# Articles – Titles, References, and Abstracts about Mind on Myocardial Ischemia / Infarction

PubMed search on September 4, 2024, on this exact search query:

> ((“stress”[All Fields] OR “stressed”[All Fields] OR “stresses”[All Fields] OR “stressful”[All Fields] OR “stressfulness”[All Fields] OR “stressing”[All Fields]) AND (“social stress”[All Fields] OR “psychosocial stress”[All Fields] OR “psychophysiological stress”[All Fields] OR “mental stress”[All Fields]) AND (“myocardial infarction”[All Fields] OR “myocardial ischemia”[All Fields])) AND ((“2000"[Date – Publication] : “3000”[Date – Publication]))

This turned out 390 articles. I shifted these to extract the relevant ones, retaining 164 articles.

## Contents

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1. Cairns M, Odendaal C, O'Brien C, Marais E, Oestlund I, Storbeck KH, Sishi B, Joseph D, Smith C, Essop MF. The effects of chronic stress on rat heart function following regional ischemia: a sex-dependent investigation. Am J Physiol Heart Circ Physiol. 2024 Aug 23. doi: 10.1152/ajpheart.00424.2024. Epub ahead of print. PMID: 39178027.

Chronic psychosocial stress is a recognized, yet understudied risk factor for heart disease, with potential sex-specific effects. We investigated whether chronic stress triggers sex-dependent cardiac dysfunction in isolated Wistar rat hearts subjected to ischemia-reperfusion injury. The experimental cohort underwent 1 hour of daily restraint stress for four weeks versus matched controls, followed by euthanasia (sodium pentobarbitone) and heart excision for *ex vivo* perfusion. Blood analysis revealed sex-specific alterations in stress hormones and inflammatory markers. Compared to controls, chronic restraint stress (CRS) males displayed decreased plasma brain-derived neurotrophic factor (BDNF) levels *($p<0.05$)*, while CRS females exhibited elevated plasma adrenocorticotropic hormone (ACTH) *($p<0.01$)* and reduced corticosterone *($p<0.001$)* alongside lower serum estradiol *($p<0.001$)* and estradiol/ progesterone ratio *($p<0.01$)*. Of note, CRS females showed increased serum cardiac troponin T ($p<0.05$) and tumor necrosis factor-alpha (TNF-a) *($p<0.01$)* with suppressed interleukin (IL)-1a, IL-1β, IL-6, and IL-10 levels *($p<0.05$)* when compared to controls. *Ex vivo* Langendorff perfusions revealed that CRS female hearts displayed impaired post-ischemic functional recovery for baseline stroke volume *($p<0.01$)*, work performance *($p<0.05$)*, aortic output *($p<0.05$)*, coronary flow *($p<0.01$)*, and overall cardiac output *($p<0.01$)* when compared to matched controls and CRS males *($p<0.05$)*. Our findings reveal intriguing sex-specific responses at both the systemic and functional levels in stressed hearts. Here, the dysregulation of stress hormones, pro-inflammatory state, and potential underlying cardiomyopathy in females following the stress protocol renders them more prone to damage following

myocardial ischemia. This study emphasizes the importance of incorporating sex as a biological variable in cardiac research focusing on stress-related cardiomyopathy.

2. Liu Y, Jiang W, Wang H, Xu M, Liao Y, Zhou H, Bai B, Liu F, Yin H, Liu Q, Liang Y, Yu X, Guo L, Wang S, Ma H, Geng Q. Objective Ischemia, Subjective Angina, and Psychological Distress in Angina With No Obstructive Coronary Disease. J Am Heart Assoc. 2024 Aug 6;13(15):e034644. doi: 10.1161/JAHA.124.034644. Epub 2024 Jul 31. PMID: 39082421.

**Background:** Angina with no obstructive coronary disease (ANOCA) and ischemia with no obstructive coronary disease, prevalent yet underrecognized conditions, mostly affect women. Previous studies rarely distinguished between them. We aimed to compare the prevalence of objective ischemia through various examinations in women with ANOCA and assess the impact of objective and subjective ischemia on their mental health.

**Methods and results:** A total of 84 eligible women with ANOCA and 42 controls underwent mental stress, pharmacological stress, exercise stress, and Holter testing. Objective evidence of myocardial ischemia was assessed by positron emission tomography-computed tomography and ECG, and subjective symptoms were graded using the Canadian Cardiovascular Society scale (CCS). Psychological assessments were conducted using 6 scales. Among 84 women with ANOCA, 37 (44%) received a diagnosis of ischemia with no obstructive coronary disease following mental stress testing, 20 (28.6%) through pharmacological stress testing, 14 (21.2%) via exercise stress testing, and 24 (32.9%) from Holter. Mental stress-induced myocardial ischemia was more prevalent ($P<0.05$). Among 54 patients with ANOCA who completed all tests, 30% showed no ischemia, and only 1 (1.9%) showed ischemia in all tests. In addition, patients with ANOCA had higher psychological scores than controls ($P<0.01$). No significant differences was observed in psychological scores between ANOCA with positive and negative ischemia test results ($P>0.05$). However, ANOCA with milder angina (CCS I) exhibited higher scores across the Hospital Anxiety and Depression Scale, State-Trait Anxiety Inventory, Perceived Stress Scale, and Posttraumatic Stress Disorder Checklist-Civilian Version and a higher prevalence of Type D personality traits ($P<0.05$).

**Conclusions:** In patients with ANOCA, the positive rate of myocardial ischemia exhibits variability among several noninvasive tests. A worsened psychological state is more closely linked to milder angina symptoms than to ischemia performance, highlighting the importance of focusing on symptom management in their psychological care.

3. Peng X, Li D, Quan J, Wu C, Li H, Liu E, Hu L, Huang S, Kong L, Chen X, Yang H, Liang H, Wang S, Ma H, Geng Q. A multimodal physiological and psychological dataset for human with mental stress induced myocardial ischemia. Sci Data. 2024 Jun 27;11(1):704. doi: 10.1038/s41597-024-03462-2. PMID: 38937514; PMCID: PMC11211436.

Accurate differentiation between angina with no obstructive coronary arteries (ANOCA) and mental stress-induced myocardial ischemia (MSIMI) is crucial for tailored treatment strategies, yet public data scarcity hampers understanding. Given the higher incidence of both conditions in women, this study prospectively enrolled 80 female ANOCA and 39 age-matched female controls, subjecting them to three types of mental stress tasks. ECGs were continuously monitored across Rest, Stress, and Recover stages of the mental stress tasks, with PET/CT imaging during the Stress stage to evaluate myocardial perfusion. With PET/CT serving as the gold standard for MSIMI diagnosis, 35 of the 80 ANOCA patients were diagnosed as MSIMI. Using ECG variables from different stages of mental stress tasks, we developed five machine learning models to diagnose MSIMI. The results showed that ECG data from different stages provide valuable information for MSIMI classification. Additionally, the dataset encompassed demographic details, physiological, and blood sample test results of the patients. We anticipate this new dataset will significantly push further progress in ANOCA and MSIMI research.

4. Liu F, Wang H, Bai B, Yin H, Liu Y, Wang Y, Liu Q, Wang S, Ma H, Geng Q. Obstructive Sleep Apnea as a Key Contributor to Mental Stress-Induced Myocardial Ischemia in Female Angina Patients with No Obstructive Coronary Artery Disease. Nat Sci Sleep. 2024 Jun 17;16:823-832. doi: 10.2147/NSS.S445219. PMID: 38911317; PMCID: PMC11192149.

**Purpose:** Mental stress induced myocardial ischemia (MSIMI) is regarded as the primary cause of the angina with no obstructive coronary artery disease (ANOCA). Obstructive sleep apnea (OSA) is autonomously linked to obstructive coronary heart disease, hypertension, and sudden cardiac death. Similar to the impact of psychological stress on the cardiovascular system, individuals with OSA experience periodic nocturnal hypoxia, resulting in the activation of systemic inflammation, oxidative stress, endothelial dysfunction, and sympathetic hyperactivity. The

contribution of OSA to MSIMI in ANOCA patients is unclear. To explore the prevalence of OSA in ANOCA patients and the correlation between OSA and MSIMI, a prospective cohort of female ANOCA patients was recruited.

**Patients and methods:** We recruited female patients aged 18 to 75 years old with ANOCA and evaluated MSIMI using positron emission tomography-computed tomography. Subsequently, Level III portable monitors was performed to compare the relationship between OSA and MSIMI.

**Results:** There is higher REI (7.8 vs 2.6, *P*=0.019), ODI (4.7 vs 9.2, *P*=0.028) and percentage of OSA (67.74% vs 33.33%, *P*=0.004) in MSIMI patients. The patients diagnosed with OSA demonstrated higher myocardial perfusion imaging scores (SSS: 1.5 vs 3, *P* = 0.005, SDS: 1 vs 3, P = 0.007). Adjusted covariates, the risk of developing MSIMI remained 3.6 times higher in OSA patients (β=1.226, OR = 3.408 (1.200-9.681), *P* = 0.021).

**Conclusion:** Patients with MSIMI exhibit a greater prevalence of OSA. Furthermore, the myocardial blood flow perfusion in patients with OSA is reduced during mental stress.

5. Osei J, Vaccarino V, Wang M, Shah AS, Lampert R, Li LY, Ko YA, Pearce BD, Kutner M, Garcia EV, Piccinelli M, Raggi P, Bremner JD, Quyyumi AA, Sun YV, Ahmed H, Haddad G, Daaboul O, Roberts T, Stefanos L, Correia L, Shah AJ. Stress-Induced Autonomic Dysfunction is Associated With Mental Stress-Induced Myocardial Ischemia in Patients With Coronary Artery Disease. Circ Cardiovasc Imaging. 2024 Jun;17(6):e016596. doi: 10.1161/CIRCIMAGING.124.016596. Epub 2024 Jun 13. PMID: 38868952; PMCID: PMC11187646.

**Background:** Mental stress-induced myocardial ischemia (MSIMI) is associated with adverse cardiovascular outcomes in individuals with coronary artery disease, but the mechanisms underlying this phenomenon are unknown. We examined the relationship between stress-induced autonomic dysfunction, measured by low heart rate variability (HRV) in response to stress, and MSIMI in patients with stable coronary artery disease. We hypothesized that stress-induced autonomic dysfunction is associated with higher odds of MSIMI.

**Methods:** In 735 participants with stable coronary artery disease, we measured high- and low-frequency HRV in 5-minute intervals before and during a standardized

laboratory-based speech stressor using Holter monitoring. HRV at rest and stress were categorized into low HRV (first quartile) versus high HRV (second to fourth quartiles); the low category was used as an indicator of autonomic dysfunction. Multivariable logistic regression models were used to examine the association of autonomic dysfunction with MSIMI.

**Results:** The mean age was 58 (SD, ±10) years, 35% were women, 44% were Black participants, and 16% developed MSIMI. Compared with high HRV during stress, low HRV during stress (both high and low frequencies) was associated with higher odds of MSIMI after adjusting for demographic and clinical factors (odds ratio for high-frequency HRV, 2.1 [95% CI, 1.3-3.3]; odds ratio for low-frequency HRV, 2.1 [95% CI, 1.3-3.3]). Low-frequency HRV at rest was also associated with MSIMI but with slightly reduced effect estimates.

**Conclusions:** In individuals with coronary artery disease, mental stress-induced autonomic dysfunction may be a mechanism implicated in the causal pathway of MSIMI.

6. Kaul S. Diagnosis of Mental Stress-Induced Myocardial Ischemia: A Physician's Enigma. J Am Soc Echocardiogr. 2024 May 24:S0894-7317(24)00262-1. doi: 10.1016/j.echo.2024.05.012. Epub ahead of print. PMID: 38797331.

NO ABSTRACT

7. Kong B, Fei H, Cheng S, Ma H, Yin H, Li M, Liu Q, Liu Y, Bai B, Liu F, Guo L, Geng Q. Mental Stress-Induced Myocardial Ischemia Detected by Global Longitudinal Strain and Quantitative Myocardial Contrast Echocardiography in Women With Nonobstructive Coronary Artery Disease. J Am Soc Echocardiogr. 2024 May 16:S0894-7317(24)00231-1. doi: 10.1016/j.echo.2024.05.008. Epub ahead of print. PMID: 38761987.

**Background:** The utility of radionuclide myocardial perfusion imaging including positron emission tomography (PET) for diagnosing mental stress-induced myocardial ischemia (MSIMI) is clinically restricted. This study aims to assess the diagnostic performance of novel echocardiographic techniques, including automated

strain and quantitative myocardial contrast echocardiography (MCE) with dedicated software and deep neural network model, for MSIMI detection. The secondary objective was to explore the correlation between changes in myocardial blood flow and MSIMI.

**Methods:** Seventy-two female patients ages 18 to 75 with angina and nonobstructive coronary artery disease (ANOCA) and 23 healthy controls were prospectively recruited. Both echocardiography with contrast agent and PET imaging were performed during structured mental stress testing. Mental stress-induced myocardial ischemia was defined as a summed difference score ≥3 on PET. Echocardiographic parameters including left ventricular global longitudinal strain, β, and A × β were obtained, and their trends during mental stress testing were observed. ΔGLS was defined as the ratio of difference between global longitudinal strain values at stress and rest to the rest data. β reserve and A×β reserve were respectively calculated.

**Results:** Thirty-two ANOCA patients (44%) and 1 control (4%) were diagnosed with MSIMI ($P < .01$). For ANOCA patients with MSIMI, left ventricular GLS, β, and A × β declined to varied extents during mental stress testing compared with those without MSIMI and the controls ($P < .05$). Bland-Altman plots demonstrated good consistency between β reserve and A × β reserve output by the deep neural network model and iMCE software. Receiver operating characteristic curve analyses showed that ΔGLS, β reserve, and A × β reserve demonstrated favorable ability to predict MSIMI, especially the combination of A × β reserve using iMCE analysis and ΔGLS (area under the curve, 0.94; sensitivity, 83%; specificity, 97%).

**Conclusions:** Novel technologies in echocardiography exhibit the potential to be a clinical alternative to cardiac PET for effectively detecting MSIMI. Attenuated myocardial blood flow response during structured mental stress testing was correlated with MSIMI, providing a reasonable explanation for the chest discomfort persisting in ANOCA women.

8. Sun W, Mei L, Zhang A, Lai S, Qu X. Computed tomography myocardial perfusion imaging to detect myocardial ischemia in patients with anxiety and obstructive coronary heart disease post-exposure to mental stressors. Sci Rep. 2024 May 9;14(1):10685. doi: 10.1038/s41598-024-61568-4. PMID: 38724607; PMCID: PMC11082233.

This study aims to measure myocardial blood flow (MBF) using dynamic CT-myocardial perfusion imaging (CT-MPI) combined with mental stressors in patients with obstructive coronary artery disease (OCAD) and in patients with anxiety and no

obstructive coronary artery disease (ANOCAD). A total of 30 patients with OCAD with 30 patients with ANOCAD were included in this analysis. Using the 17-segment model, the rest and stress phase MBF of major coronary arteries in participants were recorded respectively. Compared with ANOCAD patients, OCAD patients were more likely to have localized reduction of MBF ($p < 0.05$). For patients with ANOCAD, both global MBF and MBF of the main coronary arteries in the stress phase were lower than those in the rest phase (all $p < 0.05$), but there was no significant difference in MBF among the main coronary arteries in the rest or stress phase ($p = 0.25$, $p = 0.15$). For patients with OCAD, the MBF of the target area was lower than that of the non-target area in both the rest and stress phase, and the MBF of the target area in the stress phase was lower than that in the rest phase (all $p < 0.05$). However, there was no significant difference in MBF between the rest or stress phase in the non-target area ($p = 0.73$). Under mental stress, the decrease in MBF in ANOCAD patients was diffuse, while the decrease in MBF in OCAD patients was localized. Dynamic CT-MPI combined with mental stressors can be used to detect MBF changes in anxiety patients.

9. Gaffey AE, Spatz ES. Psychological Health and Ischemic Heart Disease in Women: A Review of Current Evidence and Clinical Considerations across the Healthspan. Curr Atheroscler Rep. 2024 Mar;26(3):45-58. doi: 10.1007/s11883-023-01185-0. Epub 2024 Jan 19. PMID: 38240928; PMCID: PMC11219074.

**Purpose of review:** Psychological health encompasses a constellation of negative and positive factors-i.e., psychosocial stress, depression, anxiety, trauma, loneliness and social isolation, anger and hostility, optimism, and a sense of purpose. This narrative review presents current evidence at the intersection of psychological health, risk of ischemic heart disease (IHD), and IHD-related outcomes, with an emphasis on associations in women.

**Recent findings:** For women, relations between psychological health and IHD reflect important sex and gender differences in biological and psychosocial factors. Although efforts devoted to understanding psychological health and IHD risk have varied by psychological factor-scientific evidence is strongest for psychosocial stress and depression, while anxiety, trauma, and positive psychological factors warrant more investigation-less optimal psychological health is consistently associated with an earlier and greater risk of IHD morbidity and mortality in women. Still, many past prospective studies of psychological factors and IHD risk had a limited representation of women, did not include analyses by sex, or failed to account for other influential,

sex-specific factors. Thus, there are multiple pathways for further, rigorous investigation into psychological health-IHD associations, mechanisms, and empirically supported psychological interventions to mitigate IHD risk among women. Given the robust evidence linking psychological health with women's risk for IHD, implementing routine, brief, psychological screening is recommended. Significant life events, developmental milestones specific to women, and IHD diagnoses or events could cue further psychological assessment and referral, efforts which will mutually strengthen the evidence for integrated psychological and IHD care and delivery of such care to this vulnerable group.

### 10. Ong HT, Chen J. Mental stress, atheroma, myocardial ischaemia and injury: the link is inflammation. Gen Psychiatr. 2023 Dec 26;36(6):e101282. doi: 10.1136/gpsych-2023-101282. PMID: 38155845; PMCID: PMC10753718.

Increasing observational and experimental trial data have shown that mental stress can lead to an increase in adverse clinical cardiovascular events. Mental stress affects the heart by inducing ischaemia and precipitating myocardial infarction (MI) or direct myocardial injury. Mental stress leads to systemic inflammation. Inflammation is known to cause rapid atheromatous plaque progression, instability and thrombosis-the classic type 1 MI. Inflammation can also lead to type 2 MI or myocarditis and injury. The published data linking systemic inflammation, mental stress and cardiovascular disease will be reviewed to establish the linkage between mind and heart, thereby highlighting the importance of holistically managing the patient, not only addressing separate organ systems. Finally, recent trial evidence showing the value of anti-inflammatory drugs in cardiovascular and mental conditions will be briefly considered.

11. Moazzami K, Garcia M, Sullivan S, Lewis TT, Bremner JD, Razavi AC, Shallenberger L, Sun YV, Raggi P, Shah AJ, Quyyumi AA, Vaccarino V. Association Between Symptoms of Chronic Psychological Distress and Myocardial Ischemia Induced by Mental Stress in Patients With Coronary Artery Disease. J Am Heart Assoc. 2023 Nov 7;12(21):e030305. doi: 10.1161/JAHA.123.030305. Epub 2023 Nov 6. PMID: 37929719; PMCID: PMC10727402.

Background Mental stress-induced myocardial ischemia is a frequent phenomenon in patients with coronary artery disease and is associated with a greater risk of future cardiovascular events. The association between chronic symptoms of psychological distress and mental stress-induced ischemia is not clear. Methods and Results We used a composite score of psychological distress derived from symptoms of depression, posttraumatic stress disorder, anxiety, anger, and perceived general stress. Participants underwent myocardial perfusion imaging with both mental (public speaking task) and conventional (exercise or pharmacological) stress testing. Overall, 142 (15.9%) patients experienced mental stress-induced myocardial ischemia. After adjusting for demographic factors, medical history, and medication use, patients in the highest tertile of psychological distress score had 35% higher odds of having mental stress-induced ischemia compared to those in the lowest tertile (odds ratio [OR], 1.35 [95% CI, 1.06-2.22]). Stratified analyses showed that the association between psychological distress score and mental stress-induced myocardial ischemia was significantly associated only within the subgroup of patients with a prior myocardial infraction, with patients with a prior myocardial infarction in the highest tertile having a 93% higher odds of developing myocardial ischemia with mental stress (95% CI, 1.07-3.60). There was no significant association between psychological distress and conventional stress-induced ischemia (OR, 1.19 [95% CI, 0.87-1.63]). Conclusions Among patients with a history of myocardial infarction, a higher level of psychosocial distress is associated with mental stress-induced myocardial ischemia but not with ischemia induced by a conventional stress test.

12. Moazzami K, Cheung B, Sullivan S, Shah A, Almuwaqqat Z, Alkhoder A, Mehta PK, Pearce BD, Shah AJ, Martini A, Obideen M, Nye J, Bremner JD, Vaccarino V, Quyyumi AA. Hemodynamic Reactivity to Mental Stress in Patients With Coronary Artery Disease. JAMA Netw Open. 2023 Oct 2;6(10):e2338060. doi: 10.1001/jamanetworkopen.2023.38060. PMID: 37847500; PMCID: PMC10582791.

**Importance:** The clinical significance of hemodynamic reactivity to mental stress in the population with coronary artery disease (CAD) is unclear.

**Objective:** To investigate the association between hemodynamic reactivity to mental stress and the risk of adverse cardiovascular events in patients with stable CAD.

**Design, setting, and participants:** This cohort study included individuals with stable CAD from 2 prospective studies from a university-based hospital network: the Mental Stress Ischemia Prognosis Study (MIPS) and the Myocardial Infarction and Mental Stress Study 2 (MIMS2). Participants were enrolled between June 2011 and March 2016 and followed up for a median of 6.0 (IQR, 5.6-6.0) years in MIPS and 4.6 (IQR, 3.8-5.3) years in MIMS2. Data were analyzed from December 1, 2022, to February 15, 2023.

**Exposures:** The rate-pressure product (RPP) was calculated as the mean systolic blood pressure times the mean heart rate at rest. Rate-pressure product reactivity was calculated as the maximum RPP during a standardized mental stress test minus the RPP at rest.

**Main outcomes and measures:** The primary outcome was a composite of cardiovascular death or nonfatal myocardial infarction. The secondary end point additionally included hospitalizations for heart failure.

**Results:** From the total of 938 individuals from the pooled cohort (mean [SD] age, 60.2 [10.1] years; 611 [65.1%] men), 631 participated in MIPS and 307 in MIMS2. A total of 373 individuals (39.8%) were Black, 519 (55.3%) were White, and 46 (4.9%) were of unknown race or ethnicity. The RPP increased by a mean (SD) of 77.1% (23.1%) during mental stress (mean [SD] absolute change, 5651 [2878]). For every SD decrease in RPP reactivity with mental stress, the adjusted hazard ratios for the primary and secondary end points were 1.30 (95% CI, 1.04-1.72) and 1.30 (95% CI, 1.06-1.56), respectively, in MIPS and 1.41 (95% CI, 1.06-1.97) and 1.21 (95% CI, 1.02-1.60), respectively, in MIMS2. In the pooled sample, when RPP reactivity to mental stress was added to a model including traditional clinical risk characteristics, model

discrimination for adverse events improved (increase in C statistic of 5% for the primary end point; P = .009).

**Conclusions and relevance:** In this cohort study of individuals with stable CAD, a blunted cardiovascular reactivity to mental stress was associated with adverse outcomes. Future studies are needed to assess the clinical utility of mental stress reactivity testing in this population.

13. Almuwaqqat Z, Garcia EV, Cooke CD, Garcia M, Shah AJ, Elon L, Ko YA, Sullivan S, Nye J, Van Assen M, De Cecco C, Raggi P, Bremner JD, Quyyumi AA, Vaccarino V. Quantitation of diffuse myocardial ischemia with mental stress and its association with cardiovascular events in individuals with recent myocardial infarction. J Nucl Cardiol. 2023 Oct;30(5):2029-2038. doi: 10.1007/s12350-023-03212-8. Epub 2023 Mar 29. PMID: 36991249; PMCID: PMC11057358.

Microcirculatory dysfunction during psychological stress may lead to diffuse myocardial ischemia. We developed a novel quantification method for diffuse ischemia during mental stress (dMSI) and examined its relationship with outcomes after a myocardial infarction (MI). We studied 300 patients ≤ 61 years of age (50% women) with a recent MI. Patients underwent myocardial perfusion imaging with mental stress and were followed for 5 years. dMSI was quantified from cumulative count distributions of rest and stress perfusion. Focal ischemia was defined in a conventional fashion. The main outcome was a composite outcome of recurrent MI, heart failure hospitalizations, and cardiovascular death. A dMSI increment of 1 standard deviation was associated with a 40% higher risk for adverse events (HR 1.4, 95% CI 1.2-1.5). Results were similar after adjustment for viability, demographic and clinical factors and focal ischemia. In sex-specific analysis, higher levels of dMSI (per standard deviation increment) were associated with 53% higher risk of adverse events in women (HR 1.5, 95% CI 1.2-2.0) but not in men (HR 0.9, 95% CI 0.5-1.4), P 0.001. A novel index of diffuse ischemia with mental stress was associated with recurrent events in women but not in men after MI.

14. Sun W, Zhang A, Mei L, Liu X, Li Z, Qu X. Dynamic myocardial perfusion computed tomography with mental stress test to detect changes in myocardial microcirculation in patients with anxiety and no obstructive coronary artery disease. Eur Radiol. 2023 Sep;33(9):6522-6533. doi: 10.1007/s00330-023-09607-y. Epub 2023 Apr 10. PMID: 37036482.

**Objective:** Mental stress can induce myocardial ischemia in patients with anxiety and other psychological disorders. Computed tomography myocardial perfusion imaging (CT-MPI) has the potential to quantitatively diagnose myocardial ischemia. The aim of this study was to measure changes in myocardial microcirculation perfusion (MMP) in patients with anxiety who have angina symptoms/ischemia but no obstructive coronary artery disease (INOCA) using dynamic CT-MPI in combination with a mental stress test.

**Methods:** Patients with INOCA were divided into five subgroups (none, minimal, mild, moderate, and severe) according to the generalized anxiety disorder scale. Patients underwent dynamic CT-MPI with mental stress testing using a series of the standardized color word/arithmetic stressors. Myocardial blood flow (MBF) during resting and stress phases of CT-MPI was recorded.

**Results:** Fifty-eight patients with 986 segments were included for final analysis. Compared to patients with none, minimal, mild, and moderate anxiety, those with severe anxiety had the largest rate of MBF decrease and the largest MBF decrease value. At the same time, those with no anxiety had the largest rate of MBF increase, the largest MBF increase value (all $p < 0.05$). As anxiety intensified, the rate of MBF increased and the MBF value increased ($r = -0.24$, $r = -0.27$, $p < 0.05$). Concomitantly, the rate of MBF decreased and the MBF value decreased ($r = 0.63$, $r = 0.43$, $p < 0.05$).

**Conclusions:** Dynamic CT-MPI with a mental stress test can be used to evaluate MMP in patients with anxiety and INOCA. Mental stress resulted in significant differences in changes in the rate and value of MBF among patients with different anxiety degrees.

**Key points:** • Dynamic CT-MPI with mental stress test worked well to quantitatively evaluate myocardial microcirculation perfusion in patients with anxiety and INOCA. • The rates of MBF decrease and MBF decrease value were positively correlated with anxiety degree of anxiety patients with INOCA. • MBF change derived from CT-MPI with mental stress test had a good performance to predicting anxiety degree of patients with anxiety and INOCA.

15. Nawar A, Gazi AH, Chan M, Sanchez-Perez JA, Rahman FN, Ziegler C, Daaboul O, Haddad G, Al-Abboud OA, Ahmed H, Murrah N, Vaccarino V, Shah AJ, Inan OT. Towards Quantifying Stress in Patients with a History of Myocardial Infarction: Validating ECG-Derived Patch Features. Annu Int Conf IEEE Eng Med Biol Soc. 2023 Jul;2023:1-4. doi: 10.1109/EMBC40787.2023.10340614. PMID: 38083211.

Patients with prior myocardial infarction (MI) have an increased risk of experiencing a secondary event which is exacerbated by mental stress. Our team has developed a miniaturized patch with the capability to capture electrocardiogram (ECG), seismocardiogram (SCG) and photoplethysmogram (PPG) signals which may provide multimodal information to characterize stress responses within the post-MI population in ambulatory settings. As ECG-derived features have been shown to be informative in assessing the risk of MI, a critical first step is to ensure that the patch ECG features agree with gold-standard devices, such as the Biopac. However, this is yet to be done in this population. We, thus, performed a comparative analysis between ECG-derived features (heart rate (HR) and heart rate variability (HRV)) of the patch and Biopac in the context of stress. Our dataset contained post-MI and healthy control subjects who participated in a public speaking challenge. Regression analyses for patch and Biopac HR and HRV features (RMSSD, pNN50, SD1/SD2, and LF/HF) were all significant ($p<0.001$) and had strong positive correlations ($r>0.9$). Additionally, Bland-Altman analyses for most features showed tight limits of agreement: 0.999 bpm (HR), 11.341 ms (RMSSD), 0.07% (pNN50), 0.146 ratio difference (SD1/SD2), 0.750 ratio difference (LF/HF).Clinical relevance- This work demonstrates that ECG-derived features obtained from the patch and Biopac are in agreement, suggesting the clinical utility of the patch in deriving quantitative metrics of physiology during stress in post-MI patients. This has the potential to improve post-MI patients' outcomes, but needs to be further evaluated.

16. Dhaibar HA, Kamberov L, Carroll NG, Amatya S, Cosic D, Gomez-Torres O, Vital S, Sivandzade F, Bhalerao A, Mancuso S, Shen X, Nam H, Orr AW, Dudenbostel T, Bailey SR, Kevil CG, Cucullo L, Cruz-Topete D. Exposure to Stress Alters Cardiac Gene Expression and Exacerbates Myocardial Ischemic Injury in the Female Murine Heart. Int J Mol Sci. 2023 Jul 1;24(13):10994. doi: 10.3390/ijms241310994. PMID: 37446174; PMCID: PMC10341935.

Mental stress is a risk factor for myocardial infarction in women. The central hypothesis of this study is that restraint stress induces sex-specific changes in gene expression in the heart, which leads to an intensified response to ischemia/reperfusion injury due to the development of a pro-oxidative environment in female hearts. We challenged male and female C57BL/6 mice in a restraint stress model to mimic the effects of mental stress. Exposure to restraint stress led to sex differences in the expression of genes involved in cardiac hypertrophy, inflammation, and iron-dependent cell death (ferroptosis). Among those genes, we identified tumor protein p53 and cyclin-dependent kinase inhibitor 1A (p21), which have established controversial roles in ferroptosis. The exacerbated response to I/R injury in restraint-stressed females correlated with downregulation of p53 and nuclear factor erythroid 2-related factor 2 (Nrf2, a master regulator of the antioxidant response system-ARE). S-female hearts also showed increased superoxide levels, lipid peroxidation, and prostaglandin-endoperoxide synthase 2 (Ptgs2) expression (a hallmark of ferroptosis) compared with those of their male counterparts. Our study is the first to test the sex-specific impact of restraint stress on the heart in the setting of I/R and its outcome.

17. Gupta MD, Kunal S, Jha M, Girish MP, Mishra P, Shukla M, Bundela N, Batra V, Bansal A, Mukhopadhyay S, Yusuf J. Psychosocial stress and well-being in patients presenting with acute myocardial infarction in a tertiary care center. Indian Heart J. 2023 Jul-Aug;75(4):298-303. doi: 10.1016/j.ihj.2023.06.006. Epub 2023 Jun 14. PMID: 37328136; PMCID: PMC10421977.

**Background:** Psychosocial factors such as stress have been previously implicated as a risk factor for cardiovascular diseases (CVDs). There is little evidence regarding the prevalence of stress among patients with acute myocardial infarction (AMI).

**Methods:** A total of 903 patients with AMI enrolled in the North Indian ST-Segment Elevation Myocardial Infarction (NORIN-STEMI) registry were included in this study. Perceived stress in these subjects was evaluated using the Perceived Stress Scale-10 questionnaire while the World health Organization (WHO-5) Well-being Index was used to evaluate psychological well-being. All these patients were followed up for one month and major adverse cardiac events (MACE) were determined.

