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The Relationship Between Mental Stress-Induced Microvolt T-Wave Alternans (MTWA) and Inflammation in Post-Myocardial Infarction (MI) Patients

By

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Degree to be awarded: MPH
Department of Epidemiology

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The Relationship Between Mental Stress-Induced Microvolt T-Wave Alternans (MTWA) and Inflammation in Post-Myocardial Infarction (MI) Patients

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2010

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An abstract of
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Abstract

The Relationship Between Mental Stress-Induced Microvolt T-Wave Alternans (MTWA) and Inflammation in Post-Myocardial Infarction (MI) Patients

By Jiemin Wang

Background: Psychological stress can provoke both fatal ventricular tachyarrhythmias (VTAs) and acute inflammatory response in post-MI patients. Microvolt T-wave alternans (MTWA) is a predictor for future VTAs and an important clinical tool for sudden cardiac death (SCD) risk stratification in these venerable patients. The relationship between mental stress-induced MTWA and inflammatory response has not been investigated to date. We aim to examine the association between inflammatory responses to acute mental stress and mental stress-induced TWA in post-MI patients in this study.

Methods and Results: TWA induced by experimental psychological stress was assessed from digitized ambulatory ECGs by modified moving average analysis in 95 young and middle-aged post-MI subjects. The marker of inflammatory response—interleukin-6 (IL-6) was measured at 0 minutes, 60 minutes and 90 minutes after stress respectively. Subjects also underwent exercise as a control comparison. MTWA increased with both mental stress and exercise ($P<0.0001$). Both stresses induced significant increase in IL-6 at 90 minutes after stress ($P= 0.013$ for mental stress; $P= 0.035$ for exercise). The mental stress-induced TWA positively associated with increased IL-6 level at 90 minutes after stress ($P=0.047$). This effect was independent of cardiovascular risk factors, chronic psychological stress, heart function, mental-stress induced ischemia and medications. An opposite trend of IL-6 in response to exercise with exercise-induced TWA was found in multivariable analyses ($P=0.053$).

Conclusion: Acute mental stress can elicit significant increases of TWA in patients who are younger than 60 years old and have survived from a recent myocardial infarction. The subjects with a higher (vs. lower) IL-6 level at 90 minutes after mental stress also have higher TWA during mental stress. In contrast, exercise-induced TWA tends to be inversely associated with IL-6 level at 90 minutes after stress. This may help to risk-stratify post-MI patients regarding mental stress-induced SCD and to understand specific mechanisms linking inflammation and mental stress-induced TWA, which differs from that with exercise.

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Table of Contents

Background

Patients who have experienced a myocardial infarction (MI) are at particular risk for sudden cardiac death (SCD), mostly resulting from ventricular tachyarrhythmias (VTAs) that are preceded by repolarization heterogeneity (1). Psychological stress can provoke fatal VTAs and SCD in such vulnerable patients (2), but accurate patient stratification regarding the future risk for mental-stress induced arrhythmic events is still an open question in clinical practice.

Microvolt T-wave alternans (MTWA), a marker of repolarization heterogeneity, describes a subtle beat-to-beat fluctuation in the ST segment or T-wave morphology noted on an electrocardiogram (ECG). A wealth of evidence has established MTWA as a predictor for future VTAs and an important clinical tool for SCD risk stratification in post-MI patients (3, 4). Experimental psychological stress has been proven to increase the magnitude of TWA in patients with implantable cardiac defibrillators (ICDs) (5, 6), and TWA induced by mental stress predicts future VTAs as well (7), providing a possible pathway linking psychological stress and SCD, as well as a potential risk stratifier for mental-stress induced SCD. However, these studies were conducted primarily in patients with severely reduced left ventricular ejection fraction (LVEF). Few studies have attempted to establish mental stress-induced TWA in post-MI patients, especially those with a preserved heart function. Risk stratification of mental-stress induced SCD in post-MI patients is of important clinical implications since these patients are highly vulnerable and may ultimately benefit from advanced therapies such as ICDs.

Inflammation has long been a robust risk factor for MI and overall cardiovascular mortality (8, 9). Recent literature revealed that greater burden of inflammation, assessed by IL-6 levels, was independently associated with SCD risk (10), indicating the possibility of involvement of inflammation in arrhythmogenesis. Acute mental arousal has been demonstrated to elicit increases in inflammatory markers in patients with coronary artery disease (CAD) (11). Whether those with a higher inflammatory response to mental stress are also more likely to have an arrhythmia compared to those with a lower response has not been examined to date. Understanding the relationship between inflammation and TWA during mental stress may help to identify those at higher risk of mental stress-induced SCD and also to explain pathophysiological mechanisms.

