WHEN IS A HOT FLASH NOT JUST A HOT FLASH?

*Understanding the links between hot flashes and cardiovascular risk*

Rebecca C. Thurston, PhD
Departments of Psychiatry, Psychology, and Epidemiology
University of Pittsburgh
Vasomotor Symptoms (VMS)

- Hot flashes, night sweats
- Over 70% of women experience during menopausal transition
- Can persist for decades (10 years!)
Hot Flashes Duration

% US women

Birth

Final Menstrual Period (FMP)

Death
Long understood to have important impact on quality of life

Few medical implications?
Is a Hot Flash *Just* a Hot Flash?

- WHI and HERS: women with baseline VMS highest CVD risk with HT use
  - WHI (older women) Rossouw et al., 2007
  - HERS (women with CHD) Huang et al., 2009
VMS and Subclinical CVD
Subclinical Cardiovascular Disease (CVD) Measures

- FMD: Endothelial dysfunction (lower worse)
  - Early in CVD
- Calcification: Calcified plaques
- IMT: Thickness of intimal and medial layers
Study of Women’s Health Across the Nation (SWAN)

Hot Flashes

Subclinical Cardiovascular Disease (CVD)
- Flow mediated dilation (FMD)
- Calcification
- Intima media thickness (IMT)

CV Risk Factors?
Study of Women’s Health Across the Nation (SWAN)

SWAN (N=3302) SWAN Heart (N=557)
Pittsburgh, Chicago

Baseline Yrs 4-7
- FMD: Brachial artery ultrasound
- Calcification: EBT aorta
- IMT: Carotid artery ultrasound

Annually:
- Demographic, Health behaviors, Affect
- Hot flashes
- SBP, DBP, BMI
- Blood Draw: E2, lipids, glucose

Follow up Yrs 6-9
- IMT

Baseline

1 2 3 4 5 6 7 8 9 10 11 12 13
Hot Flashes & Flow Mediated Dilation

Age, site, race, lumen diameter, BMI, education, DBP, HT use, HDL, LDL, triglycerides, glucose, diabetes history, lipid med use, smoking, physical activity, E2, cycle day of blood draw

(Thurston et al., 2008, Circulation)
Hot Flashes & Aortic Calcification

(Thurston et al., 2008, Circulation)

Age, site, race, education, BMI, smoking, SBP, antidepressant use, HT, menopausal status, depressive sx, phys activity, glucose, HDL, LDL, triglycerides, diabetes hx, cycle day, E2
Cross Sectional Association between Hot Flashes and IMT

<table>
<thead>
<tr>
<th>Hot flashes in past 2 weeks</th>
<th>IMT (mm)</th>
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</thead>
<tbody>
<tr>
<td>None</td>
<td>0.68</td>
</tr>
<tr>
<td>1-5 Days</td>
<td>0.69</td>
</tr>
<tr>
<td>6+ Days</td>
<td>0.70</td>
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</tbody>
</table>

age, site, race, education, BMI, smoking status, SBP, HDL, LDL, triglycerides, glucose, diabetes status/meds, CVD status/meds, HT use, E2, cycle day of blood draw

(Thurston et al., 2011, Menopause)
Association between Hot Flashes Across Visits and IMT

age, site, race, education, BMI, smoking status, SBP, HDL, LDL, triglycerides, glucose, diabetes status/meds, CVD status/meds, HT use, E2, cycle day of blood draw

(Thurston et al., 2011, *Menopause*)
More evidence: Hot Flashes and Flow Mediated Dilation

(Bechlioulis et al 2010, JCEM)
More Evidence: VMS and IMT

(Ozkaya et al 2011, Int J of Gyn & Obstet)
Summary of Subclinical CVD findings

- Positive findings
  - VMS and IMT (Ozkaya et al., 2011; Thurston et al., 2011)
  - VMS (duration) and aortic calcification (Thurston et al., 2010)
  - VMS and FMD/aortic calcification (Thurston et al., 2008; Bechlioulis et al 2010)

- Negative findings: Coronary artery calcification
  - WHI: women with hysterectomy (Allison et al., 2010)
  - KEEPS: healthy early perimenopausal women (Wolff et al., 2013)
Hot Flashes and Subclinical CVD

- Women with hot flashes may have higher subclinical CVD
  - Older or with some elevated CVD risk factors?
- Not explained by CVD risk factors, E2
- Mechanisms?
VMS and the Autonomic Nervous System
VMS and Autonomic Nervous System

- Etiology of VMS: Role of autonomic nervous system speculated
- Reduced parasympathetic (vagal) control of heart rate linked to elevated CVD risk
- High frequency heart rate variability (HF-HRV)
Study Question

Hot Flashes \rightarrow \text{Cardiac vagal control (HF-HRV)}
VMS and the Autonomic Nervous System

- Controlled laboratory studies
- “Real world” ambulatory studies
Physiologic Measurement of Hot Flashes
Hot Flash Diary

