Postmenopausal Physiological Changes

Robert R. Freedman

Abstract The hallmark of menopause is the marked reduction of estradiol levels due to ovarian failure. This, among other factors result in hot flashes, the most common menopausal symptom. Hot flashes (HFs) can be measured objectively, both inside and outside the laboratory, using sternal skin conductance, an electrical measure of sweating. We have found that HFs are triggered by small elevations in core body temperature (T_C), acting within a greatly reduced thermoneutral zone. This reduction is caused by elevated central sympathetic activation, among other factors. There is a circadian rhythm of HFs peaking at 1825 h. Imaging studies have shown that hot flash activation begins in the brainstem, followed by the insula and by the prefrontal cortex. HFs in the first, but not the second half of the night can produce awakenings and arousals. This is because rapid eye movement (REM) sleep suppresses thermoregulatory effector responses, which include hot flashes.

Keywords Hot flash · Menopause · Sleep · Thermoregulation

Contents

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1 Introduction

Menopause, defined as the final menstrual period, represents the permanent cessation of menses due to loss of ovarian follicular function, generally caused by aging. In practice, 1 year after the final menstrual period is usually employed to mark the onset of menopause. In Western societies, menopause occurs at an average of 51.4 ± 5 years, ranging from approximately 40–60 years (North American Menopause Society 2007).

Physiologically, the hallmark of menopause is the marked reduction of estradiol levels to 10 % or less of those found during reproductive years (North American Menopause Society 2007). Additionally, levels of FSH (follicular stimulating hormone) and LH (luteinizing hormone) increase following menopause. The most common symptom of menopause is the hot flash (HF) which forms the basis of the present chapter.

Hot flashes (HFs) are reported as feelings of intense warmth along with sweating, flushing, and chills. Sweating is generally reported in the face, neck, and chest. HFs usually last for 1–5 min, with some lasting as long as an hour (Kronenberg 1990). The median duration of symptoms is about 4 years, with some lasting as long as 20 years (Feldman et al. 1985). In one U.S. study, 87 % of the women reported daily HFs and about a third of those reported more than 10 per day (Kronenberg 1990). There is some racial and ethnic variation of HFs with Caucasian women reporting the highest prevalence and Japanese and Chinese women reporting the lowest (Gold et al. 2006).

2 Physiologic Events of the Hot Flash

Peripheral vasodilation, demonstrated by elevated skin temperature and blood flow, occurs during HFs in all areas that have been studied (Fig. 1). Skin temperature increases in the digits, face, arms, chest, abdomen, back, and legs (Freedman 1998; Molnar 1975; Kronenberg et al. 1984; Tataryn et al. 1980; Ginsburg et al. 1981) and blood flow in these areas is elevated, as well (Kronenberg et al. 1984; Tataryn et al. 1980; Ginsburg et al. 1981).

Sweating and skin conductance, an electrical measure of this, also increases during HFs (Fig. 1). Molnar (1975) determined the whole body sweat rate to be about 1.3 g/min in one subject. We measured sweating and skin conductance from the sternum at the same time in 14 women (Freedman 1998). We found a close temporal correspondence between both measures, which were significantly elevated. Measurable sweating occurred in 90 % of the HFs.

Core body temperature (T_C) also increases prior to HFs. We measured T_C and sternal skin conductance during 77 HFs in 10 menopausal women who reported frequent symptoms (Freedman et al. 1995). We found small but significant T_C elevations before the majority of HFs and replicated these findings in two subsequent studies (Freedman 1998; Freedman and Woodward 1996).