The present study exams the relationship between acute inflammatory responses to acute mental stress, as measured by IL-6, and mental stress-induced TWA in patients with MI within the past 6 months. To investigate whether these mechanistic pathways are specific to mental stress, we also examined exercise-induced TWA and inflammation as a control comparison. We hypothesized TWA increases during acute mental stress, and that those with a higher (vs. lower) inflammatory response to mental stress, but not exercise stress, also had higher stress-induced TWA.

Methods

Study Population

Study participants were recruited as part of the Myocardial Infarction and Mental Stress Study (MIMS) (12), consisting 98 patients who were 38 to 60 years of age and admitted with a confirmed diagnosis of MI within the past 6 months at Emory-affiliated hospitals between July 2009 and April 2012. Details of our recruitment strategy and number of eligible and excluded patients have been described (12). The Emory Institutional Review Board approved the study and all patients provided informed consent.

Study Design

Study subjects underwent two stress tests in randomized order, one with mental stress, and the other with exercise. Two stresses were performed on separate days within one week (on average, 4 days apart). All anti-ischemic medications were held for 24 hours prior to tests. Demographic and psychosocial data were collected at the first visit prior to cardiac testing. Ambulatory ECGs (Holters) with modified II and V1 leads were recorded on GE Medical (Milwaukee, WI) SEER digital system throughout the whole testing for each subject. Holter data were then exported to a GE Ambulatory ECG Analysis System (MARS) for blinded offline analyses of TWA by a trained reader. In order to evaluate patient's myocardial infusion under stress, all subjects underwent three single photon emission computed tomography (SPECT) imaging scans, one with rest, one with mental stress and the other with exercise. At the end of the study protocol, medical records were abstracted for clinical information, including catheterization data at the time of MI and the information of medication uses.

Mental Stress Procedure

Participants rested for 30 minutes in a quiet, dimly lit, temperature-controlled room before stress testing. Mental stress was then induced by a standardized public speaking task (13), which required patients to imagine a real-life stressful situation and make up a realistic story around this scenario. They were given two minutes to prepare a speech and three minutes to deliver it in front of a video camera and a small audience. Blood samples were collected from the indwelling IV catheters before (0 minutes) stress, and at 60 and 90 minutes after the stress task for measurement of IL-6. One minute after the onset of the mental stress subjects were intravenously injected with Technetium-99m (^{99m}Tc sestamibi), followed a minimum of 45 minutes later by a gated SPECT scan. Holter recordings of rest, stress and recovery periods were obtained with a SEER device by GE and stored digitally.

Exercise Stress Procedure

Subjects underwent the Bruce protocol for exercise stress by walking on a treadmill. Exercise target was set at 85% of predicted heart rate according to the patient's sex and age. Blood samples were collected at the same times as the mental stress. Holter and SPECT scan were obtained in the same way as the mental stress test. Patients who were unable to reach target heart rate were given regadenoson 0.4 mg for ischemia testing, but were excluded from this analysis.

Measurement of TWA

The modified moving average (MMA) analysis was used to measure TWA. The MMA approach provides a robust, dynamic assessment of TWA through principles of noise reduction by filtering, exclusion of aberrant beats, and use of continuous waveform

averaging (3). MMA-based TWA studies with ambulatory ECG recordings in both exercise (14-16) and mental stress (7) scenarios validated the concept that TWA represents a continuum of risk, with higher TWA levels indicating greater risk.

In the present study, TWA was assessed quantitatively over 5-minutes intervals during rest (10 minutes after the starting of rest), stress and recovery periods (5 min after the start of recovery). The waveforms of each Holter recording were classified by software and verified by an experienced reader. After careful editing and exclusion of segments with significant artifact, TWA magnitudes were then computed, and the peak value of each interval was recorded. Two leads (II, V1) were evaluated, and the lead with higher TWA during stress for each subject was used for baseline and recovery as well. TWA was not measured in ECG portions with heart rate greater than 120 beats/min, excessive noise, or segments in which ectopic or premature beats constitute more than 20% of beats (3).

Measurements of Inflammation Markers

For IL-6 measures, blood samples were collected in EDTA tubes, placed immediately on ice, and centrifuged at 4°C for 10 minutes at 3000 rpm. Plasma was separated, coded, stored at –80°C. Study showed that IL-6 had a delayed response to acute mental stress, which went higher 45 min after stress and even higher 105min after stress but not immediately post-stress (17). Therefore, plasma IL-6 concentrations were measured by enzyme-linked immunosorbent assay (R&D Systems, Minneapolis, Minn.) at time 0 as baseline level, and at 60 min and 90 min after stress as a reflection of inflammation response in current study.