**Results:** A majority of patients with AMI had either severe (478 [52.9%]) or moderate stress (347 [38.4%]) while low stress levels were observed in 78 [8.6%] patients. Additionally, most of the patients with AMI (478 [53%]) had WHO-5 well-being index <50%. Subjects with severe stress were younger (50.86 ± 13.31; P < 0.0001), more likely to be males (403 [84.30%]; P = 0.027), were less likely to have optimal level of physical activity (P < 0.0001) and had lower WHO-5 well-being score (45.54 ± 1.94%; P < 0.0001) as compared to those with low and moderate stress levels. On 30-days follow-up, subjects with moderate/severe stress had higher MACE however, the difference was non-significant (2.1% vs 1.04%; P = 0.42).

**Conclusion:** A high prevalence of perceived stress and low well-being index was observed in patients presenting with AMI in India.

18. Helman TJ, Headrick JP, Stapelberg NJC, Braidy N. The sex-dependent response to psychosocial stress and ischaemic heart disease. Front Cardiovasc Med. 2023 Apr 21;10:1072042. doi: 10.3389/fcvm.2023.1072042. PMID: 37153459; PMCID: PMC10160413.

Stress is an important risk factor for modern chronic diseases, with distinct influences in males and females. The sex specificity of the mammalian stress response contributes to the sex-dependent development and impacts of coronary artery disease (CAD). Compared to men, women appear to have greater susceptibility to chronic forms of psychosocial stress, extending beyond an increased incidence of mood disorders to include a 2- to 4-fold higher risk of stress-dependent myocardial infarction in women, and up to 10-fold higher risk of Takotsubo syndrome-a stress-dependent coronary-myocardial disorder most prevalent in post-menopausal women. Sex differences arise at all levels of the stress response: from initial perception of stress to behavioural, cognitive, and affective responses and longer-term disease outcomes. These fundamental differences involve interactions between chromosomal and gonadal determinants, (mal)adaptive epigenetic modulation across the lifespan (particularly in early life), and the extrinsic influences of socio-cultural, economic, and environmental factors. Pre-clinical investigations of biological

mechanisms support distinct early life programming and a heightened corticolimbic-noradrenaline-neuroinflammatory reactivity in females vs. males, among implicated determinants of the chronic stress response. Unravelling the intrinsic molecular, cellular and systems biological basis of these differences, and their interactions with external lifestyle/socio-cultural determinants, can guide preventative and therapeutic strategies to better target coronary heart disease in a tailored sex-specific manner.

19. Bremner JD, Piccinelli M, Garcia EV, Moncayo VM, Elon L, Nye JA, Cooke CD, Washington BP, Ortega RA, Desai SR, Okoh AK, Cheung B, Soyebo BO, Shallenberger LH, Raggi P, Shah AJ, Daaboul O, Jajeh MN, Ziegler C, Driggers EG, Murrah N, De Cecco CN, van Assen M, Krafty RT, Quyyumi AA, Vaccarino V. A Pilot Study of Neurobiological Mechanisms of Stress and Cardiovascular Risk. Med Res Arch. 2023 Apr;11(4):3787. doi: 10.18103/mra.v11i4.3787. Epub 2023 Apr 25. PMID: 37484871; PMCID: PMC10361343.

**Objective:** Coronary heart disease is a leading cause of death and disability. Although psychological stress has been identified as an important potential contributor, mechanisms by which stress increases risk of heart disease and mortality are not fully understood. The purpose of this study was to assess mechanisms by which stress acts through the brain and heart to confer increased CHD risk.

**Methods:** Coronary Heart Disease patients (N=10) underwent cardiac imaging with [Tc-99m] sestamibi single photon emission tomography at rest and during a public speaking mental stress task. Patients returned for a second day and underwent positron emission tomography imaging of the brain, heart, bone marrow, aorta (indicating inflammation) and subcutaneous adipose tissue, after injection of [$^{18}$F]2-fluoro-2-deoxyglucose for assessment of glucose uptake followed mental stress. Patients with (N=4) and without (N=6) mental stress-induced myocardial ischemia were compared for glucose uptake in brain, heart, adipose tissue and aorta with mental stress.

**Results:** Patients with mental stress-induced ischemia showed a pattern of increased uptake in the heart, medial prefrontal cortex, and adipose tissue with stress. In the heart disease group as a whole, activity increase with stress in the medial prefrontal brain and amygdala correlated with stress-induced increases in spleen ($r=0.69$, $p=0.038$; and $r=0.69$, $p=0.04$ respectfully). Stress-induced frontal lobe increased uptake correlated with stress-induced aorta uptake ($r=0.71$, $p=0.016$). Activity in

insula and medial prefrontal cortex was correlated with post-stress activity in bone marrow and adipose tissue. Activity in other brain areas not implicated in stress did not show similar correlations. Increases in medial prefrontal activity with stress correlated with increased cardiac glucose uptake with stress, suggestive of myocardial ischemia (r=0.85, p=0.004).

**Conclusions:** These findings suggest a link between brain response to stress in key areas mediating emotion and peripheral organs involved in inflammation and hematopoietic activity, as well as myocardial ischemia, in Coronary Heart Disease patients.

20. Kim JH, Almuwaqqat Z, Martini A, Liu C, Ko YA, Sullivan S, Dong T, Shah AJ, Bremner JD, Pearce BD, Nye JA, Vaccarino V, Quyyumi AA. Mental Stress-Induced Change in Plasma Stromal Cell-Derived Factor-1 and Adverse Cardiovascular Outcomes: A Cohort Study. CJC Open. 2023 Jan 28;5(4):325-332. doi: 10.1016/j.cjco.2023.01.006. PMID: 37124969; PMCID: PMC10140748.

**Background:** Acute psychological stress can provoke mental stress-induced myocardial ischemia (MSIMI) in coronary artery disease (CAD). Stromal cell-derived factor 1 (SDF1) is released in response to hypoxia, and higher levels of SDF1 are associated with adverse outcomes. We examined whether an increase in SDF1 level in response to mental stress predicts adverse outcomes in CAD patients.

**Methods:** A total of 554 patients with stable CAD (mean age 63 years; 76% male; 26% Black) underwent standardized mental stress testing. Plasma SDF1 levels were measured at rest and 90 minutes after mental stress, and MSIMI was evaluated by 99mTc-sestamibi perfusion imaging. Participants were followed for 5 years for the primary endpoint of composite of death and myocardial infarction (MI) and the secondary endpoint of composite of death, MI, and heart failure hospitalization. Cox hazard models were used to assess the association between SDF1 change and incident adverse events.

**Results:** Mean (standard deviation) SDF1 change with mental stress was +56.0 (230) pg/mL. During follow-up, a rise of 1 standard deviation in SDF1 with mental stress was associated with a 32% higher risk for the primary endpoint of death and MI (95% confidence interval, 6%-64%), independent of the resting SDF1 level, demographic and clinical risk factors, and presence of ischemia. A rise of 1 standard deviation in SDF1 was associated with a 33% (95% confidence interval, 11%-59%) increase in the

risk for the secondary endpoint, independent of the resting SDF1 level, demographic, and clinical risk factors and presence of ischemia.

**Conclusions:** An increase in SDF1 level in response to mental stress is associated with a higher risk of adverse events in stable CAD, independent of MSIMI.

21. Sullivan S, Young A, Garcia M, Almuwaqqat Z, Moazzami K, Hammadah M, Lima BB, Hu Y, Jajeh MN, Alkhoder A, Elon L, Lewis TT, Shah AJ, Mehta PK, Bremner JD, Quyyumi AA, Vaccarino V. Sex Differences in Vascular Response to Mental Stress and Adverse Cardiovascular Events Among Patients With Ischemic Heart Disease. Arterioscler Thromb Vasc Biol. 2023 Apr;43(4):e112-e120. doi: 10.1161/ATVBAHA.122.318576. Epub 2023 Mar 1. PMID: 36857628; PMCID: PMC10164352.

**Background:** Microvascular measures of vascular dysfunction during acute mental stress may be important determinants of major adverse cardiovascular events (MACE), especially among younger and middle-aged women survivors of an acute myocardial infarction.

**Methods:** In the MIMS2 study (Myocardial Infarction and Mental Stress 2), individuals who had been hospitalized for a myocardial infarction in the past 8 months were prospectively followed for 5 years. MACE was defined as a composite index of cardiovascular death and first/recurring events for nonfatal myocardial infarction and hospitalizations for heart failure. Reactive hyperemia index and flow-mediated dilation were used to measure microvascular and endothelial function, respectively, before and 30 minutes after a public-speaking mental stress task. Survival models for recurrent events were used to examine the association between vascular response to stress (difference between poststress and resting values) and MACE. Reactive hyperemia index and flow-mediated dilation were standardized in analyses.

**Results:** Of 263 patients (the mean age was 51 years; range, 25-61), 48% were women, and 65% were Black. During a median follow-up of 4.3 years, 64 patients had 141 adverse cardiovascular events (first and repeated). Worse microvascular response to stress (for each SD decrease in the reactive hyperemia index) was associated with 50% greater risk of MACE (hazard ratio, 1.50 [95% CI, 1.05-2.13]; $P$=0.03) among women only (sex interaction: $P$=0.03). Worse transient endothelial dysfunction in response to stress (for each SD decrease in flow-mediated dilation) was associated with a 35% greater risk of MACE (hazard ratio, 1.35 [95% CI, 1.07-1.71]; $P$=0.01), and the association was similar in women and men.

**Conclusions:** Peripheral microvascular dysfunction with mental stress was associated with adverse events among women but not men. In contrast, endothelial dysfunction was similarly related to MACE among both men and women. These results suggest a female-specific mechanism linking psychological stress to adverse outcomes.

22. Mehta PK, Sharma A, Bremner JD, Vaccarino V. Mental Stress-Induced Myocardial Ischemia. Curr Cardiol Rep. 2022 Dec;24(12):2109-2120. doi: 10.1007/s11886-022-01821-2. Epub 2022 Nov 2. PMID: 36322365; PMCID: PMC9628301.

**Purpose of review:** To summarize recent evidence on mental stress-induced myocardial ischemia (MSIMI), its mechanisms, and clinical significance.

**Recent findings:** MSIMI can occur in patients with normal cardiac stress testing, is only weakly related to severity of coronary artery disease (CAD), and it is often silent. Among patients with CAD, MSIMI is associated with a twofold increased risk of major adverse cardiovascular events compared to those who do not have MSIMI. Certain groups such as young women with myocardial infarction and those with psychological comorbidities are more susceptible to MSIMI. Abnormal microvascular vasoreactivity and inflammation are implicated mechanisms in MSIMI. Increased brain activity in regions that modulate autonomic reactivity to emotional stress and fear is associated with MSIMI. MSIMI has important prognostic implications in patients with CAD. Stress can no longer be ignored as a risk factor in cardiology care. Clinical trials testing effective strategies to target MSIMI are needed.

23. Suglia SF, Hardy ST, Cammack AL, Kim YJ, Pearce BD, Shah AJ, Sullivan S, Wittbrodt M, Bremner JD, Vaccarino V. Child Maltreatment and Inflammatory Response to Mental Stress Among Adults Who Have Survived a Myocardial Infarction. Psychosom Med. 2022 Nov-Dec 01;84(9):1013-1020. doi: 10.1097/PSY.0000000000001114. Epub 2022 Aug 2. PMID: 35980788; PMCID: PMC9643601.

**Objective:** Experiences of child maltreatment are associated with cardiovascular risk and disease in adulthood; however, the mechanisms underlying these associations are poorly understood.

**Methods:** We examined associations between retrospectively self-reported exposure to child maltreatment (Early Trauma Inventory Self-Report Short Form) and

inflammatory responses to mental stress among adults (mean age = 50 years) who recently had a myocardial infarction ( n = 227). Inflammation was assessed as blood interleukin-6 (IL-6), matrix metalloproteinase-9 (MMP-9), and monocyte chemoattractant protein-1 concentrations, measured before and after a standardized public speaking stress task. We used mixed linear regression models adjusting for cardiovascular disease severity, medication usage, and psychosocial, demographic, and life-style factors.

**Results:** In women, increases in IL-6 levels and MMP-9 levels with stress were smaller in those exposed to sexual abuse, relative to those unexposed (IL-6 geometric mean increases = 1.6 [95% confidence interval {CI} = 1.4-1.9] pg/ml versus 2.1 [95% CI = 1.8-2.4] pg/ml; MMP-9 geometric mean increases = 1.0 [95% CI = 0.9-1.2] ng/ml versus 1.2 [95% CI = 1.1-1.4] ng/ml). No differences were noted for emotional or physical abuse. By contrast in men, individuals exposed to sexual abuse had larger IL-6 responses than those not exposed to abuse.

**Conclusions:** These findings suggest sex differences in stress response among survivors of a myocardial infarction exposed to abuse early in life. They also underscore the importance of examining sex as an effect modifier of relationships between exposure to early life adversity and inflammatory responses to mental stressors in midlife.

24. Sullivan S, Young A, Garcia M, Almuwaqqat Z, Moazzami K, Hammadah M, Lima BB, Driggers EG, Levantsevych O, Alkhalaf M, Jajeh MN, Alkhoder A, Elon L, Gooding H, Lewis TT, Shah AJ, Bremner JD, Quyyumi AA, Vaccarino V. Gender Disparities Between Neighborhood Social Vulnerability and Psychological Distress Among Patients with Heart Disease. J Womens Health (Larchmt). 2022 Oct;31(10):1440-1449. doi: 10.1089/jwh.2021.0505. Epub 2022 Aug 12. PMID: 35960809; PMCID: PMC9618377.

***Background:*** Psychological stress disorders are twice as prevalent in women with ischemic heart disease compared to men. The disproportionate psychological health experience of these women is not well understood. The objective of this study was to examine whether neighborhood social factors are associated with disparities in psychological health by gender. ***Materials and Methods:*** We studied 286 patients with heart disease recruited from Emory-based hospitals in the Myocardial Infarction and Mental Stress 2 Study (*n* = 286). A global measure of psychological distress was

calculated by taking an average of ranks across symptom scales for depression, post-traumatic stress disorder, anxiety, anger, and perceived stress. The social vulnerability index (SVI) was developed by the Centers for Disease Control and Prevention and was used to rank patients' census tracks on 14 social factors. Beta coefficients for mean ranks in psychological distress scores were estimated per 10-unit increase in SVI percentile ranking using multilevel regression models. ***Results:*** The mean age of the sample was 51 years, 49% were women, and 66% African American. After adjusting for demographics, cardiovascular risk factors, and antidepressant use, each 10-unit increase in SVI percentile ranking was associated with 4.65 (95% CI: 0.61-8.69; $p$ = 0.02) unit increase in mean scores for psychological distress among women only (SVI-by-gender-interaction = 0.01). These associations were driven by the SVI themes of lower socioeconomic status and poorer access to housing and transportation. ***Conclusion:*** Neighborhood social vulnerability may be a psychosocial stressor that potentiates women's susceptibility to adverse psychological and cardiovascular health.

25. Poitras M, Narvaez Linares NF, Lambert M, Browndyke JN, Plamondon H. Women with Myocardial Infarction Present Subtle Cognitive Difficulties on a Neuropsychological Battery After Exposure to a Social Stressor. Psychol Res Behav Manag. 2022 Sep 23;15:2761-2771. doi: 10.2147/PRBM.S379381. PMID: 36176378; PMCID: PMC9514296.

**Objective:** Myocardial infarction (MI) is the primary cause of mortality and morbidity in women, but its sequelae remain largely understudied. Given the heart-brain relationship, our study aimed to further understand stress's impact on regulating cognitive function post-MI. Specifically, our study evaluated the effect of stress induced using the Trier Social Stress Test (TSST), on neuropsychological function in women who have or have not experienced MI.

**Methodology:** To do so, women (mean age = 59.41 yrs) with ($WHx_{MI}$ = 13) or without () a history of MI were exposed to the TSST prior to completion of a series of standardized neuropsychological tests: the Montreal Cognitive Assessment (MoCA), Control Oral Word Association (COWA), Rey Complex Figure and Recognition (RCFT), Trail Making Test (TMT), and Auditory Consonant Triagrams (ACT).

**Results:** Our findings support MI to be associated with impairments in working memory affecting immediate recall of ACT, as well as visuospatial impairments in the RCFT copy trial, marked by poorer drawing accuracy and incorrect placement of

figure elements. Overall, $WHx_{MI}$ required more time to complete the neuropsychological assessment ($WHx_{MI}$ 166.57 ± 12, 155.00 ± 6.57; $p < 0.01$).

**Conclusion:** Together, these findings support cognitive impairments noted following a social stressor to remain subtle in $WHx_{MI}$. Our study highlights the need for the development of more sensitive tools to screen for neuropsychological impairments in women with MI and the importance of assessing performance in a variety of testing conditions.

## 26. Vancheri F, Longo G, Vancheri E, Henein MY. Mental Stress and Cardiovascular Health-Part I. J Clin Med. 2022 Jun 10;11(12):3353. doi: 10.3390/jcm11123353. PMID: 35743423; PMCID: PMC9225328.

Epidemiological studies have shown that a substantial proportion of acute coronary events occur in individuals who lack the traditional high-risk cardiovascular (CV) profile. Mental stress is an emerging risk and prognostic factor for coronary artery disease and stroke, independently of conventional risk factors. It is associated with an increased rate of CV events. Acute mental stress may develop as a result of anger, fear, or job strain, as well as consequence of earthquakes or hurricanes. Chronic stress may develop as a result of long-term or repetitive stress exposure, such as job-related stress, low socioeconomic status, financial problems, depression, and type A and type D personality. While the response to acute mental stress may result in acute coronary events, the relationship of chronic stress with increased risk of coronary artery disease (CAD) is mainly due to acceleration of atherosclerosis. Emotionally stressful stimuli are processed by a network of cortical and subcortical brain regions, including the prefrontal cortex, insula, amygdala, hypothalamus, and hippocampus. This system is involved in the interpretation of relevance of environmental stimuli, according to individual's memory, past experience, and current context. The brain transduces the cognitive process of emotional stimuli into hemodynamic, neuroendocrine, and immune changes, called fight or flight response, through the autonomic nervous system and the hypothalamic-pituitary-adrenal axis. These changes may induce transient myocardial ischemia, defined as mental stress-induced myocardial ischemia (MSIMI) in patients with and without significant coronary obstruction. The clinical consequences may be angina, myocardial infarction, arrhythmias, and left ventricular dysfunction. Although MSIMI is associated with a substantial increase in CV mortality, it is usually underestimated because it arises without pain in most cases. MSIMI occurs at lower levels of cardiac work than exercise-induced ischemia, suggesting that the impairment of myocardial blood flow

is mainly due to paradoxical coronary vasoconstriction and microvascular dysfunction.

27. Dasa O, Mahmoud AN, Kaufmann PG, Ketterer M, Light KC, Raczynski J, Sheps DS, Stone PH, Handberg E, Pepine CJ. Relationship of Psychological Characteristics to Daily Life Ischemia: An Analysis From the National Heart, Lung, and Blood Institute Psychophysiological Investigations in Myocardial Ischemia. Psychosom Med. 2022 Apr 1;84(3):359-367. doi: 10.1097/PSY.0000000000001044. PMID: 35067655; PMCID: PMC8976783.

**Objective:** Cardiac ischemia during daily life is associated with an increased risk of adverse outcomes. Mental stress is known to provoke cardiac ischemia and is related to psychological variables. In this multicenter cohort study, we assessed whether psychological characteristics were associated with ischemia in daily life.

**Methods:** This study examined patients with clinically stable coronary artery disease (CAD) with documented cardiac ischemia during treadmill exercise (n = 196, mean [standard deviation] age = 62.64 [8.31] years; 13% women). Daily life ischemia (DLI) was assessed by 48-hour ambulatory electrocardiophic monitoring. Psychological characteristics were assessed using validated instruments to identify characteristics associated with ischemia occurring in daily life stress.

**Results:** High scores on anger and hostility were common in this sample of patients with CAD, and DLI was documented in 83 (42%) patients. However, the presence of DLI was associated with lower anger scores (odds ratio [OR] = 2.03; 95% confidence interval [CI] = 1.12-3.69), reduced anger expressiveness (OR = 2.04; 95% CI = 1.10-3.75), and increased ratio of anger control to total anger (OR = 2.33; 95% CI = 1.27-4.17). Increased risk of DLI was also associated with lower hostile attribution (OR = 2.22; 95% CI = 1.21-4.09), hostile affect (OR = 1.92; 95% CI = 1.03-3.58), and aggressive responding (OR = 2.26; 95% CI = 1.25-4.08). We observed weak inverse correlations between DLI episode frequency and anger expressiveness, total anger, and hostility scores. DLI was not associated with depression or anxiety measures. The combination of the constructs low anger expressiveness and low hostile attribution was independently associated with DLI (OR = = 2.59; 95% CI = 1.42-4.72).

**Conclusions:** In clinically stable patients with CAD, the tendency to suppress angry and hostile feelings, particularly openly aggressive behavior, was associated with DLI. These findings warrant a study in larger cohorts, and intervention studies are needed

to ascertain whether management strategies that modify these psychological characteristics improve outcomes.

28. Kim YJ, Levantsevych OM, Elon L, Lewis TT, Suglia SF, Bremner JD, Quyyumi AA, Pearce B, Raggi P, Vaccarino V, Shah AJ. Early life stress and autonomic response to acute mental stress in individuals with coronary heart disease. J Trauma Stress. 2022 Apr;35(2):521-532. doi: 10.1002/jts.22766. Epub 2022 Jan 15. PMID: 35032417; PMCID: PMC9109683.

Early life stress (ELS) has been associated with an increased risk of cardiovascular disease. We examined whether ELS was associated with autonomic function and stress reactivity among individuals with coronary heart disease (CHD). We included patients with stable CHD from two parallel studies, the Mental Stress Ischemia Prognosis Study (MIPS) and the Myocardial Infarction and Mental Stress Study 2 (MIMS2), and assessed ELS using the Early Trauma Inventory-Self-Report-Short Form. Participants underwent a laboratory-based mental stress task while undergoing ambulatory electrocardiographic monitoring. We used multivariate linear regression models to estimate the associations between ELS and heart rate variability (HRV; low frequency [LF], high frequency [HF], and LF and HF [LH] ratio). The analytic sample included 405 MIPS and 284 MIMS2 participants. Most participants endorsed at least one experience of ELS (92.2%). Although we did not observe associations between ELS and HRV outcomes in the overall sample, ELS was associated with lower LH ratio HRV during recovery in the posttraumatic stress disorder (PTSD) subgroup, ELS x PTSD interaction, p = .041. In the MIMS2 subgroup, ELS was associated with lower resting period LF HRV, $\hat{B}\hat{B}$ = -0.16 ln $ms^2$ ; 95% CI [-0.31, -0.02]. Exposure to physical trauma was associated with decreased HF HRV overall reactivity only among participants with high to moderate depressive symptoms, $\hat{B}\hat{B}$ = -0.52 ln $ms^2$ vs. $\hat{B}\hat{B}$ = 0.01 ln $ms^2$ , p = .013. Overall, heterogeneous associations between ELS and HRV emerged, suggesting the need for additional research regarding longer-term ambulatory HRV.

29. Bravo PE, Cappola TP. Mental Stress-Induced Myocardial Ischemia: When the Mind Controls the Fate of the Heart. JAMA. 2021 Nov 9;326(18):1803-1804. doi: 10.1001/jama.2021.18766. PMID: 34751723; PMCID: PMC9208308.

**Coronary heart disease (CHD)** is the leading cause of mortality globally, and patients who have chronic forms of CHD experience substantial morbidity, including high rates of recurrent cardiac events and eventual onset of heart failure.[1,2] Further research to identify vulnerable populations, improve risk stratification, and understand nontraditional risk factors is essential to reduce the public health burden of CHD.

In this context, sufficient evidence now suggests that mental stress can trigger myocardial infarction,[3,4] reversible cardiomyopathy,[5] and sudden cardiac death in susceptible individuals.[6] The link between mental stress and CHD was first described over a century ago[7] and has become an important topic of research over the past 40 years.[3,4] In a meta-analysis of 20 studies involving 3164 individuals with CHD, mental stress provoked in a controlled environment (eg, public speaking, mental arithmetic, anger recall) was associated with inducing myocardial ischemia in 32% of patients with CHD in the form of either transient regional wall motion abnormalities on echocardiography, ST-segment deviation on electrocardiography, or reversible defects on myocardial perfusion imaging with single-photon emission computed tomography (SPECT).[4] Another meta-analysis of 5 studies involving 555 individuals suggested that presence of so-called mental stress–induced myocardial ischemia in patients with CHD was associated with increased risk of recurrent cardiac events and mortality compared with individuals with CHD but without mental stress–induced myocardial ischemia, with absolute rates of these outcomes of 34% vs 14%, respectively.[3]

Although suggestive, these prior studies were limited by small sample sizes (largest single outcomes study, n = 182), lack of racial, ethnic, and gender diversity, and use of relatively less sensitive techniques to detect ischemia (mainly echocardiography and electrocardiography).[3] Therefore, it is unclear whether the increased risk of cardiac events associated with mental stress–induced myocardial ischemia can be generalized to larger populations with CHD.[8] Moreover, the underlying mechanisms of and the interplay between mental stress ischemia and conventional stress ischemia induced during exercise or pharmacological stress have not been sufficiently explored.

In this issue of *JAMA*,[9] Vaccarino and colleagues present the largest (n = 918) and most diverse (34% women, 40% Black individuals) observational study investigating the association between mental stress ischemia, conventional stress ischemia, and future cardiac events in patients with known CHD using contemporary myocardial perfusion SPECT imaging. The study consisted of a pooled analysis of 2 parallel prospective studies, with similar protocols, involving patients with established CHD: the Mental Stress Ischemia Prognosis Study (MIPS; n = 618) and the Myocardial Infarction and

Mental Stress Study 2 (MIMS2; n = 300). After enrollment, all participants underwent both mental stress testing with public speaking challenge and conventional stress testing with either exercise (69%) or pharmacologic SPECT (31%) to provoke ischemia.

Overall, mental stress ischemia was observed in 16% of participants, conventional stress ischemia in 31%, and both in 10%. After a median 5-year follow-up, the primary end point of cardiovascular death or myocardial infarction occurred in 17% of study participants, and a secondary end point that also included heart failure hospital admission occurred in 35%. In all models tested, presence of mental stress ischemia showed significant associations with both the primary (pooled adjusted hazard ratio [HR], 2.5; 95% CI, 1.8–3.5) and secondary (pooled adjusted HR, 2.0; 95% CI, 1.5–2.8) end points. Presence of conventional stress ischemia showed similar associations with primary (adjusted HR, 2.0; 95% CI, 1.3–2.0) and secondary (adjusted HR, 1.6; 95% CI, 1.3–2.0) end points. However, analyses based on the specific ischemia phenotype demonstrated that participants with evidence of both phenotypes had the strongest association with the primary end point (HR, 3.8; 95% CI, 2.6–5.6), followed by individuals with mental stress ischemia only (HR, 2.0; 95% CI, 1.1–3.7). In contrast, conventional stress ischemia alone was not significantly associated with the primary outcome (HR, 1.4; 95% CI, 0.9–2.1) when compared with individuals without myocardial ischemia by either intervention. Similar associations were apparent for the secondary end point.

The results of the study by Vaccarino et al largely confirm prior observations from smaller studies and extend the generalizability of the findings to women, Black individuals, and younger individuals with stable CHD, populations that are often underrepresented in biomedical research. In addition, this study reports for the first time the complex interplay that seems to exist between inducible ischemia by mental stress and conventional stress testing, which can result in distinct ischemia phenotypes that may have different risk profiles. In particular, it is remarkable that mental stress ischemia (without conventional stress ischemia) appears to be a stronger risk factor than conventional stress ischemia (without concomitant mental stress ischemia) for cardiovascular death, nonfatal myocardial infarction, or heart failure hospital admission.

From a pathophysiological perspective, mental stress ischemia and conventional stress ischemia appear to arise through different mechanisms. Mental stress may lead to an adrenergic surge, but unlike exercise-induced ischemia, mental stress ischemia typically occurs at a lower cardiac work-load and is not associated with angiographic CHD severity.[10] Moreover, mental stress ischemia ensues independent of hemodynamic changes, implying that myocardial oxygen demand and CHD burden play relatively minor roles. Invasive studies have shown that in mental stress ischemia, coronary blood flow decreases while the coronary diameter does not significantly change at the site of atherosclerotic disease, suggesting an impairment in the coronary microcirculation. Patients with mental stress ischemia also have an impaired vasodilatory response to intracoronary acetylcholine infusion, in keeping with coronary endothelial dysfunction.[8] By comparison, vasodilators used to induce conventional stress ischemia increase coronary blood flow through endothelium-independent mechanisms[11] and exercise mainly induces endothelium-dependent changes in coronary flow.[12]

Thus, presence of mental stress ischemia as assessed through SPECT appears to be primarily a marker of coronary endothelial dysfunction, whereas presence of conventional stress ischemia is a more mixed picture that encompasses impaired endothelium-independent vasoreactivity, endothelial dysfunction, degree of coronary atherosclerosis, and increased myocardial oxygen demand. These underlying differences may account for the discrepancies in outcome associated with both types of ischemia, and may also help explain the relatively higher risk observed in patients with mental stress ischemia only than in patients with conventional stress ischemia only. For example, emerging evidence indicates that patients with CHD and coronary endothelial dysfunction have generally worse outcomes than their counterparts with endothelium-independent dysfunction.[13] Consequently, it is plausible that coexistence of endothelium-dependent and endothelium-independent microvascular dysfunction, as elicited by mental stress ischemia and conventional stress ischemia, respectively, may portend the highest risk as suggested by the current study.[9]

In summary, the study by Vaccarino and colleagues provides compelling evidence demonstrating a strong association between mental stress ischemia and the risk of future cardiac events and mortality among individuals with stable CHD. However, several clinically relevant questions remain for future studies, including the following: To what extent is mental stress ischemia therapeutically modifiable? Can screening for and treatment of mental stress ischemia lead to improved outcomes? Is mental stress testing reproducible and feasible in clinical practice? Are there additional at-risk populations in whom mental stress ischemia testing should be considered? Answers to these important questions will help determine whether mental stress should become an actionable clinical item in the management of individuals with known or suspected CHD.

30. Vaccarino V, Almuwaqqat Z, Kim JH, Hammadah M, Shah AJ, Ko YA, Elon L, Sullivan S, Shah A, Alkhoder A, Lima BB, Pearce B, Ward L, Kutner M, Hu Y, Lewis TT, Garcia EV, Nye J, Sheps DS, Raggi P, Bremner JD, Quyyumi AA. Association of Mental Stress-Induced Myocardial Ischemia With Cardiovascular Events in Patients With Coronary Heart Disease. JAMA. 2021 Nov 9;326(18):1818-1828. doi: 10.1001/jama.2021.17649. PMID: 34751708; PMCID: PMC8579237.

**Importance:** Mental stress-induced myocardial ischemia is a recognized phenomenon in patients with coronary heart disease (CHD), but its clinical significance in the contemporary clinical era has not been investigated.

**Objective:** To compare the association of mental stress-induced or conventional stress-induced ischemia with adverse cardiovascular events in patients with CHD.

**Design, setting, and participants:** Pooled analysis of 2 prospective cohort studies of patients with stable CHD from a university-based hospital network in Atlanta, Georgia: the Mental Stress Ischemia Prognosis Study (MIPS) and the Myocardial Infarction and Mental Stress Study 2 (MIMS2). Participants were enrolled between June 2011 and March 2016 (last follow-up, February 2020).

**Exposures:** Provocation of myocardial ischemia with a standardized mental stress test (public speaking task) and with a conventional (exercise or pharmacological) stress test, using single-photon emission computed tomography.

**Main outcomes and measures:** The primary outcome was a composite of cardiovascular death or first or recurrent nonfatal myocardial infarction. The secondary end point additionally included hospitalizations for heart failure.

**Results:** Of the 918 patients in the total sample pool (mean age, 60 years; 34% women), 618 participated in MIPS and 300 in MIMS2. Of those, 147 patients (16%) had mental stress-induced ischemia, 281 (31%) conventional stress ischemia, and 96 (10%) had both. Over a 5-year median follow-up, the primary end point occurred in 156 participants. The pooled event rate was 6.9 per 100 patient-years among patients with and 2.6 per 100 patient-years among patients without mental stress-induced ischemia. The multivariable adjusted hazard ratio (HR) for patients with vs those without mental stress-induced ischemia was 2.5 (95% CI, 1.8-3.5). Compared with patients with no ischemia (event rate, 2.3 per 100 patient-years), patients with mental stress-induced ischemia alone had a significantly increased risk (event rate, 4.8 per 100 patient-years; HR, 2.0; 95% CI, 1.1-3.7) as did patients with both mental stress ischemia and conventional stress ischemia (event rate, 8.1 per 100 patient-years; HR, 3.8; 95% CI, 2.6-5.6). Patients with conventional stress ischemia alone did not have a significantly increased risk (event rate, 3.1 per 100 patient-years; HR, 1.4; 95% CI, 0.9-2.1). Patients with both mental stress ischemia and conventional stress ischemia had an elevated risk compared with patients with conventional stress ischemia alone (HR, 2.7; 95% CI, 1.7-4.3). The secondary end point occurred in 319 participants. The event rate was 12.6 per 100 patient-years for patients with and 5.6 per 100 patient-years for patients without mental stress-induced ischemia (adjusted HR, 2.0; 95% CI, 1.5-2.5).

