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Original Article

ORIGINAL ARTICLE

Changes in heart rate and blood pressure during nocturnal hot flashes associated with and without awakenings

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Abstract

Hot flashes (HFs) are a hallmark of menopause in midlife women. They are beyond bothersome symptoms, having a profound impact on quality of life and wellbeing, and are a potential marker of cardiovascular (CV) disease risk. Here, we investigated the impact on CV functioning of single nocturnal HFs, considering whether or not they were accompanied by arousals or awakenings. We investigated changes in heart rate (HR, 542 HFs), blood pressure (BP, 261 HFs), and pre-ejection period (PEP, 168 HFs) across individual nocturnal physiological HF events in women in the menopausal transition or post-menopause (age: 50.7 ± 3.6 years) (n = 86 for HR, 45 for BP, 27 for PEP). HFs associated with arousals/awakenings (51.1%), were accompanied by an increase in systolic (SBP; ~6 mmHg) and diastolic (DBP; ~5 mmHg) BP and HR (~20% increase), sustained for several minutes. In contrast, HFs occurring in undisturbed sleep (28.6%) were accompanied by a drop in SBP and a marginal increase in HR, likely components of the heat dissipation response. All HFs were accompanied by decreased PEP, suggesting increased cardiac sympathetic activity, with a prolonged increase for HFs associated with sleep disruption. Older age predicted greater likelihood of HF-related sleep disturbance. HFs were less likely to wake a woman in rapid-eye-movement and slow-wave sleep. Findings show that HFs associated with sleep disruption, which are in the majority and more likely in older women, lead to increases in HR and BP, which could have long-term impact on nocturnal CV restoration in women with multiple HFs.

Statement of Significance

Hot flashes (HFs) are a common symptom that can persist for several years across menopause and are a known marker of cardiovascular (CV) disease risk. They often disrupt sleep, which could impact nocturnal CV recovery. We show that waking up with a HF, beyond the HF itself, is associated with CV activation, including increased blood pressure, heart rate, and cardiac sympathetic activity, which could be a pathway towards increased CV risk in midlife women. Women with multiple nocturnal HFs that wake them up may lose the benefit of the CV "holiday" that accompanies restful sleep. Also, older age predicts HF-associated sleep disruption, suggesting that the CV impact may be more relevant in older women.

Key words: vasomotor symptoms; blood pressure; REM sleep; sympathetic nervous system; menopause

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Introduction

Hot flashes (HFs) are a hallmark of the menopausal transition, being reported by up to 80% of women [1–3] and lasting a median duration of 7.4 years [1]. HF frequency varies between women, ranging from hourly to weekly [4], and can occur both day and night (night sweats) [4].

HFs emerge when estradiol levels decline and are a thermoregulatory phenomenon, characterized by a heat dissipation response, including increased cutaneous vasodilation and sweating that last a few minutes [5]. As such, HFs can be identified by a sudden increase in sternal skin conductivity due to increased sweating. Studies in awake women having HFs have shown that vasodilation is mediated by a transient increase in skin sympathetic nerve activity [6] and is accompanied by increased heart rate (HR) and decreased mean arterial pressure [6, 7].

Recent studies have pointed to HFs being beyond "bothersome" symptoms, showing that they are markers of higher risk of subclinical cardiovascular (CV) disease. Specifically, presence and/or severity of HFs has been associated with higher blood pressure (BP), poorer endothelial function and flow-mediated dilation, more aortic calcification, and higher carotid intima-media thickness (reviewed in [8]), with some relationships being stronger in women with an early onset of HFs [9]. Women with HFs are also more likely to have an adverse adipokine profile [10], higher lipid and lipoprotein levels [11], insulin resistance [12], and possibly increased risk for subsequent CV disease events [8]. Most studies have been cross-sectional and relied on self-reported HFs; underlying mechanisms linking HFs with markers of subclinical CV risk are not fully understood, and the HF may itself be just one indicator of underlying risk, reflecting system instability.

An unexplored factor that could contribute to increased CV risk in women with multiple HFs is HF-related sleep disturbance. Sleep and the CV system are intimately connected, with sleep providing a "CV holiday" [13], with an overall wake-to-sleep reduction in CV effort (decreases in BP, HR, cardiac output). Arousal from sleep can disrupt this CV holiday [14], which is a pathway to adverse CV health [13]. Higher nocturnal BP is a strong predictor of adverse CV events in hypertensive and general populations [15, 16], and is associated with reduced endothelial function [15].

HFs are associated with poorer self-reported sleep quality and chronic insomnia [17–19], with longitudinal data showing that women reporting moderate-severe HFs are almost three times more likely to report frequent nocturnal awakenings compared to women without HFs [18]. While studies linking self-reported HFs with poor perceived sleep quality are consistent, literature linking objective HFs and objective poor sleep quality are conflicting (see [17] for review), with some studies showing a poorer polysomnographic (PSG)-defined sleep profile [20] and others showing no difference in PSG measures [21] in women with objective HFs compared with asymptomatic women. Analysis of individual HF events and PSG measures in women with HFs are also inconsistent, with some studies reporting that awakenings are more likely to occur before than after an HF [21], and others reporting that HFs occur before an awakening only in the first half of the night [22], or that the majority of HFs coincide with awakenings [23–25], with no differences in the first and second part of the night [23]. In an experimental model of simulated menopause (treatment with a Gonadotropin-releasing hormone [GnRH] agonist), Joffe and colleagues [26] found that the majority (66%) of HFs coincided with wake or N1 sleep. Some of the variability in the findings in the literature might relate to inter- and intra-individual differences in the extent to which HFs disrupt sleep. For example, a more detailed analysis of HF-related sleep disruption revealed that HF-associated wake time was responsible for almost a third of total wakefulness, on average, however there was wide variance between women (some HFs occurred without disturbing sleep, while others were associated with awakenings of different durations, depending on the time taken to fall asleep again) [23].

Awakenings associated with HFs could disrupt CV recovery across the night. However, little work has examined CV changes associated with nocturnal HFs, and none has considered effects of HF-awakenings versus the HF itself. Some studies show that women reporting HFs have higher SBP and DBP [27], with higher DBP being particularly evident at night [28] compared to asymptomatic women. Also, the presence of nocturnal HFs is associated with an increased risk of coronary heart disease [29]. Thurston and colleagues [30] considered HR variability changes around physiological HFs recorded in women across 24 hours, and found a significant reduction in vagal-related activity during an HF, with the reduction being greater for HFs recorded during self-reported sleep periods. We previously reported that HR increased and vagal-related activity decreased in association with HFs in undisturbed sleep, indicating a direct effect of the HF itself [31]. In another study of ambulatory BP in women with severe HFs, half of the HFs self-reported at night were associated with substantially higher SBP and DBP within 15 minutes after the HF relative to average nocturnal values [32]. However, sleep stages and physiological HFs were not measured, therefore, this analysis is restricted to HFs recalled by women. The relationship between HFs, sleep/wake episodes, and CV function, therefore, remains to be determined.

Here we aimed to investigate changes in BP and HR recorded continuously across individual HFs, categorized according to whether or not they were associated with simultaneous arousal/awakening (Arousal HF); delayed awakening (Delayed Arousal HF); or without sleep disruption (Sleep HF). In this way, we could differentiate effects on CV functioning of the HF alone from effects of the HF combined with immediate or delayed awakenings. We also assessed pre-ejection period (PEP), derived from impedance cardiography (ICG), and specifically reflective of beta-adrenergic influences upon the heart [33]. We hypothesized that HFs associated with sleep disruption would be associated with a greater CV response compared to HFs in undisturbed sleep. We also investigated if subject characteristics (e.g. menopausal stage, age, body mass index [BMI], depression symptoms), and sleep stage and time of night in which the HF occurred, predicted the likelihood of HF-associated sleep disruption.