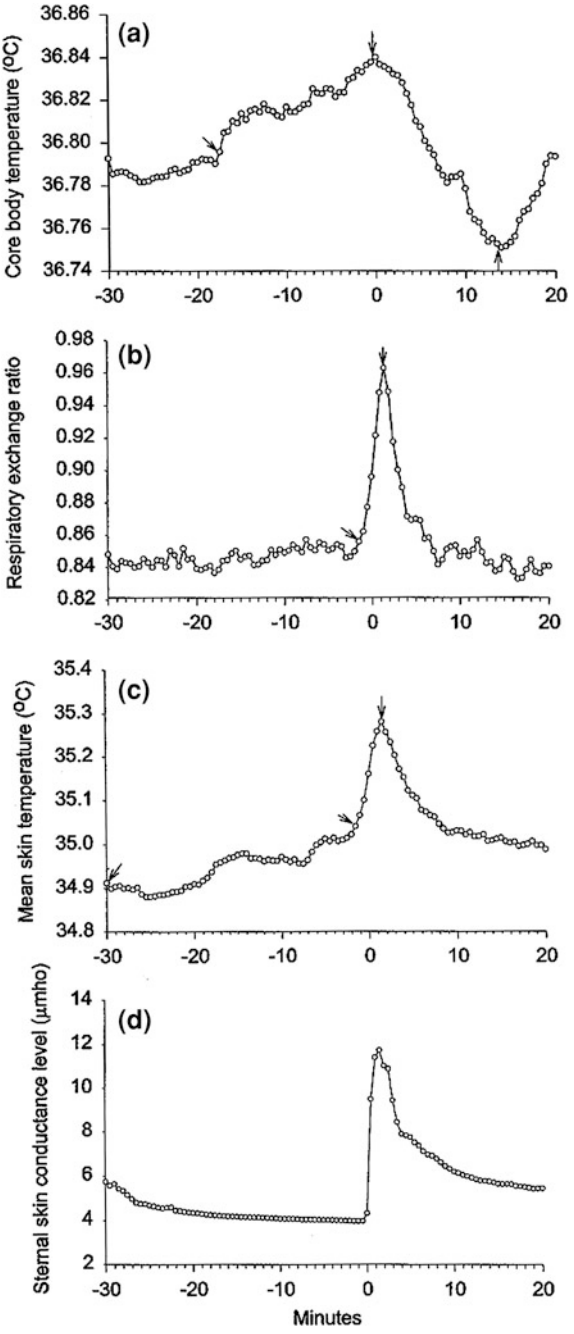

Fig. 1 **a** Core body temperature (means) during menopausal hot flashes. **b** Respiratory exchange ratio (means) during hot flashes. **c** Mean skin temperature (means) during hot flashes. **d** Sternal skin conductance (means) during hot flashes. Time 0 is the beginning of the sternal skin conductance response. Intervals between arrows are significantly different from each other at $P < 0.05$, Duncan's test

The T_C elevations could be caused by increased metabolic rate (heat production) and/or peripheral vasoconstriction (decreased heat loss). We did find significant increases in metabolic rate (Fig. 1), but they occurred at the same time as the peripheral vasodilation and sweating; peripheral vasoconstriction did not occur (Freedman 1998). Therefore, the T_C elevations are not caused by metabolic rate elevations. Small increases in heart rate, about 7–15 beats/min do occur along with the metabolic rate increases (Molnar 1975; Kronenberg et al. 1984) and palpitations are sometimes reported.

3 Objective Measurement of Hot Flashes

Typically, diaries are used to assess treatment outcome in HF studies. However, there are several problems with these measures. Errors in compliance are major sources of bias (Takarangi et al. 2006). Also, HFs occurring during sleep are not accurately reported because recall of these events is usually poor and many HFs do not produce awakenings (Freedman 2010). Finally, placebo effects as large as 40–50 %, occur with self-reports (Stone et al. 2003). Therefore, objective measures of HFs have been developed.

Increased skin conductance recorded from the sternum is presently the best objective marker of HFs. An increase in this measure $\geq$ 2 μmho (electrical unit of conductance) within 30 s corresponded with 95 (Freedman 1989), 90 (Freedman et al. 1992), and 80 % of reported HFs (de Bakker and Everaerd 1996). These results have been independently replicated (de Bakker and Everaerd 1996). Moreover, these results have been extended to men with HFs due to androgen therapy for prostate cancer (Hanisch et al. 2007).