- Occurrence
- Severity
- Bothersome
- Emotions
- …
Reduced Cardiac Vagal Control During Hot Flashes: Laboratory

* p < 0.05 vs. minute zero

(Thurston et al. 2010, *Menopause*)
Reduced Cardiac Vagal Control During Hot Flashes: Ambulatory (24 hrs)

HF-HRV (lnmsec²)

Minutes surrounding hot flash

Pre-flash: p<0.0001
Post-flash: p<0.0001

(Thurston et al., 2012, Menopause)
Autonomic Nervous System and Hot Flashes

- Others similar findings: Freedman et al., 2011; deZambotti et al., 2013; Hoikkala et al., 2010

- Mechanism linking hot flashes to CVD risk?

- Insight into etiology of hot flashes
  - Autonomic nervous system?
VMS and CVD risk factors (traditional and novel)
Hot Flashes and Systolic Blood Pressure

(Gerber et al. 2007, Menopause)
Hot Flashes and LDL Cholesterol

![Graph showing the relationship between hot flashes and LDL cholesterol levels.](image)

- **SWAN Visit**
  - None
  - 1-5 Days
  - 6+ Days

**p<0.001**

- Hot flashes in past two weeks
- Covariates: age, site, race, education, menopausal status, alcohol use, physical activity, smoking, anxiety, BMI, CVD status/medication, lipid lowering medication

(Thurston et al., 2012, *Obstet Gynecol*)
Hot Flashes and HOMA

p<0.0001

Hot flashes in past two weeks
Covariates: Age, site, race, education, menopausal status, alcohol, smoking, physical activity, smoking, anxiety, BMI, heart, BP or lipid lowering med

(Thurston et al., JCEM, 2012)
Hot Flashes and TPA-antigen

Hot flashes in past two weeks
Covariates: education, menopausal status, alcohol, parity, smoking, exercise, affect, BMI, CV meds, diabetes/insulin, steroids, pain med, antidepressants

(Thurston et al., 2011, Menopause)
Hot Flashes and P-selectin

(Bechlioulis et al 2012, JCEM)
VMS and CVD Risk

- Subclinical CVD
- Autonomic nervous system
- Blood pressure
- Lipids
- Insulin resistance
- Inflammatory/hemostatic factors
Studies of CVD events: Very few

- VMS in context of HT use → elevated risk (older women): WHI & HERS (Rossouw et al., 2007; Huang et al., 2009)

- Early VMS → reduced risk, Later VMS → higher risk: WHI-OS (Szmuilowicz et al., 2011)

- Night sweats → increased CHD events: EPOS (Gast et al., 2011)
Considerations

- Age of onset: older? (see poster 107)
- Duration or burden of VMS: More persistent/ frequent/ severe?
- Existing CVD risk profile: Women with elevated CVD risk factors?
- VMS measures: Brief, self-report measures, recall and reporting biases
- Post-hoc analyses
Hot Flashes and CVD Risk

- Study designed to address relations between hot flashes and CVD risk
  - Comprehensively study mechanisms linking hot flashes and CVD risk: R01HL105647, N=300 (PI: Thurston)
(Dennerstein et al., 2000; Kronenberg, 1999; Mosca, 1997; Tunstall-Pedoe, 1998)
Implications?

- Possibly …… midlife marker of CVD risk
  - Aggressive risk factor reduction among women with hot flashes?
- Improve health of midlife women
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Thank you!
Extra slides
Hot Flashes and Triglycerides

Hot flashes in past two weeks
Covariates: age, site, race, education, menopausal status, alcohol use, physical activity, smoking, anxiety, BMI, CVD status/medication, lipid lowering medication

(Thurston et al., 2012, Obstet Gynecol)
Hot Flashes and ApoB

![Graph showing ApoB levels across SWAN visits]

- **None:** Yellow line
- **1-5 Days:** Blue line
- **6+ Days:** Red line

**p < 0.0001**

- **Hot flashes in past two weeks**
- **Covariates:** age, site, race, education, menopausal status, alcohol use, physical activity, smoking, anxiety, BMI, CVD status/medication, lipid lowering medication

(Thurston et al., 2012)
Hot Flashes and Factor VIIc

Hot flashes in past two weeks

Covariates: education, menopausal status, alcohol, parity smoking, exercise, affect, BMI, CV meds, diabetes/insulin, steroids, pain med, antidepressants

(Thurston et al., 2011, *Menopause*)
Duration of Hot Flash reporting over 8 yrs and Aortic Calcification, HT users

\[ b = 2.87, \ SE = 1.21, \ p<0.05 \]

Covariates: age, race, smoking, SBP, LDL, HDL, triglycerides, glucose, BMI, education, alcohol use, BP med use, lipid med use, yrs since FMP, time difference between measurements

(Thurston et al., 2010, *Menopause*)
VMS and IMT by Obesity Status

(Thurston et al., 2011, Menopause)