**Conclusions and relevance:** Among patients with stable coronary heart disease, the presence of mental stress-induced ischemia, compared with no mental stress-induced ischemia, was significantly associated with an increased risk of cardiovascular death or nonfatal myocardial infarction. Although these findings may provide insights into mechanisms of myocardial ischemia, further research is needed to assess whether testing for mental stress-induced ischemia has clinical value.

31. Duan XC, Liu MY. [Early diagnosis and treatment of mental-stress induced myocardial ischemia]. Zhonghua Nei Ke Za Zhi. 2021 Oct 1;60(10):921-924. Chinese. doi: 10.3760/cma.j.cn112138-20210816-00556. PMID: 34551485.

[Article in Chinese]

32. McKinnon II, Shah AJ, Lima B, Moazzami K, Young A, Sullivan S, Almuwaqqat Z, Garcia M, Elon L, Bremner JD, Raggi P, Quyyumi AA, Vaccarino V, Lewis TT. Everyday Discrimination and Mental Stress-Induced Myocardial Ischemia. Psychosom Med. 2021 Jun 1;83(5):432-439. doi: 10.1097/PSY.0000000000000941. PMID: 34080584; PMCID: PMC8225242.

**Objective:** Mental stress-induced myocardial ischemia (MSIMI), a transient myocardial ischemic response to mental stress, is associated with poorer outcomes among patients with coronary heart disease and is more likely to occur among women. However, predictors of MSIMI are not well explored. The current study investigated the association between experiences of everyday discrimination and MSIMI among patients with recent myocardial ischemia and contrasted the results with conventional stress-induced myocardial ischemia (CSIMI). We examined sex differences in associations.

**Methods:** We studied 295 post-MI patients (145 women, 150 men). Provocation of myocardial ischemia with mental stress (speech task) and conventional stress (exercise or pharmacologic) was assessed by myocardial perfusion imaging. Frequency of exposure to everyday discrimination was assessed via questionnaire using the Everyday Discrimination Scale (EDS).

**Results:** The mean age was 51 years in both women and men, and the EDS score ranged from 10 to 38 (mean [standard deviation] = 17 [6] years). After multivariable analysis, each standard deviation increase in the EDS score (more frequent exposure) was associated with an increased odds of MSIMI (odds ratio [OR] = 1.57 [1.10-2.23]). The EDS score was not associated with CSIMI (OR = 0.86 [0.64-1.17]). Women demonstrated a twofold increase (OR = 1.96 [1.13-3.38], p = .02) in the adjusted odds of MSIMI, with each standard deviation increase in the EDS score compared with a 1.4-fold increase (OR = 1.40 [0.80-2.44], p = .24) among men; however, interaction was not statistically significant.

**Conclusions:** Among post-MI patients, everyday discrimination was positively associated with occurrence of MSIMI, but not with CSIMI; associations were more pronounced among women.

33. Zoofaghari S, Nikaen F, Bahramsari S, Hashemzadeh M, Dorooshi G. Myocardial infarction without coronary artery occlusion following mental stress. J Res Med Sci. 2021 Feb 27;26:12. doi: 10.4103/jrms.JRMS_128_20. PMID: 34084191; PMCID: PMC8106406.

Myocardial infarction (MI) with nonobstructive coronary arteries (MINOCA) is syndrome with clinical evidence of acute MI (AMI) with normal coronary arteries. This study reports the case of a 23-year-old single woman referring to the hospital with clinical manifestations of MI, with electrocardiography findings of slow ventricular tachycardia or accelerated idioventricular rhythm and atrioventricular dissociation, and high troponin levels, which was admitted with the diagnosis of MINOCA due to mental stress (grief) and was discharged after 4 days of monitoring and following stabilization of conditions and absence of symptoms. Other causes of MINOCA ruled out through imaging studies. Mental stress can lead to MINOCA.

34. Moazzami K, Sullivan S, Lima BB, Kim JH, Hammadah M, Almuwaqqat Z, Shah AJ, Hajjar I, Goldstein FC, Levey AI, Bremner JD, Quyyumi AA, Vaccarino V. Mental stress-induced myocardial ischemia and cognitive impairment in coronary atherosclerosis. J Psychosom Res. 2021 Feb;141:110342. doi: 10.1016/j.jpsychores.2020.110342. Epub 2020 Dec 25. PMID: 33360843; PMCID: PMC7857648.

**Objective:** To understand if presence of mental stress-induced myocardial ischemia (MSIMI) is associated with higher prevalence of cognitive impairment at baseline and its decline over time.

**Methods:** A cohort of participants with stable coronary atherosclerosis underwent acute mental stress testing using a series of standardized speech/arithmetic stressors. The stress/rest digital vasomotor response to mental stress (sPAT) was assessed to measure microvascular constriction during mental stress. Patients received 99mTc-sestamibi myocardial perfusion imaging at rest, with mental stress and with conventional (exercise/pharmacological) stress. Cognitive function was assessed both

at baseline and at a 2 year follow-up using the Trail Making Test parts A and B and the verbal and visual memory subtests of the Wechsler Memory Scale.

**Results:** We studied 486 individuals (72% male, 32.1% Black, 62 ± 9 (mean ± SD) years old). After multivariable adjustment for baseline demographics, risk factors, and medication use, presence of MSIMI was associated with 21% and 20% slower completion of Trail-A and Trail-B, respectively (p for all <0.01). After a 2-year follow-up period, presence of MSIMI was associated with a 33% slower completion of Trail-B, denoting cognitive decline (B = 0.33, 95% CI, 0.04, 0.62). A lower sPAT, indicating greater vasoconstriction, mediated the association between MSIMI and worsening Trail-B performance by 18.2%. Ischemia with a conventional stress test was not associated with any of the cognitive tests over time.

**Conclusion:** MSIMI is associated with slower visuomotor processing and worse executive function at baseline and with greater decline in these abilities over time.

35. Waller C, Rhee DS, Gröger M, Rappel M, Maier T, Müller M, Rottler E, Nerz K, Nerz C, Brill S, Becker HP, Radermacher P. Social Stress-Induced Oxidative DNA Damage Is Related to Prospective Cardiovascular Risk. J Clin Med. 2020 Nov 23;9(11):3783. doi: 10.3390/jcm9113783. PMID: 33238572; PMCID: PMC7700520.

Psychosocial stress increases cardiovascular risk, which coincides with enhanced oxidative DNA damage. Increased sympathetic tone-related catecholamine release causes oxidative stress, which contributes to catecholamine-related cardiotoxicity. Therefore, we tested the hypothesis whether acute psychosocial stress induces oxidative DNA damage, its degree being related to the cardiovascular risk profile and depending on the sympathetic stress response. After assessment of the prospective cardiovascular Münster score (PROCAM) to determine the risk of acute myocardial infarction, 83 male and 12 female healthy volunteers underwent the Trier social stress test for groups (TSST-G). Heart rate variability was quantified by measuring the standard deviation (SDNN) and root mean square of successive differences (RMSSD) between normal-to-normal inter-beat intervals. Salivary α-amylase (sAA) activity was assessed as a surrogate for noradrenaline plasma concentrations. Oxidative DNA damage was determined using whole-blood single-cell gel electrophoresis ("tail moment" in the "comet assay"). A total of 33 subjects presented with a prospective risk of myocardial infarction (risk+) vs. 59 subjects without risk (risk-). The TSST-G stress significantly increased blood pressure, heart rate, and sAA in both groups,

while oxidative DNA damage was only increased in the risk+ group. Immediately after the TSST-G, the "tail moment" showed significant inverse linear relations with both SDNN and RMSSD. Acute psychosocial stress may cause oxidative DNA damage, the degree of which is directly related to the individual cardiovascular risk profile and depends on the stress-induced increase in the sympathetic tone.

36. Meadows JL, Shah S, Burg MM, Pfau S, Soufer R. The Foundational Role of Cardiovascular Imaging in the Characterization of Mental Stress-Induced Myocardial Ischemia in Patients with Coronary Artery Disease. Curr Cardiol Rep. 2020 Oct 10;22(12):162. doi: 10.1007/s11886-020-01407-w. PMID: 33037938.

**Purpose of review:** Mental stress-provoked myocardial ischemia (MSIMI) is an ischemic phenomenon provoked by the experience of psychologically stressful circumstances. While MSIMI was initially identified 50 years ago during activities of daily living through the use of wearable Holter monitor, subsequent research utilized the technologies of cardiac imaging-ventriculography and myocardial perfusion-under controlled conditions to pursue an understanding of pathophysiology and prognosis. This work revealed that MSIMI occurs in almost half of patients with stable coronary artery disease (CAD) and is associated with cardiac events and early mortality. We provide a focused review of the instrumental role that cardiac imaging has played in elucidating how stress affects cardiac physiology and how emerging diagnostic techniques will allow for further research on stress-mediated changes in the coronary macro- and microvasculature.

**Recent findings:** Observations about the cardiac response to mental stress diverge from underlying cornerstones of the traditional CAD paradigm which is based upon myocardial oxygen demand and the degree of epicardial coronary stenosis. Evidence from studies utilizing non-invasive and invasive studies of coronary perfusion indicates perturbations in the microvascular compartment in response to mental stress. Cardiovascular imaging enjoined with mental stress provocation may be a commanding tool to advance our understanding of non-obstructive CAD and the coronary microvasculature. This further understanding will facilitate incorporation of mental stress testing in the clinical care of patients with discrepant diagnostic work-up of CAD and in patients who experience anginal symptoms due to non-exertional and/or emotional triggers. Such algorithms will be crucial to identify treatment targets to modify the risk associated with mental stress-associated ischemia and adverse prognosis.

37. Shah SM, Meadows JL, Burg MM, Pfau S, Soufer R. Effects of Psychological Stress on Vascular Physiology: Beyond the Current Imaging Signal. Curr Cardiol Rep. 2020 Oct 9;22(12):156. doi: 10.1007/s11886-020-01406-x. PMID: 33037500.

**Purpose of review:** This review describes the effects of psychological stress on the physiology of the entire vascular system, from individual cellular components to macrovascular and microvascular responses, and highlights the importance of the vascular system in the context of current limitations in cardiac imaging for evaluation of the cardiovascular response to mental stress.

**Recent findings:** The physiological responses that mediate vascular changes are based on evolutionary needs, but there is increasing evidence that the long-term consequences of psychological stress can precipitate the development and progression of cardiovascular disease (CVD). While there is an extensive body of literature describing localized physiological responses or overt cardiovascular manifestations, often framed within the organ-specific scope of cardiovascular imaging, there has not been a comprehensive description of the global vascular effects of psychological stress. Given the global nature of these processes, targeted cardiovascular imaging modalities may be insufficient. Here we approach the vascular response to mental stress systematically, describing the effects on the endothelium, vascular smooth muscle, and adventitia. We then address the mental stress effects on large vessels and the microvascular compartment, with a discussion of the role of microvascular resistance in the pathophysiology of mental stress-induced myocardial ischemia. Vascular responses to psychological stress involve complex physiological processes that are not fully characterized by routine cardiovascular imaging assessments. Future research incorporating standardized psychological assessments targeted toward vascular mechanisms of stress responses is required to guide the development of behavioral and therapeutic interventions.

38. Schmidt K, Lima ADS, Schmitt KR, Moraes MA, Schmidt MM. Stress in Women with Acute Myocardial Infarction: A Closer Look. Arq Bras Cardiol. 2020 Oct;115(4):649-657. English, Portuguese. doi: 10.36660/abc.20190282. PMID: 33111864; PMCID: PMC8386975.

**Background:** Women seem to be more susceptible to psychosocial stress than men, and stress is associated with worse outcomes after acute myocardial infarction (AMI).

**Objectives:** To investigate whether the female gender is an independent predictor of risk for stress and to compare stress levels between women and men after AMI.

**Methods:** Cross-sectional study of a case series. Patients aged 18 to 65 years who were treated for AMI at the study facility between January 2017 and June 2018 were eligible. The presence of stress was assessed using Lipp's Stress Symptoms Inventory for Adults (ISSL), which categorizes stress into four phases (alertness, resistance, near-exhaustion, and exhaustion), through a list of physical and psychological symptoms. Data were analyzed using SPSS Version 24.0. The significance level was set at $p<0.05$.

**Results:** Of the 330 respondents, 89% of women and 70% of men experienced stress. The female gender was associated with nearly threefold higher odds of experiencing stress (EXP (B)2.79, $p = 0.02$). Regarding the phases of stress, women were more often in the near-exhaustion and exhaustion phases, while men were more often in the resistance phase.

**Conclusions:** This study showed that women are most often in the third and fourth phases of stress, i.e., in situations of long-standing psychosocial stress. These findings can assist in the development of gender-specific strategies for health promotion and disease prevention, aiming to minimize the effects of stress in this population.

39. Huan N, Yu Y, Wang P, Wang C. Research progress regarding the diagnosis and treatment of mental stress-induced myocardial ischemia. Anatol J Cardiol. 2020 Sep;24(3):126-136. doi: 10.14744/AnatolJCardiol.2020.69447. PMID: 32870175; PMCID: PMC7585978.

Myocardial ischemia resulting from psychological stress [mental stress-induced myocardial ischemia (MSIMI)] refers to the condition wherein psychosocial and psychological stimulations cause myocardial ischemia in patients with coronary heart disease, which is different from drug-induced myocardial ischemia. Therefore, this condition often escapes diagnosis, portends clinical risk, and affects the quality of life of MSIMI survivors. MSIMI is closely related to the poor prognosis of cardiovascular diseases, especially in young women, according to recent randomized, controlled trials (RCTs) on MSIMI. These RCTs involved different sample sizes, interventional measures, and detection techniques. Moreover, differences exist regarding the prevalence rate, distribution characteristics, possible pathogenesis, and clinical significance. Nevertheless, currently, the diagnostic criteria, pathogenesis, and treatment of MSIMI are still in the clinical exploration stage. Hence, considering

recent RCTs, this paper summarizes the research status of MSIMI from the aspects of pathogenesis, diagnosis, and treatment strategies to provide a theoretical basis for the follow-up diagnostic methods and treatment guidelines for MSIMI.

40. von Känel R, Merz F, Pfister H, Brückl T, Zimmermann P, Uhr M, Holsboer F, Höhne N, Ising M. Acute Stress-Induced Coagulation Activation in Patients With Remitted Major Depression Versus Healthy Controls and the Role of Stress-Specific Coping. Ann Behav Med. 2020 Aug 8;54(8):611-618. doi: 10.1093/abm/kaaa001. PMID: 32044917.

**Background:** Depressed patients have an increased risk of myocardial infarction, for which acute stress is a frequent trigger. Prothrombotic changes could be one involved mechanism that can be modulated by psychological coping.

**Purpose:** We examined the effects of remitted major depression and situation-specific coping strategies on stress-induced coagulation activation.

**Methods:** Forty patients with remitted depression and 23 healthy controls underwent the Trier Social Stress Test, rating applied coping strategies thereafter. Blood was sampled at baseline and 15 and 45 min poststress to measure fibrinogen, von Willebrand factor (VWF) and D-dimer. Coagulation activation over time was quantified as area under the curve (AUC) with respect to baseline activity. Standardized z-scores of individual coagulation AUC measures were added up to a prothrombotic index.

**Results:** Stress provoked significant VWF ($p = .024$) and D-dimer ($p = .002$) responses. Remitted depressed patients used positive distraction coping more frequently than controls did ($p = .030$). Coagulation AUC measures were similar in both groups. In all participants, higher positive coping total ($p = 0.009$), driven by devaluation/defense ($p = .022$) and distraction ($p = .004$) coping, was associated with a lower prothrombotic index. In controls, but not in remitted depressed patients, higher positive coping total ($p = .008$), driven by higher devaluation/defense ($p = .010$) and distraction ($p = .023$) coping, was associated with lower VWF AUC.

**Conclusions:** Despite the use of favorable coping strategies in a specific stress situation, remitted depressed patients may benefit less from a positive effect of positive situational coping on coagulation activation than controls. Such a mechanism could partially explain the increased risk of myocardial infarction in depressed individuals.

41. Moazzami K, Wittbrodt MT, Lima BB, Nye JA, Mehta PK, Pearce BD, Almuwaqqat Z, Hammadah M, Levantsevych O, Sun YV, Raggi P, Garcia EV, Goetz M, Quyyumi AA, Bremner JD, Vaccarino V, Shah AJ. Higher Activation of the Rostromedial Prefrontal Cortex During Mental Stress Predicts Major Cardiovascular Disease Events in Individuals With Coronary Artery Disease. Circulation. 2020 Aug 4;142(5):455-465. doi: 10.1161/CIRCULATIONAHA.119.044442. Epub 2020 Jun 11. PMID: 32522022; PMCID: PMC7677173.

**Background:** Psychological stress is a risk factor for major adverse cardiovascular events (MACE) in individuals with coronary artery disease. Certain brain regions that control both emotional states and cardiac physiology may be involved in this relationship. The rostromedial prefrontal cortex (rmPFC) is an important brain region that processes stress and regulates immune and autonomic functions. Changes in rmPFC activity with emotional stress (reactivity) may be informative of future risk for MACE.

**Methods:** Participants with stable coronary artery disease underwent acute mental stress testing using a series of standardized speech/arithmetic stressors and simultaneous brain imaging with high-resolution positron emission tomography brain imaging. We defined high rmPFC activation as a difference between stress and control scans greater than the median value for the entire cohort. Interleukin-6 levels 90 minutes after stress, and high-frequency heart rate variability during stress were also assessed. We defined MACE as a composite of cardiovascular death, myocardial infarction, unstable angina with revascularization, and heart failure hospitalization.

**Results:** We studied 148 subjects (69% male) with mean±SD age of 62±8 years. After adjustment for baseline demographics, risk factors, and baseline levels of interleukin-6 and high-frequency heart rate variability, higher rmPFC stress reactivity was independently associated with higher interleukin-6 and lower high-frequency heart rate variability with stress. During a median follow-up of 3 years, 34 subjects (21.3%) experienced a MACE. Each increase of 1 SD in rmPFC activation with mental stress was associated with a 21% increase risk of MACE (hazard ratio, 1.21 [95% CI, 1.08-1.37]). Stress-induced interleukin-6 and high-frequency heart rate variability explained 15.5% and 32.5% of the relationship between rmPFC reactivity and MACE, respectively. Addition of rmPFC reactivity to conventional risk factors improved risk reclassification for MACE prediction, and C-statistic improved from 0.71 to 0.76 ($P$=0.03).

**Conclusions:** Greater rmPFC stress reactivity is associated with incident MACE. Immune and autonomic responses to mental stress may play a contributory role.

42. Moazzami K, Wittbrodt MT, Alkhalaf M, Lima BB, Nye JA, Mehta PK, Quyyumi AA, Vaccarino V, Bremner JD, Shah AJ. Association Between Mental Stress-Induced Inferior Frontal Cortex Activation and Angina in Coronary Artery Disease. Circ Cardiovasc Imaging. 2020 Aug;13(8):e010710. doi: 10.1161/CIRCIMAGING.120.010710. Epub 2020 Aug 10. PMID: 32772572; PMCID: PMC7422935.

**Background:** The inferior frontal lobe is an important area of the brain involved in the stress response, and higher activation with acute mental stress may indicate a more severe stress reaction. However, it is unclear if activation of this region with stress correlates with angina in individuals with coronary artery disease.

**Methods:** Individuals with stable coronary artery disease underwent acute mental stress testing using a series of standardized speech/arithmetic stressors in conjunction with high resolution positron emission tomography imaging of the brain. Blood flow to the inferior frontal lobe was evaluated as a ratio compared with whole brain flow for each scan. Angina was assessed with the Seattle Angina Questionnaire's angina frequency subscale at baseline and 2 years follow-up.

**Results:** We analyzed 148 individuals with coronary artery disease (mean age [SD] 62 [8] years; 69% male, and 35.8% Black). For every doubling in the inferior frontal lobe activation, angina frequency was increased by 13.7 units at baseline ([Formula: see text], 13.7 [95% CI, 6.3-21.7]; *P*=0.008) and 11.6 units during follow-up ([Formula: see text], 11.6 [95% CI, 4.1-19.2]; *P*=0.01) in a model adjusted for baseline demographics. Mental stress-induced ischemia and activation of other brain pain processing regions (thalamus, insula, and amygdala) accounted for 40.0% and 13.1% of the total effect of inferior frontal lobe activation on angina severity, respectively.

**Conclusions:** Inferior frontal lobe activation with mental stress is independently associated with angina at baseline and during follow-up. Mental stress-induced ischemia and other pain processing brain regions may play a contributory role.

43. Liu M, Liu J, Zhang L, Xu W, He D, Wei W, Ge Y, Dandu C. An evidence of brain-heart disorder: mental stress-induced myocardial ischemia regulated by inflammatory cytokines. Neurol Res. 2020 Aug;42(8):670-675. doi: 10.1080/01616412.2020.1783879. Epub 2020 Jun 23. PMID: 32573395.

**Objective:** Underlying Coronary Artery Disease (CAD) complicated by Mental Stress-Induced Myocardial Ischemia (MSIMI) has been linked with an increased risk for adverse cardiovascular events and even sudden death. However, the underlying mechanisms of MSIMI remain unknown. In this study, we investigated cytokine levels at baseline inflammation status and during acute inflammatory responses to mental stress in patients with known CAD who presented with MSIMI.

**Method:** 77 patients with known CAD were recruited and all underwent echocardiography before and during arithmetic stress task. MSIMI was diagnosed by new or worsening wall motion abnormalities greater than or equal to a 5% reduction of left ventricle ejection fraction. Inflammatory markers were measured both before and immediately after the Mental Stress (MS) by ELISA kits. Repeated measures models were used to report the responses and mixed linear regression models were used to report the differences between MSIMI negative and positive patients.

**Result:** MS induced a significant increase in Stromal Cell-Derived Factor-1α (SDF-1α) and Monocyte Chemoattractant Protein-1 (MCP-1) in all subjects; 20.78% of the patients with known CAD developed MSIMI during the arithmetic task. MSIMI positive patients had significantly lower baseline levels of Interleukin-1β (IL-1β) and Tumor Necrosis Factor-α (TNF-α), but a higher response in levels of SDF-1α than MSIMI negative patients.

**Conclusion:** MS can induce acute inflammatory responses. MSIMI is associated with lower levels of IL-1β and TNF-α at baseline and higher levels of SDF-1α in response to MS.

44. Zhang L, Bao Y, Wang X, Zhou Y, Tao S, Xu W, Liu M. A meta-analysis on the prevalence, associated factors and diagnostic methods of mental stress induced myocardial ischemia. J Transl Med. 2020 May 29;18(1):218. doi: 10.1186/s12967-020-02383-z. PMID: 32471451; PMCID: PMC7257246.

**Background:** The high prevalence of mental stress induced myocardial ischemia (MSIMI) causes double risk of adverse cardiac events in patients with MSIMI. However, multiple types of mental stress, diagnostic techniques, and diagnostic measurements may increase the complexity and heterogeneity in the assessment of MSIMI. Therefore, we performed this meta-analysis to assess the prevalence, associated factors, and diagnostic methods of MSIMI.

**Methods:** We systematically searched PubMed, EMBACE, Web of Science, CNKI, Wanfang through 1 Feb 2020 in English and Chinese. Review Manager (RevMan) Version 5.3 and Stata 12.0 were used for data analyses.

**Results:** Twenty articles were enrolled. The pooled estimates for the prevalence of MSIMI in CAD patients was 32%. Potential associated factors of MSIMI involved history of post myocardial infarction (MI), or coronary artery bypass graft (CABG) (RR: 1.29, 95% CI 1.00-1.66, P = 0.05; RR: 1.59, 95% CI 1.00-2.52, P = 0.05). Evidence supported that diagnostic methods could influence the prevalence of MSIMI. Significant differences of MSIMI prevalence were found in different types of mental stress (Public Speaking: 22%; Mental arithmetic: 26%; Anger recall: 34%; Two types: 37%; Three or more than three types: 43%, P = 0.02), diagnostic techniques (SPECT: 26%; RNV: 38%; ECG: 16%; Echocardiography: 41%; Two types: 43%, P < 0.0001), and diagnostic measurements (LVEF decrease: 19%; WMA: 51%; ST depression: 16%; MPD: 26%; Two or more than two measurements: 45%, P < 0.00001). Moreover, univariate meta-regression demonstrated that MSIMI was linked with mental stress (exp(b): 1.0508, SE: 0.0201, P: 0.018).

**Conclusions:** This meta-analysis implicated that patients with diabetes, post MI or CABG might be more vulnerable to MSIMI. However, the prevalence of MSIMI could be influenced by diagnostic methods, especially the adopted types of mental stress, diagnostic techniques and measurements. Therefore, it is necessary to formulate a standard diagnostic method for MSIMI, which should be adequate, assessable, and affordable worldwide. Registration PROSPERO. Online Protocol: CRD42020162822.

45. Lima BB, Hammadah M, Pearce BD, Shah A, Moazzami K, Kim JH, Sullivan S, Levantsevych O, Lewis TT, Weng L, Elon L, Li L, Raggi P, Bremner JD, Quyyumi A, Vaccarino V. Association of Posttraumatic Stress Disorder With Mental Stress-Induced Myocardial Ischemia in Adults After Myocardial Infarction. JAMA Netw Open. 2020 Apr 1;3(4):e202734. doi: 10.1001/jamanetworkopen.2020.2734. PMID: 32286655; PMCID: PMC7156990.

**Importance:** Posttraumatic stress disorder (PTSD) is prevalent among patients who survived an acute coronary syndrome and is associated with adverse outcomes, but the mechanisms underlying these associations are unclear.

**Objective:** To evaluate the association of PTSD with mental stress-induced myocardial ischemia among individuals who survived a myocardial infarction (MI).

**Design, setting, and participants:** This cross-sectional study included 303 patients aged 18 to 60 years enrolled from a university-affiliated network. Participants had a verified history of MI within 8 months. Data were collected from June 2011 to March 2016, and data analysis was conducted from March to June 2019.

**Exposures:** A clinical diagnosis of PTSD (lifetime and current) was obtained using the Structured Clinical Interview from the Diagnostic and Statistical Manual of Mental Disorders (Fourth Edition), and PTSD symptom subscales were assessed with the civilian version of the PTSD Symptom Checklist.

**Main outcomes and measures:** Patients received technetium 99m-labeled sestamibi myocardial perfusion imaging at rest, with mental stress (ie, a speech task) and conventional stress (ie, exercise or pharmacologic). A summed difference score (ie, the difference between stress and rest scores) was used to assess ischemia under both stress conditions.

**Results:** Among 303 participants (148 [48.8%] women; 198 [65.3%] African American; mean [SD] age, 51 [7] years), the prevalence of PTSD was 14.5% (44 patients). Patients with PTSD had a higher rate of ischemia with mental stress than those without PTSD (12 of 44 [27.3%] vs 38 of 259 [14.7%]; P = .04) and more than twice the mean number of ischemic segments (1.2 [95% CI, 0.5-1.8] vs 0.5 [95% CI, 0.3-0.7]; P < .001), but there was no difference in conventional stress ischemia (10 of 44 [22.7%] vs 60 of 259 [23.2%]; P = .91). Increasing levels of PTSD symptoms were associated with higher odds of ischemia with mental stress (adjusted odds ratio [OR] per 5-point score increase, 1.18; 95% CI 1.04-1.35; P = .01) but not with conventional

stress (adjusted OR per 5-point score increase, 1.05; 95% CI, 0.92-1.21; P = .47). Reexperiencing trauma was the symptom cluster most robustly associated with the presence of ischemia with mental stress (adjusted OR per 5-point score increase, 1.87; 95% CI 1.21-2.91; P = .005), followed by avoidance and numbing (adjusted OR per 5-point score increase, 1.51; 95% CI, 1.07-2.14; P = .02).

**Conclusions and relevance:** In this study of young and middle-aged individuals with MI, with a large representation of women and patients from racial/ethnic minority groups, PTSD was associated with the development of myocardial ischemia with mental stress. A higher ischemic response to mental stress represents a potential pathway associating PTSD with adverse outcomes after MI.

46. Kim JH, Almuwaqqat Z, Hammadah M, Liu C, Ko YA, Lima B, Sullivan S, Alkhoder A, Abdulbaki R, Ward L, Bremner JD, Sheps DS, Raggi P, Sun YV, Shah AJ, Vaccarino V, Quyyumi AA. Peripheral Vasoconstriction During Mental Stress and Adverse Cardiovascular Outcomes in Patients With Coronary Artery Disease. Circ Res. 2019 Oct 25;125(10):874-883. doi: 10.1161/CIRCRESAHA.119.315005. Epub 2019 Sep 25. PMID: 31550998; PMCID: PMC7134565.

**Rationale:** Excessive vasoconstriction in response to mental stress may be a potential mechanism by which acute psychological stress leads to adverse cardiac events.

**Objectives:** We investigated whether excessive digital vasoconstriction during acute mental stress predicts adverse cardiovascular outcomes among patients with coronary artery disease.

**Methods and results:** Five hundred forty-nine patients with stable coronary artery disease (age 63±9, 76% male, 29% black) underwent mental stress testing with a standardized public speaking stressor and followed prospectively for cardiovascular end points. Digital pulse wave amplitude was continuously measured using peripheral artery tonometry (PAT, Itamar Inc). Stress/rest PAT ratio (sPAT) of pulse wave amplitude during mental stress/baseline was calculated and dichotomized by the median value into low and high sPAT ratio groups. Upon 3-year follow-up, Fine and Gray's subdistribution hazard ratios were used to examine the association between sPAT ratio and the composite end point of cardiovascular death, myocardial infarction, revascularization, and hospitalization for heart failure. The median sPAT ratio was 0.68 (interquartile range, 0.48-0.88), indicating 32% vasoconstriction with mental stress. Men were more likely to have low sPAT ratio than women (odds ratio, 1.79; *P*=0.007) while those on β-blockers were less likely to have low sPAT ratio (odds

ratio, 0.52; *P*=0.003). After adjusting for demographic and cardiovascular risk factors, medications, and rate-pressure product change during mental stress, those with low sPAT ratio were at significantly higher risk of adverse outcomes (subdistribution hazard ratio, 1.77 [95% CI, 1.12-2.80]).

**Conclusions:** Greater peripheral vasoconstriction with mental stress, denoted by a low sPAT ratio, is associated with a higher risk of adverse cardiovascular outcomes in patients with coronary artery disease.

47. Lima BB, Hammadah M, Kim JH, Uphoff I, Shah A, Levantsevych O, Almuwaqqat Z, Moazzami K, Sullivan S, Ward L, Kutner M, Ko YA, Sheps DS, Bremner JD, Quyyumi AA, Vaccarino V. Association of Transient Endothelial Dysfunction Induced by Mental Stress With Major Adverse Cardiovascular Events in Men and Women With Coronary Artery Disease. JAMA Cardiol. 2019 Oct 1;4(10):988-996. doi: 10.1001/jamacardio.2019.3252. PMID: 31509180; PMCID: PMC6739728.

**Importance:** Acute mental stress can result in transient endothelial dysfunction, but the prognostic relevance of this phenomenon is unknown.

**Objective:** To determine the association between mental stress-induced impairment in endothelium-dependent relaxation as assessed by brachial artery flow-mediated vasodilation and adverse cardiovascular outcomes among individuals with stable coronary artery disease.

**Design, setting, and participants:** This cohort study was conducted at a university-affiliated hospital network between June 2011 and August 2014. A cohort of individuals with stable coronary artery disease were included. Data analysis took place from November 2018 to May 2019.