The skin conductance measure is also useful because it can be recorded outside the laboratory in daily life. Using the same recording methods with ambulatory monitors, we found an agreement of 85 % between the skin conductance criterion and patient event marks (Freedman 1989). A second study found an agreement of 77 % (Freedman et al. 1992).

However, the major drawback of skin conductance recording is that it requires the use of electrodes and gel, which must be changed every 24 h. Therefore, the author has invented a miniature, hygrometric HF recorder which requires neither electrodes nor gel (Freedman and Wasson 2007). This device will record all HFs for 1 month using a single hearing aid battery. It attaches to the skin with a double-sided sticky collar. A simple computer scoring program has been developed which will score 1 week of 24 h data in <5 min.

In a recent study of patient satisfaction with the recorder, the author obtained positive responses from patients regarding the ease of use and appearance of the recorder (Freedman and Wasson 2007; Freedman 2009).

4 Endocrinology of Hot Flashes

Since HFs occur in the vast majority of women having natural or surgical menopause, estrogens are clearly involved in their etiology. This is consistent with the fact that estrogen therapy virtually eliminates HFs. However, estrogen reduction alone does not explain the occurrence of HFs because there are no relationships between these symptoms and plasma, urinary, or vaginal (Askel et al. 1976) levels of estrogens, nor are there differences in plasma levels between women with and without HFs (Freedman et al. 1995; Askel et al. 1976). Additionally, clonidine reduces HF frequency but does not change estrogen levels (Schindler et al. 1979), and prepubertal girls have low estrogen levels but no HFs. Therefore, estrogen withdrawal is necessary but not sufficient to explain the occurrence of HFs.

A temporal relationship was observed between HFs and LH pulses (Casper et al. 1979; Tataryn et al. 1979). However, further work demonstrated that women with isolated gonadotropin deficiency had HFs but no LH pulses (Gambone et al. 1984), and those with hypothalamic amenorrhea had LH pulses but no HFs. Also, HFs occurs in women with LH suppression from GnRH compounds (Casper and Yen 1981; DeFazio et al. 1983), in women with pituitary insufficiency and hypoestrogenism (Meldrum et al. 1981), and in hypophysectomized women, who have no LH pulses (Mulley et al. 1977).

Subsequently, an opiate system was hypothesized in the etiology of HFs. Jeffcoate (1981) showed that an opiate antagonist reduced HF and LH pulse frequencies, although other research failed to replicate these results (DeFazio et al. 1984). Thus, the evidence for opiate involvement in HFs is inconsistent.

Norepinephrine (NE) plays an important role in thermoregulation acting, in part, through α_2-adrenergic receptors. Injected into the preoptic hypothalamus, NE causes heat dissipation responses followed by a decline in T_C (Brück and Zeisberger 1990). Additionally, gonadal steroids modulate central NE activity (Insel and Motulsky 1987). Although plasma NE levels do not change during HFs (Kronenberg et al. 1984; Casper et al. 1979), these do not represent levels in the brain (Kopin et al. 1984).

We addressed these issues using pharmacologic probes. In a controlled, laboratory investigation (Freedman et al. 1990), we showed that yohimbine, a α_2-adrenergic antagonist that elevates brain NE (Goldberg and Robertson 1983), triggered HFs in symptomatic but not asymptomatic menopausal women, while clonidine, a α_2 agonist, ameliorated them. Postmortem studies have shown that most α_2 receptors in the human brain are inhibitory (Sastre and Garcia-Sevilla 1994). Blockade of these receptors with yohimbine would increase NE release, whereas clonidine would reduce it (Starke et al. 1989; Charney et al. 1982).

Furthermore, estrogens modulate brain adrenergic receptors (Etgen et al. 2001; Ansonoff and Etgen 2001). Taken together, these data formed the basis of our theory that elevated brain NE, in conjunction with estrogen withdrawal, are part of the etiology of HFs.