Methods

Sample

Eighty-six women who had at least one objectively recorded HF during an overnight laboratory PSG recording were included in this analysis. Sample characteristics are presented in Table 1. Women were participating in a multi-night study, as described elsewhere [34, 35]. Briefly, women aged between 43–60 years old in the early (n = 46, persistent difference of 7 days or more

Table 1. Characteristics and polysomnographic variables (mean [*SD*]) for the sample of 86 women included in the analysis

Demographics	
Sample, No.	
•Early menopausal transition	46
•Late menopausal transition	31
•Post-menopause	9
Caucasian, No.	64
	Mean (*SD*)
Age, years	50.7 (3.6)
Body mass index, kg m^{-2}	24.4 (4.0)
Beck depression inventory (BDI-II)[a], score	6.6 (5.5)
Pittsburgh sleep quality index (PSQI)[a], score	7.4 (4.0)
Pre-sleep arousal	
Presleep arousal scale (PSAS), score	
•PSAS-somatic	11.4 (3.1)
•PSAS-cognitive	10.2 (6.0)
Polysomnographic variables[b]	
Time in bed, minutes	439.4 (55.3)
Sleep onset latency, minutes	11.7 (11.1)
Total sleep time (TST), minutes	368.8 (49.2)
Wakefulness after sleep onset, minutes	58.9 (36.0)
Stage N1, %TST	8.8 (4.3)
Stage N2, %TST	53.6 (7.8)
Stage N3, %TST	14.4 (7.9)
Rapid-eye-movement (REM) sleep, %TST	23.1 (4.6)
Arousal Index, No./hour	9.5 (5.3)
Awakening Index, No./hour	3.5 (1.6)
Physiological hot flashes	
Hot flashes (No. per night)	6.3 (6.1) (median of 5)

[a]Data unavailable in 1 or 2 women.
[b]PSG measures were averaged across nights if a participant had multiple nights before averaging across the group.

in the length of consecutive cycles) or late (n = 31, increased variability in cycle length and the occurrence of amenorrhea of ≥60 days) menopausal transition or early post-menopause (n = 9, first 1–6 years after final menses), according to Stages of Reproductive Aging Workshop criteria [36], were recruited from the community. Inclusion criteria were: intact uterus and at least one ovary; absence of severe mental or medical conditions requiring medications known to affect sleep and/or the CV system (e.g. antihypertensives, hypnotics, antidepressants), absence of hormone therapy/contraception for the preceding 3 months, absence of sleep-related breathing/leg movement disorders (assessed with clinical PSG). All but three women were nonsmokers. The study was reviewed and approved by the SRI International Institutional Review Board, and all participants provided written, informed consent.

Questionnaires

Women completed the Beck Depression Inventory (BDI-II) [37] to assess depression symptoms; the Pittsburgh sleep quality index (PSQI) to assess sleep quality [38]; and the presleep arousal scale (PSAS), to assess cognitive and somatic arousal during the falling asleep process [39].

Physiological assessments

Recordings were made using dedicated inputs to Compumedics amplifiers (Compumedics, Abbotsford, Victoria, Australia). PSG, electrocardiography (ECG), and skin conductance (SC) were recorded in all women. Beat-to-beat BP and ICG data were only available in a subset of women who completed that part of the protocol. Specifically, beat-to-beat BP data were available in 45 women (21 early menopausal transition, 15 late menopausal transition, 9 early post-menopause) and ICG data were available in 27 women (9 early menopausal transition, 9 late menopausal transition, 9 early post-menopause). There were no differences in demographics or sleep continuity measures between the groups with and without BP or ICG data. Signal processing was performed using customized processing scripts for Matlab (MathWorks, Natick, MA).

Sleep.

Recordings included electroencephalography (EEG; 256 Hz sampled, 0.3–35 Hz filtered), bilateral electrooculography, submental electromyography, collected according to standard criteria [40] using Compumedics amplifiers and ProFusion software (Compumedics, Abbotsford, Victoria, Australia). Sleep was scored in 30-second epochs (wake, N1, N2, N3, rapid-eye-movement [REM sleep]) by experienced scorers blinded to the presence of any HF events. Brief arousals (≥3 seconds, <15 seconds) were marked according to standard rules (abrupt shift of EEG frequency including alpha, theta and/or frequencies >16 Hz [but not spindles] that lasts ≥ 3 seconds [40]).

Heart rate.

ECG was recorded via Ag/AgCl Meditrace surface spot electrodes in a modified D2 Einthoven configuration, sampled at 512 Hz. Signals were digitally filtered with a fourth-order Butterworth bandpass filter (upper: 0.5 Hz; lower: 35 Hz), applied in forward and backward directions to avoid phase shifts. Customized algorithms were applied to compute normal-to-normal inter-beat-intervals via automatic detection of R peaks to derive HR.

Blood pressure.

BP raw waveforms were obtained using Portapres technology (Model-2; TNO TPD Biomedical Instrumentation, Amsterdam, NL), a validated method allowing prolonged noninvasive BP measurements [41]. The BP signal was obtained from the index and middle fingers of the non-dominant hand using inflatable cuffs and photoplethysmography (PPG) sensors to measure the blood volume. The blood volume at zero transmural pressure is estimated via oscillometry, and the cuff pressure is continually varied to maintain this blood volume throughout the cardiac cycle via a fast servo-control system. The applied time-varying cuff pressure is, therefore, equal to arterial BP. The device has been shown to achieve BP errors within Association for the Advancement of Medical Instrumentation limits of 5 mmHg bias and 8 mmHg precision [42]. Despite some limitation in absolute BP estimates, this method allows reliable estimation of BP changes [43], the focus of our investigation. Measurements alternated between fingers every 30 minutes to minimize discomfort. Automatic algorithms were developed to identify and exclude data corresponding to calibration and cuff switching and to detect systolic peaks and diastolic troughs, from which SBP and DBP were derived.

Sympathetic activity.

ICG dZ/dt (Ω), that is, the rate of change in the impedance waveform on a given beat, was recorded with HIC-4000 Bioelectric

ICG (Bio-Impedance Technology, Inc., Chapel Hill, NC), using a dual-spot electrode 4-lead 8-point connection arrangement [44]. A low-intensity (4 mA) alternating current of high frequency (100 kHz) was used for the ICG circuit (sampling rate: 1024 Hz). Signals were digitally filtered with a fourth-order Butterworth bandpass filter (upper: 0.5 Hz; lower: 25 Hz), applied in forward and backward directions. ICG cardiac cycles were identified using the ECG R peaks as reference. Automatic algorithms were developed to detect and remove ICG cycles corrupted by noise and artifacts [45, 46]. B points were then detected on the clean ICG cycles using an automatic B-point detection algorithm [47]. The algorithms used to remove artifact from ICG and ECG signals and to measure PEP have been shown to achieve up to 96% accuracy when compared to expert manual scoring [45–47].

PEP(s) was calculated as the time interval between the Q-point (beginning of the electrical systole; determined by a fixed interval [35 ms] backward from the ECG R-wave peak) on the ECG signal and the B point (opening of the aortic valve) on the ICG dZ/dt signal. PEP is inversely related to beta-adrenergic sympathetic nervous system activity [33, 48].

Post-processing of all CV measures

An outlier removal algorithm was developed to remove corrupted cardiac cycles (data points > 10 scaled median absolute deviations from the median). Corrupted data segments <10 seconds were replaced by interpolating the remainder of the data. Uncorrupted CV parameters were then averaged over 30-second bins corresponding to the scored PSG. Thirty-second data segments containing more than 70% corrupted cardiac cycles were identified as corrupted. Corrupted segments of data that were shorter than 300 seconds were replaced by interpolating the remainder of the data; the rest of them were excluded. An expert visually checked the performance of the outlier detection algorithm on approximately 10% of randomly selected data.

Hot flashes.

