram); and respiratory rate. Changes in cardiac vagal control as assessed by respiratory sinus arrhythmia during VMS, relative to periods before and after VMS, were tested in linear mixed models.

Results: Significant decreases in respiratory sinus arrhythmia were observed during physiologically measured VMS relative to periods preceding (b[SE] = 0.13 (0.004), $P < 0.0001$) and after the vasomotor symptoms (b[SE] = 0.13 (0.004), $P < 0.0001$), adjusted for age, race, body mass index, and sleep/wake status. Decreases were observed for women not aware of their VMS, and differences persisted controlling for respiration rate. Interactions indicated that respiratory sinus arrhythmia decreases were most pronounced during sleep and for younger women.

Conclusions: Physiologically measured VMS were accompanied by an inhibition of cardiac vagal control in a large sample of women. Changes were observed irrespective of whether the VMS were reported, were most pronounced during sleep, and were greatest among younger women. These findings contribute to the understanding of vasomotor symptom physiology.

Key Words: Autonomic nervous system – Cardiac vagal control – Heart rate variability – Hot flashes – Vasomotor symptoms.

Vasomotor symptoms (VMS), or hot flashes and night sweats, are common during the menopausal transition, experienced by over 70% of women.[1] Frequent or severe VMS last much longer than was previously thought (for an average of 7-10 y).[2,3] For many women, VMS are associated with impairments in quality of life, mood, and sleep.[4-6] New data also have indicated that VMS may be linked to physical health, including indicators of cardiovascular disease (CVD) risk.[7,8] In the wake of findings of potential risk associated with the most effective treatment for VMS, hormone therapy,[9] a large number of women have discontinued hormone therapy,[10] and no other comparatively effective treatment options have emerged. Thus, there has been great interest in clarifying the underlying physiology of VMS to better understand this common midlife experience, to inform new treatments for VMS, and to elucidate the implications of VMS for the health of midlife women.

Despite their ubiquity, the physiology of VMS is not well established. Some work has implicated the autonomic nervous

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system and its innervation of cardiac and vascular tissue in the etiology of VMS. Alpha sympathetic control of the skin vasculature is important for thermoregulation, and vagal and beta sympathetic control directly influences cardiac function (heart rate [HR], contractility).[11,12] Vagal activation often, though not uniformly, acts to counter sympathetic activation. Some early research shows increased plasma levels of epinephrine[13] and of a metabolite of brain norepinephrine occurring with VMS.[14] Recently, investigators have been using electrocardiogram (ECG)-assessed HR variability (HRV), an index of autonomic control of HR. One HRV index is respiratory sinus arrhythmia (RSA), which provides an index of parasympathetic, or vagal control of the heart.[11,15] Although some limited research[16-18] suggests acute vagal withdrawal occurring during physiologically assessed VMS, this work has notable limitations, including being based upon very small sample sizes.

In this study, we examined whether physiologically monitored VMS are accompanied by acute reductions in cardiac vagal control during wake and sleep among 215 women undergoing 24 hours of ambulatory ECG and physiologic and diary VMS monitoring. We further considered changes in HR and respiration during VMS. Finally, we considered changes in cardiac vagal control, with VMS as a function of whether or not the VMS was reported.

METHODS

Study sample

The study sample included 215 late perimenopausal (no menstrual period in the prior 2-12 mo) and postmenopausal (no menstrual period in the prior 12 mo)[19] women participating in a study about VMS and cardiovascular function. All women were between ages 40 and 60, showed evidence of VMS on skin conductance monitoring, and had at least 17 hours (75%) of valid ECG and sternal skin conductance data. Exclusion criteria included hysterectomy and/or oophorectomy; current smoking; reported heart disease, stroke, or arrhythmia; pregnancy; use of oral or transdermal estrogen or progesterone, gabapentin, insulin, clonidine, beta blockers, calcium channel blockers, selective serotonin reuptake inhibitor or serotonin norepinephrine reuptake inhibitor antidepressants within the past 3 months; and currently undergoing chemotherapy for cancer. Two hundred and fifteen women (152 non-Hispanic white, 55 African American, and 8 women of other ethnicities) were included in primary analytic models.