5 Thermoregulation and Hot Flashes

T_C in homeotherms is regulated between an upper threshold for sweating and a lower threshold for shivering. Between these thresholds is a neutral zone within which major thermoregulatory responses (sweating, shivering) do not occur (Savage and Brengelmann 1996). Small adjustments within the neutral zone are performed by changes in peripheral blood flow.

According to this theory, the heat dissipation responses of the hot flash (sweating, peripheral vasodilation) would be provoked if T_C crossed the upper threshold. We had already demonstrated T_C increases before most HFs (Freedman 1998; Freedman et al. 1995; Freedman and Woodward 1996). We therefore chose to study the width of the thermoneutral zone in women with and without HFs.

Previous research showed that warm, ambient temperatures and peripheral body heating could provoke HFs (Freedman 1989; Freedman et al. 1992) suggesting that the upper threshold is lowered in women with HFs. We then demonstrated that the lower threshold is elevated in these women by inducing shivering while measuring T_C (Freedman and Woodward 1995). We then measured the upper and lower thresholds using ambient heating and cooling in women with and without HFs. We measured the thermoneutral zone to be 0.0 °C in the symptomatic women and 0.4 °C in the asymptomatic women (Freedman and Krell 1999). We then replicated the T_C sweating threshold findings using exercise. When sweating thresholds were reached, all symptomatic but no asymptomatic women demonstrated objective and subjective HFs. Sweat rates in the former group were twice those of the later group.

Thus, we believe that HFs are triggered by T_C elevations acting within a greatly narrowed thermoneutral zone in postmenopausal women with HFs. A HF, consisting of sweating and peripheral vasodilation, is provoked when T_C reaches the upper threshold. T_C then declines, and when the lower threshold is crossed, shivering occurs. What biochemical mechanisms account for this?

Basic science investigations have found that increased brain NE narrows the width of the thermoneutral zone (Brück and Zeisberger 1990). Conversely, clonidine lowers NE release, raises the sweating threshold, and reduces the shivering threshold. We therefore hypothesize that increased brain NE narrows the thermoneutral zone in menopausal women with HFs.

We determined the T_C sweating threshold in women with and without HFs during I.V. clonidine and placebo (Freedman and Dinsay 2000). We showed that clonidine significantly elevated the sweating threshold compared to placebo in the women with HFs, whereas the opposite occurred in the women without HFs. We therefore believe that clonidine reduces HFs by raising the T_C sweating threshold.

We then conducted a similar study to examine the mechanism through which estrogen ameliorates HFs (Freedman and Blacker 2002). Symptomatic menopausal women were randomly assigned to receive 1 mg/day 17 β-estradiol P.O. or placebo for 90 days. We found that the T_C sweating threshold was significantly

elevated and HF frequency significantly ameliorated in the E_2 but not the placebo group. Thus, estrogen ameliorates HFs by raising the T_C sweating threshold, but we do not know the precise mechanisms of this.

6 Circadian Rhythm of Hot Flashes

Given this mechanism, we sought to determine if HF occurrence was related to the T_C circadian rhythm. Using 24 h ambulatory monitoring, we recorded sternal SCL to detect HFs, ambient temperature, skin temperature, and T_C (ingested radio telemetry pill) (Freedman et al. 1995). Cosinor analysis revealed an HF circadian rhythm with a peak at 1825 h (Fig. 2). The majority of HFs were preceded by T_C elevations ($P < 0.05$). HFs began at significantly higher T_C levels (36.82 ± 0.04 °C) compared with all nonflash periods (36.70 ± 0.005 °C). We then replicated these findings in symptomatic women with breast cancer using a whole-room calorimeter (Carpenter et al. 2004).

7 Imaging Studies

We were interested to determine the brain areas associated with the physiologic and phenomenological aspects of the HF and employed functional magnetic resonance imaging (fMRI) to do this. In the first study, we used symptomatic menopausal women and asymptomatic amenorrheic women and induced HFs and sweating (measured with sternal SCL) in the scanner (Freedman et al. 2006). Significant areas of activation in the symptomatic women included the insular and the anterior cingulate cortex. Sweating in the amenorrheic women was associated with activation in the anterior cingulate and superior frontal gyrus. We believe the insular activation is associated with the "rush of heat" described during menopausal HFs.

