Menopausal Hot Flashes and Carotid Intima Media Thickness Among Midlife Women

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Background and Purpose—There has been a longstanding interest in the role of menopause and its correlates in the development of cardiovascular disease (CVD) in women. Menopausal hot flashes are experienced by most midlife women; emerging data link hot flashes to CVD risk indicators. We tested whether hot flashes, measured via state-of-the-art physiologic methods, were associated with greater subclinical atherosclerosis as assessed by carotid ultrasound. We considered the role of CVD risk factors and estradiol concentrations in these associations.

Methods—A total of 295 nonsmoking women free of clinical CVD underwent ambulatory physiologic hot flash assessments; a blood draw; and carotid ultrasound measurement of intima media thickness and plaque. Associations between hot flashes and subclinical atherosclerosis were tested in regression models controlling for CVD risk factors and estradiol.

Results—More frequent physiologic hot flashes were associated with higher carotid intima media thickness (for each additional hot flash: β [SE]=0.004 [0.001]; P=0.0001; reported hot flash: β [SE]=0.008 [0.002]; P=0.002, multivariable) and plaque (eg, for each additional hot flash, odds ratio [95% confidence interval] plaque index ≥2=1.07 [1.003–1.14]; P=0.04, relative to no plaque, multivariable) among women reporting daily hot flashes; associations were not accounted for by CVD risk factors or by estradiol. Among women reporting hot flashes, hot flashes accounted for more variance in intima media thickness than most CVD risk factors.

Conclusions—Among women reporting daily hot flashes, frequent hot flashes may provide information about a woman’s vascular status beyond standard CVD risk factors and estradiol. Frequent hot flashes may mark a vulnerable vascular phenotype among midlife women.

Key Words: atherosclerosis ■ cardiovascular diseases ■ hot flashes ■ intima media thickness ■ menopause ■ vasomotor symptoms ■ women

Cardiovascular disease (CVD) is the leading cause of death among women.1 As women typically manifest with atherosclerotic CVD postmenopausally, on average 10 years after men, there has been a longstanding interest in the role of the menopause transition and its correlates in the development of atherosclerotic CVD in women.2 The focus of this work has largely been on the hormonal changes associated with menopause. Recent data have also considered how other menopause-related factors, including menopausal symptoms, relate to CVD risk in women.

Hot flashes are the classic menopausal symptom, reported by >70% of midlife women.3 For one third of women, hot flashes are frequent or severe.4 The impact of hot flashes on quality of life is well documented,5 and hot flashes are strong drivers of healthcare utilization.6 However, hot flashes are thought to have few implications for women’s physical health.

Newer data challenge that assumption. Post hoc analyses from large hormone therapy trials suggested that the CVD risk with hormone therapy use was highest among older women reporting moderate-severe hot flashes at baseline.7,8 Later observations from cohort studies suggest that greater hot flash reporting may be associated with a poorer CVD risk factor profile9,10 and higher subclinical atherosclerosis11–14 beyond standard risk factors. However, studies specifically designed to test relations among hot flashes and CVD risk are absent. The limitations in this literature, including retrospective hot flash measures vulnerable to multiple biases,15,16 exclusion of highly symptomatic women,8,17 the group most affected, and contradictory findings,17 have limited conclusions about the precise nature of hot flash–CVD risk associations.

In a sample of nonsmoking women without clinical CVD, we used state-of-the-art ambulatory physiologic and prospective ecological momentary reports of hot flashes to test
whether hot flashes (presence and frequency) were associated with subclinical atherosclerosis as assessed by carotid intima media thickness (IMT) and plaque. Carotid IMT and plaque are widely used and well-validated indicators of subclinical atherosclerosis predictive of later clinical CVD, including among relatively low-risk samples (eg, midlife women).18–20 They are preferable to other widely used subclinical atherosclerosis indices (eg, coronary artery calcification) that show a high rate of zero readings among midlife women.21 We tested the role of standard and novel CVD risk factors in these relations. Finally, as endogenous estradiol has been implicated in hot flashes and atherosclerosis in women,22 we considered estradiol concentrations in these relations.