Design and procedures

Women were recruited from the community via advertisements, mailings, and postings on message boards. After a telephone and inperson screening, height and weight were measured, questionnaires administered, and participants equipped with an ambulatory monitor (VU-AMS, VU University Amsterdam, www.vu-ams.nl, Amsterdam, the Netherlands)[20-22] that they wore for 24 hours as they went about their daily activities. This portable device worn in a pouch around the waist measures sternal skin conductance (for VMS), ECG (for HRV), and thoracic impedance (for respiration) continuously. Women were also provided with an electronic diary to be completed during waking hours when experiencing a VMS. Procedures were approved by the University of Pittsburgh Institutional Review Board. Participants provided written informed consent.

Measures

VMS

Sternal skin conductance was sampled at 1 Hz from the sternum via a 0.5-V constant voltage circuit passed between two Ag/AgCl electrodes (UFI) filled with 0.05 M KCl Velvachol/glycol paste.[23] Participants were instructed to avoid exercising and showering during monitoring. At the end of monitoring, data were downloaded, and VMS were scored using UFI software (DPSv3.7; Morro Bay, CA). This software automatically flags skin conductance rises of 2 μmho in 30 seconds, the standard criterion for VMS.[24] All events were also visually reviewed. Given that some women show submaximal VMS failing to reach the 2 μmho criterion,[25,26] all potential VMS events (submaximal VMS that show the characteristic hot flash pattern[27]) were also visually inspected, and events showing the characteristic pattern yet below 2 micromho/30 second rise were coded and independently verified by two coders. This coding approach has been shown to be reliable ($\kappa = 0.86$).[25,26] A 20-minute lockout period was implemented after the start of the VMS during which no VMS were coded. Women were also asked to report VMS they subjectively experienced by completing a portable electronic diary (Palm Z22, Palm, Inc) and pressing event mark buttons on the monitor that provided a date and time-stamped event mark.

HR, HRV, and respiration

HR was measured by ECG via three Ag/AgCl electrodes (Ultratrace 1690, Conmed; Utica, NY) in a standard three-lead configuration sampled at 1 kHz via the VU-AMS. Respiration was measured via thoracic impedance, sampled at 1 kHz via 4 Ag/AgCl electrodes.[20,28] Thoracic impedance to index respiration rate is preferable in the ambulatory setting for participant comfort and data quality.[29]

Each heartbeat or R-wave marker in the ECG signal were assessed for artifacts by an artifact detection algorithm (VU-AMS.5fs software; VU University Amsterdam, www.vu-ams.nl, Amsterdam, the Netherlands). All data were also reviewed and edited in detail by trained coders for the classification of normal from ectopic and artifactual beats, the latter being removed or interpolated. Minutes with 25% or more ectopic beats were eliminated. Minute-by-minute estimates of HR and RSA were conducted using VU-AMS software in accordance with guidelines.[11,15] RSA was scored by VU-AMS software based on the peak-valley method. This method uses the interbeat interval (IBI) time series extracted from the ECG together with the respiration signal obtained from the thorax impedance change signal to obtain heart

period variability that is associated with respiration.[15,28,29] RSA indexes changes in HR that occur during each respiratory cycle. HR increases during inspiration and decreases during expiration, variations which are largely vagally mediated.[15] RSA is computed for each respiratory cycle from the shortest IBI during an interval, starting at the beginning of inspiration and ending 1,000 ms after the end of inspiration, and the longest IBI during an interval, starting at the beginning of expiration and ending 1,000 ms after the end of expiration. RSA is calculated by subtracting the shortest IBI from the longest IBI. For secondary analyses SDNN (standard deviation of all normal R-R intervals) and a time domain approach to calculating HRV was also calculated.[11]

Covariates

Height and weight were measured via a fixed stadiometer and a calibrated balance beam scale, respectively. Demographics, menstrual history, and health behaviors were assessed by demographic and medical history questionnaires. Sleep/wake times were determined from a sleep diary completed before the women went to bed at night and upon waking the following morning. Race/ethnicity was determined in response to "How would you describe your primary racial or ethnic group?" Menopause status was obtained from reported bleeding patterns, categorized as perimenopausal (bleeding in previous 3 mo with decrease in cycle predictability in the past year, or >3 to <12 mo amenorrhea), or postmenopausal (>12 mo amenorrhea).[19] Time since the final menstrual period was calculated from the recalled date of the woman's last menstrual period.