Other Measurements

Information on demographic factors (age, gender, race, education and income level) was collected using standard questionnaires from population studies. Weight and height were measured to calculate body mass index (kg/m^2). A detailed medical history including traditional CAD risk factors (hypertension, hyperlipidemia and diabetes) and medication use (angiotensin-converting-enzyme inhibitor, beta-blockers, anti-depressants and statins) was obtained by a research nurse. CAD severity was quantified using the Gensini semiquantitative angiographic scoring system (18), which was obtained from subject's angiographic data. Left ventricular ejection fraction (LVEF) was also derived from ventriculogram or echocardiogram. Beck Depression Inventory II (BDI-II) (19), a reliable and valid self-report measure of depression, was administrated to measure subject's depressive symptoms. A total score was computed as a continuous variable. The Early Trauma Inventory (ETI), an reliable and valid instrument for measurement of childhood traumatic experiences (20), was also assessed as a general stress marker. Stress induced myocardial perfusion abnormalities were detected by SPECT and quantified by means of the Emory Cardiac Toolbox software (21). Detailed method of measuring stress-induced ischemia has been described in our previous studies (12, 22).

Statistical Analysis

Analysis was computed using SAS 9.4 for Windows. Significance level was set at 0.05. For descriptive analysis, data are presented as mean ± SD for normally distributed variables, median (interquartile range, IQR) for variables with skewed distribution, or percentages when appropriate. TWA and IL-6 values were transformed logarithmically for statistical analyses to achieve a normal distribution. Repeated measures ANOVA tests

were performed for comparisons of TWA across different periods (rest, stress and recovery). Differences of TWA and IL-6 responses between mental stress and exercise were examined with paired *t* tests.

Since heart rate (HR) largely impacts the magnitude of TWA (3), we adopted the HR correction method described by Kop *et al* (5). TWA values ($\hat{y}$) were predicted by regression ($\hat{y} = a + b \times HR$) with concomitant HR measures (n= 501). Values of a and b were based on the regression equation. Residualized-TWA values were then calculated as the difference between the observed (y) and predicted ($\hat{y}$) TWA values: y -$\hat{y}$ to minimum the effect of HR on TWA. Residualized-TWAs were used to compare mental and exercise TWAs (a secondary analysis) because exercise generally causes higher heart rate elevations than mental stress, and therefore the raw TWA values could not be directly compared.

Because repeated TWA measures were taken from each patient, mixed linear regression models were constructed in multivariable analyses to examine the association of IL-6 with TWA, adjusting for possible confounding factors. The primary predictor was IL-6 at 90 minutes after stress because of a delayed response of IL-6 to mental stress. In a series of cumulative hierarchical models, we adjusted for a set of factors that were considered either possible confounding factors or mediators of the relationships under study (Figure1). IL-6 measured at other points and the changes of post-stress IL-6 from baseline were also examined respectively in multivariable models as secondary analyses.

Results

Study Population

Among the 98 participants enrolled in the study, 3 subjects were excluded from the TWA analysis for missing or poor-quality Holter data, making 95 eligible for mental-stress induced TWA analysis. For exercise induced TWA, 22 were excluded because of failure to take exercise test or to reach target heart rate, 4 were further excluded as a result of the occurrence of atrial fibrillation or excessive ventricular ectopic contractions during exercise, or poor-quality Holter data. In sum, 72 patients were available for exercise-induced TWA. Since IL-6 data were missing for some subjects, a total of 81 and 63 subjects were included in the final multivariable analyses for mental stress and exercise stress respectively (Figure2).

There are no differences of any baseline covariates between subjects who were excluded from the exercise stress analysis and those who were included. The patients with missing IL -6 data were similar to those without missing data with some exceptions; they were more likely to be women (27.7% versus 2.1% $P<0.001$), current smokers (29.6% versus 8.8%, $P=0.01$), and on anti-depressants treatment (41.7% versus 10.8%, $P=0.005$).

The mean age of included subjects was 50 years, ranging from 38 to 60. Overall, 50% of the participants were female and 54% were African-American (Table 1). Forty-five percent of the patients had an ST-elevation MI, 86% had previous revascularization procedures. Most subjects (89.5%) had preserved heart function (LVEF>40%), with the median LVEF 55% and the range from 20% to 75%. Only 6 patients (6.3%) had an LVEF less than 30%.

Stress Induced Inflammatory Response

Both mental stress and exercise resulted in significant higher IL-6 level at 90 minutes after stress compared to baseline IL-6 level (1.37±0.78 versus 1.02±0.81 *ln pg/ml*, *P*= 0.013 for mental stress; 0.98±0.70 versus 0.70±0.79 *ln pg/ml*, *P*= 0.035 for exercise; Figure 3). IL-6 levels at 60 minutes after both stresses had a trend of increase, but were not significantly higher as compared with baseline levels (1.18±0.74 versus 1.02±0.81 *ln pg/ml*, *P*=0.39 for mental stress; 0.89±0.68 versus 0.70±0.79 *ln pg/ml*, *P*=0.19 for exercise). With regard to the change of IL-6 from baseline to 90 minutes after stress, the effects of mental stress and exercise were similar (0.36±0.53 vs. 0.27±0.45 *ln pg/ml*, *P*=0.196). It is of note that baseline IL-6 level was higher with mental stress than with exercise (1.02±0.81 vs. 0.70±0.79 *ln pg/ml*, *P*<0.0001), possibly indicating that subjects already experienced some degree of stress before the speaking task.