Methods

Study Sample

The study sample comprised 304 late perimenopausal (2-12-month amenorrhea) and postmenopausal (≥12-month amenorrhea) non-smoking women aged 40 to 60. By design, half of the women reported daily hot flashes or night sweats, and half reported no hot flashes or night sweats in the past 3 months. Of the 1929 women who underwent telephone screening, 304 were interested, eligible, and enrolled and had usable physiologic hot flash monitoring data (≥70% of 24 hours). Exclusion criteria were based on factors having a major impact on study measures or safety and included hysterectomy and bilateral oophorectomy; history of heart disease, stroke, arrhythmia, ovarian/gynecological cancer, pheochromocytoma, pancreatic tumor, kidney failure, seizures, Parkinson disease, Raynaud phenomenon; current pregnancy; or having used select medications in the past 3 months (oral/transdermal estrogen or progesterone, selective estrogen receptor modulators, selective serotonin reuptake inhibitors, serotonin norepinephrine reuptake inhibitors, gabapentin, insulin, β-blockers, calcium channel blockers, α-2 adrenergic agonists, and other antiarrhythmic agents). Women who had undergone uterine ablation, endarterectomy, or lymph node removal or who were undergoing dialysis or chemotherapy was also excluded.

Of the 304 women, 4 women were excluded because of missing carotid data (equipment failure or poor image) and 5 women excluded because of missing blood marker data (Homeostatic Model Assessment: n=3; low-density lipoprotein cholesterol: n=2). Excluded women had higher triglycerides than included women (P<0.05). A total of 295 women were included in final models.

Design and Procedures

Women were recruited from the community via advertisements, mailings, and message boards. Participants underwent physical measurements, hot flash monitoring, a blood draw, and a carotid artery ultrasound. Procedures were approved by the University of Pittsburgh Institutional Review Board. Participants provided written, informed consent.

Measures

Hot Flashes

Participants completed 3 days of ambulatory hot flash monitoring, the first 24 hours of which included physiologic hot flash monitoring. Women were equipped with a hot flash monitor (VU-AMS, VU University Amsterdam, Netherlands), electronic diary, and wrist actigraph. The VU-AMS is a wearable monitor that quantifies hot flashes via sternal skin conductance, a validated physiologic measure of hot flashes.23 Women reported hot flashes by completing an electronic diary (Palm Z22) and pressing event mark buttons on the VU-AMS monitor and actigraph, providing date and time-stamped hot flash reports. Participants wore the VU-AMS monitor for 24 hours, after which time they removed it and stored it in a provided case. For the remaining 2 days, women carried the diary and actigraph. After monitoring, hot flash data were downloaded and scored via UFI software (DPSv3.7; Morro Bay, CA) according to validated methods that have demonstrated reliability, including in the present laboratory (κ=0.86).23,24

Carotid Ultrasound

Trained and certified sonographers at the University of Pittsburgh’s Ultrasound Research Laboratory obtained bilateral carotid images via B-mode ultrasound using a Sonoline Antares (Siemens, Malvern, PA) high-resolution duplex scanner equipped with a VF10-5 transducer. Digitized images were obtained from 8 locations (4 locations each from the left and right carotid arteries): near and far walls of the distal common carotid artery, far walls of the carotid bulb, and internal carotid artery. Images were read using semiautomated reading software.25 Values were obtained by electronically tracing the lumen–intima interface and the media–adventitia interface across a 1-cm segment for each of these eight segments. Average and maximal values were recorded for each of the 8 locations; the mean of the average and maximal readings across the 8 locations comprised mean and maximal IMT, respectively. Reproducibility of IMT measures was excellent (intraclass correlation coefficient between sonographers 0.87–0.94, between readers=0.94–0.99).