Statistical analysis

The RSA and SDNN values were log (ln)-transformed for analysis due to skewness. Consistent with previous work,[16,17] pre-VMS, VMS, and post-VMS time periods were identified by comparing RSA during the minute at which the onset of the VMS occurred (ie, minute zero) to each of the preceding and following intervals within a single mixed-effects regression. Three periods were yielded: a pre-VMS period, ranging from 8 to 2 minutes before flash onset; a VMS period, ranging from 1 minute before 5 min after VMS onset; and a post-VMS period, ranging from 6 to 12 minutes after onset. These 6-minute pre-VMS and post-VMS periods were next entered into subsequent models as within-woman factors, with the during-flash time segment considered the referent. We also considered longer pre-VMS and post-VMS intervals (encompassing the 20 min before and after the VMS),[17] and findings were comparable, so analytic models with VMS intervals of equal length (6 min) are presented here.

Relations between VMS intervals, RSA, heart rate, and respiration were estimated with linear mixed-effects models, with random intercepts for VMS nested within participants and maximum likelihood estimation. The within-group correlation structure was modeled as a first-order continuous autoregressive, nested within VMS and participants. Covariates included age, race/ethnicity, and body mass index (BMI) (note that menopause stage was not related to RSA). Physiologically detected VMS (regardless of whether they were reported) and onset times were used for all primary models; subjective VMS (regardless of whether they were physiologically detected) and times were considered in secondary models. Additional models considered RSA changes during physiologically detected VMS that were also reported, physiologically detected VMS that were not reported, and reported VMS that lacked a corresponding physiologically detected VMS. Respiratory rate was added to covariate-adjusted models to examine whether it accounted for any relations between (physiologically detected or self-reported) VMS and RSA. Further, given potential dependence of HRV on HR, in secondary analyses, we used the formula of Monfredi to correct for HR level ($SDNN/exp^{[HR/58.8]}$).[30] Interactions between VMS period and sleep/wake status, VMS reporting status, menopause stage, time since the final menstrual period, age, and race/ethnicity in relation to RSA were tested with cross-product terms for VMS intervals and the relevant moderator via the likelihood ratio test. Analyses were performed with SAS v9.4 (SAS Institute, Cary, NC). Models were two-sided (alpha = 0.05).

RESULTS

Participants were on average 54 years old, postmenopausal, normotensive, and overweight (Table 1). Of the 215 women, 148 (69%) women reported having VMS and 67 (31%) reported that they did not have VMS in the past 3 months. The sample showed a median of 10 physiologically detected VMS/24 hours (7 wake, 3 sleep) and reported 3 VMS/24 hours (2 wake, 0 sleep). The women who reported having VMS reported a median of 6 VMS/24 hours. The total number of VMS across the sample was 2,386 physiologically detected VMS and 958 self-reported VMS.

We found a significant reduction in RSA observed during the VMS period relative to the periods before and after physiologically detected VMS (Table 2, Fig. 1A). Reductions were somewhat more pronounced during sleep than during wake (interaction $P < 0.0001$), differences that were not fully due to the higher RSA during sleep (interaction $P < 0.0001$ when controlling for average preflash RSA level). We also examined subjectively reported VMS and found significant reductions in RSA during subjectively reported VMS (Table 2, Fig. 1B).

Both HR and respiratory rate significantly increased during physiologically detected VMS as compared with pre-VMS and post-VMS periods (Fig. 2; HR: pre-VMS b[SE] = −3.56 [0.08], $P < 0.0001$; post-VMS b[SE] = −3.77 [0.07], $P < 0.0001$; respiratory rate: pre-VMS b[SE] = −0.38 [0.02], $P < 0.0001$; post-VMS b[SE] = −0.40 [0.02], $P < 0.0001$; both models relative to VMS period and adjusted for age, BMI, race/ethnicity, wake/sleep). Changes were similar for self-reported VMS (Fig. 1, Supplemental Digital Content 1, http://links.lww.com/MENO/A145). Given the role of respiration in RSA, we examined RSA changes during VMS also controlling for respiration, and findings persisted

