International Journal of Cardiology xxx (2017) xxx–xxx

Contents lists available at ScienceDirect

International Journal of Cardiology

journal homepage: www.elsevier.com/locate/ijcard

Mental stress peripheral vascular reactivity is elevated in women with coronary vascular dysfunction: Results from the NHLBI-sponsored Cardiac Autonomic Nervous System (CANS) study☆

Puja K. Mehta [a,*], Melody Hermel [b], Michael D. Nelson [b], Galen Cook-Wiens [c], Elizabeth A. Martin [b], Ayman A. Alkhoder [a], Janet Wei [b], Margo Minissian [b], Chrisandra L. Shufelt [b], Sailaja Marpuri [b], David Hermel [b], Amit Shah [d], Michael R. Irwin [e], David S. Krantz [f], Amir Lerman [g], C. Noel Bairey Merz [b]

[a] Emory Clinical Cardiovascular Research Institute, Emory University School of Medicine, Atlanta, GA, United States
[b] Barbra Streisand Women's Heart Center, Cedars-Sinai Heart Institute, Los Angeles, CA, United States
[c] Biostatistics and Bioinformatics Research Center, Cedars-Sinai Medical Center, Los Angeles, CA, United States
[d] Department of Epidemiology, Rollins School of Public Health, Emory University, United States
[e] Cousins Center for Psychoneuroimmunology, Semel Institute for Neuroscience, David Geffen SOM at UCLA, United States
[f] Department of Medical and Clinical Psychology, Uniformed Services University, Bethesda, MD, United States
[g] Cardiovascular Diseases, Mayo Clinic, Rochester, MN, United States

ARTICLE INFO

Article history:
Received 28 April 2017
Received in revised form 26 September 2017
Accepted 17 October 2017
Available online xxxx

Keywords:
Vascular reactivity
Mental stress
Microvascular dysfunction
Women heart disease

ABSTRACT

Background: Women with chest pain, ischemia, and no obstructive coronary artery disease often have coronary vascular dysfunction (CVaD). Peripheral vascular reactivity to mental stress may contribute mechanistic understanding of stress-induced ischemia in women with CVaD.
Methods: 62 women (41 CVaD and 21 controls) underwent mental stress testing (MST) with anger recall, mental arithmetic, and forehead cold pressor (COP) challenge. Emotional arousal was measured (Likert scale). Reactive hyperemia index (RHI) was calculated before and after MST by peripheral arterial tonometry (PAT). Stress PAT ratio (SPR) of pulse amplitude during stress to rest was obtained to measure vasoconstriction. Wilcoxson rank sum test was used for analysis.
Results: Mean age of CVaD and control groups was 58 ± 9 and 55 ± 10 years ($p = 0.73$). Baseline RHI correlated with coronary endothelial function ($r = 0.36$, $p = 0.03$) and inversely with RHI change post-MST ($r = -0.51$, $p < 0.001$). During MST, 10% of controls reported chest pain vs. 41% of CVaD subjects ($p = 0.01$). RHI did not change significantly after MST in either group. CVaD subjects had lower SPR vs. controls during mental arithmetic (0.54 [0.15, 1.46] vs. 0.67 [0.36, 1.8], $p = 0.039$), not evident in the other tasks. Vasoconstriction inversely correlated with anxiety ($r = -3.4$, $p = 0.03$), frustration ($r = -0.37$, $p = 0.02$), and feeling challenged ($r = -0.37$, $p = 0.02$) in CVaD but not controls.
Conclusions: Mental stress peripheral vascular reactivity is elevated in women with CVaD compared to controls. Elevated vascular reactivity may be one contributor to stress-induced chest pain in CVaD. Interventions that modulate vasoconstrictive responses may be of benefit and should be tested in clinical trials in women with CVaD.

1. Background

Chest pain with evidence of myocardial ischemia and no obstructive coronary arteries occurs more commonly in women and is associated with an adverse prognosis [1–3]. Approximately 50% of these women have coronary vascular dysfunction (CVaD) [2,4]. CVaD encompasses endothelial and non-endothelial dependent macro- and microvascular dysfunction, and data from the Women's Ischemia Syndrome Evaluation (WISE) and other studies indicate that CVaD is associated with adverse cardiovascular prognosis, including myocardial infarction, stroke, congestive heart failure, and sudden cardiac death [3,5–7]. Invasive coronary reactivity testing (CRT) can be performed to clarify the diagnosis when CVaD is suspected [8].

Women with CVaD also often present with non-exertional, emotional stress-induced chest pain; while anxiety/pain disorders and abnormal cardiac nociception are also relatively more common in women with chest pain [9,10], the mechanistic pathways of emotional stress-induced chest pain are not well understood. Acute mental stress has been associated with endothelial dysfunction and impaired vasoreactivity in patients

☆ nih.gov identifier: NCT01568177.