SC was sampled at 16 Hz using a BioDerm Skin Conductance Meter (model 2701, UFI) connected to two Ag/AgCl electrodes placed on either side of the sternum, with a 0.5 V constant voltage circuit between them. Physiological HFs were automatically detected based on a ≥1.5 μmho rise in SC within 30 seconds, using a customized algorithm [49] with the threshold set at 1.5 μmho. Algorithms were used to detect HFs and determine the timing of their onset, as well as to reject noise and artifacts by analyzing the SC level and slope [49]. HF candidates accompanied by a very fast change in SC (not physiologically possible) were rejected, and a 10-minute refractory period following an HF was applied during which any HF candidates are removed. To detect HF-onset, the SC signal was filtered, the slope within a 30-second window following the HF was calculated, and the first sample at which the slope reached at least 0.02 $\mu S\ s^{-1}$ was marked as HF-onset [49]. All HFs were then manually checked to examine the shape of each HF: submaximal HFs (lower than the 2 μmho threshold [50]), but with a characteristic HF shape were included, as suggested by others [30, 51, 52]. Indeed, the 2 μmho threshold has poor sensitivity (up to 47% of HFs reported by women did not correspond to a sufficient SC increase) [53], and lowering the threshold increases sensitivity while maintaining specificity [51].

HF categories

Given the known increase in skin blood flow even before an increase in sweat rate [4], we marked a 60-second window as "HF-onset," which encompassed the start of the increase in sweat rate and the 30 seconds immediately prior to that. We then categorized HFs based on the presence of PSG-defined wake time and sleep stage composition and brief arousals during the 4-minute period (Figure 1) encompassing HF-onset, using modified criteria from [31]. The following categories were formed:

Arousal HF when the 90-second pre-HF-onset period consisted of sleep (N1, N2, N3, or REM sleep) and the HF-onset window contained at least 1 epoch of wake or arousal. The 90-second post-HF-onset period consisted of wake and/or sleep.

Delayed Arousal HF when wakefulness did not occur until the post-HF-onset period.

Sleep HF when the 90-second pre-HF-onset period, HF-onset, and 90-second post-HF-onset period contained only sleep epochs. There were no brief arousals during HF-onset.

Ambiguous HF when the pre-HF-onset period contained all wake or mixed wake/sleep epochs. (Excluded from analysis of CV changes across HF events due to variability in CV measures in the pre-HF-onset period).

We used stringent criteria for defining sleep disruption during HF-onset by considering the presence of even brief arousals. Brief arousals were allowed to occur during the rest of the period, regardless of HF category.

Data analysis

The period of analysis was the 15-minute period around each HF, divided into 30-second epochs (~5 minutes before, and ~ 10 minutes after the HF, Figure 1). Statistical analyses were conducted using Hierarchical linear models (type of repeated-measures mixed model) to account for between-woman and between-night random effects. Repeated-measure models take into account the fact that there are multiple measurements on study participants so that precision is not overestimated (as would occur if individual HFs were treated as independent). Hierarchical linear models using Stata's mixed commands were used to examine whether values for each CV variable across 30-second epochs of the pre-HF-onset period (90 seconds before HF-onset), HF-onset (60 seconds), and post-HF-onset period (90 seconds after HF-onset) as well as for early (between 90 seconds and 270 seconds after HF-onset) and late (between 300 seconds and 570 seconds after HF-onset) recovery periods differed from baseline (between 90 seconds and 270 seconds before HF-onset) and whether the magnitude of that difference differed between HF types (i.e. Arousal HF, Delayed Arousal HF, Sleep HF). The independent variable was a categorical variable for HF type, where the excluded category (represented by the constant term in the regression equation) was Sleep HF. Statistical significance was calculated using Wald's test. For tests comparing HF categories, the Wald test compared the expected value for an HF category with that of another category. For analyses examining differences across the HF relative to baseline, the Wald's test determined whether the difference between baseline and each 30-second epoch was statistically greater than zero for each HF category. HFs with missing CV data were excluded from analysis for that particular model.

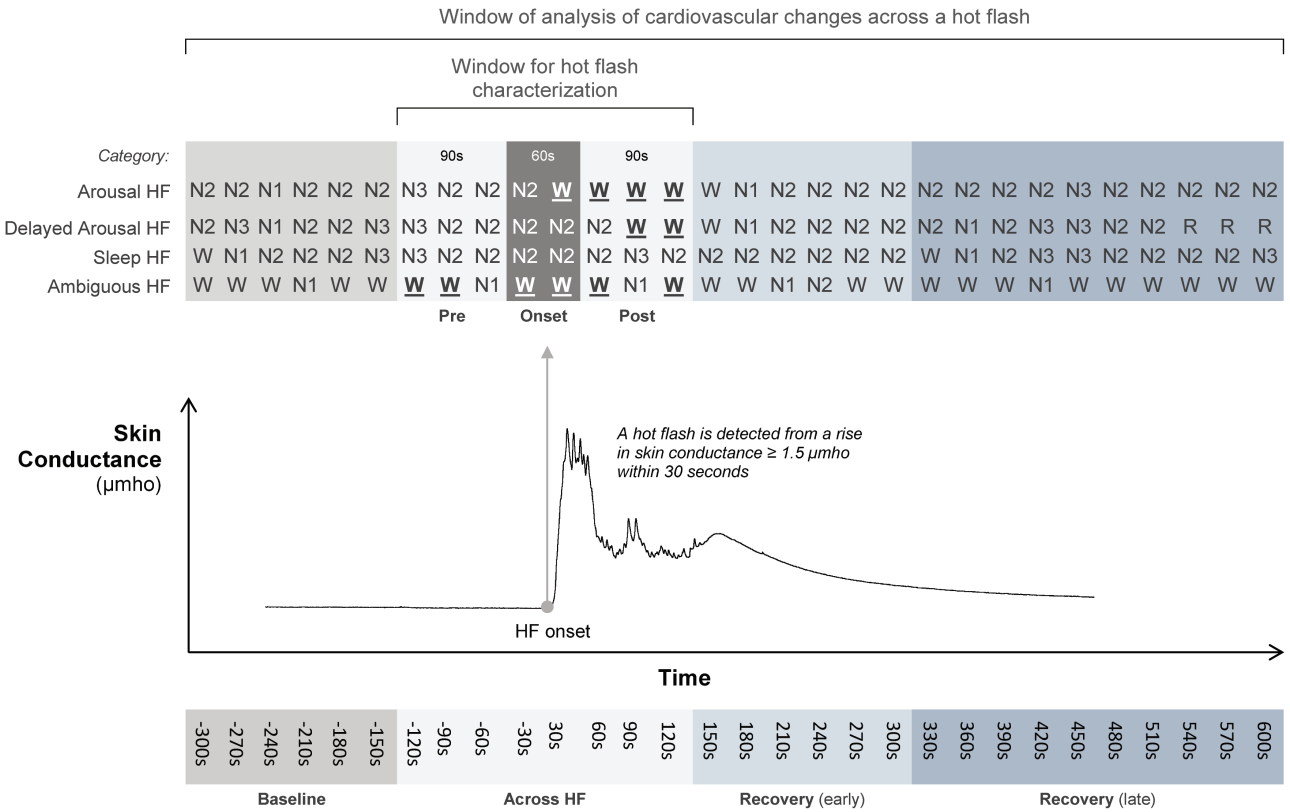

Figure 1. HFs were categorized based on sleep stage composition in 30-second epochs around HF-onset (60 seconds) and across 90-second pre-HF-onset and 90-second post-HF-onset. Bottom panel shows an example of a physiological HF (skin conductance rise of ≥1.5 µmho within 30 seconds) recorded from sternum skin conductance time-aligned with the PSG sleep stages; arrow reflects rise in skin conductance marking HF-onset. The complete analysis window is divided into baseline, HF, early, and late recovery periods. N1, N2, N3, refer to sleep stages; W = wakefulness.

Repeated-measures mixed ordinal logistic models using Stata's meologit commands were used for analyses determining whether the proportions of each sleep stage in the pre-HF-onset period differed across HF categories and whether proportions of each HF category differed across hours of the night. Finally, mixed logistic models using Stata's melogit commands were used to determine if characteristics (menopausal stage; age; BMI; sleep quality from PSQI; depression symptoms from BDI; presleep cognitive and somatic arousal from PSAS) predicted the likelihood of having HF-associated sleep disturbance (combined Arousal and Delayed Arousal HF categories).