**Exposures:** Study participants were subjected to a laboratory mental stress task (public speaking).

**Main outcomes and measures:** Flow-mediated vasodilation was measured before and 30 minutes after a public-speaking mental stress task. We examined the association of the rest (prestress), poststress, and δ flow-mediated vasodilation (poststress minus prestress levels) with an adjudicated composite end point of adverse events, including cardiovascular death, myocardial infarction, unstable angina leading to revascularization, and heart failure hospitalization, after adjusting for sociodemographic factors, medical history, and depression.

**Results:** A total of 569 patients were included (mean [SD] age, 62.6 [9.3] years; 420 men [73.8%]). Flow-mediated vasodilation decreased from a mean (SD) of 4.8% (3.7%) before mental stress to 3.9% (3.6%) after mental stress (a 23% reduction; P < .001), and 360 participants (63.3%) developed transient endothelial dysfunction (a decrease in flow-mediated vasodilation). During a median (interquartile range) follow-up period of 3.0 (2.9-3.1) years, 74 patients experienced a major adverse cardiovascular event. The presence of transient endothelial dysfunction with mental stress was associated with a 78% increase (subdistribution hazard ratio [sHR], 1.78 [95% CI, 1.15-2.76]) in the incidence of major adverse cardiovascular event. Both the δ flow-mediated vasodilation (sHR, 1.15 [95% CI, 1.03-1.27] for each 1% decline) and poststress flow-mediated vasodilation (sHR, 1.14 [95% CI, 1.04-1.24] for each 1% decline) were associated with major adverse cardiovascular event. Risk discrimination statistics demonstrated a significant model improvement after addition of either poststress flow-mediated vasodilation (change in the area under the curve, 0.05 [95% CI, 0.01-0.09]) or prestress plus δ flow-mediated vasodilation (change in the area under the curve, 0.04 [95% CI, 0.00-0.08]) compared with conventional risk factors.

**Conclusions and relevance:** In this study, transient endothelial dysfunction with mental stress was associated with adverse cardiovascular outcomes in patients with coronary artery disease. Endothelial responses to stress represent a possible mechanism through which psychological stress may affect outcomes in patients with coronary artery disease.

48. Saelee R, Vaccarino V, Sullivan S, Hammadah M, Shah A, Wilmot K, Abdelhadi N, Elon L, Pimple P, Kaseer B, Levantsevych O, Bremner JD, Lewis TT. Longitudinal associations between self-reported experiences of discrimination and depressive symptoms in young women and men post- myocardial infarction. J Psychosom Res. 2019 Sep;124:109782. doi: 10.1016/j.jpsychores.2019.109782. Epub 2019 Jul 19. PMID: 31371836; PMCID: PMC6673666.

**Objectives:** Research suggests that following a myocardial infarction (MI), women under the age of 60 have more elevated depressive symptoms and adverse outcomes than similarly aged men. Identifying risk factors that contribute to gender differences in depressive symptoms among this group may be critical to the development of psychosocial interventions. Experiences of discrimination may be an important correlate of depressive symptoms in this group; however, studies of this relationship have largely been cross-sectional and focused on healthy populations.

This study examines longitudinal associations among gender, discrimination, and depressive symptoms in a young post-MI cohort.

**Methods:** Participants were 313 adults from the Myocardial Infarction and Mental Stress Ischemia Study 2 of young (≤60 yrs) post-MI patients. At baseline and 6 month follow-up, depressive symptoms were measured with the Beck Depression Inventory-II and discrimination was assessed with the 10-item version Everyday Discrimination scale. Linear regression models were used to assess the longitudinal association between reports of discrimination and depressive symptoms adjusted for sociodemographic characteristics, psychosocial factors and health status indicators and tested for gender differences.

**Results:** The mean age was 51.2, 49.6% were women, and 69.5% were African-American. Although the discrimination-by-gender interaction was marginally significant (p=.09) in the fully adjusted model, findings suggest that the association between changes in reports of discrimination and depressive symptoms over time may be more pronounced for women (β=.61, standard error=.15, p<.001) than men (β=.27, standard error=.13, p=.033).

**Conclusion:** Our findings suggest that discrimination is a risk factor for depressive symptoms in young post-MI populations over time.

49. Kasher N, Wittbrodt MT, Alam ZS, Lima BB, Nye JA, Campanella C, Ladd S, Hammadah M, Shah AJ, Raggi P, Quyyumi AA, Vaccarino V, Bremner JD. Sex differences in brain activation patterns with mental stress in patients with coronary artery disease. Biol Sex Differ. 2019 Jul 12;10(1):35. doi: 10.1186/s13293-019-0248-4. PMID: 31300046; PMCID: PMC6626382.

**Background:** Stress is an important contributor to myocardial ischemia and the progression of coronary artery disease (CAD), and women are more susceptible than men to these effects. Little is known, however, about the neural basis of these sex differences.

**Methods:** We investigated sex differences in neural correlates of mental stress in a sample of 53 female and 112 male participants (N = 165) with CAD, with and without mental stress-induced myocardial ischemia (MSI), during exposure to mental arithmetic tasks and public speaking stress tasks using high-resolution positron emission tomography (HR-PET) and radiolabeled water imaging of the brain.

**Results:** Women compared to men had significantly greater activation with stress in the right frontal (BA 9, 44), right parietal lobe (Area 3, 6, 40), right posterior cingulate gyrus (BA 31), bilateral cerebellum, and left temporal/fusiform gyrus (BA 37) and greater deactivation in bilateral anterior cingulate gyrus (BA 24, 32), bilateral medial frontal gyrus (BA 6, 8, 9, 10), right parahippocampal gyrus, and right middle temporal gyrus (BA 21). Women with MSI (but not those without MSI) showed significantly greater activation than men in the right posterior cingulate gyrus (BA 31) and greater deactivation in several frontal and temporal lobe areas.

**Conclusion:** Men and women with CAD show differences in responses to stress in brain limbic areas that regulate emotion, and these functional responses differ by MSI status. Our results suggest that the cingulate gyrus may be involved in sex differences in MSI.

50. Liu MY, Yang Y, Zhang LJ, Pu LH, He DF, Liu JY, Hafeez A, Ding YC, Ma H, Geng QS. Potential predictors for mental stress-induced myocardial ischemia in patients with coronary artery disease. Chin Med J (Engl). 2019 Jun 20;132(12):1390-1399. doi: 10.1097/CM9.0000000000000260. PMID: 31205095; PMCID: PMC6629334.

**Background:** Mental stress-induced myocardial ischemia (MSIMI) is closely associated with adverse cardiac events in patients with coronary artery disease (CAD) and we aimed to determine whether biomarkers and blood pressure could be potential predictors of MSIMI.

**Methods:** This study enrolled 82 patients with documented CAD between June 1, 2017 and November 9, 2017. Patient blood samples were obtained at resting period and at the end of mental arithmetic. Then, patients were assigned to MSIMI positive group and MSIMI negative group. The main statistical methods included linear regression, receiver operating characteristic (ROC) curves, and logistic regression.

**Results:** Patients with CAD with MSIMI had significantly greater median resting N-terminal pro-brain natriuretic peptide (NT-proBNP, 141.02 [45.85-202.76] pg/mL vs. 57.95 [27.06-117.64] pg/mL; Z = -2.23, P = 0.03) and mean systolic blood pressure (SBP) (145.56 ± 16.87 mmHg vs. 134.92 ± 18.16 mmHg, Z = -2.13, P = 0.04) when compared with those without MSIMI. After 5-min mental stress task, those who developed MSIMI presented higher elevation of median post-stressor high sensitivity cardiac troponin I (hs-cTnI, 0.020 [0.009-0.100] ng/mL vs. 0.009 [0.009-0.010] ng/mL; Z = -2.45, P = 0.01), post-stressor NT-proBNP (138.96 [39.93-201.56] pg/mL vs. 61.55 [25.66-86.50] pg/mL; Z = -2.15, P = 0.03) compared with those without MSIMI. Using

the ROC curves, and after the adjustment for basic characteristics, the multiple logistic regression analysis showed that patients presenting a post-stressor hs-cTnI ≥ 0.015 ng/mL had seven-fold increase in the risk of developing MSIMI (odds ratio [OR]: 7.09; 95% confidence interval [CI]: 1.65-30.48; P = 0.009), a rest NT-proBNP ≥ 80.51 pg/mL had nearly eight-fold increase (OR: 7.85; 95% CI: 1.51-40.82; P = 0.014), a post-stressor NT-proBNP ≥ 98.80 pg/mL had 35-fold increase (OR: 34.96; 95% CI: 3.72-328.50; P = 0.002), a rest SBP ≥ 129.50 mmHg had 11-fold increase (OR: 11.42; 95% CI: 1.21-108.17; P = 0.034).

**Conclusions:** The present study shows that CAD patients with higher hs-cTnI level, and/or greater NT-proBNP and/or SBP are at higher risk of suffering from MSIMI when compared with those without MSIMI, indicating that hs-cTnI, NT-proBNP, SBP might be potential predictors of MSIMI.

51. Scheer FAJL, Chellappa SL, Hu K, Shea SA. Impact of mental stress, the circadian system and their interaction on human cardiovascular function. Psychoneuroendocrinology. 2019 May;103:125-129. doi: 10.1016/j.psyneuen.2019.01.016. Epub 2019 Jan 16. PMID: 30682628; PMCID: PMC6686856.

The risk for adverse cardiovascular events (e.g., myocardial infarction, sudden cardiac death) peaks in the morning, possibly due to the effects of the endogenous circadian system on cardiovascular risk factors, or the occurrence in the morning of specific triggers, such as mental stress. To assess any interacting effects on cardiovascular function of mental stress and the circadian system, 12 healthy adults underwent a 240-h protocol with all measurements and behaviors scheduled evenly across the circadian cycle. Mental stress was repeatedly induced by performance-motivated serial addition tasks. Cardiovascular measures included hemodynamic function (heart rate, blood pressure), circulating catecholamines (epinephrine, norepinephrine), and estimates of sympathovagal balance and cardiac vagal modulation derived from heart rate variability analyses. Mental stress increased hemodynamic function, sympathovagal balance and epinephrine, and decreased cardiac vagal modulation. Endogenous circadian variation occurred in all cardiovascular measures: sympathovagal balance peaked in the circadian morning (~9 AM), cardiac vagal modulation in the circadian night (~4 AM), and heart rate and circulating catecholamines in the late circadian morning/early afternoon (~12 PM). Importantly, the effects of mental stress and the endogenous circadian system on cardiovascular function occurred in conjunction, such that mental stress in the circadian morning

caused greatest sympathovagal balance. This summation of effects could contribute to the increased morning cardiovascular vulnerability.

52. Pimple P, Hammadah M, Wilmot K, Ramadan R, Al Mheid I, Levantsevych O, Sullivan S, Lima BB, Kim JH, Garcia EV, Nye J, Shah AJ, Ward L, Raggi P, Bremner JD, Hanfelt J, Lewis TT, Quyyumi AA, Vaccarino V. The Relation of Psychosocial Distress With Myocardial Perfusion and Stress-Induced Myocardial Ischemia. Psychosom Med. 2019 May;81(4):363-371. doi: 10.1097/PSY.0000000000000674. PMID: 30676537; PMCID: PMC6955148.

**Objective:** Mental stress-induced myocardial ischemia is a frequent phenomenon in patients with coronary artery disease (CAD). The link between an integrated measure of chronic psychosocial distress and mental stress-induced myocardial ischemia, and whether it differs by sex, has not been examined before.

**Methods:** We used latent class analysis to derive a composite measure of psychosocial distress integrating scales of depression, posttraumatic stress, anxiety, anger, hostility, and perceived stress in 665 individuals with stable CAD. Participants underwent myocardial perfusion imaging with mental stress and perfusion defects were quantified at rest (summed rest score), with mental stress (summed stress score), and their difference (summed difference score), the latter being an index of inducible ischemia.

**Results:** The M (SD) age was 63 (9) years, and 185 (28%) were women. Latent class analysis characterized the study sample into four distinct classes of incremental psychosocial distress. In women, class 4 (highest distress) had an adjusted 4.0-point higher summed rest score (95% confidence interval = 0.2-7.7) as compared with class 1 (lowest distress), whereas no difference was observed in men (-0.87 points, 95% confidence interval = -3.74 to 1.99, p = .04 for interaction). There was no association between the psychosocial distress latent variable and summed difference score in either women or men.

**Conclusions:** Among patients with CAD, a higher level of psychosocial distress is not associated with mental stress ischemia, but it is associated with more resting (fixed) perfusion abnormalities in women only, as well as with blunted hemodynamic response to mental stress in both men and women.

53. Tomaszewski M, Topyła W, Kijewski BG, Miotła P, Waciński P. Does gender influence the outcome of ischemic heart disease? Prz Menopauzalny. 2019 Apr;18(1):51-56. doi: 10.5114/pm.2019.84158. Epub 2019 Apr 9. PMID: 31114459; PMCID: PMC6528044.

Diseases of the cardiovascular system (myocardial infarction, stroke, heart failure, hypertensive heart disease, cardiomyopathy) account for 40% of all deaths in men and up to 49% of all deaths in women. For a long time it was thought that the clinical picture of ischemic heart disease in men and women was similar. Now, however, there are more reports suggesting that diverse manifestations of the symptoms of ischemic disease may be related to differences between sexes. The disparity between women and men is also evident in the diagnostic process, and various pathological mechanisms of cardiovascular diseases, in particular myocardial ischemia in men and women, affect the differences in the results of diagnostic tests. Vasomotor dysfunction is particularly frequent in women, as their coronary vessels are more sensitive to the catecholamines released during mental stress, resulting in spasm and ischemic myocardium. Moreover, a much lower dose of acetylcholine induced vasoconstriction, which indicates that women are more sensitive to this neurotransmitter. Therefore, coronary vasomotor disorders in the form of epicardial and microvascular dysfunction are more often seen in women. All these mentioned factors resulted in higher mortality and poorer quality of life of women suffering from ischemic heart disease.

54. Moscona JC, Peters MN, Maini R, Katigbak P, Deere B, Gonzales H, Westley C, Baydoun H, Yadav K, Ters P, Jabbar A, Boulad A, Mahata I, Gadiraju TV, Nelson R, Srivastav S, Irimpen A. The Incidence, Risk Factors, and Chronobiology of Acute Myocardial Infarction Ten Years After Hurricane Katrina. Disaster Med Public Health Prep. 2019 Apr;13(2):217-222. doi: 10.1017/dmp.2018.22. Epub 2018 Apr 12. PMID: 29644946.

**Objective:** The purpose of this study was to investigate the 10-year impact of Hurricane Katrina on the incidence of acute myocardial infarction (AMI) along with contributing risk factors and any alteration in chronobiology of AMI.

**Methods:** A single-center, retrospective, comparison study of AMI incidence was performed at Tulane University Health Sciences Center from 2 years before Hurricane Katrina to 10 years after Hurricane Katrina. A 6-year, pre-Katrina and 10-year, post-Katrina cohort were also compared according to pre-specified demographic, clinical, and chronobiological data.

**Results:** AMI incidence increased from 0.7% (150/21,079) to 2.8% (2,341/84,751) post-Katrina (P<0.001). The post-Katrina cohort had higher rates of coronary artery disease (36.4% vs. 47.9%, P=0.01), diabetes mellitus (31.3% vs. 39.9%, P=0.04), hyperlipidemia (45.4% vs. 59.3%, P=0.005), smoking (34.4% vs. 53.8%, P<0.001), drug abuse (10.2% vs. 15.4%, P=0.02), psychiatric illness (6.7% vs. 14.9%, P<0.001), medication non-adherence (7.3% vs. 15.3%, P<0.001), and lack of employment (7.2% vs. 16.4%, P<0.001). The post-Katrina group had increased rates of AMI during nights (29.8% vs. 47.8%, P<0.001) and weekends (16.1% vs. 29.1%, P<0.001).

**Conclusions:** Even 10 years after the storm, Hurricane Katrina continues to be associated with increased incidence of AMI, higher prevalence of traditional cardiovascular and psychosocial risk factors, and an altered chronobiology of AMI toward nights and weekends. (Disaster Med Public Health Preparedness. 2019;13:217-222).

55. Nero D, Agewall S, Daniel M, Caidahl K, Collste O, Ekenbäck C, Frick M, Henareh L, Jernberg T, Malmqvist K, Schenck-Gustafsson K, Spaak J, Sörensson P, Sundin Ö, Y-Hassan S, Hofman-Bang C, Tornvall P. Personality Traits in Patients with Myocardial Infarction with Nonobstructive Coronary Arteries. Am J Med. 2019 Mar;132(3):374-381.e1. doi: 10.1016/j.amjmed.2018.11.010. Epub 2018 Nov 30. PMID: 30503881.

**Objective:** The purpose of this study was to describe type A behavior pattern and trait anger in patients with myocardial infarction with nonobstructive coronary arteries (MINOCA) and compare them with patients with coronary heart disease and healthy controls. Type A behavior pattern and anger have been linked to coronary heart disease in previous studies. This is the first study to assess type A behavior pattern and trait anger in MINOCA patients.

**Methods:** One hundred MINOCA patients, consecutively recruited during 2007-2011 at 5 coronary care units in Stockholm, were matched for sex and age to 100 coronary heart disease patients and 100 healthy controls. All participants completed the

Bortner Rating Scale to quantify type A behavior pattern and the Spielberger Trait Anger Scale to quantify anger 3 months after the acute event.

**Results:** MINOCA patients' Bortner Rating Scale score was 70.9 ± 10.8 (mean ± SD) and Spielberger Trait Anger Scale score was 14 (12-17) (median; interquartile range). Coronary heart disease patients' Bortner Rating Scale score was 70.5 ± 10.2 and Spielberger Trait Anger Scale score was 14 (12-17). Healthy controls' Bortner Rating Scale score was 71.9 ± 9.1 and Spielberger Trait Anger Scale score was 13 (11-16).

**Conclusion:** We found no significant differences in Bortner Rating Scale score and Spielberger Trait Anger Scale score among MINOCA, coronary heart disease patients, and healthy controls, regardless of whether total scores, subscales, or cutoffs were used to classify type A behavior pattern and trait anger. However, we cannot exclude the existence of an occasional episode of anger or mental stress in relation to the coronary event. This is the first study to assess type A behavior pattern and trait anger in patients with MINOCA, and future studies need to confirm the current findings before any firm conclusions can be made.

56. Almuwaqqat Z, Sullivan S, Hammadah M, Lima BB, Shah AJ, Abdelhadi N, Fang S, Wilmot K, Al Mheid I, Bremner JD, Garcia E, Nye JA, Elon L, Li L, O'Neal WT, Raggi P, Quyyumi AA, Vaccarino V. Sex-Specific Association Between Coronary Artery Disease Severity and Myocardial Ischemia Induced by Mental Stress. Psychosom Med. 2019 Jan;81(1):57-66. doi: 10.1097/PSY.0000000000000636. PMID: 30571661; PMCID: PMC6800112.

**Objective:** It is unclear whether mental stress-induced myocardial ischemia (MSIMI) is related to obstructive coronary artery disease (CAD). We examined this question and contrasted results with ischemia induced by conventional stress testing (CSIMI). Because women are more susceptible to ischemia without coronary obstruction than men, we examined sex differences.

**Methods:** We studied 276 patients 61 years and younger with recent myocardial infarction. CAD severity was quantified using the log-transformed Gensini Score (lnGS) and the Sullivan Stenosis Score. Patients underwent myocardial perfusion imaging with mental stress (public speaking) and conventional (exercise or pharmacological) stress testing. MSIMI and CSIMI were defined as a new or worsening perfusion defect.

**Results:** The prevalence of MSIMI was 15% in men and 20% in women. The median GS for patients with MSIMI was 65.0 in men and 28.5 in women. In logistic regression models adjusted for demographic and cardiovascular risk factors, CAD severity was associated with CSIMI in the full sample (odds ratio [OR] = 1.49, 95% [CI], 1.14-1.95, per 1-unit increase in lnGS), with no significant difference by sex. Although CAD severity was not associated with MSIMI in the entire sample, results differed by sex. CAD severity was associated with MSIMI among men (OR = 1.95, 95% CI, 1.13-3.36, per 1-unit increase in lnGS), but not among women (OR = 1.02, 95% CI, 0.74-1.42, p = .042 for interaction). Analysis using Sullivan Stenosis Score yielded similar results.

**Conclusions:** Findings suggest that CAD severity is related to MSIMI in men but not women. MSIMI in women may therefore be driven by alternative mechanisms such as coronary microvascular disease.

57. Lima BB, Hammadah M, Wilmot K, Pearce BD, Shah A, Levantsevych O, Kaseer B, Obideen M, Gafeer MM, Kim JH, Sullivan S, Lewis TT, Weng L, Elon L, Li L, Bremner JD, Raggi P, Quyyumi A, Vaccarino V. Posttraumatic stress disorder is associated with enhanced interleukin-6 response to mental stress in subjects with a recent myocardial infarction. Brain Behav Immun. 2019 Jan;75:26-33. doi: 10.1016/j.bbi.2018.08.015. Epub 2018 Aug 30. Erratum in: Brain Behav Immun. 2019 May;78:204-205. doi: 10.1016/j.bbi.2019.03.019. PMID: 30172946; PMCID: PMC6279471.

**Background:** Posttraumatic Stress Disorder (PTSD) is prevalent among patients who survived an acute coronary syndrome, and is associated with adverse outcomes, but the mechanisms underlying these associations are unclear. Individuals with PTSD have enhanced sensitivity of the noradrenergic system to stress which may lead to immune activation. We hypothesized that survivors of a myocardial infarction (MI) who have PTSD would show an enhanced inflammatory response to acute psychological stress compared to those without PTSD.

**Methods:** Individuals with a verified history of MI within 8 months and a clinical diagnosis of current PTSD underwent a mental stress speech task. Inflammatory biomarkers including interleukin-6 (IL-6), high-sensitivity C reactive protein (HsCRP), matrix metallopeptidase 9 (MMP-9), intercellular adhesion molecule (ICAM)-1,

vascular cell adhesion molecule (VCAM)-1 and monocyte chemoattractant protein (MCP)-1 were measured at rest and 90 min after mental stress.

**Results:** Among 271 patients in the study (mean age 51 ± 7 years, 50% female, 60% African-American), the prevalence of PTSD was 12%. Mental stress resulted in a significant increase in IL-6, but the increase was more marked in patients with PTSD (126% increase) than those without (63% increase) ($p = 0.001$). MCP-1 showed a modest increase with stress which was similar in patients with PTSD (9% increase) and without PTSD (6% increase) ($p = 0.35$). CRP did not increase with stress in either group.

**Conclusion:** MI patients with current PTSD exhibit enhanced IL-6 response to psychosocial stress, suggesting a mechanistic link between PTSD and adverse cardiovascular outcomes as well as other diseases associated with inflammation.

58. Bremner JD, Campanella C, Khan Z, Shah M, Hammadah M, Wilmot K, Al Mheid I, Lima BB, Garcia EV, Nye J, Ward L, Kutner MH, Raggi P, Pearce BD, Shah AJ, Quyyumi AA, Vaccarino V. Brain Correlates of Mental Stress-Induced Myocardial Ischemia. Psychosom Med. 2018 Jul/Aug;80(6):515-525. doi: 10.1097/PSY.0000000000000597. PMID: 29794945; PMCID: PMC6023737.

**Objective:** Coronary artery disease (CAD) is a major cause of morbidity and mortality, and despite important advances in our understanding of this disorder, the underlying mechanisms remain under investigation. Recently, increased attention has been placed on the role of behavioral factors such as emotional stress on CAD risk. Brain areas involved in memory and the stress response, including medial prefrontal cortex, insula, and parietal cortex, also have outputs to the peripheral cardiovascular system. The purpose of this study was to assess the effects of mental stress on brain and cardiac function in patients with CAD.

**Methods:** CAD patients (N = 170) underwent cardiac imaging with [Tc-99m] sestamibi single-photon emission tomography at rest and during a public speaking mental stress task. On another day, they underwent imaging of the brain with [O-15] water positron emission tomography (PET) during mental stress (arithmetic and public speaking) and control conditions.

**Results:** Patients with mental stress-induced myocardial ischemia showed increased activation with stress in anterior cingulate, inferior frontal gyrus, and parietal cortex ($p < .005$). This was seen with both arithmetic stress and public speaking stress.

Arithmetic stress was additionally associated with left insula activation, and public speaking with right pre/postcentral gyrus and middle temporal gyrus activation ($p < .005$).

**Conclusions:** These findings suggest that mental stress-induced myocardial ischemia is associated with activation in brain areas involved in the stress response and autonomic regulation of the cardiovascular system. Altered brain reactivity to stress could possibly represent a mechanism through which stress leads to increased risk of CAD-related morbidity and mortality.

59. Hammadah M, Kim JH, Al Mheid I, Samman Tahhan A, Wilmot K, Ramadan R, Alkhoder A, Khayata M, Mekonnen G, Levantsevych O, Bouchi Y, Kaseer B, Choudhary F, Gafeer MM, Corrigan FE 3rd, Shah AJ, Ward L, Kutner M, Bremner JD, Sheps DS, Raggi P, Vaccarino V, Samady H, Mavromatis K, Quyyumi AA. Coronary and Peripheral Vasomotor Responses to Mental Stress. J Am Heart Assoc. 2018 May 3;7(10):e008532. doi: 10.1161/JAHA.118.008532. PMID: 29728013; PMCID: PMC6015339.

**Background:** Coronary microvascular dysfunction may contribute to myocardial ischemia during mental stress (MS). However, the role of coronary epicardial and microvascular function in regulating coronary blood flow (CBF) responses during MS remains understudied. We hypothesized that coronary vasomotion during MS is dependent on the coronary microvascular endothelial function and will be reflected in the peripheral microvascular circulation.

**Methods and results:** In 38 patients aged 59±8 years undergoing coronary angiography, endothelium-dependent and endothelium-independent coronary epicardial and microvascular responses were measured using intracoronary acetylcholine and nitroprusside, respectively, and after MS induced by mental arithmetic testing. Peripheral microvascular tone during MS was measured using peripheral arterial tonometry (Itamar Inc, Caesarea, Israel) as the ratio of digital pulse wave amplitude compared to rest (peripheral arterial tonometry ratio). MS increased the rate-pressure product by 22% (±23%) and constricted epicardial coronary arteries by -5.9% (-10.5%, -2.6%) (median [interquartile range]), $P$=0.001, without changing CBF. Acetylcholine increased CBF by 38.5% (8.1%, 91.3%), $P$=0.001, without epicardial coronary diameter change (0.1% [-10.9%, 8.2%], $P$=not significant). The MS-induced CBF response correlated with endothelium-dependent CBF changes with acetylcholine ($r$=0.38, $P$=0.03) but not with the response to nitroprusside. The

peripheral arterial tonometry ratio also correlated with the demand-adjusted change in CBF during MS ($r$=-0.60, $P$=0.004), indicating similarity between the microcirculatory responses to MS in the coronary and peripheral microcirculation.

**Conclusions:** The coronary microvascular response to MS is determined by endothelium-dependent, but not endothelium-independent, coronary microvascular function. Moreover, the coronary microvascular responses to MS are reflected in the peripheral microvascular circulation.

60. Pimple P, Hammadah M, Wilmot K, Ramadan R, Al Mheid I, Levantsevych O, Sullivan S, Garcia EV, Nye J, Shah AJ, Ward L, Mehta P, Raggi P, Bremner JD, Quyyumi AA, Vaccarino V. Chest Pain and Mental Stress-Induced Myocardial Ischemia: Sex Differences. Am J Med. 2018 May;131(5):540-547.e1. doi: 10.1016/j.amjmed.2017.11.026. Epub 2017 Dec 7. PMID: 29224740; PMCID: PMC5910270.

**Background:** Mental stress-induced myocardial ischemia is a frequent phenomenon in patients with coronary artery disease. Women with coronary artery disease tend to have more mental stress-induced myocardial ischemia and more chest pain/anginal symptoms than men, but whether the association between mental stress-induced myocardial ischemia and angina burden differs in women and men is unknown.

**Methods:** This was a cross-sectional study with experimental manipulation of 950 individuals with stable coronary artery disease. Chest pain/angina frequency in the previous 4 weeks was assessed with the Seattle Angina Questionnaire's angina-frequency subscale. Mental stress-induced myocardial ischemia was assessed with myocardial perfusion imaging during mental stress (standardized public speaking task). Presence of mental stress-induced myocardial ischemia was based on expert readers and established criteria. A conventional (exercise or pharmacologic) stress test was used as a control condition.

**Results:** Overall, 338 individuals (37%) reported angina; 112 (12%) developed mental stress-induced myocardial ischemia, and 256 (29%) developed conventional stress ischemia. Women who reported angina had almost double the probability to develop mental stress-induced myocardial ischemia (19% vs 10%, adjusted prevalence rate ratio, 1.90; 95% confidence interval, 1.04-3.46), whereas there was no such difference in men (11% vs 11%, adjusted prevalence rate ratio, 1.09; 95% confidence interval, 0.66-1.82). No association was found between angina symptoms and conventional stress ischemia for women or men. Results for ischemia as a continuous variable were similar.

**Conclusions:** In women, but not in men, anginal symptoms may be a marker of vulnerability toward ischemia induced by psychologic stress. These results highlight the psychosocial origins of angina in women and may have important implications for the management and prognosis of women with angina.

61. Hammadah M, Al Mheid I, Wilmot K, Ramadan R, Alkhoder A, Obideen M, Abdelhadi N, Fang S, Ibeanu I, Pimple P, Mohamed Kelli H, Shah AJ, Pearce B, Sun Y, Garcia EV, Kutner M, Long Q, Ward L, Bremner JD, Esteves F, Raggi P, Sheps D, Vaccarino V, Quyyumi AA. Association Between High-Sensitivity Cardiac Troponin Levels and Myocardial Ischemia During Mental Stress and Conventional Stress. JACC Cardiovasc Imaging. 2018 Apr;11(4):603-611. doi: 10.1016/j.jcmg.2016.11.021. Epub 2017 Mar 15. PMID: 28330661; PMCID: PMC5814354.

**Objectives:** This study sought to investigate whether patients with mental stress-induced myocardial ischemia will have high resting and post-mental stress high-sensitivity cardiac troponin I (hs-cTnI).

**Background:** Hs-cTnI is a marker of myocardial necrosis, and its elevated levels are associated with adverse outcomes. Hs-cTnI levels may increase with exercise in patients with coronary artery disease. Mental stress-induced myocardial ischemia is also linked to adverse outcomes.

**Methods:** In this study, 587 patients with stable coronary artery disease underwent technetium Tc 99m sestamibi-single-photon emission tomography myocardial perfusion imaging during mental stress testing using a public speaking task and during conventional (pharmacological/exercise) stress testing as a control condition. Ischemia was defined as new/worsening impairment in myocardial perfusion using a 17-segment model.

**Results:** The median hs-cTnI resting level was 4.3 (interquartile range [IQR]: 2.9 to 7.3) pg/ml. Overall, 16% and 34.8% of patients developed myocardial ischemia during mental and conventional stress, respectively. Compared with those without ischemia, median resting hs-cTnI levels were higher in patients who developed ischemia either during mental stress (5.9 [IQR: 3.9 to 8.3] pg/ml vs. 4.1 [IQR: 2.7 to 7.0] pg/ml; $p < 0.001$) or during conventional stress (5.4 [IQR: 3.9 to 9.3] pg/ml vs. 3.9 [IQR: 2.5 to 6.5] pg/ml; $p < 0.001$). Patients with high hs-cTnI (cutoff of 4.6 pg/ml for men and 3.9 pg/ml for women) had greater odds of developing mental (odds ratio [OR]: 2.4; 95% confidence interval [CI]: 1.5 to 3.9; $p < 0.001$) and conventional (OR:

2.4; 95% CI: 1.7 to 3.4; p < 0.001) stress-induced ischemia. Although there was a significant increase in 45-min post-treadmill exercise hs-cTnI levels in those who developed ischemia, there was no significant increase after mental or pharmacological stress test.

**Conclusions:** In patients with coronary artery disease, myocardial ischemia during either mental stress or conventional stress is associated with higher resting levels of hs-cTnI. This suggests that hs-cTnI elevation is an indicator of chronic ischemic burden experienced during everyday life. Whether elevated hs-cTnI levels are an indicator of adverse prognosis beyond inducible ischemia or whether it is amenable to intervention requires further investigation.