* Corresponding author at: 1462 Clifton Rd NE, Suite 505, Atlanta, GA 30322, United States.
E-mail address: pkmehta@emory.edu (P.K. Mehta).

https://doi.org/10.1016/j.ijcard.2017.10.061
0167-5273/

with obstructive CAD [11,12]. This may result in mental stress-induced myocardial ischemia (MSIMI), which is more common in women with CAD. Patients with MSIMI are also more likely to have exaggerated peripheral vasoconstriction during mental stress [12,13]. Further evidence suggests that mental stress induces peripheral vasoreactivity, which may be useful in the detection of MSIMI in patients with CAD [14–18]. However, it is not known whether women with CVaD and no obstructive CAD have abnormal peripheral vasoreactivity during acute mental stress. Hence, this study evaluated peripheral vascular reactivity to acute mental stress in women with CVaD as compared to reference control subjects.

2. Methods

2.1. CVaD subjects

44 CVaD women enrolled in the NHLBI-sponsored Women's Ischemia Syndrome Evaluation — Coronary Vascular Dysfunction (WISE-CVD) study (PI: Bairey Merz) at a single site (Cedars-Sinai Medical Center) were recruited and enrolled in the NHLBI-sponsored Cardiac Autonomic Nervous System (CANS) substudy between October 2010 and June 2015. These women had persistent chest pain, evidence of myocardial ischemia by routine stress testing, and no obstructive CAD on invasive coronary angiography. Inclusion and exclusion criteria were as previously published for WISE-CVD [19]. Three subjects who did not have coronary reactivity testing (CRT) to diagnose CVaD were excluded due to inadequate data. The study was IRB approved, and all subjects were provided informed consent.

2.2. Coronary reactivity testing (CRT)

Clinically-indicated invasive CRT was performed to diagnose CVaD as previously described [8]. Briefly, after confirmation of no obstructive CAD by angiography, a Doppler Flowire (Volcano®) was placed in the proximal left anterior descending artery and vasoactive agents (adenosine 18 and 36 μg, acetylcholine 36.4 μg, and nitroglycerin 200 μg) were used to assess endothelial and non-endothelial dependent, macro- and micro-vascular function, using previously published methods [7,20]. The peak coronary flow reserve (CFR) response to either dose of adenosine was used for analysis. Abnormal CRT responses were defined as the following four pathways: (a) an abnormal non-endothelial microvascular response was CFR < 2.5 to intracoronary adenosine; (b) an abnormal endothelial microvascular response was change in coronary blood flow (CBF) ≤ 50% to high dose acetylcholine; (c) an abnormal endothelial macro-vascular response was <5% change in coronary artery diameter to high dose acetylcholine; and (d) an abnormal non-endothelial macro-vascular response was change in coronary artery diameter < 20% to nitroglycerin [8,21]. Coronary endothelial dysfunction was defined as abnormal coronary diameter response or abnormal coronary blood flow to acetylcholine. Patients with at least one abnormal pathway were included in the study.

2.3. Mental stress testing (MST)

MST was performed in the morning after an overnight fast; caffeine was withheld for 24 h and smoking was prohibited for at least 6 h. Subjects were asked to withhold caffeine and medications for 24 h (beta blocker, short acting calcium channel blocker, angiotensin-converting enzyme inhibitors and angiotensin receptor blockers, renin blockers, and ranolazine) or for 48 h (long acting calcium channel blockers and nitrates) when medically able. After IV placement, subjects rested for 30 min in a quiet, dimly lit, temperature-controlled room. A mood survey with Likert scale [22–25] questions was administered to assess subjective levels of psychological stress, including anxiety, frustration, anger, and irritation. Baseline blood pressure, heart rate, and reactive hyperemia index (RHI) by peripheral arterial tonometry (PAT) were measured. All subjects underwent MST in a supine position via a standardized protocol (Appendix Fig. 1).

Two mental stress tests were administered in counterbalanced order with a 2-min rest period between each stress test task: (*a*) *4-min anger recall speech task* modified from Ironson et al. [26] requires the subject to recall a situation of extreme anger or frustration and (*b*) *4-min mental arithmetic task*, which requires the subject to count backwards by 7's from a randomly chosen number. These are standard MST tasks that have been used successfully by our group and others [22,24,27]. During the 2-min rest period in between tasks, blood pressure and heart rate were assessed to ensure a return to baseline levels, prior to proceeding with the next task. During the MST tasks, BP was monitored every minute by automated cuff, and heart rate and rhythm continuously monitored. For the first 26 subjects, one lead ECG monitoring was used, but for better detection of ST segment changes, we changed to 12 lead ECG monitoring (Mortara Instruments®) for the later subjects. Likert scale was re-administered after each MST task. PAT pulse amplitude was continuously monitored during MST.