Results

Hot flashes

Women contributed 1–13 HFs per night, from 1 to 7 PSG recordings, for a total of 546 physiological HFs detected from 175 nights. A small number of HFs were excluded from analysis for HR (n = 4), BP (n = 10), and ICG (n = 20) due to signal drop-outs (e.g. due to sensor loosening/detachment) around the HF-onset period. Due to differences in the number of women providing data for each signal, and missing data, number of HF events analyzed varied per signal: HR analysis was based on 542 HFs; BP analysis on 261 HFs; and PEP analysis on 168 HFs.

PSG variables are presented in Table 1. 51.1% of detected HFs were clearly associated with sleep disruption (27.7% for Arousal HF and 23.4% for Delayed Arousal HF categories). For Arousal HF, the majority (67.6%) were associated with an awakening rather than brief arousal at HF-onset. Of those associated with an arousal, the majority (67.3%) converted to an awakening in the following 90 seconds (post-HF-onset). 28.6% of HFs occurred in undisturbed sleep (Sleep HF category). The remaining HFs (20.3%) were ambiguous (the pre-HF period contained wake or mixed wake-sleep stages such that CV measures were variable before HF-onset) and were excluded from analysis. Figure 2 shows sleep stage composition across the window of analysis, showing the distinction between HF categories.

HR across HFs

Figure 3 shows HR plotted across each HF category. While HR appears to be higher during baseline for Sleep HF relative to other categories, there was no significant difference in baseline HR, after accounting for between-women and night-to-night variability. Comparisons of HR in pre-HF-onset, HF-onset, and post-HF-onset periods relative to baseline for each HF category are shown in Table 2. For Arousal HF, HR began to increase relative to baseline before HF-onset (p < 0.001), and peaked during HF-onset and 30 seconds after (+12.0 bpm, on average). For Delayed Arousal HF, HR was significantly higher during HF-onset relative to baseline (p < 0.001), peaking 60 seconds post-HF-onset (+11.9 bpm, on average). For Sleep HF, HR began to increase 30 seconds before HF-onset relative to baseline (p = 0.01), peaking between 60–90 seconds post-HF-onset (+2.9 bpm, on average).

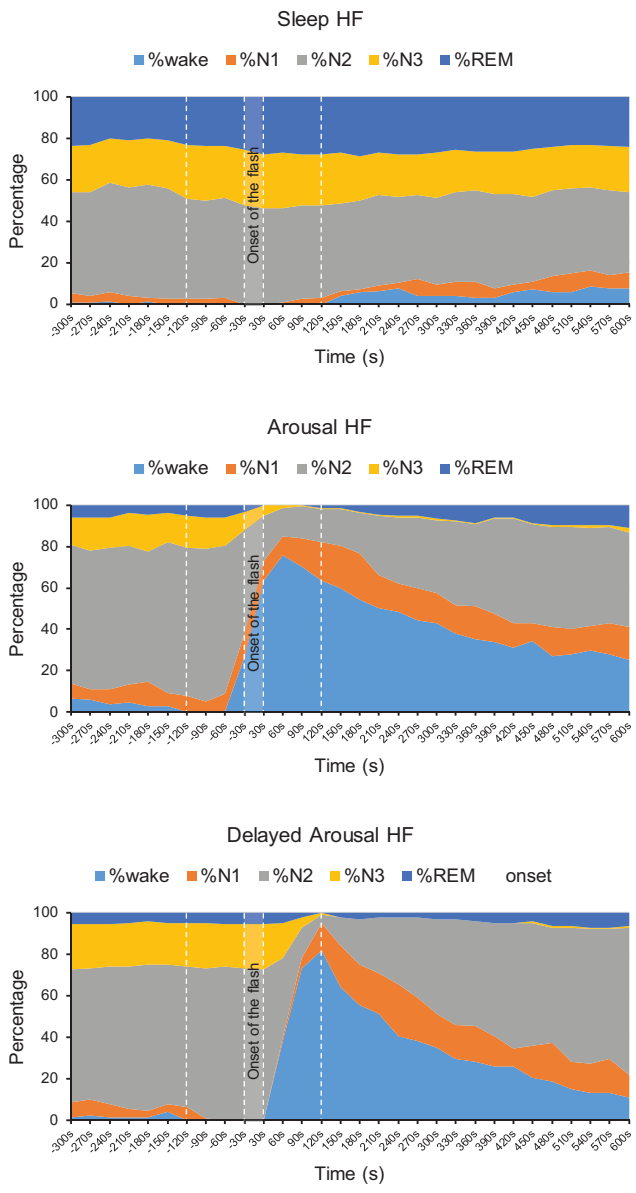

Figure 2. Stacked area graphs illustrating sleep stage composition in each 30-second bin (percentage of total) as a function of time across HF-onset for HF categories (Sleep HF, Arousal HF, Delayed Arousal HF). Outer white dotted lines highlight HF characterization windows of pre-HF-onset, HF-onset, and post-HF-onset).

The magnitude of the HR increase during HF-onset was greater for Arousal HF than for Sleep HF ($\chi^2 = 158.7$, $p < 0.001$) and Delayed Arousal HF ($\chi^2 = 130.0$, $p < 0.001$). The magnitude of the HR increase after HF-onset was greater for Delayed Arousal HF compared to Sleep HF ($\chi^2 = 99.7$, $p < 0.001$; Figure 3). Finally, HR remained significantly higher in the early recovery period compared to baseline ($p < 0.001$) for all HF types (Arousal HF $\chi^2 = 42.7$; Delayed Arousal HF $\chi^2 = 49.1$; Sleep HF $\chi^2 = 41.8$). HR continued to be higher in the late recovery period relative to baseline for Sleep HF ($\chi^2 = 11.4$, $p < 0.01$) and Arousal HF ($\chi^2 = 9.6$, $p < 0.01$) but not for Delayed Arousal HF.

SBP and DBP Across HFs.

There was no significant difference in baseline levels of SBP or DBP between HF categories. As shown in Figure 4 and Table 2, for Arousal HF, SBP was higher relative to baseline post-HF-onset ($p = 0.03$), with the maximum increase occurring 90 seconds after HF-onset (+6.7 mmHg, on average). As shown in Table 2, for Delayed Arousal HF, SBP was significantly lower during HF-onset relative to baseline (–8.3 mmHg, on average) before it began to rise again, being significantly higher than baseline 90 seconds post-HF-onset ($p = 0.047$, +3.9 mmHg, on average). For Sleep HF, SBP was lower during HF-onset ($p < 0.01$, –5.4 mmHg, on average) relative to baseline.

Changes in DBP were similar to those in SBP across HFs (Figure 5 and Table 2). For Arousal HF, DBP was higher relative to baseline during HF-onset ($p = 0.03$), with the maximum increase 90 seconds after HF-onset (+5.4 mmHg, on average). For Delayed Arousal HF, DBP was lower during HF-onset relative to baseline ($p = 0.02$) and then began to rise after HF-onset, being higher than baseline 60 seconds after HF-onset ($p < 0.01$). DBP did not change across the HF relative to baseline for Sleep HF.

Between HF analyses showed that the magnitude of the increase in SBP after HF-onset was greater for Arousal HF ($\chi^2 = 11.3$, $p < 0.001$) and Delayed Arousal HF ($\chi^2 = 6.1$, $p = 0.01$) across the post-HF-onset period, relative to Sleep HF. Similarly, the increase in DBP after HF-onset was greater for Arousal HF ($\chi^2 = 7.6$, $p < 0.01$) and tended to be greater for Delayed Arousal HF ($\chi^2 = 3.1$, $p = 0.08$), relative to Sleep HF.