Stress Induced TWA

Significant increases in TWA magnitudes were observed in both stresses. Mental stress induced a mean TWA magnitude of 23.2±17.1μV, as compared with a mean of 46.4±37.4μV with exercise (Table 2). After logarithmic transformation for normality, *ln* TWA was found to increase from baseline (2.42±0.57 *ln* μV) to mental stress (2.96±0.58 *ln* μV, *P*<0.0001). The magnitude decreased close to baseline level at 5 minutes after mental stress (2.50±0.65 *ln* μV, *P*=0.521). Exercise also provoked significantly higher TWA level (3.60±0.69 *ln* μV) than baseline TWA (2.62±0.58 *ln* μV, *P*<0.0001), which decreased to baseline level quickly as well. No differences in TWA magnitudes were found between rest and recovery periods for both mental stress (*P*=0.913) and exercise

(*P*=1.000). The baseline TWA with mental stress was similar to that with exercise (*P*=0.079), and so was the TWA of recovery (*P*=0.446, Figure 4).

The increase of TWA with mental stress (0.54±0.76 *ln* μV) was significantly lower than that with exercise (0.98±0.91*ln* μV, *P*=0.0003). However, exercise also induced twice heart rate response (32±15 bpm) as much as that with mental stress (16±13 bpm, *P*<0.0001). We further compared HR-adjusted TWA to account for the effect of different HR change (Table 3). The change of residualized-TWA remained higher with exercise (*P*=0.031, Table 3).

Relationship Between IL-6 and TWA

The association between IL-6 and TWA were tested by building mixed linear regression models (Table 4). IL-6 levels at 90 minutes after stress showed a positive association with mental-induced TWA in the unadjusted model (Model 1, *P*=0.043), and the association persisted after adjustments for all possible confounders and mediators (Model 6, *P*=0.047). There were no significant effects with LVEF (*P*=0.256) and mental stress-induced ischemia (*P*=0.296) on TWA in multivariable model (Model 6). A trend of negative correlation with exercise-induced TWA was found after adjustment for hierarchal sets of covariates (*P*=0.053, Table 4). Mental-stress induced TWA was also positively associated with baseline IL-6 level after adjusting for covariates (Table 5, *P*=0.049), but not in unadjusted model (*P*=0.912). Models with IL-6 at other time points or the change in IL-6 levels had no significant estimates (Table 5).

Discussion

The present study demonstrates that acute mental stress can elicit significant increases of TWA in young and middle-aged patients who have survived from a recent myocardial infarction. Although the increase in TWA with mental stress is relatively lower as compared to that with exercise, the effect of mental stress on TWA is impressive given mental stress only induces modest increases in heart rate. The mental-stress induced TWA, but not exercise-induced TWA, positively correlates with IL-6 level after stress, a measure of inflammatory response to stress. This effect is independent of cardiovascular risk factors, chronic psychological stress, heart function, mental-stress induced ischemia and medications.

The present study is the first to address the relationship between inflammatory responses and TWA in experimental mental stress test. The multivariable analyses reveal a positive association between mental-stress induced TWA and IL-6 at 90 minutes after stress despite demographic, behavioral, psychological factors, traditional cardiovascular risk factors, CAD severity, heart function, stress-induced ischemia, and medications. The reason why only IL-6 at 90 minutes, but not at baseline or 60 minutes after stress, has positive association with TWA could be partially explained by the delayed response of IL-6 to mental stress. IL-6 starts to increase about 45 minutes after mental stress rather than immediately post stress (17).

Our findings are supported by other research that has found an association between inflammation and sudden cardiac death (SCD). The Cardiovascular Health Study (CHS) with 5806 participants reported a robust association of IL-6 with SCD risk despite traditional risk factors, incident myocardial infarction, and heart failure (10),

suggesting involvement of inflammatory responses in arrhythmogenesis. Our study builds upon these findings by specifying that the inflammation induced by acute mental stress, not exercise stress, is a signal of increased repolarization heterogeneity during acute mental stress. This has implications for states of chronic mental stress such as depression, which also associates with increased inflammation (23) and may be linked to SCD (24).