TABLE 1. *Participant characteristics (N = 215)*

Age, M (SD)	53.9 (3.8)
Race/ethnicity, N (%)	
White	152 (70.7)
Black	55 (25.6)
Asian/Hispanic/mixed	8 (3.7)
Menopause stage, N (%)	
Perimenopausal	34 (15.8)
Postmenopausal	181 (84.2)
Education, N (%)	
High school/some college/vocational	100 (46.5)
College graduate	57 (26.5)
>College	58 (27.0)
BMI, M (SD)	28.8 (6.6)
SBP, M (SD)	120.1 (13.9)
DBP, M (SD)	71.1 (8.9)
CESD, M (SD)	8.0 (7.8)
Self-rated health, N (%)	
Good/fair/poor	68 (31.6)
Very good	93 (43.3)
Excellent	54 (25.1)
RSA, median (IQR)	
Total	36.9 (26.5, 48.1)
Wake	32.4 (24.6, 42.5)
Sleep	44.0 (34.2, 60.9)
Heart rate, beats/min, M (SD)	
Total	77.4 (10.1)
Wake	81.9 (10.2)
Sleep	67.6 (9.4)
Respiration rate, breaths/min, M (SD)	
Total	16.3 (1.7)
Wake	17.0 (1.6)
Sleep	14.8 (2.2)
Physiologic hot flashes, number/woman, median (IQR)	
Total	10 (4-16)
Wake[a]	7 (3-12)
Sleep[b]	3 (1-4)
Self-reported hot flashes, number/woman, median (IQR)	
Total	3 (0-7)
Wake[a]	2 (0-6)
Sleep[b]	0 (0-1)

BMI, body mass index; CESD, Center for Epidemiologic Studies Depression Scale; DBP, diastolic blood pressure; IQR, interquartile range; SBP, systolic blood pressure; SD, standard deviation.
[a]Number of hot flashes/monitoring time standardized to 17-hour waking period.
[b]Number of hot flashes/monitoring time standardized to 7-hour sleep period.

for physiologically detected and self-reported VMS (physiologically detected: pre-VMS b[SE] = 0.09 [0.004], post-VMS b[SE] = 0.10 [0.004], $P < 0.0001$; self-reported: pre-VMS b[SE] = 0.09 [0.006], post-VMS b[SE] = 0.10 [0.006], $P < 0.0001$; both models relative to VMS period and adjusted for age, BMI, race/ethnicity, wake/sleep, respiration rate). Further, given the potential dependence of HRV on HR, we used a formula that corrects for HR level in examining autonomic changes during VMS ($SDNN/exp^{[HR/58.8]}$)[30] and findings persisted (relative to VMS period: pre-VMS b[SE] = −0.10 [0.005], post-VMS b[SE] = −0.07 [0.005], $P < 0.0001$; adjusted for age, BMI, race/ethnicity, wake/sleep).

We next examined RSA changes during physiologically detected VMS that were also reported (VMS, n = 783), self-reported VMS that were *not* physiologically detected (n = 174), and physiologically detected VMS that were not reported (n = 1,585; Table 3). Although all types of VMS showed significant reductions in RSA, examination of effect sizes indicated particularly pronounced associations for VMS that were both physiologically detected and reported. Further, as many women who showed VMS here (31%) denied having current VMS, we examined whether the RSA changes during the physiologically detected VMS of women who denied currently having VMS were comparable to those women who reported having VMS. Reductions in RSA during VMS among women who did not report having VMS were slightly smaller (interaction $P = 0.002$), but also statistically significant (Table 1 and Fig. 2, Supplemental Digital Content 1 and 2, http://links.lww.com/MENO/A145 and http://links.lww.com/MENO/A146).