There were no significant differences between baseline and recovery periods for SBP for any of the HF categories. For DBP, in early recovery, levels remained higher than baseline for Arousal HF ($\chi^2 = 3.9$, $p = 0.047$) but returned to baseline levels in late recovery. For Delayed Arousal HF and Sleep HF, DBP no longer differed from baseline during recovery periods.

PEP across HFs.

As shown in Figure 6 and Table 2, for Arousal HF, PEP significantly shortened (increase in sympathetic activity) during HF-onset relative to baseline ($p < 0.001$), and continued to be shorter 30–90 seconds post-HF-onset ($p < 0.001$). For Delayed Arousal HF, PEP was significantly shorter 30–90 seconds post-HF-onset relative to baseline ($p < 0.001$). Finally, for Sleep HF, PEP was significantly shorter during HF-onset ($p = 0.02$) and 30 seconds post-HF-onset ($p = 0.03$) relative to baseline. There was no difference in the magnitude of PEP shortening (increase in sympathetic activity) across HF categories. Finally, PEP levels in early recovery were still lower than baseline for both Arousal HF ($\chi^2 = 6.9$, $p < 0.01$) and Delayed Arousal HF ($\chi^2 = 7.1$, $p < 0.01$) but returned to baseline levels during the late recovery period. For Sleep HF, PEP during recovery had returned to baseline levels.

Factors predicting HF-associated arousal

Sleep stage composition in the pre-HF period differed between HF categories: The pre-HF period for Sleep HFs was less likely to contain N2 sleep (48% vs 70%) and more likely to contain REM sleep (24% vs 6%) than Arousal and Delayed Arousal HFs ($p < 0.01$, Figure 2). The pre-HF-onset period for Sleep HF was also less likely than Arousal HF to contain N1 sleep (3% vs 7%, $p = 0.036$) and more likely to contain N3 sleep (26% vs 15%, $p = 0.018$). Sleep stage composition in the pre-HF-onset period did not differ between Arousal and Delayed Arousal HFs. The

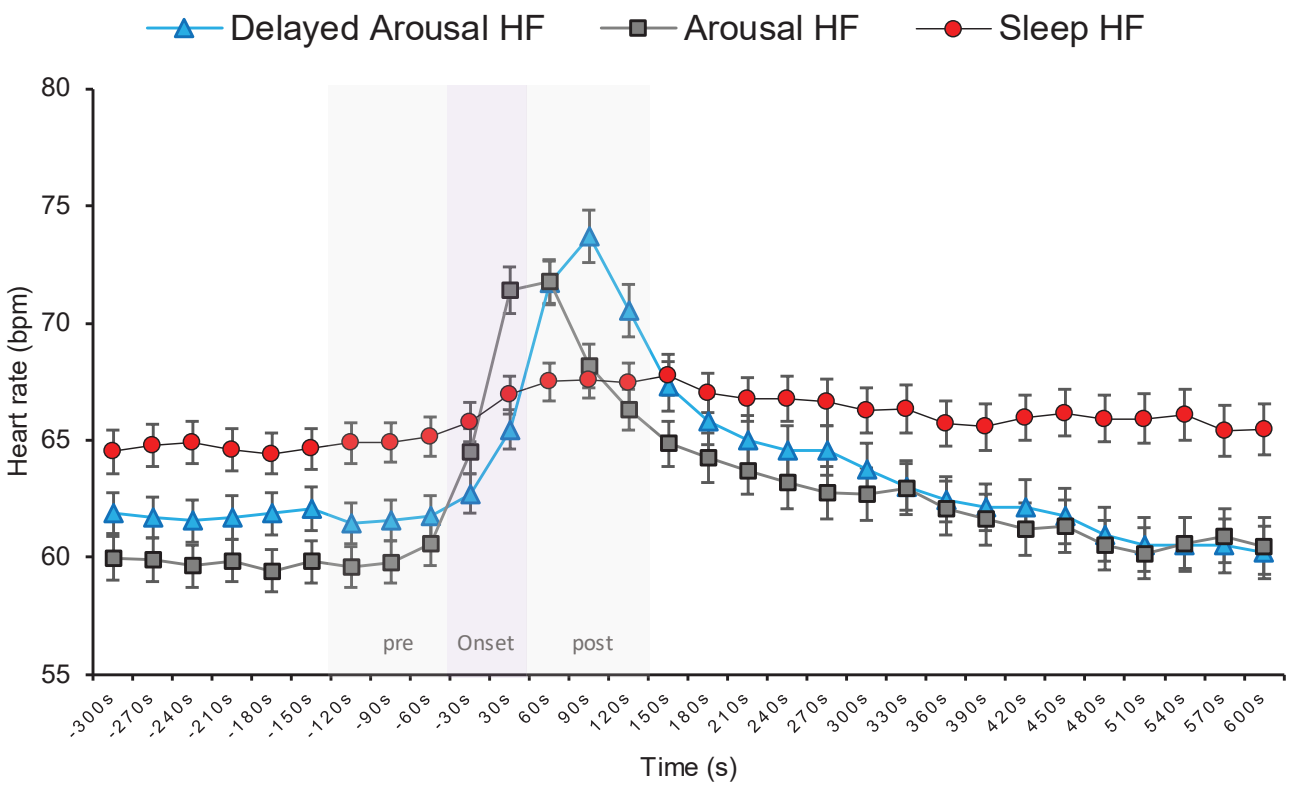

Figure 3. Heart rate (unadjusted mean ± standard error [SEM]) across HFs according to category (Arousal Hot Flash, Delayed Arousal Hot Flash, Sleep Hot Flash). Analysis adjusted for between-women and between-night variability showed no significant differences between categories in baseline HR.

Table 2. Results of statistical comparisons of changes in heart rate, systolic and diastolic blood pressure, and pre-ejection period across pre-HF-onset, HF-onset, and post-HF-onset, relative to baseline for three different categories of HFs recorded during overnight sleep (Arousal HF, Delayed Arousal HF, Sleep HF)

HF category	Heart rate			Systolic blood pressure			Diastolic blood pressure			Pre-ejection period[a]		
Relative to baseline	Pre-HF- onset	HF-onset	Post-HF-onset	Pre-HF-onset	HF-onset	Post- HF-onset	Pre-HF-onset	HF-onset	Post- HF-onset	Pre-HF-onset	HF-onset	Post-HF-onset
Arousal HF	↑ (χ^2 = 14.1, p < 0.001)	↑ (χ^2 = 120, p < 0.001)	↑ (χ^2 = 128, p < 0.001)	ns	ns	↑ (χ^2 = 4.5, p = 0.03)	ns	↑ (χ^2 = 4.5, p = 0.03)	↑ (χ^2 = 19.6, p < 0.001)	ns	↓ (χ^2 = 16.4, p < 0.001)	↓ (χ^2 = 18.7 p < 0.001)
Delayed Arousal HF	ns	↑ (χ^2 = 26.3 p < 0.001)	↑ (χ^2 = 251, p < 0.001)	ns	↓ (χ^2 = 5.5, p = 0.02)	↑ (χ^2 = 3.9, p = 0.047)	ns	↓ (χ^2 = 5.6, p = 0.02)	↑ (χ^2 = 7.9, p < 0.01)	ns	↓ (trend) p = 0.07	↓ (χ^2 = 11.7, p < 0.001)
Sleep HF	↑ (χ^2 = 6.6, p = 0.01)	↑ (χ^2 = 8.9, p < 0.01)	↑ (χ^2 = 24, p < 0.001)	ns	↓ (χ^2 = 7.6, p < 0.01	↓ (χ^2 = 4.8, p = 0.03)	ns	ns	ns	ns	↓ (χ^2 = 5.7, p = 0.02)	↓ (χ^2 = 4.9, p = 0.03)

ns, not significant.
[a]Decreased PEP reflects increased sympathetic activity.

distribution of HF categories across hours of the night is shown in Supplementary Figure 1.