A small number of studies have demonstrated that mental stress could increase TWA magnitude in ICD patients, the majority of whom had ischemic heart disease and decreased LVEF (5, 7). These findings, however, have limited generalizability, as the greatest number of SCD events occurs in patients with LVEF>35% (25, 26). Our study has consistent findings in a different sample of post-MI patients with mostly normal ejection fractions (89.5%). Of note, we did not find an interaction with systolic dysfunction. The finding of present study has important clinical implications in terms of risk stratification of mental-stress induced SCD. Mental stress is common in daily life, and avoidance of mental stress is difficult for most post-MI patients. Therefore, accurate patient stratification regarding the future risk for mental stress-induced arrhythmic events is crucial for prevention of SCD. Mental stress-induced TWA has shown a significant predictive value of VTAs similar to that for exercise-induced TWA (7). Thus, mental stress-induced TWA level may help identify high-risk population for mental-stress induced SCD. We further demonstrated higher inflammatory response to mental stress is associated with a higher level of TWA during mental stress, which may have implications on treatment and risk stratification.

The mechanism linking inflammation and mental-stress induced TWA is unclear. Yue *et. al.* found an association between ECG parameters reflecting abnormal

repolarization (prolonged QT interval, lower T wave amplitude) and elevated levels of inflammatory markers, and hypothesized an inflammation–repolarization ion channel link (27). We cannot validate this hypothesis because our primary inflammation marker was IL-6 at 90 minutes after stress, thus mental stress-induced TWA preceded the increases of IL-6. Although we did find an association of TWA with baseline IL-6 in mental stress after adjustments for covariates, the effect did not persist in unadjusted analysis and in exercise test. Therefore, further study is needed to elucidate this assumption. More likely, there may be common pathways involving autonomic activation triggered by psychological stress. In studies by Lampert *et. al.,* increased TWA correlated with increased catecholamines—a marker of sympathetic activation— during mental stress (6). Sympathetic activation during the early stages of stress induces inflammatory response as well (28). Although we have adjusted for heart rate that partially accounts for the effect of sympathetic activation, there might be residual effect on TWA beyond the effects of heart rate.

The reason why we found an opposite trend of inflammation with exercise-induced TWA may relate to the anti-inflammatory properties of exercise-induced IL-6 (29). Previous literature suggested that exercise-induced IL-6 reflects activation of the "classic" signaling pathway, with a subsequent rise in circulating levels of the anti-inflammatory cytokines and the release of cortisol from the adrenal glands (30, 31), rather than the "trans-signaling" pathway, which is associated with the pro-inflammatory effects of IL-6 pathology (31). Our study indicates the increase in IL-6 with exercise is protective with regard to SCD, which is consistent with previous studies suggesting an anti-inflammatory role of IL-6 in exercise, and may relate to long-term benefits of

physical training. The results also imply that the pathophysiological mechanisms of mental stress–induced arrhythmias and inflammatory responses differ from those induced by exercise, reflecting differential autonomic, central nervous system, and immunological responses.

Our study has several strengths. By broadly characterizing our cohort, we could adjust for an extensive number of confounding factors that are important, but not routinely assessed in clinical practice, such as psychological conditions and mental stress-induced myocardial ischemia. This can be important, as both inflammation and TWA can also increase in relation with stress-induced myocardial ischemia. Nonetheless, previous studies have suggested that mental stress-induced myocardial ischemia is not associated with TWA (5, 6). We also quantified TWA as a continuous variable in the analyses, which increased our power and overcome the small sample size (3, 32). This is justified by the dose-response relationship between cardiovascular mortality and SCD, as they increase by 55% and 58% per 20μV of TWA, respectively (16). Finally, exercise data were available as a control comparison, which provided added data that this relationship is specific to mental stress.

The study has the inherent limitations of observational studies that the findings may have been affected by residual confounding and do not establish causality. Nonetheless, the experimental design allows us to attribute within-subject changes specifically to mental or exercise stress. The findings may be generalizable only to patients aged less than 60 years with a previous MI. Therefore, larger samples in other age groups are also needed. A large number of patient also were excluded due to noise, which may have introduced bias if patients with a higher stress response were more likely

to cause motion artifact. Additionally, most patients were taking beta-blockers; although medications were held for 24 hours prior to test, the magnitudes of stress-induced TWA could still be blunted as a result of long half-lives of beta-blockers (33). Nonetheless, this may better represent daily life scenario, and was adjusted in the analysis. Finally, only one marker of inflammation was measured in our study, reducing the sensitivity with which we could measure a high inflammatory response. However, IL-6 is considered to be an excellent indicator of inflammation, as other markers such as C-reactive protein have not been noted to associate with SCD (10).

In conclusion, we found that acute mental stress can elicit significant increases of TWA in young and middle-aged post-MI patients. Patients with a higher inflammatory response during mental stress also had higher stress-induced TWA compared to those with a lower inflammatory response. A trend in the opposite direction was found for patients with high inflammatory responses to exercise. Although the mechanisms are unclear, current study provides an insight of the role of mental-stress induced inflammation in pathogenesis, risk stratification and treatment of SCD during mental stress. Additional studies that explore this relationship and translate these findings into clinical practice are needed.

