Journal of Psychosomatic Research 78 (2015) 433–437

Contents lists available at ScienceDirect

Journal of Psychosomatic Research

Angina and mental stress-induced myocardial ischemia

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ARTICLE INFO

Article history:
Received 11 April 2014
Received in revised form 11 February 2015
Accepted 12 February 2015

Keywords:
Coronary artery disease
Angina
Stress

ABSTRACT

Objective: Mental stress-induced myocardial ischemia is a common phenomenon in patients with coronary artery disease (CAD) and an emerging prognostic factor. Mental stress ischemia is correlated with ambulatory ischemia. However, whether it is related to angina symptoms during daily life has not been examined.
Methods: We assessed angina frequency (past month) in 98 post-myocardial infarction (MI) subjects (age 18–60 years) using the Seattle Angina Questionnaire. Patients underwent [^{99m}Tc]sestamibi SPECT perfusion imaging at rest, after mental stress, and after exercise/pharmacological stress. Summed scores of perfusion abnormalities were obtained by observer-independent software. A summed difference score (SDS), the difference between stress and rest scores, was used to quantify myocardial ischemia under both stress conditions.
Results: The mean age was 50 years, 50% were female and 60% were non-white. After adjustment for age, sex, smoking, CAD severity, depressive, anger, and anxiety symptoms, each 1-point increase in mental stress–SDS was associated with 1.73-unit increase in the angina frequency score (95% CI: 0.09–3.37) and 17% higher odds of being in a higher angina frequency category (OR: 1.17, 95% CI: 1.00–1.38). Depressive symptoms were associated with 12% higher odds of being in a higher angina frequency category (OR: 1.12, 95% CI: 1.03–1.21). In contrast, exercise/pharmacological stress-induced SDS was not associated with angina frequency.
Conclusion: Among young and middle-aged post-MI patients, myocardial ischemia induced by mental stress in the lab, but not by exercise/pharmacological stress, is associated with higher frequency of retrospectively reported angina during the day. Psychosocial stressors related to mental stress ischemia may be important contributory factor to daily angina.

Introduction

Myocardial ischemia in response to a standardized mental stress challenge can be induced in approximately one-third to one-half of patients with coronary artery disease (CAD) [1,2] and is associated with a 2- to 3-fold increased risk of future cardiac events [3]. Mental stress-induced myocardial ischemia is correlated with myocardial ischemia in daily life measured with ambulatory electrocardiographic monitoring [4,5].

Although previous literature suggests that mental stress-induced ischemia is a silent phenomenon [1], its association with angina symptoms during daily life has not been extensively evaluated. Daily life angina is an important dimension of CAD patients' quality of life, and patients' perspectives about the impact of CAD on their health status is increasingly recognized as an essential outcome in clinical care [6]. Psychosocial factors, especially depression and anxiety, have been found to influence angina symptoms [7–9], especially in younger population [7] and mental stress-induced ischemia could be an intermediate pathway for this association.

In a sample of young or middle-aged patients with a recent myocardial infarction (MI) with large representation of women and African Americans, we sought to examine the association between propensity to develop mental stress ischemia and presence, frequency, and severity of angina symptoms in the previous month. Furthermore, we contrasted the results for mental stress ischemia to those for physical stress ischemia, which was examined as a control condition using exercise or pharmacological stress testing.

Methods

Between July 2009 and April 2012, the Myocardial Infarction and Mental Stress Study enrolled 98 patients (49 male and 49 females) between ages 38 and 60 years with a documented history of MI in the

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http://dx.doi.org/10.1016/j.jpsychores.2015.02.007
0022-3999/

previous 6 months. Inclusion and exclusion criteria and details of sampling were described elsewhere [10]. The study protocol was approved by the Emory University Institutional Review Board, and informed consent was obtained from all participants.

Each patient underwent three nuclear 99 m-Tc sestamibi-gated single-photon emission computed-tomography (SPECT) scans, one at rest, one with mental, and one with exercise/pharmacological stress. The two stresses were conducted on separate days within one week of each other (the order was balanced), and the rest scan was obtained during the first session. All testing was done after an overnight fast, and anti-ischemic medications were held for 24 hours prior to testing. Mental stress was induced by a standardized speech stressor [11]. For physical stress, most subjects were submitted to a Bruce protocol; 16 patients unable to exercise on a treadmill underwent a pharmacological stress using regadenoson (Astellas, Northbrook, IL). Myocardial perfusion was quantified by means of the Emory Cardiac Toolbox software, which provides objective (operator-independent) quantitative assessment of perfusion with established validity [12,13] and reproducibility [14,15]. The extent and the severity of perfusion defects were quantified at rest and with stresses by operator-independent summed scores using the 17-segement model [16]. In each segment, defect severity was quantified using a 5-point scale from normal (score = 0) to absent perfusion (score = 4). These scores were then summed across the 17 segments yielding a total score for rest and each stress condition. A summed difference score (SDS), quantifying the number and severity of reversible (ischemic) myocardial perfusion defects, was obtained by subtracting the rest score from each of the stress scores (mental and physical stress); a positive SDS indicates presence of reversible (ischemic) myocardial perfusion deficit.

Angina frequency during daily life was assessed with the Seattle Angina Questionnaire (SAQ)'s angina frequency subscale [17], which measures frequency of angina and use of nitroglycerin for chest pain over the previous 4 weeks. The score ranges from 0 to 100, with higher scores indicating higher frequency of angina. The SAQ angina frequency scale has been validated in a variety of populations [17,18]. In a recent trial, it was also found to correlate with electronic daily diaries for angina and nitroglycerin use cross-sectionally, as well as and longitudinally, with changes in SAQ angina frequency scores from day 1 to week 8 being correlated with changes in angina frequency documented by electronic diaries during the same period [19].