Of the factors, we considered as potential predictors of HF-associated sleep disturbance (Arousal and Delayed Arousal HF events, combined) age (χ^2 = 3.9, p = 0.047) and BMI (χ^2 = 4.53, p = 0.03) were significant: older age and higher BMI were associated with a greater likelihood of having HF-associated sleep disturbance. Follow-up analysis with age and BMI in the same model showed that each had an independent effect and that there was no age × BMI interaction effect for predicting HF-associated sleep disturbance.

Discussion

We show here that HFs accompanied by arousal from sleep are associated with tachycardia and an increase in BP that persists for several minutes. This HF phenotype is the most disruptive and predominant type of HF occurring at night. In contrast, when HFs occur in undisturbed sleep, HR increases to a lesser extent, and BP drops at HF-onset, likely reflecting decreased total peripheral resistance, a component of the heat dissipation response. Together, these findings show that HF-associated sleep disturbance is linked with substantial CV activation over and above the effect of the HF itself.

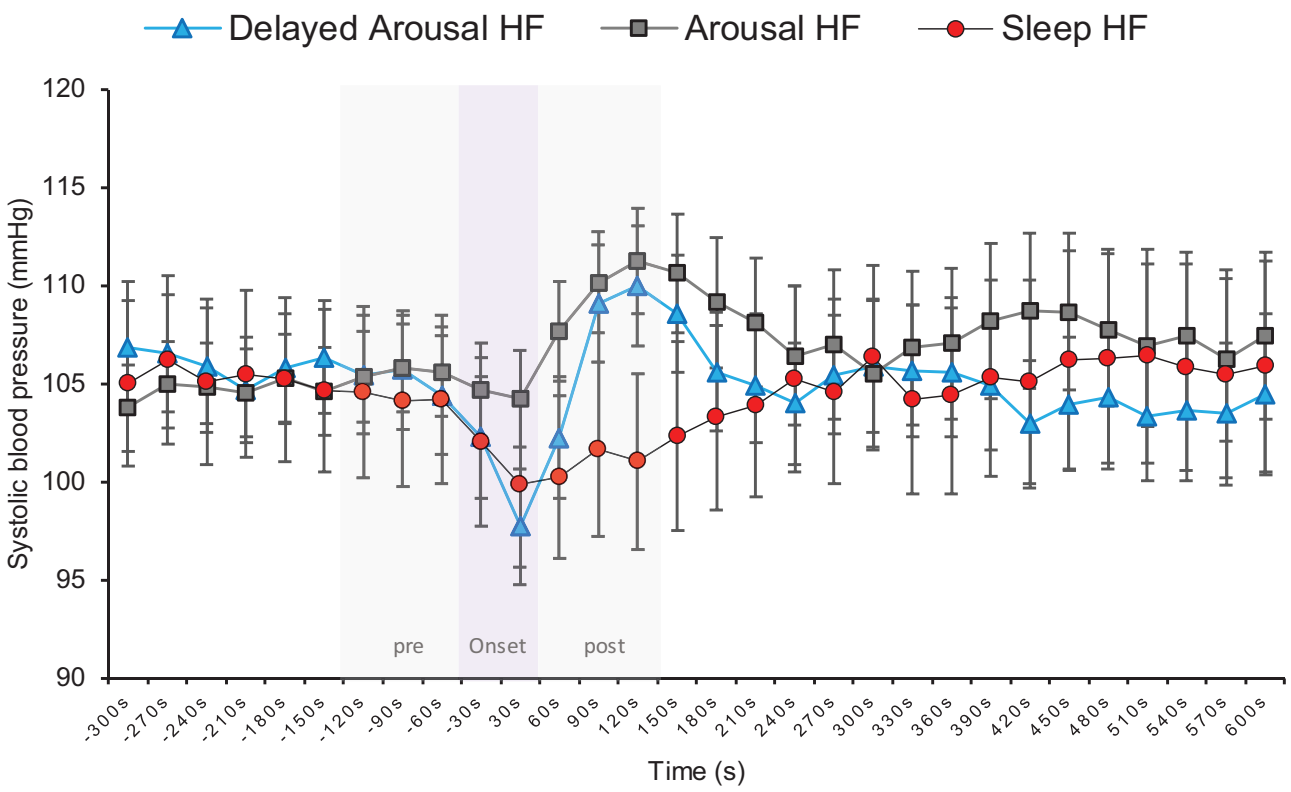

Figure 4. Systolic blood pressure (unadjusted mean ± standard error [SEM]) across hot flashes according to category (Arousal Hot Flash, Delayed Arousal Hot Flash, Sleep Hot Flash).

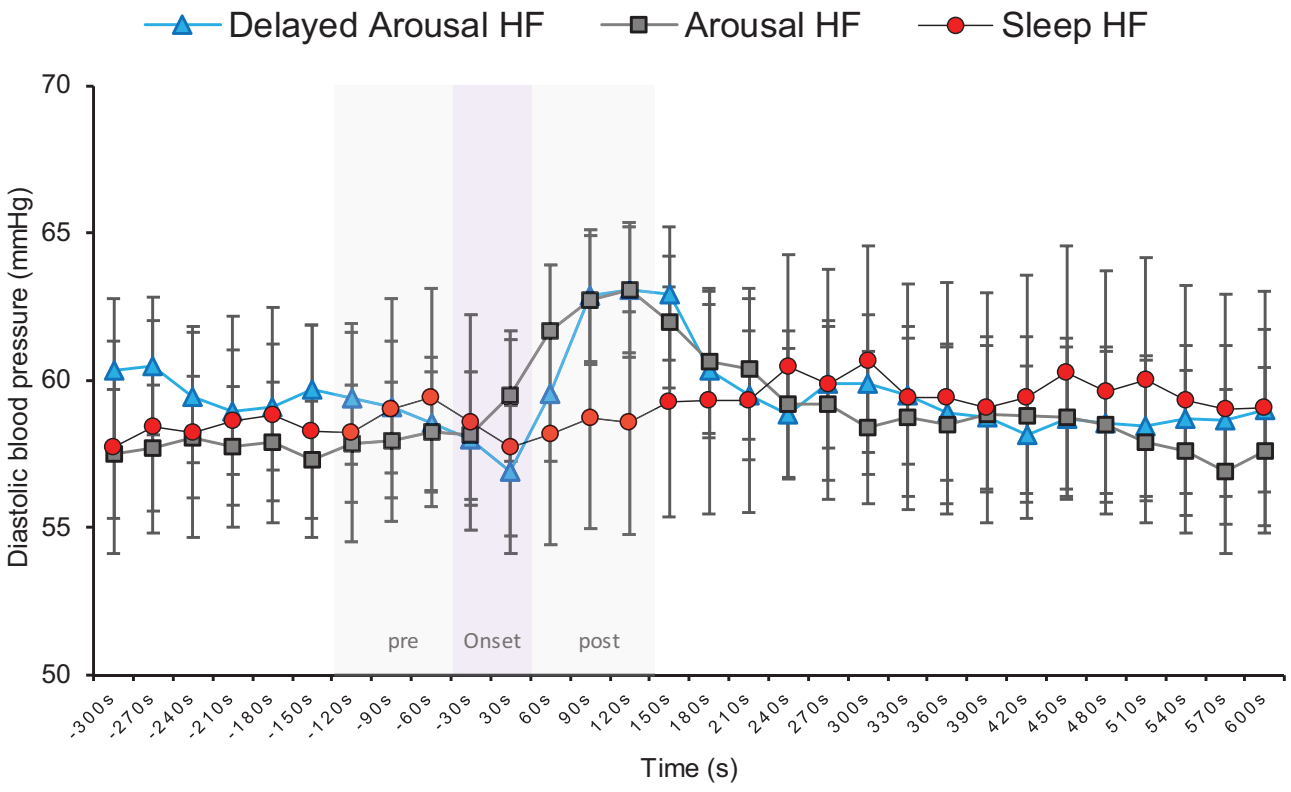

Figure 5. Diastolic blood pressure (unadjusted mean ± standard error [SEM]) across hot flashes according to category (Arousal Hot Flash, Delayed Arousal Hot Flash, Sleep Hot Flash).