At the end of MST, 3 min of modified forehead cold pressor (COP) test was performed. A 1.5 l bag filled with 800 ml crushed ice and 200 ml of water (temp 4 °C) was placed on a subject's forehead for 3 min. Hand PAT probes precluded traditional COP testing with hand in ice bucket, thus forehead COP was used. HR, BP, and PAT pulse amplitude response were also measured during COP test.

2.4. Peripheral arterial tonometry

Peripheral endothelial function and vascular reactivity were measured by peripheral arterial tonometric (PAT) plethysmographic device (EndoPAT 2000, Itamar Medical®) as previously described and during supine position, under conditions for MST described above [28,29]. The device consists of a finger probe with a transducer to assess digital volume changes accompanying pulse-waves. A pressure of 40–70 mm Hg is applied by the probe to the index fingers for venous occlusion of both hands and arterial pulse amplitude is recorded. A blood pressure cuff is placed on one arm (test arm) while amplitudes are recorded from the test arm and the contralateral arm. After 10 min of equilibration period, reactive hyperemia index (RHI) is obtained by the following: 5 min of baseline amplitude signal detection, 5 min of arterial occlusion by suprasystolic blood pressure cuff inflation, and then 6 min of post-occlusion amplitude signal detection. RHI is a unitless measure and a marker of endothelial function, and was determined at baseline and post MST by EndoPAT® automated software which takes into account the baseline signal and adjusts it to the changes in the contralateral arm [15,16,28]. RHI of <2.0 has been reported to correlate with coronary endothelial dysfunction and coronary artery disease, and is prognostic (sensitivity and specificity of ~80%) [30–32]. Peripheral vascular reactivity was determined by stress PAT ratio (SPR) which is a ratio of stress to rest pulse amplitude as previously described [15]. The lowest pulse amplitude for a 30 s segment during mental stress test task was used to compare to an average 3 min rest amplitude to obtain SPR. SPR was obtained from the arm not wearing a BP cuff and determined for each MST task, as a measure of vasoconstriction, where <0.8 is considered abnormal [28,33].

2.5. Reference control subjects

22 women were recruited from the Reference Control Study in Women (PI: Bairey Merz) at Cedars-Sinai and enrolled in the CANS study. One subject was a screen failure and excluded. Women in this group were age- and BMI-matched to the CVaD group, had no cardiac risk factors, were not on cardiac medications, and had a normal maximal exercise treadmill testing (Bruce Protocol) to serve as reference controls.

2.6. Statistical analysis

Summary data are expressed as means, standard deviations, medians, and ranges for continuous variables and frequencies (%) for categorical ones. Comparison of categorical variables between groups was done using Fisher's Exact test due to low counts in the control group. Wilcoxon Rank Sum tests were used to compare continuous outcomes between groups due to the presence of outliers. Spearman correlation coefficients are reported due to outliers. A p-value < 0.05 was considered to indicate statistical significance. Multiple linear regression was performed with RHI as the outcome and adjusted for various cardiac medications. All statistical analysis was performed using SAS (The SAS Institute, Cary, NC; ver. 9.3).

3. Results

Baseline characteristics are shown in Table 1 and demonstrate no difference between mean age and BMI between the two groups. Mean time between CRT and MST was 2.0 ± 1.6 years. There were only 7 subjects with MST within 6 months of CRT, precluding further analysis given small numbers. CRT results demonstrated that 34% had abnormal CFR (<2.5), 63% had abnormal acetylcholine diameter response, 44% had abnormal coronary blood flow change to acetylcholine, and 61% had an abnormal smooth muscle vasodilation to nitroglycerin. Only one subject had CVaD diagnosis because of abnormal nitroglycerin response with the other 3 pathways being normal. Excluding this subject did not change the overall results.

3.1. Cardiovascular reactivity and Likert scale

Hemodynamic changes to anger, mental arithmetic, and COP were similar in both groups (Appendix Table 1). There were no stress-induced arrhythmias detected on continuous rhythm monitoring during MST. During MST, 2/21 (10%) reference controls reported transient, self-limited chest pain, compared to 17/41 (41%) of CVaD subjects ($p = 0.010$). Chest pain was not associated with rhythm or ST segment changes, and no one required treatment with SL NTG for chest pain resolution during MST.

At baseline, there were no significant differences in emotional arousal measured by Likert scale subjective measures of emotion between the two groups. While both MST tasks resulted in significant

Please cite this article as: P.K. Mehta, et al., Mental stress peripheral vascular reactivity is elevated in women with coronary vascular dysfunction: Results from the NHLBI-sponsored ..., Int J Cardiol (2017), https://doi.org/10.1016/j.ijcard.2017.10.061