We conducted several additional analyses. As 19 women were taking medications that could impact autonomic function (inhaled beta agonists, anticholinergics, epinephrine), we conducted analyses without these women and findings were largely unchanged (relative to VMS period: pre-VMS b[SE] = 0.12 [0.004], post-VMS b[SE] = 0.13 [0.004], $P < 0.0001$; adjusted for age, BMI, race/ethnicity, wake/sleep). Notably, these medications were not related to RSA here ($P > 0.50$). Further, we examined any differences in RSA during VMS by age, menopause stage, time since the last menstrual period, and race/ethnicity. Significant interactions by age were observed ($P < 0.0001$), with changes in RSA during VMS somewhat more pronounced among younger women (Table 2 and Fig. 3, Supplemental Digital Content 1 and 2, http://links.lww.com/MENO/A145 and http://links.lww.com/MENO/A146). These differences were not driven by average RSA differences by age (interaction $P = 0.0004$, controlling for average RSA level). Further, there was a statistically significant interaction between race/ethnicity

TABLE 2. *Regression weights for the difference of RSA from pre and post-VMS period relative to RSA during the VMS*

	RSA (24 h)		RSA (wake)		RSA (sleep)	
	B (SE)	*P*	B (SE)	*P*	B (SE)	*P*
Physiologic VMS						
Pre-VMS period	0.13 (0.004)	<0.0001	0.11 (0.005)	<0.0001	0.16 (0.007)	<0.0001
Post-VMS period	0.13 (0.004)		0.13 (0.005)		0.13 (0.007)	
Self-report VMS		<0.0001				
Pre-VMS period	0.12 (0.007)		0.11 (0.008)	<0.0001	0.18 (0.01)	<0.0001
Post-VMS period	0.14 (0.007)		0.13 (0.008)		0.17 (0.01)	

Controlling for age, race, BMI, and (in 24-h RSA models) wake/sleep; RSA log-transformed (N = 215).
RSA, respiratory sinus arrhythmia; SE, standard error; VMS, vasomotor symptoms.

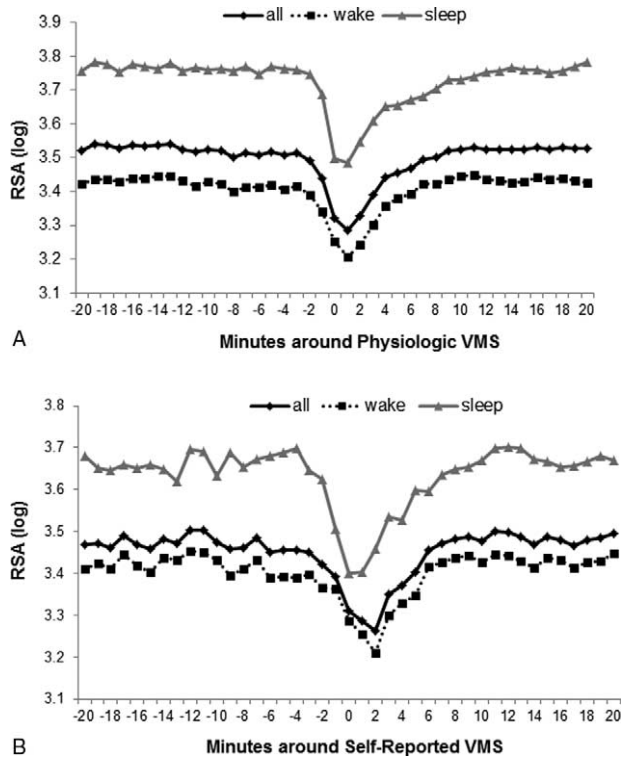

FIG. 1. Mean RSA during physiologically monitored VMS (**A**), and self-reported VMS (**B**), stratified by wake/sleep (N = 215). RSA, respiratory sinus arrhythmia; VMS, vasomotor symptoms.