Carotid plaque was defined as a distinct focal area protruding into the vessel lumen ≥50% thicker than the adjacent IMT.26 Sonographers evaluated the presence and extent of plaque in each of 5 segments of the left and right carotid artery (distal and proximal common carotid artery, carotid bulb, and proximal internal and external carotid arteries).26 Consistent with the Mannheim Consensus Statement,27 plaque was defined as a focal area protruding into the vessel lumen that was at least 50% thicker than the adjacent IMT and summarized as the presence or absence of any plaque. Additionally, for each segment, the degree of plaque was graded using the following criteria: grade 0=no observable plaque; grade 1=small plaque (<30% of the vessel diameter); grade 2=1 medium plaque (30%–50% of the vessel diameter) or multiple small plaques; grade 3=1 large plaque (>50% of the vessel diameter) or multiple plaques with at least one medium plaque. The grades from all segments of the combined left and right carotid artery were summed to create the plaque index,28 which was categorized as 0, 1, or ≥2 for analysis. Between sonographers agreement for carotid plaque assessment was good to excellent (κ statistic, κ=0.78).

Covariates

Height and weight were measured via a fixed stadiometer and balance beam scale; body mass index was calculated (kg/m²). Seated blood pressure was measured via a Dinamap device after 10-minute rest. Demographics and medical history were assessed by standard instruments. Menopause status was obtained from reported menstrual bleeding patterns.29 Depressive symptoms were assessed by the Center for Epidemiologic Studies Depression scale.30 Sleep/wake was assessed via actigraphy and sleep diary.31 Use of medications for blood pressure–lowering, lipid-lowering, or diabetes mellitus was reported and considered as covariates.

Phlebotomy was performed after a 12-hour fast. Glucose, triglycerides, and high-density lipoprotein cholesterol were measured enzymatically. Total cholesterol was determined enzymatically and low-density lipoprotein cholesterol calculated.32 Insulin was measured via radioimmunoassay. Homeostatic Model Assessment, reflecting insulin resistance, was calculated.33 C-reactive protein was measured using a high-sensitivity reagent set (Beckman Coulter, Brea, CA) and interleukin-6 with an R&D Systems (Minneapolis, MN) high-sensitivity ELISA. Estradiol was assessed via liquid chromatography-tandem mass spectrometry, the gold standard method to measure estradiol at low postmenopausal levels (lower limit of quantitation=2.5 pg/mL; lower limit of detection=1.0 pg/mL).34

Data Analysis

Homeostatic Model Assessment, triglycerides, estradiol, C-reactive protein, and interleukin-6 values were natural log transformed for analysis. Hot flashes were categorized as occurring during sleep or wake according to sleep diary and actigraph. Hot flash rates were
Results

Participants were on average 54 years of age, normotensive, overweight, and postmenopausal (Table 1). Women reporting daily hot flashes (flashers) were younger, less educated, more often non-white, and had higher diastolic blood pressure than women not reporting hot flashes (nonflashers) during the 3 months before enrollment. Across the sample, 2422 hot flashes were physiologically detected, and 2335 were reported. Among flashers, median numbers of physiologically detected and self-reported hot flashes/24 hours were 12 and 5, respectively. Among women not reporting hot flashes (nonflashers), many (46%) showed evidence of physiologic hot flashes, albeit at a low frequency (24 hours: median=0; interquartile range, 0–5).

The mean and maximal IMT were 0.68 mm (SD=0.11) and 0.85 (SD=0.16), respectively. Mean IMT did not vary by hot flash group (flasher versus nonflasher) in multivariable models (β [SE]=−0.008 [0.02]; range, 0.51–0.98, nonflasher, raw mean [SD]=0.69 [0.12]; range, 0.50–1.28). Maximal IMT also did not differ by hot flash group (β [SE]=−0.007 [0.02]; P=0.66). However, significant interactions by hot flash status and hot flash frequency did not impact hot flash–IMT associations (eg, waking physiologic hot flashes, albeit at a low frequency (24 hours: median=0; interquartile range, 0–5).

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We also considered carotid plaque. Over half the women (54%; n=160) showed no plaque, 21% (n=63) had a plaque index of 1, and 25% (n=73) had a plaque index of ≥2. Plaque did not differ by reported hot flash status (flasher versus nonflasher: plaque index ≥2, odds ratio [95% confidence interval], 1.06 [0.56–2.01]; P=0.85); plaque index 1, odds ratio [95% confidence interval], 1.08 [0.58–2.01], P=0.82, relative to no plaque, multivariable). However, interactions by hot flash
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accounted for neither by CVD risk factors nor by estradiol. With higher carotid IMT and plaque. The associations were strongest among the women at the upper median (eg, for each additional physiologic hot flashes asking women to recall their hot flashes up to