Sociodemographic factors and medical history were assessed using standardized questionnaires. Angiographic data were obtained from the coronary angiogram performed in conjunction with the index MI. CAD severity was quantified using the Gensini semi-quantitative angiographic scoring system [20], which takes into account the degree of luminal narrowing along with a multiplier for specific coronary-tree locations. The Gensini score was based on the most recent coronary catetherization procedure; if a patient underwent revascularization, the score was calculated based on the post-revascularization angiographic results for the affected coronary segment. Depressive symptoms were assessed with the Beck Depression Inventory-II (BDI-II) [21]. We also administered the State-Trait Anger Expression Inventory (STAXI-2) to measure state and trait anger [22], the State-Trait Anxiety Inventory (STAI) to measure state and trait anxiety [23], and the Cohen's perceived stress scale to quantify level of stress perceived by the subjects [24].

Baseline characteristics of the population were compared according to increasing levels of angina frequency severity using the following scale: score = 0, no reported angina; score 1–39, less than one angina episode per week (monthly angina); and score ≥ 40, one or more angina episodes per week (daily or weekly angina) [25]. Non-parametric generalized additive models [26] were used to assess the association between angina frequency as a continuous score (dependent variable) and mental or physical stress SDS as the main predictors, in separate models. We adjusted for *a priori* chosen covariates, including sociodemographic and lifestyle characteristics (age, sex, race, and current cigarette smoking), angiographic CAD severity (Gensini score), depressive symptoms (BDI-total score), trait anger (STAXI-trait score), and trait anxiety (STAI-trait score). For the physical stress models, we additionally adjusted for type of physical stress protocol (exercise or pharmacological). We also performed ordinal logistic regression, with the three levels of angina severity described above as dependent variable and a similar set of predictor variables.

Results

The mean and median age was 50 years, and 60% of patients were non-white. There were no significant differences among angina frequency subgroups in demographic, medical history, and angiographic severity of CAD, but subjects with higher angina frequency showed significantly more depressive symptoms and tended to also have higher levels of anxiety, anger and perceived stress (Table 1). Seventy (75%) subjects underwent percutaneous coronary interventions and 10 (11%) coronary artery bypass surgery after their index MI. The mean ± standard deviation for the SDS during mental stress was 2.3 ± 2.7, with range of 0–13, and for physical stress it was 2.7 ± 3.2, with range 0–13. The mean angina frequency score was 16.6 ± 21.1, with range of 0–100. Seven (9%) patients reported chest pain during exercise/pharmacological testing. These 7 subjects had a higher angina frequency score when compared with patients reporting no chest pain during exercise/pharmacological stress (38 vs. 13, $p = 0.002$). None of the patients developed chest pain during mental stress. Heart rate, systolic and diastolic blood pressure significantly increased with both mental and physical stress, but these hemodynamic changes with either mental stress or physical stress were not significantly associated with angina frequency (data not shown).

In the unadjusted model, the mental stress SDS was strongly associated with angina frequency, with each 1-point increase in SDS being associated with 2.41-unit increase in angina frequency score (95% CI: 0.87–3.95) (Table 2). This association was materially unaffected by adjustment for traditional CAD risk factors and CAD severity (age, sex, race, current cigarette smoking, and Gensini score) and remained significant even after adjustment for psychosocial risk factors (BDI-II score, trait anger and trait anxiety scores). In the fully adjusted model, each 1-point increase in mental stress SDS was associated with 1.73-unit increase in angina frequency score (95% CI: 0.09–3.37) (Table 2). Adjustment for receipt of revascularization after the infarction did not affect the results (data not shown). Using ordinal logistic regression, each 1-point increase in mental stress SDS was associated with 17% higher adjusted odds of being in a higher angina frequency category (odds ratio: 1.17, 95% CI: 1.00–1.38). Patients with the highest frequency of angina had an SDS score with mental stress that was twice as high compared with subjects in the lowest angina category (Fig. 1). Depressive symptoms were significantly associated with angina frequency, with each 1-point increase in BDI-total score being associated with 12% higher adjusted odds of being in a higher angina frequency category (odds ratio: 1.12, 95% CI: 1.03–1.21). None of the other psychosocial risk factors were independently associated with angina frequency in the final model. The addition of psychosocial factors to the model explained part of the relationship between mental stress ischemia and angina frequency (Table 2).

In contrast, we found no association between angina frequency and physical stress ischemia either in unadjusted or adjusted models (adjusted regression coefficient: 1.03, 95% CI: −0.26–2.31) (Table 2). Angiographic severity of CAD was also not associated with angina frequency.

Discussion

In a sample of young and middle-aged acute MI survivors, the degree of myocardial perfusion defect induced by mental stress (as measured by a higher SDS score), but not with physical stress, was directly associated with the retrospectively reported frequency of angina over the previous month: as the degree of overall defect with mental stress increased, the frequency of retrospectively reported angina increased. This association was independent of traditional CAD risk factors, CAD severity, and psychosocial factors. We also found that only mental stress-induced ischemia and psychosocial factors (especially depressive symptoms) were significantly associated with angina. Surprisingly, angiographic severity of CAD and a positive stress test using exercise/pharmacological testing were not associated with retrospectively reported angina symptoms during past month. Our findings challenge the commonly held notion that obstructive CAD is the main substrate for angina. Mental stress and psychosocial factors are stronger correlates of angina than CAD severity in young post-MI patients.

Consistent with our findings, previous studies found no association between exercise stress ischemia and angina history [9,27]. In the Psychophysiological Investigations of Myocardial Ischemia (PIMI) study, exercise stress ischemia was not associated with history of daily life angina, while chest pain during exercise stress testing was associated with