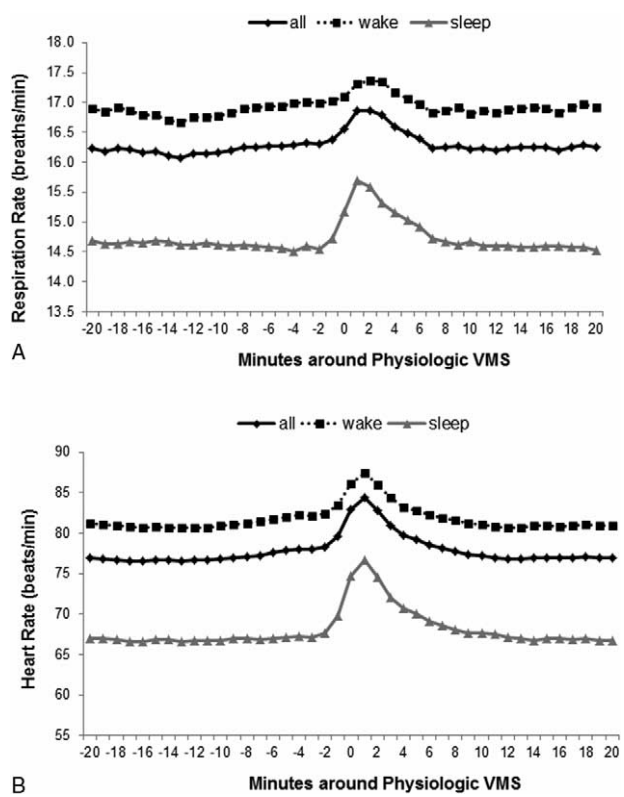

FIG. 2. Respiration rate (**A**) and mean heart rate (**B**) during physiologically monitored VMS (N = 215). VMS, vasomotor symptoms.

and VMS period ($P = 0.002$), but examination of RSA changes with VMS by race/ethnicity indicated that they were quite similar between racial/ethnic groups (Fig. 4, Supplemental Digital Content 1, http://links.lww.com/MENO/A145).

DISCUSSION

In this study we monitored 215 women over 24 hours during wake and sleep. Findings showed acute reductions in cardiac vagal control during VMS. These findings were apparent for both self-reported and physiologically assessed VMS, with particularly pronounced RSA changes during VMS that were both reported and physiologically detected. Vagal withdrawal with physiologically detected VMS was even apparent among women who were not aware of having VMS. HR and respiration rate also increased during VMS, yet the autonomic changes observed during VMS were apparent when controlling for HR level, as well as controlling for respiration rate. Further, RSA changes with VMS were observed during both wake and sleep, with slightly larger RSA declines with VMS during sleep.

This work extends prior work to a much larger sample of women. Three prior small studies showed acute reductions in cardiac vagal control during VMS, including a study of 30 women performing various tasks in the laboratory,[16] 11 women measured in the laboratory during sleep,[18] and 21 women monitored in the ambulatory setting.[17] An additional small study of 20 women indicated potential increases in sympathetic activation with physiologically detected VMS during sleep,[31] yet interpretation of this study is limited by the mixture of sympathetic and parasympathetic contributions to the lower-frequency spectral bands examined.[11] These initial studies suggest vagal withdrawal and possibly sympathetic activation during VMS. However, the small sample sizes and restriction of many of these studies to sleep limited conclusions. Our study includes a larger and more ethnically diverse sample that includes women, considers wake and sleep, and indexes respiration rate. We more definitively demonstrate increases in HR and reductions in cardiac vagal control with VMS.

Despite the prevalence of VMS, a complete understanding of their physiology has remained elusive. Notably, leading models indicate that VMS reflect altered thermoregulatory function, potentially driven by reproductive hormonal changes, yet also with potential autonomic inputs.[32] HRV reflects autonomic control of the heart, and autonomic control of other organs cannot be inferred from our data. However, other evidence more broadly supports a role of the autonomic nervous system in VMS. Prior work has indicated that alterations in sympathetic nerve activity to the skin may play a role in the VMS-associated alterations in skin blood flow.[33] Freedman et al[34] showed clonidine, a centrally acting alpha-2 adrenergic agonist to reduce VMS, and yohimbine, an alpha-2 adrenergic antagonist, to increase VMS. Other studies have suggested alterations in peripheral catecholamines[13] or central norepinephrine[14] with VMS.

TABLE 3. *Regression weights for the difference of RSA from pre and post-VMS period relative to RSA during the VMS, by physiologic occurrence and self-report of VMS, wake and sleep*

	Physiologic VMS that are reported				Physiologic VMS that were not self-reported				Self-reported VMS not physiologically detected			
	Wake		Sleep		Wake		Sleep		Wake		Sleep	
	B (SE)	*P*	B (SE)	*P*	B (SE)	*P*	B (SE)	*P*	B (SE)	*P*	B (SE)	*P*
VMS period												
Pre-VMS	0.13 (0.009)	<0.0001	0.23 (0.02)	<0.0001	0.10 (0.007)	<0.0001	0.14 (0.008)	<0.0001	0.07 (0.02)	0.001	0.13 (0.03)	<0.0001
Post-VMS	0.15 (0.009)		0.18 (0.02)		0.12 (0.007)		0.11 (0.008)		0.07 (0.02)		0.14 (0.03)	

Controlling for age, race, BMI; RSA log transformed (N = 215).
BMI, body mass index; RSA, respiratory sinus arrhythmia; SE, standard error; VMS, vasomotor symptoms.