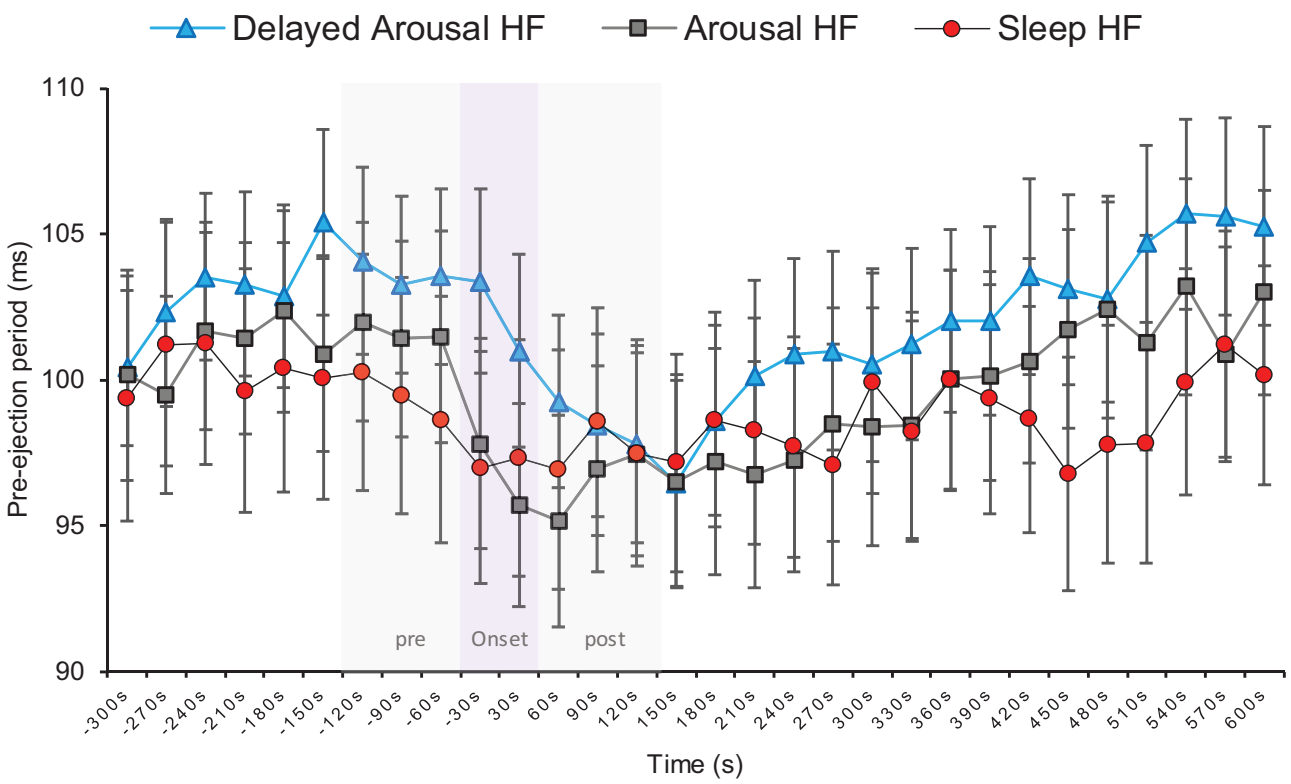

Figure 6. Pre-ejection period (unadjusted mean ± standard error [SEM], an index inversely related to cardiac sympathetic nervous system activity; lower values = greater sympathetic activity) across hot flashes according to category (Arousal Hot Flash, Delayed Arousal Hot Flash, Sleep Hot Flash).

Our finding of a pronounced increase in HR and BP in association with HF-associated arousal from sleep compliments the large body of literature showing CV activation at spontaneous arousals as well as auditory- and respiratory-evoked arousals [13]. For example, Trinder and colleagues [54] report an increase in HR averaged over 20 beats of 4.1 beats per minute, accompanied by an increase in SBP averaged over 20 beats of 6.4 mmHg following an arousal to a nonthreatening auditory stimulus in young participants. An arousal from sleep evokes an increase in peripheral and cardiac sympathetic activity, which increases vasoconstriction and HR, and leads to a surge in BP [55–57]. Similarly, we found a combination of increased BP, likely reflecting peripheral vasoconstriction, and reduced PEP, despite increased BP, suggesting both peripheral and central sympathetic activation across HF-arousal events. Arousals from sleep are a normal component of the night, but if frequent, they can dampen the reduction in CV activity that typically occurs during sleep [13]. Carrington and Trinder found that experimental arousals triggered by auditory tones (~every 1–2 minutes) across the first 90 minutes blunted the nocturnal BP dip [14]. Further, work in patients with obstructive sleep apnea has shown that a higher arousal index, beyond respiratory-related disturbances, is associated with higher diurnal and 24-hour SBP [58] and higher peripheral sympathetic activity during wakefulness in addition to increased sympathetic activity during sleep [57, 59].

HFs, and thus HF-associated awakenings, occur at a much lower frequency than do spontaneous brief arousals in healthy individuals; women had between 1–13 HFs per night in our study. However, arousal duration is an important factor to consider over and above frequency. The CV activation response at an arousal appears to have two components, the first comprising a transient "reflex" surge in BP and HR, peaking within 3–6 seconds of the stimulus, and with values returning to baseline within 10 seconds [13]. The second component depends on arousal duration; CV measures remain elevated as wakefulness persists, only returning to baseline when sleep returns [13, 54]. We found that most HF-arousal events were associated with awakenings (>15 seconds duration) rather than brief arousals and even when HF-onset was accompanied by a brief arousal, it was usually followed by a full awakening. Awakening with a HF can last from several minutes to more than an hour post HF, with HFs being responsible for, on average, almost a third of total wake time (ranging from 0% to more than 70% of total wakefulness) [23]. As such, a wake-associated increase in HR and BP following a HF could be sustained for several minutes to more than an hour post-HF. The return to sleep could depend on several factors such as discomfort due to sweating, cognitive arousal, and amount of homeostatic sleep pressure, with potentially varying effects between women on nocturnal CV recovery. Similar to our findings, others [32] reported a marked rise in BP within 15 minutes of severe nocturnal self-reported HFs, which our current data suggest were likely related to HF-associated awakenings.

Here, we focused on CV changes around individual nocturnal HFs, and it remains an open question whether having multiple HF-wake events across the night over several years impacts the CV system. We previously found that the nocturnal BP profile was altered in women in the menopausal transition with insomnia disorder, who were more likely to have physiological nocturnal HFs than controls [60]. However, having HFs (yes/no)

was not a significant factor in any models, although sample size was small and it is becoming increasingly apparent that HF characteristics beyond frequency are important, including amount of HF-associated wakefulness, age when HFs emerge, and HF trajectory patterns across the menopausal transition [9, 17, 23].

As we showed previously [23], a minority of HFs occurred without any awakenings. These HFs allowed us to examine CV changes associated with HFs independent of superimposed arousal effects. HR was higher 30 seconds before the rise in SC and remained higher than baseline for the duration of the HF, which supports our previous findings of higher HR during nocturnal HFs [31, 49], and that of others for HFs recorded when women are awake [4, 7, 30, 61]. Increased HR during HF-onset was accompanied by a shorter PEP, which returned to baseline levels soon after HF-onset. We showed previously that there is also a decline in cardiac vagal activity during Sleep HFs [31]. Taken together, these findings suggest that increased HR during a HF may be mediated by a combination of cardiac vagal withdrawal and sympathetic activation. We also found a decline in SBP and DBP across HF-onset, which likely reflects a decrease in total peripheral resistance due to the substantial increase in blood flow, particularly to the cutaneous vessels to dissipate heat, and which is apparent even in advance of a rise in SC [4, 6]. This increase in skin blood flow is neurally mediated via sympathetic cholinergic nerves that are responsible for active vasodilation [6]. Similar to our findings of a drop in SBP and DBP during HFs in asleep women, Low and colleagues [6, 7] found a decline in MAP, of about 9 mmHg during HFs in awake women, although not all women showed this response. As speculated by those authors [7], the drop in BP probably triggers a baroreflex response to increase HR (beyond the initial HR increase when an HF is triggered) such that HR continues to be higher during recovery periods, but BP returns to baseline. The CV response to a HF in undisturbed sleep, therefore, represents a normal thermoregulatory response and appears to be similar to responses to HFs while awake.