62. Vaccarino V, Sullivan S, Hammadah M, Wilmot K, Al Mheid I, Ramadan R, Elon L, Pimple PM, Garcia EV, Nye J, Shah AJ, Alkhoder A, Levantsevych O, Gay H, Obideen M, Huang M, Lewis TT, Bremner JD, Quyyumi AA, Raggi P. Mental Stress-Induced-Myocardial Ischemia in Young Patients With Recent Myocardial Infarction: Sex Differences and Mechanisms. Circulation. 2018 Feb 20;137(8):794-805. doi: 10.1161/CIRCULATIONAHA.117.030849. PMID: 29459465; PMCID: PMC5822741.

**Background:** Mental stress-induced myocardial ischemia (MSIMI) is frequent in patients with coronary artery disease and is associated with worse prognosis. Young women with a previous myocardial infarction (MI), a group with unexplained higher mortality than men of comparable age, have shown elevated rates of MSIMI, but the mechanisms are unknown.

**Methods:** We studied 306 patients (150 women and 156 men) ≤61 years of age who were hospitalized for MI in the previous 8 months and 112 community controls (58 women and 54 men) frequency matched for sex and age to the patients with MI. Endothelium-dependent flow-mediated dilation and microvascular reactivity (reactive hyperemia index) were measured at rest and 30 minutes after mental stress. The digital vasomotor response to mental stress was assessed using peripheral arterial tonometry. Patients received $^{99m}$Tc-sestamibi myocardial perfusion imaging at rest, with mental (speech task) and conventional (exercise/pharmacological) stress.

**Results:** The mean age of the sample was 50 years (range, 22-61). In the MI group but not among controls, women had a more adverse socioeconomic and psychosocial profile than men. There were no sex differences in cardiovascular risk

factors, and among patients with MI, clinical severity tended to be lower in women. Women in both groups showed a higher peripheral arterial tonometry ratio during mental stress but a lower reactive hyperemia index after mental stress, indicating enhanced microvascular dysfunction after stress. There were no sex differences in flow-mediated dilation changes with mental stress. The rate of MSIMI was twice as high in women as in men (22% versus 11%, *P*=0.009), and ischemia with conventional stress was similarly elevated (31% versus 16%, *P*=0.002). Psychosocial and clinical risk factors did not explain sex differences in inducible ischemia. Although vascular responses to mental stress (peripheral arterial tonometry ratio and reactive hyperemia index) also did not explain sex differences in MSIMI, they were predictive of MSIMI in women only.

**Conclusions:** Young women after MI have a 2-fold likelihood of developing MSIMI compared with men and a similar increase in conventional stress ischemia. Microvascular dysfunction and peripheral vasoconstriction with mental stress are implicated in MSIMI among women but not among men, perhaps reflecting women's proclivity toward ischemia because of microcirculatory abnormalities.

63. Sullivan S, Hammadah M, Al Mheid I, Wilmot K, Ramadan R, Alkhoder A, Isakadze N, Shah A, Levantsevych O, Pimple PM, Kutner M, Ward L, Garcia EV, Nye J, Mehta PK, Lewis TT, Bremner JD, Raggi P, Quyyumi AA, Vaccarino V. Sex Differences in Hemodynamic and Microvascular Mechanisms of Myocardial Ischemia Induced by Mental Stress. Arterioscler Thromb Vasc Biol. 2018 Feb;38(2):473-480. doi: 10.1161/ATVBAHA.117.309535. Epub 2017 Dec 21. PMID: 29269515; PMCID: PMC5785428.

**Objective:** To investigate sex-specific vascular mechanisms for mental stress-induced myocardial ischemia (MSIMI).

**Approach and results:** Baseline data from a prospective cohort study of 678 patients with coronary artery disease underwent myocardial perfusion imaging before and during a public speaking stressor. The rate-pressure product response was calculated as the difference between the maximum value during the speech minus the minimum value during rest. Peripheral vasoconstriction by peripheral arterial tonometry was calculated as the ratio of pulse wave amplitude during the speech over the resting baseline; ratios <1 indicate a vasoconstrictive response. MSIMI was defined as percent of left ventricle that was ischemic and as a dichotomous variable. Men (but not women) with MSIMI had a higher rate-pressure product response than

those without MSIMI (6500 versus 4800 mm Hg bpm), whereas women (but not men) with MSIMI had a significantly lower peripheral arterial tonometry ratio than those without MSIMI (0.5 versus 0.8). In adjusted linear regression, each 1000-U increase in rate-pressure product response was associated with 0.32% (95% confidence interval, 0.22-0.42) increase in inducible ischemia among men, whereas each 0.10-U decrease in peripheral arterial tonometry ratio was associated with 0.23% (95% confidence interval, 0.11-0.35) increase in inducible myocardial ischemia among women. Results were independent of conventional stress-induced myocardial ischemia.

**Conclusions:** Women and men have distinct cardiovascular reactivity mechanisms for MSIMI. For women, stress-induced peripheral vasoconstriction with mental stress, and not increased hemodynamic workload, is associated with MSIMI, whereas for men, it is the opposite. Future studies should examine these pathways on long-term outcomes.

64. Hammadah M, Sullivan S, Pearce B, Al Mheid I, Wilmot K, Ramadan R, Tahhan AS, O'Neal WT, Obideen M, Alkhoder A, Abdelhadi N, Mohamed Kelli H, Ghafeer MM, Pimple P, Sandesara P, Shah AJ, Hosny KM, Ward L, Ko YA, Sun YV, Weng L, Kutner M, Bremner JD, Sheps DS, Esteves F, Raggi P, Vaccarino V, Quyyumi AA. Inflammatory response to mental stress and mental stress induced myocardial ischemia. Brain Behav Immun. 2018 Feb;68:90-97. doi: 10.1016/j.bbi.2017.10.004. Epub 2017 Oct 3. PMID: 28986223; PMCID: PMC5808921.

**Background:** Mental stress-induced myocardial ischemia (MSIMI) is associated with increased risk of adverse cardiovascular outcomes, yet the underlying mechanisms are not well understood. We measured the inflammatory response to acute laboratory mental stress in patients with coronary artery disease (CAD) and its association with MSIMI. We hypothesized that patients with MSIMI would have a higher inflammatory response to mental stress in comparison to those without ischemia.

**Methods:** Patients with stable CAD underwent 99mTc sestamibi myocardial perfusion imaging during mental stress testing using a public speaking stressor. MSIMI was determined as impaired myocardial perfusion using a 17-segment model. Inflammatory markers including interleukin-6 (IL-6), monocyte chemoattractant protein-1 (MCP-1), matrix metallopeptidase 9 (MMP-9) and high-sensitivity C reactive protein (hsCRP) were measured at rest and 90 min after mental stress.

Results were validated in an independent sample of 228 post-myocardial infarction patients.

**Results:** Of 607 patients analyzed in this study, (mean age 63 ± 9 years, 76% male), 99 (16.3%) developed MSIMI. Mental stress resulted in a significant increase in IL-6, MCP-1, and MMP-9 (all p <0.0001), but not hsCRP. However, the changes in these markers were similar in those with and without MSIMI. Neither resting levels of these biomarkers, nor their changes with mental stress were significantly associated with MSIMI. Results in the replication sample were similar.

**Conclusion:** Mental stress is associated with acute increases in several inflammatory markers. However, neither the baseline inflammatory status nor the magnitude of the inflammatory response to mental stress over 90 min were significantly associated with MSIMI.

65. Dal Lin C, Marinova M, Rubino G, Gola E, Brocca A, Pantano G, Brugnolo L, Sarais C, Cucchini U, Volpe B, Cavalli C, Bellio M, Fiorello E, Scali S, Plebani M, Iliceto S, Tona F. Thoughts modulate the expression of inflammatory genes and may improve the coronary blood flow in patients after a myocardial infarction. J Tradit Complement Med. 2017 May 29;8(1):150-163. doi: 10.1016/j.jtcme.2017.04.011. PMID: 29322004; PMCID: PMC5755999.

**Background:** Mental stress is one of the main risk factors for cardiovascular disease. Meditation and music listening are two techniques that are able to counteract it through the activation of specific brain areas, eliciting the so-called Relaxing Response (RR). Epidemiological evidence reveals that the RR practice has a beneficial prognostic impact on patients after myocardial infarction. We aimed to study the possible molecular mechanisms of RR underlying these findings.

**Methods:** We enrolled 30 consecutive patients after myocardial infarction and 10 healthy controls. 10 patients were taught to meditate, 10 to appreciate music and 10 did not carry out any intervention and served as controls. After training, and after 60 days of RR practice, we studied the individual variations, before and after the relaxation sessions, of the vital signs, the electrocardiographic and echocardiographic parameters along with coronary flow reserve (CFR) and the carotid's intima media thickness (IMT). Neuro-endocrine-immune (NEI) messengers and the expression of inflammatory genes (p53, Nuclear factor Kappa B (NfKB), and toll like receptor 4 (TLR4)) in circulating peripheral blood mononuclear cells were also all observed.

**Results:** The RR results in a reduction of NEI molecules ($p < 0.05$) and oxidative stress ($p < 0.001$). The expression of the genes p53, NFkB and TLR4 is reduced after the RR and also at 60 days ($p < 0.001$). The CFR increases with the relaxation ($p < 0.001$) and the IMT regressed significantly ($p < 0.001$) after 6 months of RR practice.

**Conclusions:** The RR helps to advantageously modulate the expression of inflammatory genes through a cascade of NEI messengers improving, over time, microvascular function and the arteriosclerotic process.

66. Hagström E, Norlund F, Stebbins A, Armstrong PW, Chiswell K, Granger CB, López-Sendón J, Pella D, Soffer J, Sy R, Wallentin L, White HD, Stewart RAH, Held C. Psychosocial stress and major cardiovascular events in patients with stable coronary heart disease. J Intern Med. 2018 Jan;283(1):83-92. doi: 10.1111/joim.12692. Epub 2017 Oct 23. PMID: 28960596.

**Objectives:** Assess the risk of ischaemic events associated with psychosocial stress in patients with stable coronary heart disease (CHD).

**Methods:** Psychosocial stress was assessed by a questionnaire in 14 577 patients (median age 65.0, IQR 59, 71; 81.6% males) with stable CHD on optimal secondary preventive therapy in the prospective randomized STABILITY clinical trial. Adjusted Cox regression models were used to assess associations between individual stressors, baseline cardiovascular risk factors and outcomes.

**Results:** After 3.7 years of follow-up, depressive symptoms, loss of interest and financial stress were associated with increased risk (hazard ratio, 95% confidence interval) of CV death (1.21, 1.09-1.34; 1.15, 1.05-1.27; and 1.19, 1.08-1.30, respectively) and the primary composite end-point of CV death, nonfatal MI or nonfatal stroke (1.21, 1.13-1.30; 1.19, 1.11-1.27; and 1.17, 1.10-1.24, respectively). Living alone was related to higher risk of CV death (1.68, 1.38-2.05) and the primary composite end-point (1.28, 1.11-1.48), whereas being married as compared with being widowed, was associated with lower risk of CV death (0.64, 0.49-0.82) and the primary composite end-point (0.81, 0.67-0.97).

**Conclusions:** Psychosocial stress, such as depressive symptoms, loss of interest, living alone and financial stress, were associated with increased CV mortality in patients with stable CHD despite optimal medical secondary prevention treatment. Secondary prevention of CHD should therefore focus also on psychosocial issues both in clinical management and in future clinical trials.

67. Alenezi F, Brummett BH, Boyle SH, Samad Z, Babyak MA, Alzaeim N, Wilson J, Romano MMD, Sun JL, Ersboll M, O'Connor CM, Velazquez EJ, Jiang W. Usefulness of Myocardial Annular Velocity Change During Mental Stress to Predict Cardiovascular Outcome in Patients With Coronary Artery Disease (From the Responses of Mental Stress-Induced Myocardial Ischemia to Escitalopram Treatment Trial). Am J Cardiol. 2017 Nov 1;120(9):1495-1500. doi: 10.1016/j.amjcard.2017.07.039. Epub 2017 Jul 29. PMID: 28917493.

Mental stress-induced myocardial ischemia is common and a prognostic factor of adverse cardiovascular outcomes in patients with coronary artery disease (CAD). The present study aimed at examining associations between mental stress-induced myocardial annular velocity (MAV) and cardiovascular outcome in patients with CAD. MAV, specifically, diastolic early (e'), diastolic late (a'), and systolic (s') velocities were obtained at rest and during mental stress testing in 224 patients with clinically stable CAD. Using Cox regression models, age, sex, and baseline-adjusted mental stress-induced MAV measures were examined as predictors of a priori defined composite event term that comprised all-cause mortality and/or nonfatal cardiovascular events, resulting in an unplanned hospitalization (major adverse cardiovascular events [MACE]). Median follow-up was 4 years. The sample was predominantly male, Caucasian with New York Heart Association functional class I and a mean age of 63 ± 10.2 years. MS-induced changes in e' (hazard ratio [HR] = .73) and s' (HR = .73) were significant ($p < 0.05$) predictors of MACE, and the change in a' (HR = .74) was marginal ($p = 0.05$). The pattern of the relation for each MAV measure was such that patients with a greater decrease in e' and/or s' velocity had a higher probability of experiencing an MACE, and the association of the change in a' and MACE was marginal ($p = 0.05$), but the same tendency. The associations between MS-induced values of e' and a' for MACE were independent of resting levels. Mental stress-induced MAV changes independently predict an adverse cardiovascular outcome in patients with stable CAD.

68. Hammadah M, Alkhoder A, Al Mheid I, Wilmot K, Isakadze N, Abdulhadi N, Chou D, Obideen M, O'Neal WT, Sullivan S, Tahhan AS, Kelli HM, Ramadan R, Pimple P, Sandesara P, Shah AJ, Ward L, Ko YA, Sun Y, Uphoff I, Pearce B, Garcia EV, Kutner M, Bremner JD, Esteves F, Sheps DS, Raggi P, Vaccarino V, Quyyumi AA. Hemodynamic, catecholamine, vasomotor and vascular responses: Determinants of myocardial ischemia during mental stress. Int J Cardiol. 2017 Sep 15;243:47-53. doi: 10.1016/j.ijcard.2017.05.093. Epub 2017 May 25. PMID: 28571621; PMCID: PMC5532063.

**Aims:** Mental stress-induced myocardial ischemia (MSIMI) in patients with coronary artery disease (CAD) is associated with adverse cardiovascular outcomes. We aim to assess hemodynamic, neuro-hormonal, endothelial, vasomotor and vascular predictors of MSIMI.

**Methods and results:** We subjected 660 patients with stable CAD to 99mTc sestamibi myocardial perfusion imaging at rest, with mental (speech task) and with conventional (exercise/pharmacological) stress. Endothelium-dependent flow-mediated dilation (FMD), microvascular reactivity [reactive hyperemia index (RHI)] and arterial stiffness [pulse wave velocity (PWV)] were measured at rest and 30-min after mental stress. The digital microvascular vasomotor response during mental stress was assessed using peripheral arterial tonometry (PAT). A total of 106(16.1%) patients had MSIMI. Mental stress was accompanied by significant increases in rate-pressure-product (heart rate x systolic blood pressure; RPP), epinephrine levels and PWV, and significant decreases in FMD and PAT ratio denoting microvascular constriction. In comparison to those with no MSIMI, patients with MSIMI had higher hemodynamic and digital vasoconstrictive responses ($p<0.05$ for both), but did not differ in epinephrine, endothelial or macrovascular responses. Only presence of ischemia during conventional stress (OR of 7.1, 95%CI of 4.2, 11.9), high hemodynamic response (OR for RPP response≥vs<ROC cutoff of 1.8, 95%CI of 1.1, 2.8), and high digital vasoconstriction (OR for PAT ratio<vs≥ROC cutoff of 2.1, 95%CI of 1.3, 3.3) were independent predictors of MSIMI.

**Conclusion:** Ischemia during conventional stress testing and hemodynamic and vasoconstrictive responses to mental stress can help predict subjects with CAD at greater risk of developing MSIMI.

69. Wallert J, Held C, Madison G, Olsson EM. Temporal changes in myocardial infarction incidence rates are associated with periods of perceived psychosocial stress: A SWEDEHEART national registry study. Am Heart J. 2017 Sep;191:12-20. doi: 10.1016/j.ahj.2017.05.015. Epub 2017 Jun 3. PMID: 28888265.

**Background:** Psychosocial stress might trigger myocardial infarction (MI). Increased MI incidence coincides with recurrent time periods during the year perceived as particularly stressful in the population.

**Methods:** A stress-triggering hypothesis on the risk of MI onset was investigated with Swedish population data on MI hospital admission date and symptom onset date (N=156,690; 148,176) as registered from 2006 through 2013 in the national quality registry database Swedish Web-system for Enhancement and Development of Evidence-based care in Heart disease Evaluated According to Recommended Therapies (SWEDEHEART). Poisson regression was applied to analyze daily MI rates during days belonging to the Christmas and New Year holidays, turns of the month, Mondays, weekends, and summer vacation in July compared with remaining control days.

**Results:** Adjusted incidence rate ratios (IRRs) for MI rates were higher during Christmas and New Year holidays (IRR=1.07 [1.04-1.09], P<.001) and on Mondays (IRR=1.11 [1.09-1.13], P<.001) and lower in July (IRR=0.92 [0.90-0.94], P<.001) and over weekends (IRR=0.88 [0.87-0.89], P<.001), yet not during the turns of the month (IRR=1.01 [1.00-1.02], P=.891). These findings were also predominantly robust with symptom onset as alternative outcome, when adjusting for both established and some suggested-but-untested confounders, and in 8 subgroups.

**Conclusions:** Fluctuations in daily MI incidence rates are systematically related to time periods of presumed psychosocial stress. Further research might clarify mechanisms that are amenable to clinical alteration.

70. Kjellström B, Gustafsson A, Nordendal E, Norhammar A, Nygren Å, Näsman P, Rydén L, Åsberg M; PAROKRANK steering committee. Symptoms of depression and their relation to myocardial infarction and periodontitis. Eur J Cardiovasc Nurs. 2017 Aug;16(6):468-474. doi: 10.1177/1474515116686462. Epub 2016 Dec 29. PMID: 28032516.

**Background:** Psychosocial stress and depression are established risk factors for cardiovascular disease and a relationship to periodontitis has been suggested. We studied symptoms of depression and their relation to myocardial infarction and periodontitis.

**Methods:** In a Swedish case-control study, 805 patients, <75 years with a first myocardial infarction and 805 controls without myocardial infarction were matched for age, gender and geographic area. Mean age was 62±8 years and 81% were male. Standardised physical examination and dental panoramic X-ray for grading of periodontal status was performed. Medical history including risk factors related to cardiovascular disease and periodontitis was collected as was detailed information on perceived stress at home and work, and symptoms of depression (Montgomery Åsberg Depression Scale). A Montgomery Åsberg Depression Scale score ⩾13 was considered clinically relevant.

**Results:** A family history of cardiovascular disease, smoking and divorce was more frequent among patients than controls. Patients had more symptoms of depression than controls (14 vs 7%; $p<0.001$) but received less anti-depressive treatment (16 vs 42%; $p<0.001$). Symptoms of depression doubled the risk for myocardial infarction (Montgomery Åsberg Depression Scale: odds ratio 2.17 (95% confidence interval 1.41-3.34)). There was no difference in symptoms of depression between study participants with and without periodontitis.

**Conclusion:** Patients with a first myocardial infarction were more frequently depressed than matched controls without myocardial infarction, but received less anti-depressive treatment. A relationship between depression and periodontitis could not be confirmed.

71. Sun JL, Boyle SH, Samad Z, Babyak MA, Wilson JL, Kuhn C, Becker RC, Ortel TL, Williams RB, Rogers JG, O'Connor CM, Velazquez EJ, Jiang W. Mental stress-induced left ventricular dysfunction and adverse outcome in ischemic heart disease patients. Eur J Prev Cardiol. 2017 Apr;24(6):591-599. doi: 10.1177/2047487316686435. Epub 2017 Jan 9. PMID: 28067532; PMCID: PMC6093615.

Aims Mental stress-induced myocardial ischemia (MSIMI) occurs in up to 70% of patients with clinically stable ischemic heart disease and is associated with increased risk of adverse prognosis. We aimed to examine the prognostic value of indices of MSIMI and exercise stress-induced myocardial ischemia (ESIMI) in a population of ischemic heart disease patients that was not confined by having a recent positive physical stress test. Methods and results The Responses of Mental Stress Induced Myocardial Ischemia to Escitalopram Treatment (REMIT) study enrolled 310 subjects who underwent mental and exercise stress testing and were followed annually for a median of four years. Study endpoints included time to first and total rate of major adverse cardiovascular events, defined as all-cause mortality and hospitalizations for cardiovascular causes. Cox and negative binomial regression adjusting for age, sex, resting left ventricular ejection fraction, and heart failure status were used to examine associations of indices of MSIMI and ESIMI with study endpoints. The continuous variable of mental stress-induced left ventricular ejection fraction change was significantly associated with both endpoints (all p values < 0.05). For every reduction of 5% in left ventricular ejection fraction induced by mental stress, patients had a 5% increase in the probability of a major adverse cardiovascular event at the median follow-up time and a 20% increase in the number of major adverse cardiovascular events endured over the follow-up period of six years. Indices of ESIMI did not predict endpoints ( ps > 0.05). Conclusion In patients with stable ischemic heart disease, mental, but not exercise, stress-induced left ventricular ejection fraction change significantly predicts risk of future adverse cardiovascular events.

72. Hammadah M, Al Mheid I, Wilmot K, Ramadan R, Shah AJ, Sun Y, Pearce B, Garcia EV, Kutner M, Bremner JD, Esteves F, Raggi P, Sheps DS, Vaccarino V, Quyyumi AA. The Mental Stress Ischemia Prognosis Study: Objectives, Study Design, and Prevalence of Inducible Ischemia. Psychosom Med. 2017 Apr;79(3):311-317. doi: 10.1097/PSY.0000000000000442. PMID: 28002382; PMCID: PMC5373992.

**Objective:** Mental stress-induced myocardial ischemia (MSIMI) is a common phenomenon in patients with coronary artery disease (CAD), but contemporary studies of its prognostic significance and its underlying pathophysiology are limited.

**Methods:** We prospectively enrolled patients with confirmed CAD in the Mental Stress Ischemia Prognosis Study (MIPS) between 2011 and 2014. All patients underwent mental stress testing using a standardized public speaking task, and ischemia was detected by Tc-sestamibi myocardial perfusion imaging. Patients also underwent conventional stress testing for myocardial ischemia (CSIMI) using exercise or pharmacological stress testing. Furthermore, digital microvascular flow, endothelial function, arterial stiffness, and blood sample collections were performed before, during, and after mental stress. Two-year adverse clinical outcomes are being assessed.

**Results:** Six-hundred ninety-five patients completed baseline enrollment in the MIPS. Their mean (standard deviation) age was 62.9 (9.1) years, 72% were men, 30% were African American, and 32% had a history myocardial infarction. The prevalence of MSIMI and CSIMI is 16.1% and 34.7%, respectively. A total of 151 patients (22.9%) had only CSIMI, 28 (4.2%) had only MSIMI, and 78 (11.8%) had both MSIMI and CSIMI. Patients with ischemia had a lower ejection fraction and higher prevalence of previous coronary artery bypass grafting compared with those without inducible ischemia ($p < .050$). The prevalence of obstructive CAD was not statistically different between patients with and without MSIMI ($p = .426$); in contrast, it was higher in patients with CSIMI ($p < .001$).

**Conclusions:** The MIPS data will provide useful information to assess the prognostic significance and underlying mechanisms of MSIMI.

73. Feigal JP, Boyle SH, Samad Z, Velazquez EJ, Wilson JL, Becker RC, Williams RB Jr, Kuhn CM, Ortel TL, Rogers JG, O'Connor CM, Jiang W. Associations between positive emotional well-being and stress-induced myocardial ischemia: Well-being scores predict exercise-induced ischemia. J Psychosom Res. 2017 Feb;93:14-18. doi: 10.1016/j.jpsychores.2016.11.012. Epub 2016 Nov 29. PMID: 28107887; PMCID: PMC6044283.

**Objective:** Depressive symptoms have been associated with myocardial ischemia induced by mental (MSIMI) and exercise (ESIMI) stress in clinically stable ischemic heart disease (IHD) patients, but the association between positive emotions and inducible ischemia is less well characterized. The objective of this study was to examine the associations between ratings of well-being and stress-induced ischemia.

**Methods:** Subjects were adult patients with documented IHD underwent mental and exercise stress testing for the Responses of Myocardial Ischemia to Escitalopram Treatment (REMIT) trial. The General Well-Being Schedule (GWBS), with higher scores reflecting greater subjective well-being, and the Center for Epidemiologic Studies Depression Scale (CES-D) were obtained from the REMIT participants. Echocardiography was used to measure ischemic responses to mental stress and Bruce protocol treadmill exercise testing. Data were analyzed using logistic regression adjusting for age, sex, resting left-ventricular ejection fraction (LVEF), and resting wall motion score index, as well as health-related behaviors.

**Results:** GWBS scores were obtained for 210 individuals, with MSIMI present in 92 (43.8%) and ESIMI present in 64 (30.5%). There was a significant inverse correlation between GWBS-PE (Positive Emotion subscale) scores and probability of ESIMI (OR=0.55 (95%CI 0.36-0.83), p=0.005). This association persisted after additional control for CESD subscales measuring negative and positive emotions and for variables reflecting health-related behaviors. A similar inverse correlation between GWBS-PE and MSIMI was observed, but did not reach statistical significance (OR=0.81 (95%CI 0.54-1.20), p=0.28).

**Conclusion:** This is, to our knowledge, the first study demonstrating that greater levels of self-reported positive emotions are associated with a lower likelihood of ESIMI among patients with known IHD. Our results highlight the important interface functions of the central nervous and cardiovascular systems and underscore areas for future investigation.

74. Soufer R, Fernandez AB, Meadows J, Collins D, Burg MM. Body Mass Index and Risk for Mental Stress Induced Ischemia in Coronary Artery Disease. Mol Med. 2016 Sep;22:286-291. doi: 10.2119/molmed.2016.00128. Epub 2016 May 19. PMID: 27261777; PMCID: PMC5023512.

Acute emotionally reactive mental stress (MS) can provoke prognostically relevant deficits in cardiac function and myocardial perfusion, and chronic inflammation increases risk for this ischemic phenomenon. We have described parasympathetic withdrawal and generation of inflammatory factors in MS. Adiposity is also associated with elevated markers of chronic inflammation. High body mass index (BMI) is frequently used as a surrogate for assessment of excess adiposity, and associated with traditional CAD risk factors, and CAD mortality. BMI is also associated with autonomic dysregulation, adipose tissue derived proinflammatory cytokines, which are also attendant to emotion provoked myocardial ischemia. Thus, we sought to determine if body mass index (BMI) contributes to risk of developing myocardial ischemia provoked by mental stress. We performed a prospective interventional study in a cohort of 161 patients with stable CAD. They completed an assessment of myocardial blood flow with single photon emission computed tomography (SPECT) simultaneously during 2 conditions: laboratory mental stress and at rest. Multivariate logistic regression determined the independent contribution of BMI to the occurrence of mental-stress induced ischemia. Mean age was 65.6 ±9.0 years; 87.0% had a history of hypertension, and 28.6% had diabetes. Mean BMI was 30.4 ± 4.7. Prevalence of mental stress ischemia was 39.8%. BMI was an independent predictor of mental stress ischemia, OR=1.10, 95% CI [1.01-1.18] for one-point increase in BMI and OR=1.53, 95% CI [1.06-2.21] for a 4.7 point increase in BMI (one standard deviation beyond the cohort BMI mean), p=0.025 for all. These data suggest that BMI may serve as an independent risk marker for mental stress ischemia. The factors attendant with greater BMI, which include autonomic dysregulation and inflammation, may represent pathways by which high BMI contribute to this risk and serve as a conceptual construct to replicate these findings in larger CAD populations.

75. Vaccarino V, Wilmot K, Al Mheid I, Ramadan R, Pimple P, Shah AJ, Garcia EV, Nye J, Ward L, Hammadah M, Kutner M, Long Q, Bremner JD, Esteves F, Raggi P, Quyyumi AA. Sex Differences in Mental Stress-Induced Myocardial Ischemia in Patients With Coronary Heart Disease. J Am Heart Assoc. 2016 Aug 24;5(9):e003630. doi: 10.1161/JAHA.116.003630. PMID: 27559072; PMCID: PMC5079026.

**Background:** Emerging data suggest that young women with coronary heart disease (CHD) are disproportionally vulnerable to the adverse cardiovascular effects of psychological stress. We hypothesized that younger, but not older, women with stable CHD are more likely than their male peers to develop mental stress-induced myocardial ischemia (MSIMI).

**Methods and results:** We studied 686 patients (191 women) with stable coronary heart disease (CHD). Patients underwent (99m)Tc-sestamibi myocardial perfusion imaging at rest and with both mental (speech task) and conventional (exercise/pharmacological) stress testing. We compared quantitative (by automated software) and visual parameters of inducible ischemia between women and men and assessed age as an effect modifier. Women had a more-adverse psychosocial profile than men whereas there were few differences in medical history and CHD risk factors. Both quantitative and visual indicators of ischemia with mental stress were disproportionally larger in younger women. For each 10 years of decreasing age, the total reversibility severity score with mental stress was 9.6 incremental points higher (interaction, $P<0.001$) and the incidence of MSIMI was 82.6% higher (interaction, $P=0.004$) in women than in men. Incidence of MSIMI in women ≤50 years was almost 4-fold higher than in men of similar age and older patients. These results persisted when adjusting for sociodemographic and medical risk factors, psychosocial factors, and medications. There were no significant sex differences in inducible ischemia with conventional stress.

**Conclusions:** Young women with stable CHD are susceptible to MSIMI, which could play a role in the prognosis of this group.

76. Yanartas O, Sunbul M, Senkal Z, Durmus E, Kivrak T, Subasi N, Karaer G, Ergun S, Sari I, Sayar K. Increased arterial stiffness parameters in panic disorder patients in long term treatment period. Ann Gen Psychiatry. 2016 Jun 8;15:14. doi: 10.1186/s12991-016-0102-6. PMID: 27279893; PMCID: PMC4898398.

**Background:** The relationship between mental stress and cardiovascular disease has been shown in several studies. Panic disorder (PD) is also associated with cardiovascular disease due to increased risk of myocardial infarction. The aim of this study is to evaluate the association between arterial stiffness parameters and depression/anxiety scores in patients with PD.

**Methods:** The study population consisted of 25 patients with PD and 25 age-sex-matched healthy controls. Depression and anxiety levels were evaluated by Beck Depression Inventory (BDI) and Beck Anxiety Inventory (BAI), respectively. Determination of arterial stiffness parameters was conducted using a Mobil-O-Graph arteriograph system that detected signals from the brachial artery.

**Results:** While baseline characteristics were similar between two groups, BDI and BAI scores were significantly higher in patients with PD ($p < 0.005$). The pulse wave velocity (PWV) and Augmentation Index (AIx) were also significantly higher in patients with PD ($p = 0.001$, $p = 0.006$). There was a moderate correlation between PWV and AIx with BAI scores ($r = 0.442$, $p = 0.001$, $r = 0.441$, $p = 0.001$). AIx was also positively correlated with BDI scores ($r = 0.415$, $p = 0.03$).

**Conclusion:** We demonstrated a significant relationship between arterial stiffness parameters and anxiety/depression scores in patients with PD who receive antidepressant treatment.

77. Vujcic I, Vlajinac H, Dubljanin E, Vasiljevic Z, Matanovic D, Maksimovic J, Sipetic S. Psychosocial Stress and Risk of Myocardial Infarction: A Case-Control Study in Belgrade (Serbia). Acta Cardiol Sin. 2016 May;32(3):281-9. doi: 10.6515/acs20150424k. PMID: 27274168; PMCID: PMC4884755.

**Background:** The purpose of this study was to investigate which psychosocial risk factors show the strongest association with occurrence of myocardial infarction (MI) in the population of Belgrade in peacetime, after the big political changes in Serbia.

**Methods:** A case-control study was conducted involving 154 consecutive newly diagnosed patients with MI, and 308 controls matched by gender, age, and place of residence.

**Results:** According to conditional logistic regression analysis, after adjustment for conventional coronary risk factors, the odds ratios (95% confidence intervals) for work-related stressful events, financial stress, deaths and diseases, and general stress were 3.78 (1.83-7.81), 3.80 (1.96-7.38), 1.69 (1.03-2.78), and 3.54 (2.01-6.22), respectively. Among individual stressful life events, the following were independently related to MI: death of a close family member, 2.21 (1.01-4.84); death of a close friend, 42.20 (3.70-481.29); major financial problems, 8.94 (1.83-43.63); minor financial problems, 4.74 (2.02-11.14); changes in working hours, 4.99 (1.64-15.22); and changes in working conditions, 30.94 (5.43-176.31).