Our results suggest that vagal inhibition may be important to the occurrence of VMS.

These findings may contribute to the emerging literature on VMS and cardiovascular risk. In some (but not all[35]) prior studies, VMS have been linked to higher subclinical CVD[7,8,36] and a more adverse CVD risk factor profile.[37-39] Notably, reduced cardiac vagal control has been implicated in CVD development.[40] The physiologic significance of the transient reductions in cardiac vagal control with VMS observed here is not entirely clear. However, vagal withdrawal has been linked to disinhibition of inflammatory control of tissue macrophages.[41] Notably, women in this sample were having many VMS per day. The cardiovascular implications of these repeated reductions in RSA should be investigated in future work.

Given the large number of women and VMS events included examined here, we were able to test variations in RSA during VMS depending on whether the VMS was reported. Reductions in RSA were observed during both physiologically detected and self-reported VMS, with the most pronounced reductions in RSA observed during physiologically detected VMS that were also reported. It is widely observed that many VMS that are detected on physiologic monitoring are not reported,[42] similar to observations here. Interestingly, 30% of women in the present investigation denied currently having VMS, yet showed evidence of VMS on monitoring. Whether these VMS reflect actual VMS or poor specificity of sternal skin conductance monitoring remains a question. However, these VMS showed a similar autonomic signature as women who reported having VMS, supporting the events as VMS. Thus, these data indicate that RSA reductions are observed during both physiologically detected and self-reported VMS.

There were significant interactions by age, with greater reductions in RSA observed among the younger midlife women in the sample relative to the older women. These differences were not driven by baseline differences by age. There are some data indicating that the cardiovascular implications of VMS may vary by the timing of VMS in a woman's lifespan[43]; these findings suggest attention to younger midlife women. Notably, we did not observe interactions by menopause stage or time since the last final menstrual period, suggesting that this age moderation is more attributable to chronological than ovarian aging (although it is notable that date of birth is likely reported with more precision than the date of the last menstrual period). We also found significant interactions by race/ethnicity, yet the magnitude of these race-related differences were quite small.

Several limitations deserve mention. First, physiologic measures of VMS have limitations.[44] Whereas our methods of quantifying VMS addressed certain of these limitations, questions of the validity of these measures remain. However, it is notable that findings were apparent for VMS physiologically detected but not reported, supporting the significance of these events. Further, whereas the sample was large and included both white and non-white (principally African American) women, the ethnic diversity of the sample was somewhat limited; therefore findings may not generalize to other ethnic groups, particularly Hispanic and Asian women.

This study had several strengths. This study included a large sample of women studied over day and night in their home environments. Thus, it had greater power and generalizability than other studies on the topic. The women were free of major cardiovascular comorbidities. None of the women were taking medications impacting VMS or key medications impacting cardiovascular function. Although some of the women were taking medications that would have some impact on the autonomic nervous system, removal of these women did not alter findings. VMS, ECG, and respiratory rate were measured prospectively and rigorously throughout the monitoring period. Physiologic VMS measures, although subject to the caveats mentioned above, provide a more precise estimation of VMS timing and do not reply upon participant reporting. Further, we carefully considered the role of respiration, as well as potential dependence of HRV on HR. We considered VMS during wake and sleep, allowing comparisons of changes in HRV during both intervals.

CONCLUSIONS

This is the first study to examine acute changes in cardiac vagal control during physiologically assessed and self-reported VMS in a large sample of women monitored over 24 hours. This study provides further evidence that VMS are accompanied by acute increases in HR and reductions in cardiac vagal control. These changes were observed for VMS occurring during wake and sleep, for both self-reported and physiologically detected VMS, and even among women who show VMS that they do not

perceive. Together with the larger literature, they indicate vagal withdrawal during VMS and further add to the understanding of this highly prevalent experience.

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