In a second investigation (Diwadkar et al. 2013), we sought to determine the temporal sequencing of the neuronal events underlying the HF. Methods were similar to those described above. We performed fMRI in a group of postmenopausal women to measure neuronal activity in the brainstem, insula, and prefrontal cortex around the onset of an HF (detected using synchronously acquired skin conductance responses). Rise in brainstem activity occurred before the detectable onset of an HF. Insula and prefrontal activity trailed activity in the brainstem, appearing following HF onset (Fig. 3). Pre-HF brainstem responses may reflect the functional origins of internal thermoregulatory events such as HFs. By comparison, insula, and prefrontal activity may be associated with the phenomenological correlates of HFs.

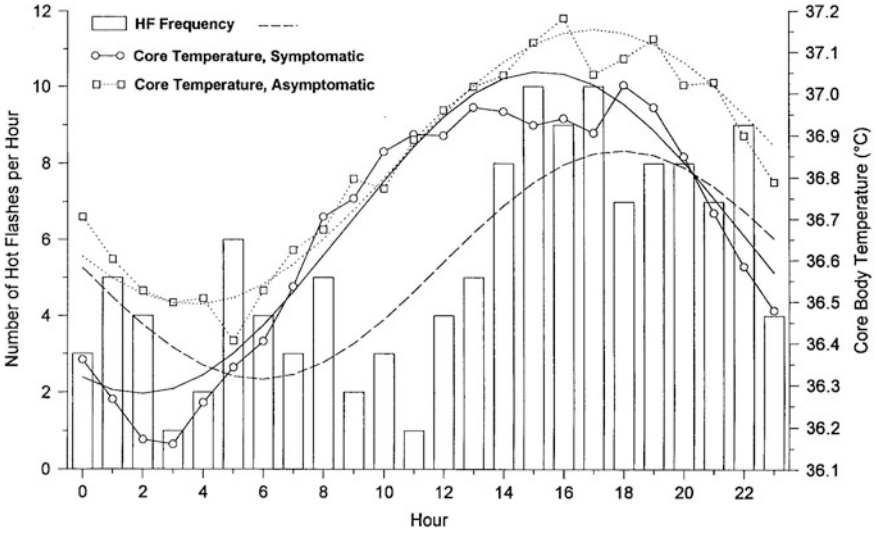

Fig. 2 Hot flash frequency and T_C during 24 h. Hot flash frequency in 10 symptomatic women (*bars*); best-fit cosine *curve* for hot flash frequency (*dashed line*); 24 h T_C data for 10 symptomatic women (O) with best-fit cosine *curve* (*solid line*); 24 h T_C data in 6 asymptomatic women (□) with best-fit cosine *curve* (*dotted line*)

8 Hot Flashes (HFs) and Sleep

Although most epidemiologic studies have found increased reports of sleep disturbance at menopause (Kravitz et al. 2003), this has not been found in most laboratory studies (Young et al. 2003). A study in our laboratory (Freedman and Roehrs 2004) found no differences among age-matched premenopausal women, postmenopausal symptomatic women, and postmenopausal asymptomatic women on any sleep measure, performance test, or questionnaire measure. Additionally, HFs did not appear to trigger awakenings or arousals based on analysis of whole-night data.

A subsequent study analyzed this last issue in greater depth by analyzing data by halves of the night (Freedman and Roehrs 2006). This was done because there is more rapid eye movement (REM) sleep in the second half of the night. It has been shown that REM sleep suppresses thermoregulatory effector responses, such as sweating and peripheral vasodilation, which constitute HFs. Indeed, it was found that HFs in the second half of the night occurred after the awakenings and arousals, whereas those in the first half of the night preceded them and could therefore trigger them.