In our study, we distinguished a sub-category of HF-disturbed sleep events: HFs in which waking lagged HF-onset. Examination of CV measures around these HFs shows components of the other two HF categories: an initial change associated with HF-onset (increase in HR and drop in BP, reflecting a heat dissipation response), and the subsequent changes associated with an awakening (substantial increase in HR and BP). It is unknown why an arousal/awakening coincides with HF-onset (defined as a sudden rise in SC) for some HFs, but is delayed or even absent in others. Possibly, the graded waking response across HFs reflects differences in intensity of the HF trigger, with Arousal HFs having the most intense trigger. Arousal threshold to various sensory stimuli is influenced by the intensity of sensory stimulation, with the percentage of experimentally induced arousals increasing with stimulus intensity [62]. Further work is needed to determine what combination of physiological measures could best be used to measure intensity/severity of an HF.

While the mechanism of an HF it not completely understood, evidence from a series of studies by Freedman and colleagues strongly supports involvement of the central sympathetic nervous system in the initiation of HFs [5]. Clonidine, an α_2-adrenergic agonist, reduces central noradrenergic activation and increases the sweating threshold, thus reducing HFs [63]. On the other hand, Yohimbine treatment, which increases brain norepinephrine, increases the number of HFs [63]. With sufficient increase in central sympathetic activation, an arousal could ensue coincident with HF-onset. For HFs with a delayed awakening, the initial stimulus may not be great enough to initiate an arousal. However, the cascade of changes that characterize a HF (sweating, change in skin blood flow and temperature, drop in BP) may trigger an awakening.

Other factors that determine likelihood of an arousal from sleep include sleep stage and sleep depth, stimulus modality, and individual characteristics (like age) [62, 64]. Sleep HFs were more likely to arise in N3 sleep. N3 (slow-wave sleep) is associated with a higher arousal threshold, at least to auditory stimuli [62, 65]. Possibly, HF-related arousal is also less likely in N3 sleep. Sleep HFs were also more likely to arise in REM sleep, which could be due to lower awakening responsiveness in REM sleep [62, 66] and/or the unique thermoregulatory nature of the HF stimulus: HFs are less likely in REM than NREM sleep [22, 23], possibly due to the lower sensitivity of the thermoregulatory system, and associated decrease in sweating responses, during REM sleep [67]. Any HFs that do occur in REM sleep, therefore, may be less intense (i.e. less likely to be associated with EEG arousal) than those in other sleep stages. We found that older age was associated with greater likelihood of having HF-associated sleep disturbance. Sleep is more vulnerable to disruption in older adults, with auditory awakening thresholds declining across adulthood [64]. Similarly, sleep might be more vulnerable to HF-related arousal in older women. Alternatively, greater exposure to HFs over time as a woman moves across the menopausal transition may lead to greater sensitization to HF-associated arousal; or HFs may be more severe in older women. We cannot differentiate these factors in our dataset. Menopausal status did not predict having HF-wake events; however, our sample mainly consisted of women in the menopausal transition. A higher BMI was also associated with a greater likelihood of having HF-associated sleep disturbance, however, since we had a cutoff for BMI of 32 Kg m^{-2}, further research is needed to determine the nature of this relationship, including whether body weight or specific aspects of body composition (e.g. percentage body fat) may account for these findings.

There is a growing body of research investigating whether HFs are associated with CV disease risk, with most studies relying on self-reports of HF frequency, severity, and bother, and some distinguishing relationships between diurnal HFs versus night sweats (reviewed in [8, 68, 69]). Findings for HF-BP relationships are mixed, with some showing relationships between HFs and higher BP [70, 71] and others showing no relationship between HFs and BP [32, 72]. Recent work by Thurston and colleagues has investigated the association between self-reported and/or physiological HFs (day and night) and preclinical CV risk markers [8]. Higher HF frequency, particularly during the day, was associated with greater carotid intima-media thickness and plaque [9]. Further work is still needed to determine whether HFs themselves provoke unfavorable changes in the vasculature, either directly or indirectly, or whether an underlying vulnerability, such as in estrogen-sympathetic nervous system dynamics, underlies both HFs and an unfavorable CV status. In this context, our data show that nocturnal HFs, whether or not linked with an arousal, are associated with increased cardiac sympathetic activation, although activation appears to be more sustained when an awakening coincides with an HF. When associated with an arousal/awakening, there

is also an increase in BP, which could have an additional detrimental impact in women with frequent HFs persisting over several years. HF-associated awake time is a critical contributor to total wakefulness across the night [23] such that just a few HF events could have a sustained disruptive effect on sleep, and consequently CV activity.

Our results should be considered in context of the study limitations. We used a convenience sample of women recruited from the community, mostly in the menopausal transition, who had at least one physiological HF during the nocturnal recording. We did not include any women seeking treatment for their symptoms. Another limitation is that we used an indirect (although validated [33, 48]) measure of cardiac sympathetic nervous system activity, derived from ICG. While reliability of absolute measures of PEP with ICG, and BP with Portapres have been questioned, they are valid at detecting changes across an event [55], such as HFs, and have the advantage of not disturbing sleep. Also, PEP and BP measures are sensitive to motion artifact; we, therefore, applied algorithms to identify and remove sections of compromised data and also manually checked the data to ensure the signals were reliable. We also used a validated algorithm to identify the time of the opening of the aortic valve [47]. We carefully categorized HFs to explore CV physiology around HF-onset depending on their association with arousals/awakenings. However, this approach meant we excluded ~20% of HFs that were ambiguous due to wake or mixed wake/sleep composition in the approach to the HF, and consequently with unstable baseline CV measures. Our conclusions, therefore, may not extend to all nocturnal HFs. Further work may examine HFs more continuously or categorize HFs in different ways, and investigate other individual or group differences within HF categories. Future analyses also could investigate further the CV responses to HFs, considering aspects of the SC signal not included here, such as HF end-points (to enable determination of HF duration), peak amplitude, and rate of change in SC. These measures could indicate physiological severity of the HF, although magnitude of the rise in SC does not necessarily correspond to subjective HF intensity or distress [53], and it is possible that a combination of physiological measures may better reflect HF severity.

Future work is also needed to investigate the additive effect of multiple HFs across the night, taking into account their association with wakefulness. Ultimately, interventions that manipulate occurrence of HFs may unveil the impact of HFs on nocturnal CV restoration, extending our results here focused on transient CV activation in association with single HF events. Also, beat-to-beat analysis of HR and BP in association with more refined EEG and SC signal analyses is necessary to determine the temporal dynamics and interactions between physiological signals across a HF. A better characterization of HFs may further advance understanding of their physiological mechanisms, severity, and impact and may ultimately lead to the determination of distinct CV risk profiles in women with HFs.

In conclusion, we have shown the different patterns of CV changes across nocturnal HFs, depending on their association with or without arousal from sleep. When HFs are associated with sleep disturbance, BP shows a sustained increase, which could potentially dampen nocturnal CV recovery in women with multiple HF-wake events, ultimately increasing risk for CV disease.

Supplementary material

Supplementary material is available at *SLEEP* online.

Supplementary Figure 1. Stacked area graph representing the proportions of hot flash categories (Arousal Hot Flash, Delayed Arousal Hot Flash, Sleep Hot Flash, Ambiguous Hot Flash) within each hour of the night. The proportion of Sleep HFs was higher in hour-2 compared to hour-7 (χ^2= 4.5, p=0.03). The proportion of Arousal HFs was lower in hour-2 than hour-5 (χ^2 = 4.5, p=0.03).

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