**Conclusions:** During this political transition period , stress at work, financial stress, and stress in general as they impacted the population of Belgrade, Serbia were strongly associated with occurence of MI.

78. Ma H, Guo L, Huang D, Wang L, Guo L, Geng Q, Zhang M. The Role of the Myocardial Microvasculature in Mental Stress-Induced Myocardial Ischemia. Clin Cardiol. 2016 Apr;39(4):234-9. doi: 10.1002/clc.22522. Epub 2016 Feb 19. PMID: 26895096; PMCID: PMC6490863.

There is increasing evidence that mental stress can manifest as physical diseases. One such condition is mental stress-induced myocardial ischemia (MSIMI); a silent, transient, myocardial ischemic response to stressful conditions. We propose that the cardiac microvasculature may be an important site for the interplay between mental

stress and MSIMI. This study is a review of the literature discussing the prevalence and emerging mechanisms underlying MSIMI. We identified several aspects underlying MSIMI, including psychological, genetic, and physiological causes. Several sources suggested that dysfunctional cardiac microvasculature might be a contributing factor in the development of stress-induced myocardial ischemia. The literature also suggested that although MSIMI has distinct features and pathophysiology, its occurrence might indicate an increased future risk of cardiovascular events. We found that dysfunctional cardiac microvasculature may be the key point of interaction between mental stress and transient myocardial ischemia and that the development of MSIMI might be a "silent" indicator for future cardiac events.

79. Kop WJ, Galvao TF, Synowski SJ, Xu W, Can A, O'Shea KM, Gould TD, Stanley WC. Effects of environmental stress following myocardial infarction on behavioral measures and heart failure progression: The influence of isolated and group housing conditions. Physiol Behav. 2015 Dec 1;152(Pt A):168-74. doi: 10.1016/j.physbeh.2015.09.024. Epub 2015 Sep 28. PMID: 26423786.

**Background:** Heart failure (HF) prognosis is negatively influenced by adverse environmental conditions associated with psychological distress and depression. The underlying mechanisms are not well understood because of insufficient experimental control in prior clinical and epidemiological studies. Using a validated animal model we examined whether distress-producing environmental manipulations (social isolation and crowding) increase HF progression following myocardial infarction (MI).

**Methods:** MI was induced using coronary artery ligation in 8-week old male Wistar rats (N=52) and results were compared to sham surgery (N=24). Housing conditions were randomly assigned at 5 days post MI or sham surgery (1/cage=isolation, 2/cage=standard reference condition, or 4/cage=crowding) and continued for 17 weeks until the end of observation. The open field test was used to test behavioral responses. Echocardiograms were obtained at weeks 8 and 16, and left ventricular (LV) weight at week 17.

**Results:** Housing conditions increased behavioral markers of distress (p=0.046) with the strongest effects for the isolated (1/cage) (p=0.022). MI did not increase distress-related behaviors compared to sham. MI-surgery resulted in characteristic HF indices

(left ventricular ejection fraction (LVEF) at week 16=46 ± 12% vs. 80 ± 7% in sham, $p<0.001$). Housing condition was not related to LVEF or LV weight ($p>0.10$).

**Conclusions:** Adverse environmental conditions, particularly isolated housing, produce increases in some of the behavioral indicators of distress. No effects of housing were found on post-MI progression of HF. The distress-HF associations observed in humans may therefore reflect common underlying factors rather than an independent causal pathway. Stronger environmental challenges may be needed in future animal research examining distress as related HF progression.


## 80. Jiang W. Emotional triggering of cardiac dysfunction: the present and future. Curr Cardiol Rep. 2015 Oct;17(10):91. doi: 10.1007/s11886-015-0635-3. PMID: 26298307.


Mental stress and emotional arousal can act as triggers of acute myocardial infarction and other adverse cardiovascular outcomes. Experimental research examining mechanisms of the adverse interplay between mind and heart has led to the discovery of mental stress-induced cardiac dysfunction or myocardial ischemia (MSIMI). Evidence about the prevalence, clinical significance, and mechanistic bases of MSIMI outlines a wide range of central and peripheral bio-pathologic processes that are associated with emotions and behaviors. MSIMI is recognized as an integrated and intermediate biomarker underpinning the negative mind-heart interplay. Particularly, MSIMI research paves the way toward investigations aiming more specifically at recognizing the susceptibilities of individuals who are prone to respond adversely to the psycho-social-environmental stress. This article reviews recent literature on MSIMI research following the comprehensive review of Strike and Steptoe Eur Heart J 24:690-703, 2003. Further, this article outlines the main steps in the identification of the specific bio-pathologic manifestations of the cardiovascular system to emotional stress. Finally, a speculative description is provided of future directions in better searching for areas that may be critical targets in resolving adverse mind-heart interplays.

81. Wawrzyniak AJ, Dilsizian V, Krantz DS, Harris KM, Smith MF, Shankovich A, Whittaker KS, Rodriguez GA, Gottdiener J, Li S, Kop W, Gottlieb SS. High Concordance Between Mental Stress-Induced and Adenosine-Induced Myocardial Ischemia Assessed Using SPECT in Heart Failure Patients: Hemodynamic and Biomarker Correlates. J Nucl Med. 2015 Oct;56(10):1527-33. doi: 10.2967/jnumed.115.157990. Epub 2015 Jul 23. PMID: 26205303; PMCID: PMC4807331.

Mental stress can trigger myocardial ischemia, but the prevalence of mental stress-induced ischemia in congestive heart failure (CHF) patients is unknown. We characterized mental stress-induced and adenosine-induced changes in myocardial perfusion and neurohormonal activation in CHF patients with reduced left-ventricular function using SPECT to precisely quantify segment-level myocardial perfusion.

**Methods:** Thirty-four coronary artery disease patients (mean age±SD, 62±10 y) with CHF longer than 3 mo and ejection fraction less than 40% underwent both adenosine and mental stress myocardial perfusion SPECT on consecutive days. Mental stress consisted of anger recall (anger-provoking speech) followed by subtraction of serial sevens. The presence and extent of myocardial ischemia was quantified using the conventional 17-segment model.

**Results:** Sixty-eight percent of patients had 1 ischemic segment or more during mental stress and 81% during adenosine. On segment-by-segment analysis, perfusion with mental stress and adenosine were highly correlated. No significant differences were found between any 2 time points for B-type natriuretic peptide, tumor necrosis factor-α, IL-1b, troponin, vascular endothelin growth factor, IL-17a, matrix metallopeptidase-9, or C-reactive protein. However, endothelin-1 and IL-6 increased, and IL-10 decreased, between the stressor and 30 min after stress. Left-ventricular end diastolic dimension was 179±65 mL at rest and increased to 217±71 after mental stress and 229±86 after adenosine ($P<0.01$ for both). Resting end systolic volume was 129±60 mL at rest and increased to 158±66 after mental stress ($P<0.05$) and 171±87 after adenosine ($P<0.07$), with no significant differences between adenosine and mental stress. Ejection fraction was 30±12 at baseline, 29±11 with mental stress, and 28±10 with adenosine (P=not significant).

**Conclusion:** There was high concordance between ischemic perfusion defects induced by adenosine and mental stress, suggesting that mental stress is equivalent to pharmacologic stress in eliciting clinically significant myocardial perfusion defects in CHF patients. Cardiac dilatation suggests clinically important changes with both

conditions. Psychosocial stressors during daily life may contribute to the ischemic burden of CHF patients with coronary artery disease.

82. Pimple P, Shah AJ, Rooks C, Bremner JD, Nye J, Ibeanu I, Raggi P, Vaccarino V. Angina and mental stress-induced myocardial ischemia. J Psychosom Res. 2015 May;78(5):433-437. doi: 10.1016/j.jpsychores.2015.02.007. Epub 2015 Feb 21. PMID: 25727240; PMCID: PMC4380582.

**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.

83. Jiang W, Boyle SH, Ortel TL, Samad Z, Velazquez EJ, Harrison RW, Wilson J, Kuhn C, Williams RB, O'Connor CM, Becker RC. Platelet aggregation and mental stress induced myocardial ischemia: Results from the Responses of Myocardial Ischemia to Escitalopram Treatment (REMIT) study. Am Heart J. 2015 Apr;169(4):496-507.e1. doi: 10.1016/j.ahj.2014.12.002. Epub 2014 Dec 17. PMID: 25819856; PMCID: PMC4382806.

**Background:** Mental stress-induced myocardial ischemia (MSIMI) is common in patients with ischemic heart disease (IHD) and associated with a poorer cardiovascular prognosis. Platelet hyperactivity is an important factor in acute coronary syndrome. This study examined associations between MSIMI and resting and mental stress-induced platelet activity.

**Methods:** Eligible patients with clinically stable IHD underwent a battery of 3 mental stress tests during the recruitment phase of REMIT study. MSIMI was assessed by echocardiography and electrocardiography. Ex vivo platelet aggregation in response to ADP, epinephrine, collagen, serotonin, and combinations of serotonin plus ADP, epinephrine, and collagen were evaluated as was platelet serotonin transporter expression.

**Results:** Of the 270 participants who completed mental stress testing, and had both resting and post-stress platelet aggregation evaluation , 43.33% (n=117) met criteria for MSIMI and 18.15% (n=49) had normal left ventricular response to stress (NLVR). The MSIMI group, relative to the NLVR groups, demonstrated heightened mental stress-induced aggregation responses, as measured by area under the curve, to collagen 10μM (6.95[5.54] vs. -14.23[8.75].; P=0.045), epinephrine 10μM (12.84[4.84] vs. -6.40[7.61].; P=0.037) and to serotonin 10 μM plus ADP 1 μM (6.64[5.29] vs. -27.34[8.34]; P<.001). The resting platelet aggregation and serotonin transporter expression, however, were not different between the two groups.

**Conclusions:** These findings suggest that the dynamic change of platelet aggregation caused by mental stress may underlie MSIMI. While the importance of these findings requires additional investigation, they raise concern given the recognized relationship between mental stress-induced platelet hyperactivity and cardiovascular events in patients with IHD.

84. Friedler B, Crapser J, McCullough L. One is the deadliest number: the detrimental effects of social isolation on cerebrovascular diseases and cognition. Acta Neuropathol. 2015 Apr;129(4):493-509. doi: 10.1007/s00401-014-1377-9. Epub 2014 Dec 24. PMID: 25537401; PMCID: PMC4369164.

The deleterious effects of chronic social isolation (SI) have been recognized for several decades. Isolation is a major source of psychosocial stress and is associated with an increased prevalence of vascular and neurological diseases. In addition, isolation exacerbates morbidity and mortality following acute injuries such as stroke or myocardial infarction. In contrast, affiliative social interactions can improve organismal function and health. The molecular mechanisms underlying these effects are unknown. Recently, results from large epidemiological trials and pre-clinical studies have revealed several potential mediators of the detrimental effects of isolation. At least three major biological systems have been implicated: the neuroendocrine (HPA) axis, the immune system, and the autonomic nervous system. This review summarizes studies examining the relationship between isolation and mortality and the pathophysiological mechanisms underlying SI. Cardiovascular, cerebrovascular, and neurological diseases including atherosclerosis, myocardial infarction, ischemic stroke and Alzheimer's disease are given special emphasis in the context of SI. Sex differences are highlighted and studies are separated into clinical and basic science for clarity.

85. Xu X, Bao H, Strait K, Spertus JA, Lichtman JH, D'Onofrio G, Spatz E, Bucholz EM, Geda M, Lorenze NP, Bueno H, Beltrame JF, Krumholz HM. Sex differences in perceived stress and early recovery in young and middle-aged patients with acute myocardial infarction. Circulation. 2015 Feb 17;131(7):614-23. doi: 10.1161/CIRCULATIONAHA.114.012826. Epub 2015 Feb 9. PMID: 25679303; PMCID: PMC4652932.

**Background:** Younger age and female sex are both associated with greater mental stress in the general population, but limited data exist on the status of perceived stress in young and middle-aged patients presenting with acute myocardial infarction.

**Methods and results:** We examined sex difference in stress, contributing factors to this difference, and whether this difference helps explain sex-based disparities in 1-month recovery using data from 3572 patients with acute myocardial infarction (2397 women and 1175 men) 18 to 55 years of age. The average score of the 14-item Perceived Stress Scale at baseline was 23.4 for men and 27.0 for women ($P<0.001$). Higher stress in women was explained largely by sex differences in comorbidities, physical and mental health status, intrafamily conflict, caregiving demands, and financial hardship. After adjustment for demographic and clinical characteristics, women had worse recovery than men at 1 month after acute myocardial infarction, with mean differences in improvement score between women and men ranging from -0.04 for EuroQol utility index to -3.96 for angina-related quality of life ($P<0.05$ for all). Further adjustment for baseline stress reduced these sex-based differences in recovery to -0.03 to -3.63, which, however, remained statistically significant ($P<0.05$ for all). High stress at baseline was associated with significantly worse recovery in angina-specific and overall quality of life, as well as mental health status. The effect of baseline stress on recovery did not vary between men and women.

**Conclusions:** Among young and middle-aged patients, higher stress at baseline is associated with worse recovery in multiple health outcomes after acute myocardial infarction. Women perceive greater psychological stress than men at baseline, which partially explains women's worse recovery.

86. Mehta PK, Wei J, Wenger NK. Ischemic heart disease in women: a focus on risk factors. Trends Cardiovasc Med. 2015 Feb;25(2):140-51. doi: 10.1016/j.tcm.2014.10.005. Epub 2014 Oct 16. PMID: 25453985; PMCID: PMC4336825.

Heart disease remains a major contributor to morbidity and mortality in women in the United States and worldwide. This review highlights known and emerging risk factors for ischemic heart disease (IHD) in women. Traditional Framingham risk factors such as hypertension, hyperlipidemia, diabetes, smoking, as well as lifestyle habits such as unhealthy diet and sedentary lifestyle are all modifiable. Health care providers should be aware of emerging cardiac risk factors in women such as adverse pregnancy outcomes, systemic autoimmune disorders, obstructive sleep apnea, and radiation-induced heart disease; psychosocial factors such as mental stress, depression, anxiety, low socioeconomic status, and work and marital stress play an important role in IHD in women. Appropriate recognition and management of an array of risk factors is imperative given the growing burden of IHD and need to deliver cost-effective, quality care for women.

87. Rorabaugh BR, Krivenko A, Eisenmann ED, Bui AD, Seeley S, Fry ME, Lawson JD, Stoner LE, Johnson BL, Zoladz PR. Sex-dependent effects of chronic psychosocial stress on myocardial sensitivity to ischemic injury. Stress. 2015;18(6):645-53. doi: 10.3109/10253890.2015.1087505. Epub 2015 Oct 12. PMID: 26458179.

Individuals with post-traumatic stress disorder (PTSD) experience many debilitating symptoms, including intrusive memories, persistent anxiety and avoidance of trauma-related cues. PTSD also results in numerous physiological complications, including increased risk for cardiovascular disease (CVD). However, characterization of PTSD-induced cardiovascular alterations is lacking, especially in preclinical models of the disorder. Thus, we examined the impact of a psychosocial predator-based animal model of PTSD on myocardial sensitivity to ischemic injury. Male and female Sprague-Dawley rats were exposed to psychosocial stress or control conditions for 31 days. Stressed rats were given two cat exposures, separated by a period of 10 days, and were subjected to daily social instability throughout the paradigm. Control rats were handled daily for the duration of the experiment. Rats were tested on the elevated plus maze (EPM) on day 32, and hearts were isolated on day 33 and subjected to 20 min ischemia and 2 h reperfusion on a Langendorff isolated heart system. Stressed male and female rats gained less body weight relative to controls, but only stressed males exhibited increased anxiety on the EPM. Male, but not female, rats exposed to psychosocial stress exhibited significantly larger infarcts and attenuated post-ischemic recovery of contractile function compared to controls. Our data demonstrate that predator stress combined with daily social instability sex-dependently increases myocardial sensitivity to ischemic injury. Thus, this manipulation may be useful for studying potential mechanisms underlying cardiovascular alterations in PTSD, as well as sex differences in the cardiovascular stress response.

88. Pimple P, Shah A, Rooks C, Bremner JD, Nye J, Ibeanu I, Murrah N, Shallenberger L, Kelley M, Raggi P, Vaccarino V. Association between anger and mental stress-induced myocardial ischemia. Am Heart J. 2015 Jan;169(1):115-21.e2. doi: 10.1016/j.ahj.2014.07.031. Epub 2014 Sep 16. PMID: 25497256; PMCID: PMC4268485.

**Background:** Mental stress-induced myocardial ischemia is associated with adverse prognosis in coronary artery disease patients. Anger is thought to be a trigger of acute coronary syndromes and is associated with increased cardiovascular risk; however, little direct evidence exists for a link between anger and myocardial ischemia.

**Methods:** [(99m)Tc]-sestamibi single-photon emission tomography was performed at rest, after mental stress (a social stressor with a speech task) and after exercise/pharmacologic stress. Summed scores of perfusion abnormalities were obtained by observer-independent software. A summed-difference score, the difference between stress and rest scores, was used to quantify myocardial ischemia under both stress conditions. The Spielberger's State-Trait Anger Expression Inventory was used to assess different anger dimensions.

**Results:** The mean age was 50 years, 50% were female, and 60% were non-white. After adjusting for demographic factors, smoking, coronary artery disease severity, depressive, and anxiety symptoms, each IQR increment in state-anger score was associated with 0.36 U-adjusted increase in ischemia as measured by the summed-difference score (95% CI 0.14-0.59); the corresponding association for trait anger was 0.95 (95% CI 0.21-1.69). Anger expression scales were not associated with ischemia. None of the anger dimensions was related to ischemia during exercise/pharmacologic stress.

**Conclusion:** Anger, both as an emotional state and as a personality trait, is significantly associated with propensity to develop myocardial ischemia during mental stress but not during exercise/pharmacologic stress. Patients with this psychologic profile may be at increased risk for silent ischemia induced by emotional stress, and this may translate into worse prognosis.

89. Wadley AJ, Veldhuijzen van Zanten JJ, Paine NJ, Drayson MT, Aldred S. Underlying inflammation has no impact on the oxidative stress response to acute mental stress. Brain Behav Immun. 2014 Aug;40:182-90. doi: 10.1016/j.bbi.2014.03.009. Epub 2014 Mar 24. PMID: 24675034.

**Introduction:** Mental stress is considered to be a trigger for acute myocardial infarction (MI), with inflammation thought to provide a mechanism. Inflammation is reciprocally linked to oxidative stress, which has also been implicated in MI. The purpose of this study was to assess the effects of experimentally-induced inflammation on the oxidative stress response to mental stress in healthy participants.

**Methods:** Healthy males undertook one of two inflammatory stimuli: typhoid vaccination (Vaccination paradigm, N=17) or eccentric exercise (Eccentric exercise paradigm, N=17). All participants completed a mental arithmetic stress task twice (within-subject design): 6h after the inflammatory stimulus, and during a control non-inflammation condition. Blood samples were taken before, immediately and 30min after the stress task. Plasma was assessed for interleukin-6 (IL-6), protein carbonyls (PC), lipid hydroperoxides (LOOH), total antioxidant capacity (TAC) and nitric oxide metabolites (NOx).

**Results:** Vaccination paradigm: IL-6, PC and NOx were significantly higher in the vaccination condition, relative to the control condition ($p<.05$). PC, TAC, LOOH and NOx were unchanged in response to mental stress in both the vaccination and control conditions. Eccentric Exercise paradigm: IL-6 and TAC were significantly higher in the eccentric exercise condition ($p<.05$), relative to the control condition. PC, TAC and NOx were unchanged in response to mental stress in both the eccentric exercise and control conditions.

**Conclusions:** Two different inflammatory paradigms were successful in increasing selective plasma markers of inflammation and oxidative stress prior to a mental stress task. However, experimentally induced transient inflammation had no impact on mental stress-induced changes in plasma LOOH, PC, TAC or NOx in young healthy participants.

90. Wei J, Pimple P, Shah AJ, Rooks C, Bremner JD, Nye JA, Ibeanu I, Murrah N, Shallenberger L, Raggi P, Vaccarino V. Depressive symptoms are associated with mental stress-induced myocardial ischemia after acute myocardial infarction. PLoS One. 2014 Jul 25;9(7):e102986. doi: 10.1371/journal.pone.0102986. PMID: 25061993; PMCID: PMC4111307.

**Objectives:** Depression is an adverse prognostic factor after an acute myocardial infarction (MI), and an increased propensity toward emotionally-driven myocardial ischemia may play a role. We aimed to examine the association between depressive symptoms and mental stress-induced myocardial ischemia in young survivors of an MI.

**Methods:** We studied 98 patients (49 women and 49 men) age 38-60 years who were hospitalized for acute MI in the previous 6 months. Patients underwent myocardial perfusion imaging at rest, after mental stress (speech task), and after exercise or pharmacological stress. A summed difference score (SDS), obtained with observer-independent software, was used to quantify myocardial ischemia under both stress conditions. The Beck Depression Inventory-II (BDI-II) was used to measure depressive symptoms, which were analyzed as overall score, and as separate somatic and cognitive depressive symptom scores.

**Results:** There was a significant positive association between depressive symptoms and SDS with mental stress, denoting more ischemia. After adjustment for demographic and lifestyle factors, disease severity and medications, each incremental depressive symptom was associated with 0.14 points higher SDS. When somatic and cognitive depressive symptoms were examined separately, both somatic [$\beta = 0.17$, 95% CI: (0.04, 0.30), $p = 0.01$] and cognitive symptoms [$\beta = 0.31$, 95% CI: (0.07, 0.56), $p = 0.01$] were significantly associated with mental stress-induced ischemia. Depressive symptoms were not associated with ischemia induced by exercise or pharmacological stress.

**Conclusion:** Among young post-MI patients, higher levels of both cognitive and somatic depressive symptoms are associated with a higher propensity to develop myocardial ischemia with mental stress, but not with physical (exercise or pharmacological) stress.

91. Wei J, Rooks C, Ramadan R, Shah AJ, Bremner JD, Quyyumi AA, Kutner M, Vaccarino V. Meta-analysis of mental stress-induced myocardial ischemia and subsequent cardiac events in patients with coronary artery disease. Am J Cardiol. 2014 Jul 15;114(2):187-92. doi: 10.1016/j.amjcard.2014.04.022. Epub 2014 May 1. PMID: 24856319; PMCID: PMC4126399.

Mental stress-induced myocardial ischemia (MSIMI) has been associated with adverse prognosis in patients with coronary artery disease (CAD), but whether this is a uniform finding across different studies has not been described. We conducted a systematic review and meta-analysis of prospective studies examining the association between MSIMI and adverse outcome events in patients with stable CAD. We searched PubMed, EMBASE, Web of Science, and PsycINFO databases for English language prospective studies of patients with CAD who underwent standardized mental stress testing to determine presence of MSIMI and were followed up for subsequent cardiac events or total mortality. Our outcomes of interest were CAD recurrence, CAD mortality, or total mortality. A summary effect estimate was derived using a fixed-effects meta-analysis model. Only 5 studies, each with a sample size of <200 patients and fewer than 50 outcome events, met the inclusion criteria. The pooled samples comprised 555 patients with CAD (85% male) and 117 events with a range of follow-up from 35 days to 8.8 years. Pooled analysis showed that MSIMI was associated with a twofold increased risk of a combined end point of cardiac events or total mortality (relative risk 2.24, 95% confidence interval 1.59 to 3.15). No heterogeneity was detected among the studies (Q=0.39, I2=0.0%, p=0.98). In conclusion, although few selected studies have examined the association between MSIMI and adverse events in patients with CAD, all existing investigations point to approximately a doubling of risk. Whether this increased risk is generalizable to the CAD population at large and varies in patient subgroups warrant further investigation.

92. Li Y, Rukshin I, Pan F, Sen S, Islam M, Yousif A, Rukshin V. The impact of the 2008-2009 economic recession on acute myocardial infarction occurrences in various socioeconomic areas of raritan bay region, new jersey. N Am J Med Sci. 2014 May;6(5):215-8. doi: 10.4103/1947-2714.132938. PMID: 24926446; PMCID: PMC4049054.

**Background:** Psychosocial stress is one important risk factor for myocardial infarction.

**Aim:** The study was to assess the impact of the 2008-2009 economic recession on myocardial infarction occurrences in different socioeconomic areas of Raritan Bay region, New Jersey.

**Materials and methods:** The patients, who were treated for acute myocardial infarction from January 2006 to June 2012, were grouped based on the average incomes of their residence districts in the Raritan Bay region. The Spearman Rank Correlation test was used to assess the correlation between the monthly occurrences of myocardial infarction and Dow Jones stock averages, as well as the correlation between the myocardial infarction occurrences and NJ State unemployment rates.

**Results:** Among 1,491 cases that were identified, 990 cases resided in areas with income below the state average and 477 were from areas above the average. After the onset of the recession, the myocardial infarction occurrences trended up in the low-income area group but not in the high-income area group; and this increasing trend is correlated with the rise in NJ State unemployment rates but not with the changes in stock averages.

**Conclusion:** Our findings suggest that unemployment contributed to an increased risk of myocardial infarction among the residents in low socioeconomic areas after the 2008-2009 economic recession.

93. Krantz DS, Burg MM. Current perspective on mental stress-induced myocardial ischemia. Psychosom Med. 2014 Apr;76(3):168-70. doi: 10.1097/PSY.0000000000000054. PMID: 24677165; PMCID: PMC8607301.

Mental stress and emotional arousal can act as triggers of myocardial infarction and other adverse cardiovascular outcomes. This editorial presents an overview of the research on mental stress-induced myocardial ischemia (MSIMI) and comments on

two investigations examining MSIMI published in this journal. These studies confirm that MSIMI is frequently observed in patients with coronary artery disease and that characteristics, such as being a woman younger than 50 years and depression, may increase the relative risk of MSIMI. The method used for determining MSIMI (i.e., assessing cardiac function as determined by echocardiography versus measurement of myocardial perfusion using single-photon emission computed tomography), as well as the nature of the mental stress protocols (i.e., one stress task versus several repeated tasks), may have important effects on the findings of MSIMI research and on their interpretation. An overview of clinical characteristics of MSIMI is presented, and the article concludes with possible directions for future MSIMI research.

94. Ersbøll M, Al Enezi F, Samad Z, Sedberry B, Boyle SH, O'Connor C, Jiang W, Velazquez EJ; REMIT Investigators. Impaired resting myocardial annular velocities are independently associated with mental stress-induced ischemia in coronary heart disease. JACC Cardiovasc Imaging. 2014 Apr;7(4):351-61. doi: 10.1016/j.jcmg.2013.10.014. Epub 2014 Mar 13. PMID: 24631512; PMCID: PMC3992174.

**Objectives:** The aim of this study was to investigate the association between resting myocardial function as assessed by tissue Doppler myocardial velocities and the propensity to develop mental stress-induced ischemia (MSIMI).

**Background:** Tissue Doppler myocardial velocities detect preclinical cardiac dysfunction and clinical outcomes in a range of conditions. However, little is known about the interrelationship between myocardial velocities and the propensity to develop MSIMI compared with exercise stress-induced myocardial ischemia.

**Methods:** Resting annular myocardial tissue Doppler velocities were obtained in 225 patients with known coronary heart disease who were subjected to both conventional exercise stress testing as well as a battery of 3 mental stress tests. Diastolic early (e') and late (a') as well as systolic (s') velocities were obtained, and the eas index, an integrated measure of myocardial velocities, was calculated as e'/(a' × s'). MSIMI was defined as: 1) the development or worsening of regional wall motion abnormality; 2) a reduction in left ventricular ejection fraction ≥ 8%; and/or 3) ischemic ST-segment changes during 1 or more of the 3 mental stress tests.

**Results:** A total of 98 of 225 patients (43.7%) exhibited MSIMI. Patients developing MSIMI had significantly lower s' (7.0 ± 1.7 vs. 7.5 ± 1.2, p = 0.016) and a' (8.9 ± 1.8 vs. 10.0 ± 1.9, p < 0.001) at baseline, whereas e' did not differ (6.5 ± 1.7 vs. 6.5 ± 1.8, p =

0.85). Furthermore, the eas index was significantly higher (0.11 ± 0.04 vs. 0.09 ± 0.03, p < 0.0001). The eas index remained significantly associated with the propensity to develop MSIMI (odds ratio per 0.05-U increase: 1.85; 95% confidence interval: 1.21 to 2.82; p = 0.004) after adjustment for resting left ventricular ejection fraction, resting wall motion index score, sex, and social circumstances of living. There was no association between resting eas index and exercise stress-induced myocardial ischemia.

**Conclusions:** MSIMI but not exercise stress-induced myocardial ischemia is independently associated with resting abnormalities in myocardial systolic and late diastolic velocities as well as the integrated measure of the eas index in patients with known coronary artery disease. (Responses of Myocardial Ischemia to Escitalopram Treatment [REMIT]; NCT00574847).

95. Vaccarino V, Shah AJ, Rooks C, Ibeanu I, Nye JA, Pimple P, Salerno A, D'Marco L, Karohl C, Bremner JD, Raggi P. Sex differences in mental stress-induced myocardial ischemia in young survivors of an acute myocardial infarction. Psychosom Med. 2014 Apr;76(3):171-80. doi: 10.1097/PSY.0000000000000045. PMID: 24608039; PMCID: PMC4008686.

**Objectives:** Emotional stress may disproportionally affect young women with ischemic heart disease. We sought to examine whether mental stress-induced myocardial ischemia (MSIMI), but not exercise-induced ischemia, is more common in young women with previous myocardial infarction (MI) than in men.

**Methods:** We studied 98 post-MI patients (49 women and 49 men) aged 38 to 60 years. Women and men were matched for age, MI type, and months since MI. Patients underwent technetium-99m sestamibi perfusion imaging at rest, after mental stress, and after exercise/pharmacological stress. Perfusion defect scores were obtained with observer-independent software. A summed difference score (SDS), the difference between stress and rest scores, was used to quantify ischemia under both stress conditions.

**Results:** Women 50 years or younger, but not older women, showed a more adverse psychosocial profile than did age-matched men but did not differ for conventional risk factors and tended to have less angiographic coronary artery disease. Compared with age-matched men, women 50 years or younger exhibited a higher SDS with mental stress (3.1 versus 1.5, p = .029) and had twice the rate of MSIMI (SDS ≥ 3; 52% versus 25%), whereas ischemia with physical stress did not differ (36% versus

25%). In older patients, there were no sex differences in MSIMI. The higher prevalence of MSIMI in young women persisted when adjusting for sociodemographic and life-style factors, coronary artery disease severity, and depression.

96. Nakamura A, Nozaki E, Fukui S, Endo H, Takahashi T, Tamaki K. Increased risk of acute myocardial infarction after the Great East Japan Earthquake. Heart Vessels. 2014 Mar;29(2):206-12. doi: 10.1007/s00380-013-0353-y. Epub 2013 Apr 20. PMID: 23604314.

Strong psychosocial stress is considered to be a precipitating factor in acute coronary events. To assess the hypothesis that the incidence of acute myocardial infarction (AMI) and its severity was remarkably heightened after the great earthquake, we retrospectively analyzed the clinical data of patients with AMI admitted to our hospital during a 3-week period between March 11 and March 31, 2011 (disaster group) as compared with AMI patients during the corresponding time period of 2010 (non-disaster group). The number of patients with AMI in the disaster group increased by about threefold (22 in the disaster group vs. seven in the non-disaster group). Compared with the previous years 2010 or 2009, the odds ratios [OR] for AMI during a 3-week period in 2011 were 4.40 (95 % confidence interval [CI]: 1.05-18.35), 5.66 (95 % CI: 1.42-22.59), respectively. Although the number of patients who underwent coronary revascularization was higher in the disaster group than in the non-disaster group (68.2 vs. 42.9 %, p = 0.0397), peak serum creatine kinase (CK)-MB level was significantly higher in the disaster group than in the non-disaster group (208.0 ± 159.0 vs. 149.3 ± 102.7 IU/l, p = 0.0431). In the disaster group, four patients died of cardiac causes, whereas no patient died in the non-disaster group (in-hospital mortality rate in the disaster vs. non-disaster group: 18.2 vs. 0 %, p = 0.0281). These results suggest that patients with AMI after the earthquake might be subject to strong psychosocial stress, and that psychological stress brought on by such disaster could trigger cardiac events and cardiac death.