This temporal relationship was replicated in a recent laboratory study of 102 women, 44–56 years of age, who complained of poor sleep (Freedman and Roehrs 2007). Fifty-three percent (53 %) of the women had apnea, restless legs, or both. The best predictors of objective sleep quality (laboratory sleep efficiency) were

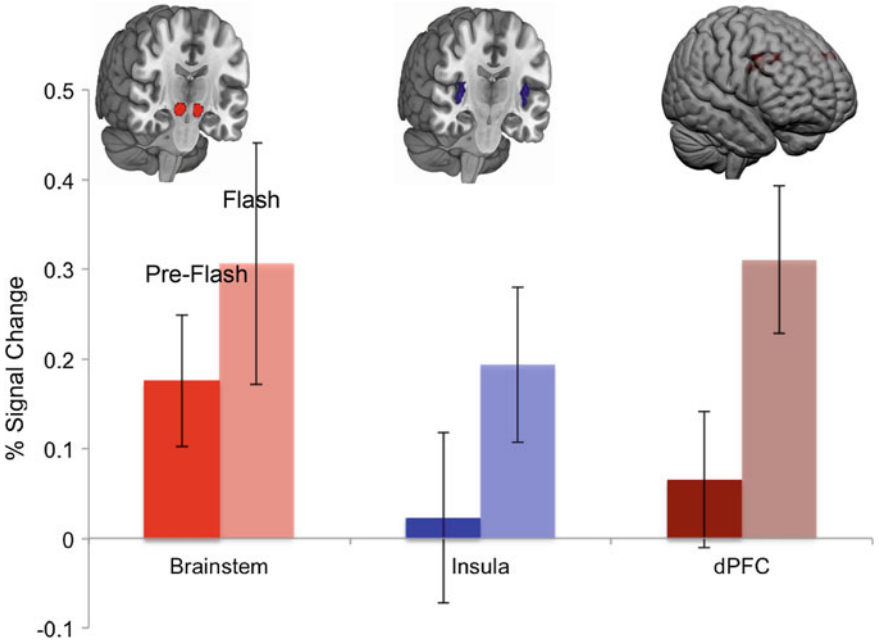

Fig. 3 Averaged activity in the pre-flash and flash windows across the three regions of interest. Images depict volume-rendered activations in the brainstem, the insula, and the dorsal prefrontal cortex successively. Data are shown collapsed across image within the pre-flash and flash windows for each subject. Relative to the pre-flash window, significantly increased activity in the flash window is seen in the insula and prefrontal cortex, but not in the brainstem. Error bars are ± SEM

apneas, periodic limb movements, and arousals ($R^2 = 0.44$, $P < 0.0001$). The best predictors of subjective sleep quality (Pittsburgh Sleep Quality Index global score) were the Hamilton anxiety score and the number of HFs in the first half of the night ($R^2 = 0.19$, $P < 0.001$). It is, therefore, possible that anxiety mediates some reports of poor sleep.

These results may explain the difference between our first laboratory study which did not analyze data by halves of the night (Young et al. 2003), and self-report studies of increased sleep disturbance at menopause (Kravitz et al. 2003). Our findings also emphasize the importance of detecting primary sleep disorders, such as apnea and periodic limb movements which are highly disruptive of sleep and can have serious medical consequences.

As described throughout this chapter, we have been interested in the role of sympathetic activation in HFs, many of which occur during sleep. It has been shown that measures of heart rate variability (HRV) in the frequency domain reflect the different components of sympathetic and parasympathetic activation. Components computed using the spectral analysis, power in HRV frequencies greater than 0.15 Hz reflects parasympathetic activation, whereas power in frequencies below 0.15 Hz reflects, in part, sympathetic activation. We performed these measurements

during laboratory sleep in 16 postmenopausal women demonstrating at least four HFs per night (Freedman et al. 2011). For the frequency bin of 0–0.15 Hz, we found that, during stage 1 sleep, power was greater during HFs compared with preceding and subsequent periods. For waking HFs, power in this band was higher before HFs than during or after them. These data are consistent with our theory of elevated sympathetic activation as a trigger for menopausal HFs.

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