We conducted several additional analyses. No significant interactions by age, race, menopause stage, time since final menstrual period, and body mass index for hot flash–IMT relations were observed. However, for plaque, significant interactions by age were observed in the total sample (P=0.04) and in flashers (P=0.04), with positive relations between hot flashes and plaque observed largely among the older (eg, ≥54, upper median) women (eg, for each additional physiologic hot flash among flashers: plaque index ≥2 odds ratio [95% confidence interval]=1.14 [1.03–1.26]; P=0.009, multivariable). Furthermore, we tested interactions for blood pressure, finding significant interactions between wakening physiologic hot flashes and diastolic blood pressure in relation to IMT among the flashers (P=0.04). Probing these interactions indicated that associations were strongest among the women at the upper median of diastolic blood pressure (≥70 mg/dL: β=0.005 [SE=0.001]; P<0.001 and <70 mg/dL: β=0.001 [SE=0.001]; P=0.59). To better understand factors that may account for hot flash–IMT relations, we considered depressive symptoms, interleukin-6, C-reactive protein, and menopause stage as additional covariates; associations between hot flashes and IMT or plaque persisted (data not shown). Finally, neither diary-rated hot flash severity nor bother were associated with outcomes (data not shown).

Discussion

We present the results from the first study designed to test associations between menopausal hot flashes and markers of carotid atherosclerosis. Among midlife women reporting daily hot flashes, a greater frequency of hot flashes was associated with higher carotid IMT and plaque. The associations were accounted for neither by CVD risk factors nor by estradiol. Among women reporting hot flashes, hot flashes accounted for more variance in IMT than in most CVD risk factors.

These findings contribute to the literature on hot flashes and markers of CVD risk. Initial observations of relations between hot flashes and CVD risk arose from post hoc analysis of large hormone therapy trials.7,8 Subsequent observations from the SWAN (Study of Women’s Health Across the Nation) and other cohort studies indicated that reported hot flashes were positively associated with subclinical atherosclerosis.11–14 In other work, we have found hot flashes associated with brain white matter hyperintensities.3,3 Not all studies have linked hot flashes to CVD risk.7,36 The existing literature has been limited by the heavy reliance on retrospective measurements of hot flashes asking women to recall their hot flashes up to

Table 2. Relation Between Hot Flashes and Carotid IMT and Plaque Among Women Reporting Daily Hot Flashes

<table>
<thead>
<tr>
<th></th>
<th>Mean IMT</th>
<th>Max IMT</th>
<th>Plaque Index, Odds Ratio (Confidence Interval)†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physiologic hot flashes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>24-h</td>
<td>0.003 (0.001)†</td>
<td>0.004 (0.001)†</td>
<td>1.00 (0.94–1.06) 1.06 (1.001–1.12)§</td>
</tr>
<tr>
<td>Wake</td>
<td>0.004 (0.001)†</td>
<td>0.005 (0.001)†</td>
<td>0.99 (0.92–1.06) 1.07 (1.003–1.14)§</td>
</tr>
<tr>
<td>Sleep</td>
<td>0.003 (0.003)</td>
<td>0.004 (0.005)</td>
<td>0.96 (0.77–1.21) 1.17 (0.96–1.42)</td>
</tr>
<tr>
<td>Self-reported hot flashes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>24-h</td>
<td>0.006 (0.002)†</td>
<td>0.007 (0.003)§</td>
<td>1.06 (0.92–1.21) 1.06 (0.93–1.21)</td>
</tr>
<tr>
<td>Wake</td>
<td>0.008 (0.002)†</td>
<td>0.009 (0.004)§</td>
<td>1.09 (0.92–1.30) 1.12 (0.95–1.32)</td>
</tr>
<tr>
<td>Sleep</td>
<td>0.008 (0.006)</td>
<td>0.01 (0.009)</td>
<td>0.98 (0.65–1.48) 1.00 (0.70–1.42)</td>
</tr>
</tbody>
</table>

Covariates: age, race, body mass index, education, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, triglycerides, systolic blood pressure, diastolic blood pressure, homeostatic model assessment, blood pressure–lowering medications, diabetes mellitus medications, and lipid-lowering medications. n=147; IMT measured in mm. IMT indicates intima media thickness. *β coefficients indicate mm increase in IMT for each additional hot flash. † Odds ratio associated with each additional hot flash, relative to no plaque. ‡P<0.01; §P<0.05; †P<0.001.