97. Soares-Filho GL, Machado S, Arias-Carrión O, Santulli G, Mesquita CT, Cosci F, Silva AC, Nardi AE. Myocardial perfusion imaging study of CO(2)-induced panic attack. Am J Cardiol. 2014 Jan 15;113(2):384-8. doi: 10.1016/j.amjcard.2013.09.035. Epub 2013 Oct 4. PMID: 24188891.

Chest pain is often seen alongside with panic attacks. Moreover, panic disorder has been suggested as a risk factor for cardiovascular disease and even a trigger for acute coronary syndrome. Patients with coronary artery disease may have myocardial ischemia in response to mental stress, in which panic attack is a strong component, by an increase in coronary vasomotor tone or sympathetic hyperactivity setting off an increase in myocardial oxygen consumption. Indeed, coronary artery spasm was presumed to be present in cases of cardiac ischemia linked to panic disorder. These findings correlating panic disorder with coronary artery disease lead us to raise questions about the favorable prognosis of chest pain in panic attack. To investigate whether myocardial ischemia is the genesis of chest pain in panic attacks, we developed a myocardial perfusion study through research by myocardial scintigraphy in patients with panic attacks induced in the laboratory by inhalation of 35% carbon dioxide. In conclusion, from the data obtained, some hypotheses are discussed from the viewpoint of endothelial dysfunction and microvascular disease present in mental stress response.

98. Ramadan R, Quyyumi AA, Zafari AM, Binongo JN, Sheps DS. Myocardial ischemia and angiotensin-converting enzyme inhibition: comparison of ischemia during mental and physical stress. Psychosom Med. 2013 Nov-Dec;75(9):815-21. doi: 10.1097/PSY.0000000000000015. Epub 2013 Oct 25. PMID: 24163387.

**Objective:** Mental stress provokes myocardial ischemia in many patients with stable coronary artery disease (CAD). Mental stress-induced myocardial ischemia (MSIMI) portends a worse prognosis, independent of standard cardiac risk factors or outcome of traditional physical stress testing. Angiotensin II plays a significant role in the physiological response to stress, but its role in MSIMI remains unknown. Our aim was to evaluate whether the use of angiotensin-converting enzyme inhibitors (ACEIs) is associated with a differential effect on the incidence of MSIMI compared with ischemia during physical stress.

**Methods:** Retrospective analysis of 218 patients with stable CAD, including 110 on ACEI, was performed. 99m-Tc-sestamibi myocardial perfusion imaging was used to define ischemia during mental stress, induced by a standardized public speaking task, and during physical stress, induced by either exercise or adenosine.

**Results:** Overall, 40 patients (18%) developed MSIMI and 80 patients (37%) developed ischemia during physical stress. MSIMI occurred less frequently in patients receiving ACEIs (13%) compared with those not on ACEIs (24%; p = .030, adjusted odds ratio = 0.42, 95% confidence interval = 0.19-0.91). In contrast, the frequency of myocardial ischemia during physical stress testing was similar in both groups (39% versus 35% in those on and not on ACEIs, respectively); adjusted odds ratio = 0.91, 95% confidence interval = 0.48-1.73).

**Conclusion:** In this retrospective study, patients using ACEI therapy displayed less than half the risk of developing ischemia during mental stress but not physical stress. This possible beneficial effect of ACEIs on MSIMI may be contributing to their salutary effects in CAD.

99. Boyle SH, Samad Z, Becker RC, Williams R, Kuhn C, Ortel TL, Kuchibhatla M, Prybol K, Rogers J, O'Connor C, Velazquez EJ, Jiang W. Depressive symptoms and mental stress-induced myocardial ischemia in patients with coronary heart disease. Psychosom Med. 2013 Nov-Dec;75(9):822-31. doi: 10.1097/PSY.0b013e3182a893ae. Epub 2013 Oct 25. PMID: 24163385; PMCID: PMC4378828.

**Objectives:** The aim of this study was to examine the associations between depressive symptoms and mental stress-induced myocardial ischemia (MSIMI) in patients with coronary heart disease (CHD).

**Methods:** Adult patients with documented CHD were recruited for baseline mental stress and exercise stress screening testing as a part of the enrollment process of the Responses of Myocardial Ischemia to Escitalopram Treatment trial. Patients were administered the Beck Depression Inventory II and the Center for Epidemiologic Studies Depression Scale. After a 24-48-hour β-blocker withdrawal, participants completed three mental stress tests followed by a treadmill exercise test. Ischemia was defined as a) any development or worsening of any wall motion abnormality and b) reduction of left ventricular ejection fraction at least 8% by transthoracic echocardiography and/or ischemic ST-segment change by electrocardiography during stress testing. MSIMI was considered present when ischemia occurred in at

least one mental test. Data were analyzed using logistic regression adjusting for age, sex, and resting left ventricular ejection fraction.

**Results:** One hundred twenty-five (44.2%) of 283 patients were found to have MSIMI, and 93 (32.9%) had ESIMI. Unadjusted analysis showed that Beck Depression Inventory II scores were positively associated with the probability of MSIMI (odds ratio = 0.1.30: 95% confidence interval = 1.06-1.60, p = .013) and number of MSIMI-positive tasks (all p < .005). These associations were still significant after adjustment for covariates (p values <.05).

**Conclusions:** In patients with CHD, depressive symptoms were associated with a higher probability of MSIMI. These observations may enhance our understanding of the mechanisms contributing to the association of depressive symptoms to future cardiovascular events. Trial Registration Clinicaltrials.gov identifier: NCT00574847.

100. Ramadan R, Sheps D, Esteves F, Zafari AM, Bremner JD, Vaccarino V, Quyyumi AA. Myocardial ischemia during mental stress: role of coronary artery disease burden and vasomotion. J Am Heart Assoc. 2013 Oct 21;2(5):e000321. doi: 10.1161/JAHA.113.000321. PMID: 24145741; PMCID: PMC3835239.

**Background:** Mental stress-induced myocardial ischemia (MSIMI) is associated with adverse prognosis in patients with coronary artery disease (CAD), yet the mechanisms underlying this phenomenon remain unclear. We hypothesized that compared with exercise/pharmacological stress-induced myocardial ischemia (PSIMI) that is secondary to the atherosclerotic burden of CAD, MSIMI is primarily due to vasomotor changes.

**Methods and results:** Patients with angiographically documented CAD underwent 99mTc-sestamibi myocardial perfusion imaging at rest and following both mental and physical stress testing, performed on separate days. The severity and extent of CAD were quantified using the Gensini and Sullivan scores. Peripheral arterial tonometry (Itamar Inc) was used to assess the digital microvascular tone during mental stress as a ratio of pulse wave amplitude during speech compared with baseline. Measurements were made in a discovery sample (n = 225) and verified in a replication sample (n = 159). In the pooled (n = 384) sample, CAD severity and extent scores were not significantly different between those with and without MSIMI, whereas they were greater in those with compared with those without PSIMI (P < 0.04 for all). The peripheral arterial tonometry ratio was lower in those with compared with those without MSIMI (0.55 ± 0.36 versus 0.76 ± 0.52, P = 0.009). In a

multivariable analysis, the peripheral arterial tonometry ratio was the only independent predictor of MSIMI (P = 0.009), whereas angiographic severity and extent of CAD independently predicted PSIMI.

**Conclusions:** The degree of digital microvascular constriction, and not the angiographic burden of CAD, is associated with MSIMI. Varying causes of MSIMI compared with PSIMI may require different therapeutic interventions that require further study.

101. Jiang W, Velazquez EJ, Kuchibhatla M, Samad Z, Boyle SH, Kuhn C, Becker RC, Ortel TL, Williams RB, Rogers JG, O'Connor C. Effect of escitalopram on mental stress-induced myocardial ischemia: results of the REMIT trial. JAMA. 2013 May 22;309(20):2139-49. doi: 10.1001/jama.2013.5566. PMID: 23695483; PMCID: PMC4378823.

**Importance:** Mental stress can induce myocardial ischemia and also has been implicated in triggering cardiac events. However, pharmacological interventions aimed at reducing mental stress-induced myocardial ischemia (MSIMI) have not been well studied.

**Objective:** To examine the effects of 6 weeks of escitalopram treatment vs placebo on MSIMI and other psychological stress-related biophysiological and emotional parameters.

**Design, setting, and participants:** The REMIT (Responses of Mental Stress Induced Myocardial Ischemia to Escitalopram Treatment) study, a randomized, double-blind, placebo-controlled trial of patients with clinically stable coronary heart disease and laboratory-diagnosed MSIMI. Enrollment occurred from July 24, 2007, through August 24, 2011, at a tertiary medical center.

**Interventions:** Eligible participants were randomized 1:1 to receive escitalopram (dose began at 5 mg/d, with titration to 20 mg/d in 3 weeks) or placebo over 6 weeks.

**Main outcomes and measures:** Occurrence of MSIMI, defined as development or worsening of regional wall motion abnormality; left ventricular ejection fraction reduction of 8% or more; and/or horizontal or down-sloping ST-segment depression of 1 mm or more in 2 or more leads, lasting for 3 or more consecutive beats, during 1 or more of 3 mental stressor tasks.

**Results:** Of 127 participants randomized to receive escitalopram (n = 64) or placebo (n = 63), 112 (88.2%) completed end point assessments (n = 56 in each group). At the end of 6 weeks, more patients taking escitalopram (34.2% [95% CI, 25.4%-43.0%]) had absence of MSIMI during the 3 mental stressor tasks compared with patients taking placebo (17.5% [95% CI, 10.4%-24.5%]), based on the unadjusted multiple imputation model for intention-to-treat analysis. A significant difference favoring escitalopram was observed (odds ratio, 2.62 [95% CI, 1.06-6.44]). Rates of exercise-induced ischemia were slightly lower at 6 weeks in the escitalopram group (45.8% [95% CI, 36.6%-55.0%]) than in patients receiving placebo (52.5% [95% CI, 43.3%-61.8%]), but this difference was not statistically significant (adjusted odds ratio; 1.24 [95% CI, 0.60-2.58]; P = .56).

**Conclusions and relevance:** Among patients with stable coronary heart disease and baseline MSIMI, 6 weeks of escitalopram, compared with placebo, resulted in a lower rate of MSIMI. There was no statistically significant difference in exercise-induced ischemia. Replication of these results in multicenter settings and investigations of other medications for reducing MSIMI are needed.

102. Jiang W, Samad Z, Boyle S, Becker RC, Williams R, Kuhn C, Ortel TL, Rogers J, Kuchibhatla M, O'Connor C, Velazquez EJ. Prevalence and clinical characteristics of mental stress-induced myocardial ischemia in patients with coronary heart disease. J Am Coll Cardiol. 2013 Feb 19;61(7):714-22. doi: 10.1016/j.jacc.2012.11.037. PMID: 23410543; PMCID: PMC3913125.

**Objectives:** The goal of this study was to evaluate the prevalence and clinical characteristics of mental stress-induced myocardial ischemia.

**Background:** Mental stress-induced myocardial ischemia is prevalent and a risk factor for poor prognosis in patients with coronary heart disease, but past studies mainly studied patients with exercise-induced myocardial ischemia.

**Methods:** Eligible patients with clinically stable coronary heart disease, regardless of exercise stress testing status, underwent a battery of 3 mental stress tests followed by a treadmill test. Stress-induced ischemia, assessed by echocardiography and electrocardiography, was defined as: 1) development or worsening of regional wall motion abnormality; 2) left ventricular ejection fraction reduction ≥ 8%; and/or 3) horizontal or downsloping ST-segment depression ≥ 1 mm in 2 or more leads lasting for ≥ 3 consecutive beats during at least 1 mental test or during the exercise test.

**Results:** Mental stress-induced ischemia occurred in 43.45%, whereas exercise-induced ischemia occurred in 33.79% (p = 0.002) of the study population (N = 310). Women (odds ratio [OR]: 1.88), patients who were not married (OR: 1.99), and patients who lived alone (OR: 2.24) were more likely to have mental stress-induced ischemia (all p < 0.05). Multivariate analysis showed that compared with married men or men living with someone, unmarried men (OR: 2.57) and married women (OR: 3.18), or living alone (male OR: 2.25 and female OR: 2.72, respectively) had higher risk for mental stress-induced ischemia (all p < 0.05).

**Conclusions:** Mental stress-induced ischemia is more common than exercise-induced ischemia in patients with clinically stable coronary heart disease. Women, unmarried men, and individuals living alone are at higher risk for mental stress-induced ischemia. (Responses of Myocardial Ischemia to Escitalopram Treatment [REMIT]; NCT00574847).

103. Schneider RH, Grim CE, Rainforth MV, Kotchen T, Nidich SI, Gaylord-King C, Salerno JW, Kotchen JM, Alexander CN. Stress reduction in the secondary prevention of cardiovascular disease: randomized, controlled trial of transcendental meditation and health education in Blacks. Circ Cardiovasc Qual Outcomes. 2012 Nov;5(6):750-8. doi: 10.1161/CIRCOUTCOMES.112.967406. Epub 2012 Nov 13. PMID: 23149426; PMCID: PMC7269100.

**Background:** Blacks have disproportionately high rates of cardiovascular disease. Psychosocial stress may contribute to this disparity. Previous trials on stress reduction with the Transcendental Meditation (TM) program have reported improvements in cardiovascular disease risk factors, surrogate end points, and mortality in blacks and other populations.

**Methods and results:** This was a randomized, controlled trial of 201 black men and women with coronary heart disease who were randomized to the TM program or health education. The primary end point was the composite of all-cause mortality, myocardial infarction, or stroke. Secondary end points included the composite of cardiovascular mortality, revascularizations, and cardiovascular hospitalizations; blood pressure; psychosocial stress factors; and lifestyle behaviors. During an average follow-up of 5.4 years, there was a 48% risk reduction in the primary end point in the TM group (hazard ratio, 0.52; 95% confidence interval, 0.29-0.92; P=0.025). The TM group also showed a 24% risk reduction in the secondary end point (hazard ratio, 0.76; 95% confidence interval, 0.51-0.1.13; P=0.17). There were reductions of 4.9

mmHg in systolic blood pressure (95% confidence interval -8.3 to -1.5 mmHg; P=0.01) and anger expression (P<0.05 for all scales). Adherence was associated with survival.

**Conclusions:** A selected mind-body intervention, the TM program, significantly reduced risk for mortality, myocardial infarction, and stroke in coronary heart disease patients. These changes were associated with lower blood pressure and psychosocial stress factors. Therefore, this practice may be clinically useful in the secondary prevention of cardiovascular disease. Clinical Trial Registration- URL: www.clinicaltrials.gov Unique identifier: NCT01299935.

104. Kivimäki M, Nyberg ST, Batty GD, Fransson EI, Heikkilä K, Alfredsson L, Bjorner JB, Borritz M, Burr H, Casini A, Clays E, De Bacquer D, Dragano N, Ferrie JE, Geuskens GA, Goldberg M, Hamer M, Hooftman WE, Houtman IL, Joensuu M, Jokela M, Kittel F, Knutsson A, Koskenvuo M, Koskinen A, Kouvonen A, Kumari M, Madsen IE, Marmot MG, Nielsen ML, Nordin M, Oksanen T, Pentti J, Rugulies R, Salo P, Siegrist J, Singh-Manoux A, Suominen SB, Väänänen A, Vahtera J, Virtanen M, Westerholm PJ, Westerlund H, Zins M, Steptoe A, Theorell T; IPD-Work Consortium. Job strain as a risk factor for coronary heart disease: a collaborative meta-analysis of individual participant data. Lancet. 2012 Oct 27;380(9852):1491-7. doi: 10.1016/S0140-6736(12)60994-5. Epub 2012 Sep 14. PMID: 22981903; PMCID: PMC3486012.

**Background:** Published work assessing psychosocial stress (job strain) as a risk factor for coronary heart disease is inconsistent and subject to publication bias and reverse causation bias. We analysed the relation between job strain and coronary heart disease with a meta-analysis of published and unpublished studies.

**Methods:** We used individual records from 13 European cohort studies (1985-2006) of men and women without coronary heart disease who were employed at time of baseline assessment. We measured job strain with questions from validated job-content and demand-control questionnaires. We extracted data in two stages such that acquisition and harmonisation of job strain measure and covariables occurred before linkage to records for coronary heart disease. We defined incident coronary heart disease as the first non-fatal myocardial infarction or coronary death.

**Findings:** 30,214 (15%) of 197,473 participants reported job strain. In 1·49 million person-years at risk (mean follow-up 7·5 years [SD 1·7]), we recorded 2358 events of incident coronary heart disease. After adjustment for sex and age, the hazard ratio for job strain versus no job strain was 1·23 (95% CI 1·10-1·37). This effect estimate was higher in published (1·43, 1·15-1·77) than unpublished (1·16, 1·02-1·32) studies. Hazard ratios were likewise raised in analyses addressing reverse causality by exclusion of events of coronary heart disease that occurred in the first 3 years (1·31, 1·15-1·48) and 5 years (1·30, 1·13-1·50) of follow-up. We noted an association between job strain and coronary heart disease for sex, age groups, socioeconomic strata, and region, and after adjustments for socioeconomic status, and lifestyle and conventional risk factors. The population attributable risk for job strain was 3·4%.

**Interpretation:** Our findings suggest that prevention of workplace stress might decrease disease incidence; however, this strategy would have a much smaller effect than would tackling of standard risk factors, such as smoking.

105. Stepanovic J, Ostojic M, Beleslin B, Vukovic O, Djordjevic-Dikic A, Giga V, Nedeljkovic I, Nedeljkovic M, Stojkovic S, Vukcevic V, Dobric M, Petrasinovic Z, Marinkovic J, Lecic-Tosevski D. Mental stress-induced ischemia in patients with coronary artery disease: echocardiographic characteristics and relation to exercise-induced ischemia. Psychosom Med. 2012 Sep;74(7):766-72. doi: 10.1097/PSY.0b013e3182689441. Epub 2012 Aug 24. Erratum in: Psychosom Med. 2012 Nov-Dec;74(9):989. Dikic, Ana Djordjevic [corrected to Djordjevic-Dikic, Ana]. Erratum in: Psychosom Med. 2012 Nov-Dec;74(9):989. doi: 10.1097/PSY.0b013e3182794f4e. PMID: 22923698.

**Objective:** The aims of this study were to investigate the incidence and parameters associated with myocardial ischemia during mental stress (MS) as measured by echocardiography and to evaluate the relation between MS-induced and exercise-induced myocardial ischemia.

**Methods:** Study participants were 79 patients (63 men; mean [M] [standard deviation {SD}] age = 52 [8] years) with angiographically confirmed coronary artery disease and previous positive exercise test result. The MS protocol consisted of mental arithmetic and anger recall task. The patients performed a treadmill exercise test 15 to 20

minutes after the MS task. Data of post-MS exercise were compared with previous exercise stress test results.

**Results:** The frequency of echocardiographic abnormalities was 35% in response to the mental arithmetic task, compared with 61% with anger recall and 96% with exercise ($p < .001$, exercise versus MS). Electrocardiogram abnormalities and chest pain were substantially less common during MS than were echocardiographic abnormalities. Independent predictors of MS-induced myocardial ischemia were: wall motion score index at rest ($p = .02$), peak systolic blood pressure ($p = .005$), and increase in rate-pressure product ($p = .004$) during MS. The duration of exercise stress test was significantly shorter ($p < .001$) when MS preceded the exercise and in the case of earlier exercise (M [SD] = 4.4 [1.9] versus 6.7 [2.2] minutes for patients positive on MS and 5.7 [1.9] versus 8.0 [2.3] minutes for patients negative on MS).

**Conclusions:** Echocardiography can be successfully used to document myocardial ischemia induced by MS. MS-induced ischemia was associated with an increase in hemodynamic parameters during MS and worse function of the left ventricle. MS may shorten the duration of subsequent exercise stress testing and can potentiate exercise-induced ischemia in susceptible patients with coronary artery disease.

### 106. Schwartz BG, French WJ, Mayeda GS, Burstein S, Economides C, Bhandari AK, Cannom DS, Kloner RA. Emotional stressors trigger cardiovascular events. Int J Clin Pract. 2012 Jul;66(7):631-9. doi: 10.1111/j.1742-1241.2012.02920.x. PMID: 22698415.

**Aims:** To describe the relation between emotional stress and cardiovascular events, and review the literature on the cardiovascular effects of emotional stress, in order to describe the relation, the underlying pathophysiology, and potential therapeutic implications.

**Materials and methods:** Targeted PUBMED searches were conducted to supplement the authors' existing database on this topic.

**Results:** Cardiovascular events are a major cause of morbidity and mortality in the developed world. Cardiovascular events can be triggered by acute mental stress caused by events such as an earthquake, a televised high-drama soccer game, job strain or the death of a loved one. Acute mental stress increases sympathetic output, impairs endothelial function and creates a hypercoagulable state. These changes have the potential to rupture vulnerable plaque and precipitate intraluminal thrombosis, resulting in myocardial infarction or sudden death.

**Conclusion:** Therapies targeting this pathway can potentially prevent acute mental stressors from initiating plaque rupture. Limited evidence suggests that appropriately timed administration of beta-blockers, statins and aspirin might reduce the incidence of triggered myocardial infarctions. Stress management and transcendental meditation warrant further study.

107. O'Donnell M, Teo K, Gao P, Anderson C, Sleight P, Dans A, Marzona I, Bosch J, Probstfield J, Yusuf S. Cognitive impairment and risk of cardiovascular events and mortality. Eur Heart J. 2012 Jul;33(14):1777-86. doi: 10.1093/eurheartj/ehs053. Epub 2012 May 2. PMID: 22551598.

**Background:** Cognitive impairment may increase the risk of all cardiovascular (CV) events. We prospectively evaluated the independent association between Mini-Mental State Examination (MMSE) score and myocardial infarction, stroke, hospital admission for heart failure and mortality, and their CV composite (major CV events), in a large high-risk CV population.

**Methods and results:** Mini-Mental State Examination was recorded at baseline in 30 959 individuals enrolled into two large parallel trials of patients with prior cardiovascular disease or high-risk diabetes and followed for a median of 56 months. We used a Cox regression model to determine the association between MMSE score and incident CV events and non-CV mortality, adjusted for age, sex, education, history of vascular events, dietary factors, blood pressure, smoking, glucose, low-density lipoprotein, high-density lipoprotein, CV medications, exercise, alcohol intake pattern, depression, and psychosocial stress. Patients were categorized into four groups based on baseline MMSE; 30 (reference), 29-27, 26-24, and <24. Compared with patients with an MMSE of 30 (n = 9624), those with scores of 29-27 [n = 13 867; hazard ratio (HR) 1.08; 95% confidence intervals (CI) 1.01-1.16], 26-24 (n = 4764; HR: 1.15; 95% CI: 1.05-1.26) and <24 (n = 2704; HR: 1.35; 95% CI: 1.21-1.50) had a graded increase in the risk of major vascular events (P < 0.0001). Mini-Mental State Examination score was significantly associated with each of the individual components of the composite, except myocardial infarction. There was also no association between baseline MMSE and hospitalization for unstable or new angina. Within MMSE domains, impairments in orientation to place (HR: 1.52; 1.25-1.85), attention-calculation (HR: 1.10; 1.02-1.18), recall (HR: 1.10; 1.04-1.16), and design copy (HR: 1.15; 1.06-1.24) were the most predictive of major vascular events and mortality. The magnitude of increased risk of CV events associated with an MMSE <24 was similar to a previous history of stroke.

**Conclusion:** In people at increased CV risk, impairments on baseline cognitive testing are associated with a graded increase in the risk of stroke, congestive heart

failure, and CV death, but not coronary events. An MMSE score of <24 increased CV disease risk to the same extent as a previous stroke.

108. Paine NJ, Bosch JA, Van Zanten JJ. Inflammation and vascular responses to acute mental stress: implications for the triggering of myocardial infarction. Curr Pharm Des. 2012;18(11):1494-501. doi: 10.2174/138161212799504713. PMID: 22364133.

There is evidence that mental stress can trigger myocardial infarction. Even though the underlying mechanisms remain to be determined, both inflammation and vascular responses to mental stress have been implicated as contributing factors. This review explores the effects of inflammation on the vascular responses to mental stress. First, the associations between inflammation and resting vascular function are discussed. It is known that increases in inflammation are associated with endothelial dysfunction, with a reduction in nitric oxide a common pathway through which inflammation can influence endothelial function. Second, the effects of mental stress on vascular responses are reviewed. There is ample evidence that in healthy participants, mental stress induces increases in forearm blood flow, which is impaired in those at risk for cardiovascular disease. Even though several mechanisms are discussed, there is evidence that nitric oxide plays an important role in stress-induced vasodilation. Finally, the influences of inflammation on the vascular responses are described. It is hypothesised that inflammation can alter vascular responses to mental stress, most likely due to lower levels of nitric oxide as a result of the inflammation. This poorer vascular response is thought to be an underlying factor through which mental stress can trigger myocardial infarction.

109. Jiang W, Velazquez EJ, Samad Z, Kuchibhatla M, Martsberger C, Rogers J, Williams R, Kuhn C, Ortel TL, Becker RC, Pristera N, Krishnan R, O'Connor CM. Responses of mental stress-induced myocardial ischemia to escitalopram treatment: background, design, and method for the Responses of Mental Stress Induced Myocardial Ischemia to Escitalopram Treatment trial. Am Heart J. 2012 Jan;163(1):20-6. doi: 10.1016/j.ahj.2011.09.018. Epub 2011 Nov 14. PMID: 22172432; PMCID: PMC3254211.

**Background:** Mental stress-induced myocardial ischemia (MSIMI) is common in patients with clinically stable coronary heart disease (CHD) and is associated with poor outcomes. Depression is a risk factor of MSIMI. The REMIT trial investigates whether selective serotonin reuptake inhibitor (SSRI) treatment can improve MSIMI. The rationale and outline of the study are described.

**Method:** In this single-center randomized clinical trial, adult patients with clinically stable CHD are recruited for baseline mental and exercise stress testing assessed by echocardiography. In addition, psychometric questionnaires are administered, and blood samples are collected for platelet activity analysis. Patients who demonstrate MSIMI, defined by new abnormal wall motion, ejection fraction reduction ≥8%, and/or development of ischemic ST change in electrocardiogram during mental stress testing, are randomized at a 1:1 ratio to escitalopram or placebo for 6 weeks. Approximately 120 patients with MSIMI are enrolled in the trial. The stress testing, platelet activity assessment, and psychometric questionnaires are repeated at the end of the 6-week intervention. The hypothesis of the study is that SSRI treatment improves MSIMI via mood regulation and modification of platelet activity.

**Conclusion:** The REMIT study examines the effect of SSRI on MSIMI in vulnerable patients with CHD and probes some potential underlying mechanisms.

110. Backé EM, Seidler A, Latza U, Rossnagel K, Schumann B. The role of psychosocial stress at work for the development of cardiovascular diseases: a systematic review. Int Arch Occup Environ Health. 2012 Jan;85(1):67-79. doi: 10.1007/s00420-011-0643-6. Epub 2011 May 17. PMID: 21584721; PMCID: PMC3249533.

**Purpose:** A systematic review was carried out to assess evidence for the association between different models of stress at work, and cardiovascular morbidity and mortality.

**Methods:** A literature search was conducted using five databases (MEDLINE, Cochrane Library, EMBASE, PSYNDEX and PsycINFO). Inclusion criteria for studies were the following: self-reported stress for individual workplaces, prospective study design and incident disease (myocardial infarction, stroke, angina pectoris, high blood pressure). Evaluation, according to the criteria of the Scottish Intercollegiate Guidelines Network, was done by two readers. In case of disagreement, a third reader was involved.

**Results:** Twenty-six publications were included, describing 40 analyses out of 20 cohorts. The risk estimates for work stress were associated with a statistically significant increased risk of cardiovascular disease in 13 out of the 20 cohorts. Associations were significant for 7 out of 13 cohorts applying the demand-control model, all three cohorts using the effort-reward model and 3 out of 6 cohorts investigating other models. Most significant results came from analyses considering only men. Results for the association between job stress and cardiovascular diseases in women were not clear. Associations were weaker in participants above the age of 55.

**Conclusions:** In accordance with other systematic reviews, this review stresses the importance of psychosocial factors at work in the aetiology of cardiovascular diseases. Besides individual measures to manage stress and to cope with demanding work situations, organisational changes at the workplace need to be considered to find options to reduce occupational risk factors for cardiovascular diseases.

111. Ravingerová T, Bernátová I, Matejíková J, Ledvényiová V, Nemčeková M, Pecháňová O, Tribulová N, Slezák J. Impaired cardiac ischemic tolerance in spontaneously hypertensive rats is attenuated by adaptation to chronic and acute stress. Exp Clin Cardiol. 2011 Fall;16(3):e23-9. PMID: 22065943; PMCID: PMC3209549.

Chronic hypertension may have a negative impact on the myocardial response to ischemia. On the other hand, intrinsic ischemic tolerance may persist even in the pathologically altered hearts of hypertensive animals, and may be modified by short- or long-term adaptation to different stressful conditions. The effects of long-term limitation of living space (ie, crowding stress [CS]) and brief ischemia-induced stress on cardiac response to ischemia/reperfusion (I/R) injury are not yet fully characterized in hypertensive subjects. The present study was designed to test the influence of chronic and acute stress on the myocardial response to I/R in spontaneously hypertensive rats (SHR) compared with their effects in normotensive counterparts. In both groups, chronic, eight-week CS was induced by caging five rats per cage in cages designed for two rats (200 cm(2)/rat), while controls (C) were housed four to a cage in cages designed for six animals (480 cm(2)/rat). Acute stress was evoked by one cycle of I/R (5 min each, ischemic preconditioning) before sustained I/R in isolated Langendorff-perfused hearts of normotensive and SHR rats. At baseline conditions, the effects of CS were manifested only as a further increase in blood pressure in SHR, and by marked limitation of coronary perfusion in normotensive animals, while no changes in heart mechanical function were observed in any of the groups. Postischemic recovery of contractile function, severity of ventricular arrhythmias and lethal injury (infarction size) were worsened in the hypertrophied hearts of C-SHR compared with normotensive C. However, myo-cardial stunning and reperfusion-induced ventricular arrhythmias were attenuated by CS in SHR, which was different from deterioration of I/R injury in the hearts of normotensive animals. In contrast, ischemic preconditioning conferred an effective protection against I/R in both groups, although the extent of anti-infarct and anti-arrhythmic effects was lower in SHR. Both forms of stress may improve the altered response to ischemia in hypertensive subjects. In contrast to short-term preconditioning stress, chronic psychosocial stress was associated with a higher risk of lethal arrhythmias and contractile failure in normotensive animals exposed to an acute ischemic challenge.

112. Doorey A, Denenberg B, Sagar V, Hanna T, Newman J, Stone PH. Comparison of myocardial ischemia during intense mental stress using flight simulation in airline pilots with coronary artery disease to that produced with conventional mental and treadmill exercise stress testing. Am J Cardiol. 2011 Sep 1;108(5):651-7. doi: 10.1016/j.amjcard.2011.04.010. Epub 2011 Jul 1. PMID: 21723529.

Mental stress increases cardiovascular morbidity and mortality. Although laboratory mental stress often causes less myocardial ischemia than exercise stress (ES), it is unclear whether mental stress is intrinsically different or differences are due to less hemodynamic stress with mental stress. We sought to evaluate the hemodynamic and ischemic response to intense realistic mental stress created by modern flight simulators and compare this response to that of exercise treadmill testing and conventional laboratory mental stress (CMS) testing in pilots with coronary disease. Sixteen airline pilots with angiographically documented coronary disease and documented myocardial ischemia during ES were studied using maximal treadmill ES, CMS, and aviation mental stress (AMS) testing. AMS testing was done in a sophisticated simulator using multiple system failures as stressors. Treadmill ES testing resulted in the highest heart rate, but AMS caused a higher blood pressure response than CMS. Maximal rate-pressure product was not significantly different between ES and AMS (25,646 vs 23,347, $p = 0.08$), although these were higher than CMS (16,336, $p < 0.0001$). Despite similar hemodynamic stress induced by ES and AMS, AMS resulted in significantly less ST-segment depression and nuclear ischemia than ES. Differences in induction of ischemia by mental stress compared to ES do not appear to be due to the creation of less hemodynamic stress. In conclusion, even with equivalent hemodynamic stress, intense realistic mental stress induced by flight simulators results in significantly less myocardial ischemia than ES as measured by ST-segment depression and nuclear ischemia.