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Tables

Table 1. Baseline Characteristics of Participants (n=95)

	Mean (SD) or Median (IQR) or %
Demographic and life-style factors	
Age, year	50 (6)
Female, %	49.5
Black race, %	53.7
Current smoking, %	28.4
Medical history and CHD risk factors	
ST-elevation MI, %	45.3
Time since MI, in months, Median, (IQR)	5.0 (2.0)
Hypertension, %	69.5
Hyperlipidemia, %	73.7
Diabetes, %	21.1
Revascularization, %	86.3
BMI, kg/m2	31.0 (6.4)
Coronary angiography data	
Gensini score, Median (IQR)	5 (16)
Left ventricular ejection fraction, Median (IQR)	55 (10)
Psychosocial factors	
Lifetime history of major depression, %	37.2
Current depression, %	6.3
Beck Depression Inventory II	11.1 (8.6)
Early Trauma Inventory	7.4 (5.4)

Medications, %	
Statins	87.4
Beta-Blockers	87.4
ACE Inhibitors*	53.7
Antidepressants	12.6
Myocardial Perfusion Imaging Data	
Mental stress induced ischemia, %	12.1
Exercise induced ischemia, %	18.3

*ACE Inhibitors (ACEI): angiotensin-converting-enzyme inhibitor.

Table 2. TWA and Heart Rate of Each Period in Stress Test

	Mental Stress		Exercise	
	TWA (μV)	HR (bpm)	TWA (μV)	HR (bpm)
Rest	13.0 (7.2)	66 (12)	16.1 (9.3)	69 (12)
Stress	23.2 (17.1)	82 (16)	46.4 (37.4)	101 (11)
Recovery	14.9 (9.6)	68 (12)	15.8 (7.9)	90 (10)

Table 3. Change of Residualized-TWA after Adjustment for HR

	Mental Stress	Exercise	*P*
Δ r-TWA (*ln* μV)	0.29±0.76	0.51±0.88	0.031
ΔHR (bpm)	16±13	32±15	<0.0001

Table 4. Models For TWA With IL-6 at 90 Minutes After Stress

	β	95% CI		P
Mental Stress				
Model 1	0.132	0.005	0.260	0.043
Model 2	0.116	-0.014	0.246	0.079
Model 3	0.112	-0.024	0.247	0.107
Model 4	0.126	-0.005	0.258	0.060
Model 5	0.129	-0.004	0.261	0.057
Model 6	0.128	0.002	0.255	0.047
Exercise				
Model 1	-0.157	-0.333	0.020	0.082
Model 2	-0.187	-0.370	-0.003	0.046
Model 3	-0.168	-0.344	0.008	0.062
Model 4	-0.174	-0.331	-0.016	0.031
Model 5	-0.174	-0.335	-0.012	0.035
Model 6	-0.148	-0.297	0.002	0.053

Model1. Adjust only for concomitant heart rate;
Model2. Adjust for heart rate and demographic factors (sex, black, current smoking);
Model3. Adjust for above covariates and cardiovascular risk factors (hypertension, hyperlipidemia, diabetes, BMI);
Model4. Adjust for above and type of MI (ST-elevated or non ST-elevated), mental stress (exercise)-induced ischemia, Gensini-score, LVEF, and time since MI (in month);
Model5. Adjust for above and psychosocial factors (BDI-score, ETI-score);
Model6. Adjust for above and medication (beta-blockers, statins, ACEI and antidepressants).

Table 5. Models For TWA With IL-6 at 0, 60 Minutes After Stress and Differences in IL-6

	Mental Stress					**Exercise Stress**				
	N	β	95% CI		P	N	β	95% CI		P
IL-6, 0 min	76	0.114	0.001	0.227	0.049	64	-0.084	-0.232	0.065	0.270
IL-6, 60 min	74	0.105	-0.021	0.232	0.102	63	-0.125	-0.289	0.039	0.136
$\Delta lnIL6\_1$	73	-0.053	-0.199	0.094	0.481	60	0.019	0.244	0.281	0.890
$\Delta lnIL6\_2$	73	-0.019	-0.193	0.156	0.835	60	-0.013	-0.223	0.196	0.900

$\Delta lnIL6\_1$*: change in IL-6 of 60 minutes from baseline;*
$\Delta lnIL6\_2$*: change in IL-6 of 90 minutes from baseline;*
All models were adjusted for concomitant heart rate, sex, black, current smoking, hypertension, hyperlipidemia, diabetes, BMI, type of MI (ST-elevated or non ST-elevated), mental stress (exercise)-induced ischemia, Gensini-score, LVEF, BDI-score, ETI-score, beta-blockers, statins, ACEI and antidepressants.