Figure. Adjusted means in average intima media thickness (IMT) by hot flash frequency among women in daily hot flash group. Quartile (Q) 1: ≤4 physiologic hot flashes, ≤1 self-reported hot flashes; Q2: 5 to 9 physiologic hot flashes, 2 to 3 self-reported hot flashes; Q3: 10 to 14 physiologic hot flashes, 4 to 5 self-reported hot flashes; Q4: ≥15 physiologic hot flashes, ≥6 self-reported hot flashes; waking hot flashes. Adjusted for age, race, body mass index, education, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, triglycerides, systolic blood pressure, diastolic blood pressure, homeostatic model assessment, blood pressure–lowering medications, diabetes mellitus medications. *P<0.05, **P<0.01, ***P<0.001 relative to Q1.
Table 3. Percent of Variance ($R^2$) in Mean Intima Media Thickness Explained by Each Variable Among Women Reporting Daily Hot Flashes (n=147)

<table>
<thead>
<tr>
<th>Variable</th>
<th>$R^2$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>4.72</td>
</tr>
<tr>
<td>Race</td>
<td>8.75</td>
</tr>
<tr>
<td>Education</td>
<td>0.98</td>
</tr>
<tr>
<td>Body mass index</td>
<td>1.50</td>
</tr>
<tr>
<td>Systolic blood pressure</td>
<td>0.19</td>
</tr>
<tr>
<td>Diastolic blood pressure</td>
<td>0.01</td>
</tr>
<tr>
<td>High-density lipoprotein cholesterol</td>
<td>0.31</td>
</tr>
<tr>
<td>Low-density lipoprotein cholesterol</td>
<td>2.71</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>0.91</td>
</tr>
<tr>
<td>Homeostatic model assessment</td>
<td>0.13</td>
</tr>
<tr>
<td>Lipid-lowering medication</td>
<td>0.99</td>
</tr>
<tr>
<td>Blood pressure–lowering medication</td>
<td>0.67</td>
</tr>
<tr>
<td>Diabetes mellitus medication</td>
<td>0.19</td>
</tr>
<tr>
<td>Physiologic waking hot flashes</td>
<td>7.86</td>
</tr>
</tbody>
</table>

physiologic hot flashes/d), a frequency found in half of the women reporting hot flashes in this sample.

This work had limitations. This observational study does not allow for conclusions about directionality or causality of relations. The use of subclinical atherosclerosis indices is necessary given the rarity of clinical events in midlife women, but limits conclusions about clinical disease. Estradiol concentrations, but not estradiol fluctuations, were quantified; yet, most of the women were postmenopausal, a time when estradiol typically stabilizes at low levels. Blood pressure variability, which has been linked to CVD risk beyond blood pressure levels alone, was not measured here and its role in these relations should be considered in future work. Although the sample was 25% non-white, Asian, and Hispanic women were underrepresented. By design, smokers, women reporting infrequent hot flashes (less than daily), and women with hysterectomy or bilateral oophorectomy were excluded. Findings cannot be generalized to these groups; future work should consider these women. Hot flashes were captured once over several days; yet, next steps should include a longitudinal study quantifying hot flashes over multiple time points.

Conclusions

More frequent hot flashes were associated with markers of carotid atherosclerosis among midlife women reporting daily hot flashes. This line of work may ultimately have clinical implications for women with frequent hot flashes. For women, midlife is typically decades before the emergence of clinical events and is a time in which CVD risk stratification can be challenging; with additional replication and extension of this work, hot flashes may ultimately assist in that effort. With further understanding of hot flash–CVD risk relations, hot flashes may have implications for understanding the accelerated changes in the vasculature occurring during menopause, changes not fully explained by reproductive hormones or aging. This body of work begins to call into question the solely incidental nature of this midlife symptom.

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Disclosures

None.

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