Figures

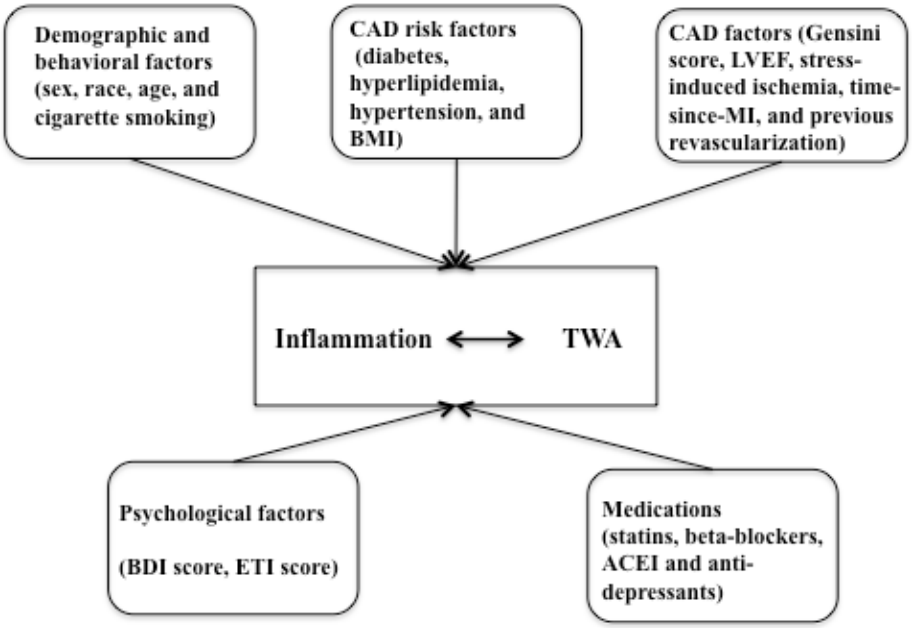

Figure 1. Covariates adjusted in multivariable analyses.

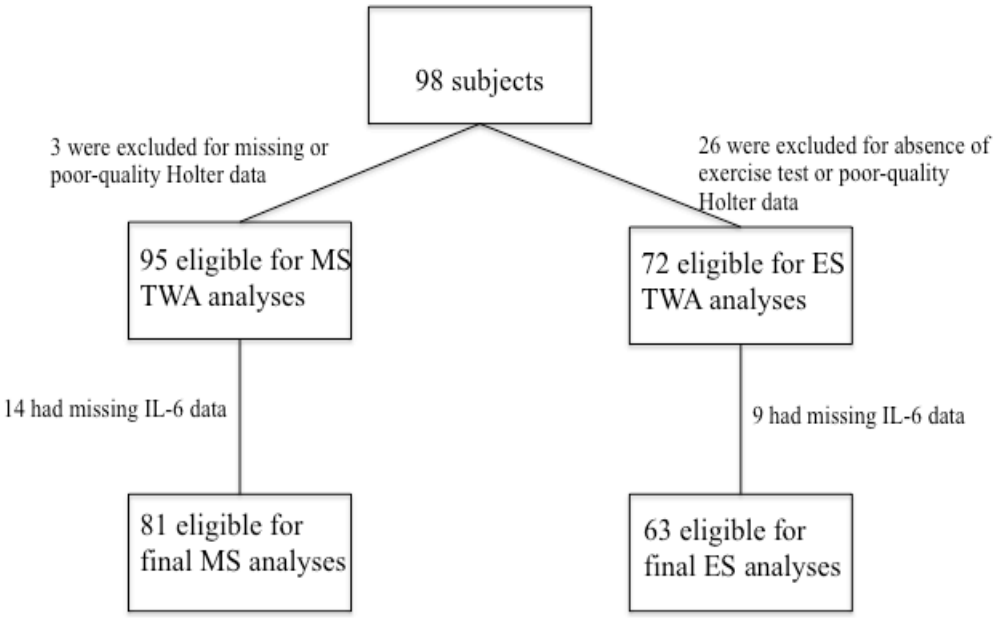

Figure 2.Study participants for each step of analyses.

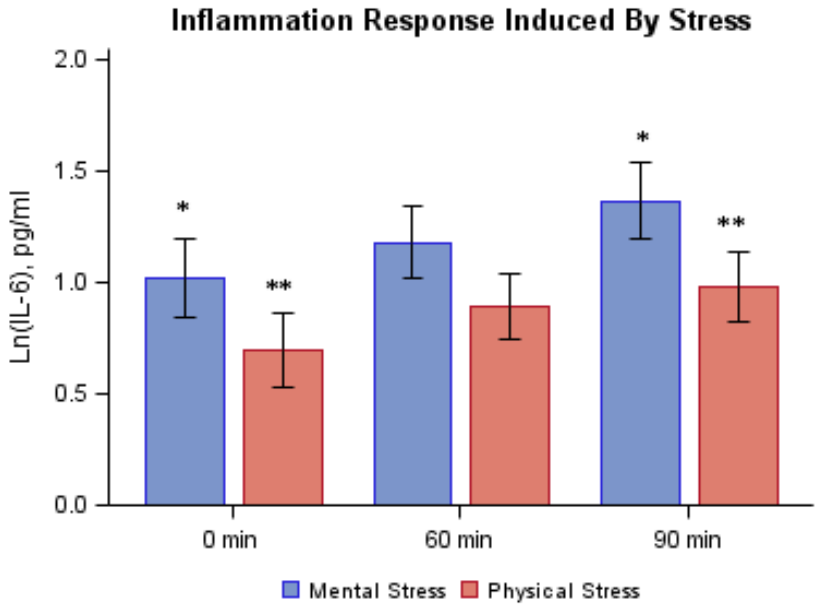

Figure 3. IL-6 Induced by Stress. The error bars represent 95% confidence intervals. There were significant differences between 90min and baseline level of IL-6 in both MS and ES (P=0.013 for mental stress, marked by *, and P=0.035 for exercise, marked by **).

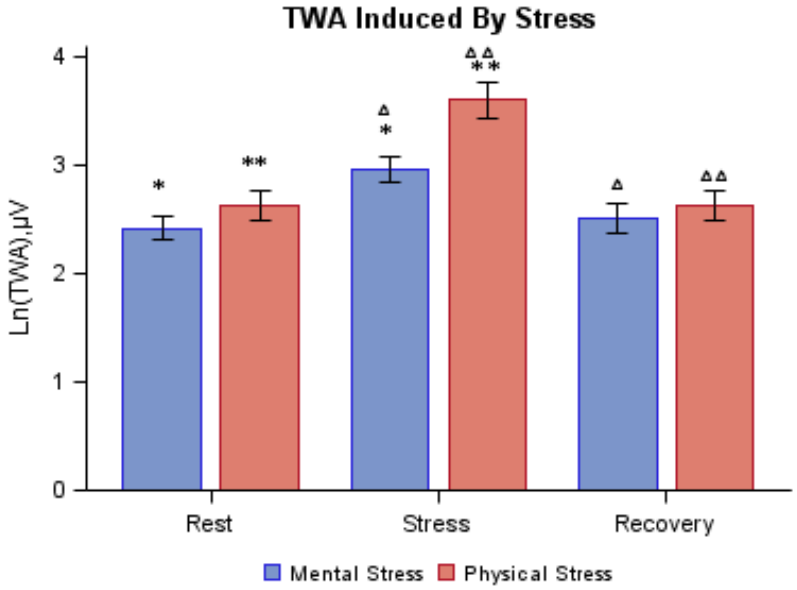

Figure 4. TWA Induced by Stress. The error bars represent 95% confidence intervals. TWAs during stresses were significantly higher than that during rest and recovery (P<0.05, marked by * and Δ for mental stress, ** and ΔΔ for exercise). No differences in TWA levels were found between rest and recovery for both stresses; the baseline and recovery TWA with mental stress were similar to that with exercise respectively (*P*>0.05).

Appendices

I. Patients inclusion and exclusion criteria for MIMS study

Inclusion Criteria:

- History of documented MI within the past 6 months
- Age 18-59

Exclusion Criteria:

- History of unstable angina, myocardial infarction, or decompensated heart failure in the past week
- Patients deemed to be unsafe to hold anti-ischemic medications for the 48 hours prior to the testing
- Systolic blood pressure >160 mm Hg or diastolic blood pressure >100 mm Hg on the day of the test
- Physical limitations with inability to exercise on a treadmill (Duke Activity Status Index [DASI]<5 METs)
- History of current alcohol or substance abuse or dependence (past year); or history of severe psychiatric disorder other than major depression, such as schizophrenia
- History of serious medical disorder other than cardiovascular disease that may interfere with the study results, e.g. cancer, renal failure
- Use of exogenous estrogens or progesterone (past 3 months)
- Current psychotropic medication treatment (past month) except treatment for depression
- Pregnancy
- Severe aortic stenosis

II. Abbreviations

MTWA or TWA: microvolt T-wave alternans

IL-6: interleukin-6

MI: myocardial infarction

SCD: sudden cardiac death

VTA: ventricular tachyarrhythmia

ICD: implantable cardioverter defibrillator

CAD: coronary artery disease

MIMS: Myocardial Infarction and Mental Stress Study

MMA: modified moving average

LVEF: left ventricular ejection fraction

SPECT: single-photon emission computed tomography

BDI: Beck Depression Inventory

ETI: Early Trauma Inventory

ACEI: angiotensin-converting-enzyme inhibitor

SD: standard deviation

IQR: interquartile range

CI: confidence interval