113. Proietti R, Mapelli D, Volpe B, Bartoletti S, Sagone A, Dal Bianco L, Daliento L. Mental stress and ischemic heart disease: evolving awareness of a complex association. Future Cardiol. 2011 May;7(3):425-37. doi: 10.2217/fca.11.13. PMID: 21627481.

The connection between cardiovascular disease and psychosocial risk factors has been the subject of an ever-growing body of literature over the last 50 years. Studies on the role of negative emotions, personality traits, chronic stress and social determinants have brought to light their possible role in triggering acute coronary syndromes, although further studies are required to clarify controversial results regarding the association between cardiovascular risk and important psychological problems such as depression and anxiety. The recognition of the role of emotional events in acute coronary syndromes paved the way for provocation experiments, aimed at inducing mental stress in a controlled setting and then documenting reversible impairment of myocardial perfusion, depolarization anomalies and arrhythmias. This ultimately led to the formalization of the concept of mental stress-induced myocardial ischemia. Accumulating evidence on the mechanistic bases of such phenomena outline a wide range of central and peripheral physiological changes associated with emotions and behaviors, whose effects are exerted on the cardiovascular system, sympathetic nervous system and the hypothalamus-hypophysis neuroendocrine axis. This article outlines the main steps in the identification of psychological aspects as cardiovascular risk factors and emphasizes the relevance of emotional stress as a trigger of acute cardiovascular events. Finally, a description is provided of the pathophysiological mechanisms behind mental stress-induced myocardial ischemia and pathways connecting the heart and brain.

114. Gafarov VV, Gafarova AV. [WHO programs "Acute Myocardial Infarction Register", MONICA: thirty years (1977-2006) of epidemiological studies of myocardial infarction in a high-risk population]. Ter Arkh. 2011;83(1):38-45. Russian. PMID: 21446201.

**Aim:** To reveal 30 year (1977-2006) trends of myocardial infarction (MI) morbidity, lethality and mortality in population of the West Siberia megapolis (Novosibirsk).

**Material and methods:** WHO programs "Acute Myocardial Infarction Register (AMIR) and MONICA covered 3 districts of Novosibirsk.

**Results:** MI morbidity in 25-64 year old population of Novosibirsk (high-risk population) in Russia is one of the highest in the world. MI morbidity was stable for 30 years excluding in 1988, 1994 and 1998 when it rose and in 2002-2004, 2006 when it lowered. Changes in mortality and lethality resemble changes in morbidity trend excluding 1977-1978 (fall) and 2002-2005 (rise). Prehospital mortality and lethality were much higher than those in hospital. Mortality and lethality in 1988, 1994, 1998 and 2002-2005 increased due to prehospital lethality and mortality, while it decreased in 1977-1978 due to hospital one. Reduction of mortality and lethality in stable MI morbidity shows improvement of medical care for MI patients, increased lethality and mortality in MI morbidity decline reflect deterioration of such care. Changes in behavioral and somatic factors of cardiovascular risk in population of Novosibirsk for 30 years were not observed while psychosocial risk factors gain a significant importance. By indirect indications, MI morbidity, mortality and lethality mark growing social stress in the population. MI mortality is 2-3 times higher than that of alcohol and is a basic factor of mortality increase in the population of Russia.

**Conclusion:** MI morbidity, mortality and lethality are markers of social stress in population.

### 115. Fiuzat M, Shaw LK, Thomas L, Felker GM, O'Connor CM. United States stock market performance and acute myocardial infarction rates in 2008-2009 (from the Duke Databank for Cardiovascular Disease). Am J Cardiol. 2010 Dec 1;106(11):1545-9. doi: 10.1016/j.amjcard.2010.07.027. Epub 2010 Oct 19. PMID: 21094353.

We sought to examine the relation between the United States economic decrease in 2008 and cardiovascular events as measured by local acute myocardial infarction (AMI) rates. Mental stress and traumatic events have been shown to be associated with increased risk of MI in patients with ischemic heart disease. This was an observational study of data from the Duke Databank for Cardiovascular Disease and includes patients undergoing angiography for evaluation of ischemic heart disease from January 2006 to July 2009. Patients with AMI occurring within 3 days before catheterization were used to calculate AMI rates. Stock market values were examined to determine the period of severe economic decrease, and time trends in AMI rates were examined over the same period. Time series models were used to assess the relation between United States stock market National Association of Securities

Dealers Automated Quotation (NASDAQ) and rates of AMI. Of 11,590 patients included in the study cohort, 2,465 patients had an AMI during this period. Time series analysis showed a significant increase in AMI rates during a period of stock market decrease from October 2008 to April 2009 ($p = 0.003$), which remained statistically significant when adjusted for seasons ($p = 0.02$). In conclusion, unadjusted and adjusted analyses of patients in the Duke Databank for Cardiovascular Disease indicated a significant correlation between a period of stock market decrease and increased AMI rates in our local cohort.

116. Leeka J, Schwartz BG, Kloner RA. Sporting events affect spectators' cardiovascular mortality: it is not just a game. Am J Med. 2010 Nov;123(11):972-7. doi: 10.1016/j.amjmed.2010.03.026. PMID: 21035586.

Physiologic and clinical triggers, including mental stress, anxiety, and anger, often precipitate acute myocardial infarction and cardiovascular death. Sporting events can acutely increase cardiovascular event and death rates. A greater impact is observed in patients with known coronary artery disease and when stressful features are present, including a passionate fan, a high-stakes game, a high-intensity game, a loss, and a loss played at home. Sporting events affect cardiovascular health through neuroendocrine responses and possibly an increase in high-risk behaviors. Acute mental stress increases the activity of the hypothalamic-pituitary-adrenocortical axis and the sympathetic-adrenal-medullary system while impairing vagal tone and endothelial function. Collectively, these mechanisms increase myocardial oxygen demand and decrease myocardial oxygen supply while also increasing the risk of arrhythmias and thrombosis. Measures can be taken to reduce cardiovascular risk, including the use of beta-blockers and aspirin, stress management, transcendental meditation, and avoidance of high-risk activities, such as smoking, eating fatty foods, overeating, and abusing alcohol and illicit drugs. Sporting events have the potential to adversely affect spectators' cardiovascular health, and protective measures should be considered.

117. Schwartz BG, Mayeda GS, Burstein S, Economides C, Kloner RA. When and why do heart attacks occur? Cardiovascular triggers and their potential role. Hosp Pract (1995). 2010;38(3):144-52. doi: 10.3810/hp.2010.06.308. PMID: 20890064.

Coronary heart disease affects 7.6% of the population in the United States, where > 900,000 myocardial infarctions (MIs) occur annually. Approximately half of all MIs have an identifiable clinical trigger. Myocardial ischemia, MI, sudden cardiac death, and thrombotic stroke each occur with circadian variation and peak after waking in the morning. In addition, physical exertion and mental stress are common precipitants of MI. Waking in the morning, physical exertion, and mental stress influence a number of physiologic parameters, including blood pressure, heart rate, plasma epinephrine levels, coronary blood flow, platelet aggregability, and endothelial function. Upregulation of sympathetic output and catecholamines increase myocardial oxygen demand and can decrease myocardial oxygen supply and promote thrombosis. Ischemia ensues when myocardial oxygen demand exceeds supply. Increases in blood pressure and ventricular contractility increase intravascular shear stress and may cause vulnerable atherosclerotic plaques to rupture, forming a nidus for thrombosis that can precipitate MI. Numerous clinical triggers of MI have been identified, including blizzards, the Christmas and New Year's holidays, experiencing an earthquake, the threat of violence, job strain, Mondays for the working population, sexual activity, overeating, smoking cigarettes, smoking marijuana, using cocaine, and particulate air pollution. Avoiding clinical triggers or participating in therapies that prevent clinical triggers from precipitating cardiac events could potentially postpone clinical events by several years and improve cardiovascular morbidity and mortality. Direct or indirect evidence suggests that the risk of triggered MIs is reduced with β-blockers, aspirin, statins, stress management, and transcendental meditation.

118. Babyak MA, Blumenthal JA, Hinderliter A, Hoffman B, Waugh RA, Coleman RE, Sherwood A. Prognosis after change in left ventricular ejection fraction during mental stress testing in patients with stable coronary artery disease. Am J Cardiol. 2010 Jan 1;105(1):25-8. doi: 10.1016/j.amjcard.2009.08.647. Epub 2009 Nov 14. PMID: 20102885; PMCID: PMC2842948.

Previous studies of patients with stable coronary artery disease have demonstrated that decreases in the left ventricular ejection fraction (LVEF) during acute mental stress are predictive of adverse clinical outcomes. The aim of the present study was to examine the prospective relation of mental stress on clinical outcomes in a sample of 138 patients with stable coronary artery disease. Patients underwent mental stress testing and were followed for a median of 5.9 years to assess the occurrence of the combined end point of myocardial infarction or all-cause mortality. There were 32 events (17 nonfatal myocardial infarctions and 15 deaths) over the follow-up period. Of the 26 patients who exhibited myocardial ischemia during mental stress testing, 11 (42%) sustained subsequent clinical events, compared to 21 of the 112 patients (19%) who showed no mental stress-induced ischemia. LVEF change during mental stress was also related to the clinical events in a graded, continuous fashion, with each 4% decrease from the LVEF at rest associated with an adjusted hazard ratio of 1.7, (95% confidence interval 1.1 to 2.6, p = 0.011). In conclusion, reductions in the LVEF during mental stress are prospectively associated with adverse clinical outcomes.

119. Milani RV, Lavie CJ. Reducing psychosocial stress: a novel mechanism of improving survival from exercise training. Am J Med. 2009 Oct;122(10):931-8. doi: 10.1016/j.amjmed.2009.03.028. Epub 2009 Aug 13. PMID: 19682669.

**Background:** Exercise training reduces mortality in patients with coronary artery disease. Behavioral characteristics, including depression, hostility, and overall psychosocial stress, have been shown to be independent risk factors for recurrent myocardial infarction and death in these patients. Exercise training can reduce these high-risk behaviors, but it remains uncertain as to what extent the health benefits of exercise training can be attributed to improving these behaviors.

**Methods:** We evaluated the impact of exercise training during cardiac rehabilitation on mortality in 53 patients with coronary artery disease with high levels of psychosocial stress and in 469 patients with coronary artery disease with low levels of psychosocial stress and compared them with 27 control patients with high psychosocial stress who did not undergo formal cardiac rehabilitation and exercise training.

**Results:** Mortality was approximately 4-fold greater in patients with high psychosocial stress than in those with low psychosocial stress (22% vs 5%; P = .003). Exercise training decreased the prevalence of psychosocial stress from 10% to 4% (P<.0001) and similarly improved peak oxygen uptake in patients with high and low psychosocial stress. Mortality in patients who improved exercise capacity by>or=10% (high exercise change) was 60% lower than in patients who had<10% improvement in exercise capacity (low exercise change) (P=.009). Mortality was lower in patients with high psychosocial stress with high exercise change compared with patients with high psychosocial stress with low exercise change (0% vs 19%; P=.009). In contrast, there was no significant improvement in mortality in patients with high versus low exercise change with low psychosocial stress (4% vs 8%; P=.14).

**Conclusion:** Psychosocial stress is an independent risk factor for mortality in patients with coronary artery disease, and exercise training can effectively reduce its prevalence. Exercise training reduces mortality in patients with coronary artery disease, and this effect seems to be mediated in part because of the salutary effects of exercise on psychosocial stress.

120. Hassan M, Mela A, Li Q, Brumback B, Fillingim RB, Conti JB, Sheps DS. The effect of acute psychological stress on QT dispersion in patients with coronary artery disease. Pacing Clin Electrophysiol. 2009 Sep;32(9):1178-83. doi: 10.1111/j.1540-8159.2009.02462.x. PMID: 19719496; PMCID: PMC2739112.

**Background:** An acute psychological stress can precipitate ventricular arrhythmias and sudden cardiac death in patients with coronary artery disease (CAD). However, the physiologic mechanisms by which these effects occur are not entirely clear. Mental stress-induced myocardial ischemia occurs in a significant percentage of the CAD population. It is unknown if the proarrhythmic effects of psychological stress are mediated through the development of myocardial ischemia.

**Objectives:** To examine the effects of psychological stress on QT dispersion (QTd) among CAD patients and whether these effects are mediated via the development of myocardial ischemia.

**Methods:** Psychological stress was induced using a public speaking task. Twelve-lead electrocardiograms (ECG) were recorded at rest, during mental stress, and during recovery. QTd was calculated as the difference between the longest and the shortest QT interval in the 12-lead ECG. Rest-stress myocardial perfusion imaging was also performed to detect mental stress-induced myocardial ischemia.

**Results:** Mental stress induced a significant increase in QTd compared to the resting condition ($P < 0.001$). This effect persisted beyond the first 10 minutes of recovery ($P < 0.001$). QTd was significantly associated with the development of mental stress ischemia with ischemic patients having significantly higher QTd during mental stress than nonischemic patients ($P = 0.006$). This finding remained significant after controlling for possible confounding factors ($P = 0.01$).

**Conclusion:** An acute psychological stress induces a significant increase in QTd, which persists for more than 10 minutes after the cessation of the stressor. This effect seems to be, at least partially, mediated by the development of mental stress-induced myocardial ischemia.

121. Hassan M, York KM, Li H, Li Q, Lucey DG, Fillingim RB, Sheps DS. Usefulness of peripheral arterial tonometry in the detection of mental stress-induced myocardial ischemia. Clin Cardiol. 2009 Sep;32(9):E1-6. doi: 10.1002/clc.20515. PMID: 19672865; PMCID: PMC6653144.

**Background:** Mental stress-induced myocardial ischemia (MSIMI) identifies a subset of coronary arterial disease (CAD) patients at increased risk for adverse cardiovascular events. Peripheral arterial vasoconstriction has been consistently reported as an underlying mechanism for ischemia development in this setting and as such affords a unique opportunity for the noninvasive detection of this phenomenon.

**Hypothesis:** We studied the usefulness of a peripheral arterial tonometry (PAT) technique in the detection of MSIMI. We sought to identify response patterns that would predict the development of MSIMI.

**Methods:** Participants were 211 patients with documented CAD. Mental stress testing was performed using a public speaking task. Rest-stress myocardial perfusion imaging was the gold standard for ischemia detection. PAT responses were assessed during the 2 phases of the stressful task (stress anticipation and the task performance) and were calculated as a ratio of stress to the resting pulse wave amplitude.

**Results:** Vascular response during the stress anticipation period (speech preparation) was more pronounced than during the actual speaking task (the mean preparation index was 0.64 +/- 0.53; the mean speech index was 0.72 +/- 0.60; P < 0.001). PAT response during speech preparation had modest accuracy for predicting MSIMI (area under the curve [AUC] was 0.63; 95% confidence interval [CI]: 0.53-0.74, P = 0.015). A PAT index < or = 0.52 was identified as the best cut off value for detecting MSIMI with a sensitivity of 76% and a specificity of 56%.

**Conclusion:** We identified a pattern of peripheral arterial response to mental stress that has a relatively modest accuracy in predicting MSIMI. Further research is needed to validate the findings of this study.

122. Soufer R, Jain H, Yoon AJ. Heart-brain interactions in mental stress-induced myocardial ischemia. Curr Cardiol Rep. 2009 Mar;11(2):133-40. doi: 10.1007/s11886-009-0020-1. PMID: 19236829; PMCID: PMC3726062.

Myocardial ischemia that results from emotional provocation occurs in as many as 30% to 50% of patients with coronary artery disease during the discourse of their lives. This emotionally provoked or mental stress ischemia is associated with poor prognosis, with emerging treatment strategies. This article outlines the conceptual constructs that support the pathophysiologic underpinnings, and biobehavioral aspects associated with this mental stress ischemia. We review a biobehavioral model in which cognitive stress is transduced in the brain. The response of the brain to psychosocial stress is a highly sophisticated and integrated process by which sensory inputs are evaluated and appraised for their importance in relation to previous experience and current goals. The biologic consequences of such stress transduced in the central nervous system has its effect on cardiovascular flow and function through changes in autonomic balance, which result in various biologic processes that culminate in the perturbation of flow and function of the heart.

123. Lingfors H, Persson LG, Lindström K, Bengtsson C, Lissner L. Effects of a global health and risk assessment tool for prevention of ischemic heart disease in an individual health dialogue compared with a community health strategy only results from the Live for Life health promotion programme. Prev Med. 2009 Jan;48(1):20-4. doi: 10.1016/j.ypmed.2008.10.009. Epub 2008 Nov 1. PMID: 19013188.

**Objective:** To evaluate the effect of an individual health dialogue on health and risk factors for ischemic heart disease in addition to that of a community based strategy.

**Method:** Inhabitants in four communities in the area of Skaraborg, Sweden were invited to a health examination including a health dialogue both at the age of 30 and 35 (target communities). In another four communities inhabitants were invited only at the age of 35 (reference communities). Health and risk factors in 35-year old inhabitants in the target communities who participated in the health dialogue in 1989-1991 and 1994-1996 were analysed and compared with 35-year olds in the reference communities participating during the same periods of time.

**Results:** Inhabitants in communities where there had been a previous individualised health intervention programme had, on the community level, a more favourable development concerning dietary habits, mental stress, body mass index, waist circumference, cholesterol, blood pressure and metabolic risk profile compared to inhabitants in communities with only a community based health intervention programme.

**Conclusions:** An individual lifestyle oriented health dialogue supported by a global health and risk assessment pedagogic tool seems to be more effective than a community health strategy only.

124. Burg MM, Graeber B, Vashist A, Collins D, Earley C, Liu J, Lampert R, Soufer R. Noninvasive detection of risk for emotion-provoked myocardial ischemia. Psychosom Med. 2009 Jan;71(1):14-20. doi: 10.1097/PSY.0b013e318187c035. Epub 2008 Oct 21. PMID: 18941131; PMCID: PMC2739989.

**Objectives:** To test an easily administered, noninvasive technology to identify vulnerability to mental stress ischemia.

**Background:** Myocardial ischemia provoked by emotional stress (MSI) in patients with stable coronary artery disease (CAD) predicts major adverse cardiac events. A clinically useful tool to risk stratify patients on this factor is not available.

**Methods:** Patients with documented CAD (n = 68) underwent single photon emission CT myocardial perfusion imaging concurrent with pulse wave amplitude assessment by peripheral arterial tonometry (PAT) during a mental stress protocol of sequential rest and anger stress periods. Heart rate and blood pressure were assessed, and blood was drawn for catecholamine assay, during rest and stress. MSI was defined by the presence of a new perfusion defect during anger stress (n = 26) and the ratio of stress to rest PAT response was calculated.

**Results:** Patients with MSI had a significantly lower PAT ratio than those without MSI (0.76 +/- 0.04 versus 0.91 +/- 0.05, p = .03). An ROC curve for optimum sensitivity/specificity of PAT ratio as an index of MSI produced a sensitivity of 0.62 and a specificity of 0.63. Among patients taking angiotensin converting enzyme (ACE) inhibitors, the sensitivity and specificity of the test increased to 0.86 and 0.73, respectively; 90% of patients without MSI were correctly identified.

**Conclusions:** PAT in concert with ACE inhibition may provide a useful approach to assess risk for MSI. Future studies should help determine how best to utilize this approach for risk assessment in the clinical setting.

## 125. Das S, O'Keefe JH. Behavioral cardiology: recognizing and addressing the profound impact of psychosocial stress on cardiovascular health. Curr Hypertens Rep. 2008 Oct;10(5):374-81. doi: 10.1007/s11906-008-0070-6. PMID: 18775114.

Psychosocial stress exerts independent adverse effects on cardiovascular health. The INTERHEART study reported that psychosocial stress accounted for approximately 30% of the attributable risk of acute myocardial infarction. Prospective studies consistently indicate that hostility, depression, and anxiety are related to increased risk of coronary heart disease and cardiovascular death. A sense of hopelessness, in particular, appears to be strongly correlated with adverse cardiovascular outcomes. Time urgency and impatience have not been consistently related to risk of coronary disease, but increase the likelihood of developing hypertension. Psychosocial stress appears to adversely affect autonomic and hormonal homeostasis, resulting in metabolic abnormalities, inflammation, insulin resistance, and endothelial dysfunction. Also, stress is often associated with self-destructive behavior and medication noncompliance. Psychosocial stress is a highly modifiable risk; many factors have been shown to be protective. These include psychosocial support,

regular exercise, stress reduction training, sense of humor, optimism, altruism, faith, and pet ownership. Simple screening questions are available to reliably indicate a patient at risk for psychosocial stress-related health problems.

126. Kriegbaum M, Christensen U, Lund R, Prescott E, Osler M. Job loss and broken partnerships: do the number of stressful life events influence the risk of ischemic heart disease in men? Ann Epidemiol. 2008 Oct;18(10):743-5. doi: 10.1016/j.annepidem.2008.04.010. Epub 2008 Aug 9. PMID: 18693037.

**Purpose:** The aim of this study was to investigate the effects of the accumulated number of job losses and broken partnerships (defined as the end of cohabitation) on the risk of fatal and nonfatal events of ischemic heart disease (IHD).

**Methods:** Prospective birth cohort study with follow-up of events of IHD from 1993 to 2004. Participants were 8365 men born in the metropolitan area of Copenhagen, Denmark, in 1953. Events of IHD were retrieved from the Danish National Patient Register and the Cause of Death Registry. Job losses and broken partnerships were identified in the Social Registers. We included mother's marital status and father's occupation at birth, body mass index at 18 years, and own educational attainment as covariates.

**Results:** We found that only broken partnerships were associated with IHD (1.28 95% confidence interval 1.02-1.58) and the subdiagnoses of other IHD (1.37 95% confidence interval 1.02-1.85). We found no indication of dose-response relationship between number of events and risk of IHD.

**Conclusion:** In this study of middle-aged men, we found only weak support for the effect of psychosocial stress on IHD measured with register based life events; we found that IHD was associated with broken partnerships but not with job loss. We did not find that the risk of incident IHD varied with the number of these stressful life events.

127. Hassan M, York KM, Li Q, Lucey DG, Fillingim RB, Sheps DS. Variability of myocardial ischemic responses to mental versus exercise or adenosine stress in patients with coronary artery disease. J Nucl Cardiol. 2008 Jul-Aug;15(4):518-25. doi: 10.1016/j.nuclcard.2008.04.005. Epub 2008 Jun 12. PMID: 18674719; PMCID: PMC2606663.

**Background:** Mental stress precipitates myocardial ischemia in a significant percentage of coronary artery disease (CAD) patients. Exercise or adenosine stresses produce different physiologic responses and cause myocardial ischemia via different mechanisms. Little is known about the comparative severity and location of myocardial ischemia provoked by these different stressors. In this study we sought to compare the within-individual ischemic responses to mental versus exercise or adenosine stress in a cohort of CAD patients.

**Methods and results:** All patients underwent mental stress and either exercise or adenosine testing within a 1-week period. Mental stress was induced via a public speaking task. Rest-stress myocardial perfusion imaging was used with all testing protocols. Participants were 187 patients (65 women [35%]) with a documented history of CAD and a mean age of 64 +/- 9 years. Mental stress-induced myocardial ischemia (MSIMI) was less prevalent and frequently of less magnitude than exercise- or adenosine-induced ischemia. Ischemia induced by exercise or adenosine testing did not accurately predict the development or the location of MSIMI. The overall concordance between these stressors for provoking ischemia was weak (percent agreement, 71%; kappa [+/- SE], 0.26 +/- 0.07). In a minority of patients (11%) mental stress provoked ischemia in the absence of exercise- or adenosine-induced ischemia. Moreover, in patients who had myocardial ischemia during both stressors, there were significant within-individual differences in the coronary artery distribution of the ischemic regions. MSIMI was more likely to occur in a single-vessel distribution (86%) compared with exercise- or adenosine-induced ischemia (54%). The stressors had moderate agreement if the ischemic region was in the right coronary artery territory (percent agreement, 76%; kappa, 0.52 +/- 0.19) or the left anterior descending coronary artery (percent agreement, 76%; kappa, 0.51 +/- 0.19) and significantly lower agreement in the left circumflex territory (percent agreement, 62%; kappa, 0.22 +/- 0.18).

**Conclusions:** Our findings indicate that mental and exercise or adenosine stresses provoke different myocardial ischemic responses. These observations suggest that exercise or adenosine testing may not adequately assess the likelihood of occurrence or severity of MSIMI and that different mechanisms are operative in each condition.

128. Anand SS, Islam S, Rosengren A, Franzosi MG, Steyn K, Yusufali AH, Keltai M, Diaz R, Rangarajan S, Yusuf S; INTERHEART Investigators. Risk factors for myocardial infarction in women and men: insights from the INTERHEART study. Eur Heart J. 2008 Apr;29(7):932-40. doi: 10.1093/eurheartj/ehn018. Epub 2008 Mar 10. PMID: 18334475.

**Aims:** Coronary heart disease (CHD) is a leading cause of death among men and women globally. Women develop CHD about 10 years later than men, yet the reasons for this are unclear. The purpose of this report is to determine if differences in risk factor distributions exist between women and men across various age categories to help explain why women develop acute MI later than men.

**Methods and results:** We used the INTERHEART global case-control study including 27 098 participants from 52 countries, 6787 of whom were women. The median age of first acute MI was higher in women than men (65 vs. 56 years; $P < 0.0001$). Nine modifiable risk factors were associated with MI in women and men. Hypertension [2.95(2.66 -3.28) vs. 2.32(2.16-2.48)], diabetes [4.26(3.68-4.94) vs. 2.67(2.43-2.94), physical activity [0.48(0.41-0.57) vs. 0.77(0.71-0.83)], and moderate alcohol use [0.41(0.34-0.50) vs. 0.88(0.82-0.94)] were more strongly associated with MI among women than men. The association of abnormal lipids, current smoking, abdominal obesity, high risk diet, and psychosocial stress factors with MI was similar in women and men. Risk factors associations were generally stronger among younger individuals compared to older women and men. The population attributable risk (PAR) of all nine risk factors exceeded 94%, and was similar among women and men (96 vs. 93%). Men were significantly more likely to suffer a MI prior to 60 years of age than were women, however, after adjusting for levels of risk factors, the sex difference in the probability of MI cases occurring before the age of 60 years was reduced by more than 80%.

**Conclusion:** Women experience their first acute MI on average 9 years later than men. Nine modifiable risk factors are significantly associated with acute MI in both men and women and explain greater than 90% of the PAR. The difference in age of first MI is largely explained by the higher risk factor levels at younger ages in men compared to women.

129. Jiang W. Impacts of depression and emotional distress on cardiac disease. Cleve Clin J Med. 2008 Mar;75 Suppl 2:S20-5. doi: 10.3949/ccjm.75.suppl_2.s20. PMID: 18540141.

Depression is a primary risk factor for ischemic heart disease (IHD) and a secondary risk factor for worsened prognosis in patients with IHD and heart failure. Mental stress-induced myocardial ischemia appears to be a significant mechanism by which depression increases the risk of death and morbidity in patients with IHD. A number of trials have evaluated the effect of therapy for depression in patients with cardiac disease, and more are ongoing. Selective serotonin reuptake inhibitors (SSRIs) are effective in improving depressive symptoms in cardiac patients and are relatively safe in these patients; tricyclic antidepressants are less safe in these patients. Early evidence suggests that antidepressant therapy with SSRIs may be associated with improved cardiac outcomes in depressed cardiac patients, but further study is needed.

130. York KM, Hassan M, Li Q, Li H, Fillingim RB, Lucey D, Bestland M, Sheps DS. Do men and women differ on measures of mental stress-induced ischemia? Psychosom Med. 2007 Dec;69(9):918-22. doi: 10.1097/PSY.0b013e31815a9245. Epub 2007 Nov 8. PMID: 17991821.

**Objective:** To consider the effects of gender on ischemia in a larger sample, with broadly defined coronary artery disease (CAD). Mental stress has been shown to cause transient myocardial ischemia in a significant percentage of people with CAD. However, little is known about the effects of mental stress on ischemic processes in women. Most studies to date either had few women or required a positive exercise stress test.

**Methods:** Participants (61 women, 93 men; average age = 63 years) had documented CAD (positive stress test, abnormal catheterization even with minimal disease, or previous myocardial infarction). They underwent mental stress testing and radionuclide perfusion imaging (stress/ rest). Cardiac function data were collected and stress was compared with baseline. The data were then submitted to a series of analyses of variance.

**Results:** A total of 50 (32%) participants exhibited reversible ischemia post psychological stress. This reflects a relative rate of 33% (n = 31 of 93) for men and 31% (n = 19 of 61) for women. No difference between men and women were

observed on any measure of hemodynamic functioning (blood pressure, heart rate, or cardiac perfusion).

**Conclusions:** Results of this study showed no significant differences between men and women on measures of hemodynamic functioning or cardiac perfusion.

131. Hassan M, York KM, Li H, Li Q, Sheps DS. Mental stress-induced myocardial ischemia in coronary artery disease patients with left ventricular dysfunction. J Nucl Cardiol. 2007 May-Jun;14(3):308-13. doi: 10.1016/j.nuclcard.2007.01.040. Epub 2007 Apr 16. PMID: 17556164.

**Background:** Reduced left ventricular ejection fraction (LVEF) is a risk factor for poor outcomes in patients with coronary artery disease (CAD). Mental stress-induced myocardial ischemia (MSIMI) also identifies a subset of CAD patients at increased risk for future cardiovascular events. Susceptibility to MSIMI in patients with CAD and reduced LVEF is unknown.

**Methods and results:** We enrolled 182 patients (67 women) with a mean age of 64 years and a documented history of CAD in this study. Baseline resting ejection fraction was determined by use of technetium 99m sestamibi gated single photon emission computed tomography. Abnormal LVEF was defined as less than 45% for men and less than 50% for women (based on published norms for our software [Cedars-Sinai Medical Center]). All participants underwent mental stress testing with a public speaking task. Rest/stress myocardial perfusion single photon emission computed tomography was performed via conventional methodology. Images were visually compared for number and severity of perfusion defects by use of a scoring method from 0 to 4. A summed difference score was calculated as the difference between summed stress and rest scores. A score of greater than 3 was considered abnormal. MSIMI developed in 19% of patients with normal LVEF and 31% of those with reduced LVEF. There is no statistically significant difference between the two groups (P = .11).

**Conclusions:** CAD patients with left ventricular dysfunction are equally susceptible to MSIMI as those with normal LVEF.

132. Lanas F, Avezum A, Bautista LE, Diaz R, Luna M, Islam S, Yusuf S; INTERHEART Investigators in Latin America. Risk factors for acute myocardial infarction in Latin America: the INTERHEART Latin American study. Circulation. 2007 Mar 6;115(9):1067-74. doi: 10.1161/CIRCULATIONAHA.106.633552. PMID: 17339564.

**Background:** Current knowledge of the impact of cardiovascular risk factors in Latin America is limited.

**Methods and results:** As part of the INTERHEART study, 1237 cases of first acute myocardial infarction and 1888 age-, sex-, and center-matched controls were enrolled from Argentina, Brazil, Colombia, Chile, Guatemala, and Mexico. History of smoking, hypertension, diabetes mellitus, diet, physical activity, alcohol consumption, psychosocial factors, anthropometry, and blood pressure were recorded. Nonfasting blood samples were analyzed for apolipoproteins A-1 and B-100. Logistic regression was used to estimate multivariate adjusted odds ratios (ORs) and their 95% confidence intervals (CIs). Persistent psychosocial stress (OR, 2.81; 95% CI, 2.07 to 3.82), history of hypertension (OR, 2.81; 95% CI, 2.39 to 3.31), diabetes mellitus (OR, 2.59; 95% CI, 2.09 to 3.22), current smoking (OR, 2.31; 95% CI, 1.97 to 2.71), increased waist-to-hip ratio (OR for first versus third tertile, 2.49; 95% CI, 1.97 to 3.14), and increased ratio of apolipoprotein B to A-1 (OR for first versus third tertile, 2.31; 95% CI, 1.83 to 2.94) were associated with higher risk of acute myocardial infarction. Daily consumption of fruits or vegetables (OR, 0.63; 95% CI, 0.51 to 0.78) and regular exercise (OR, 0.67; 95% CI, 0.55 to 0.82) reduced the risk of acute myocardial infarction. Abdominal obesity, abnormal lipids, and smoking were associated with high population-attributable risks of 48.5%, 40.8%, and 38.4%, respectively. Collectively, these risk factors accounted for 88% of the population-attributable risk.

**Conclusions:** Interventions aimed at decreasing behavioral risk factors, lowering blood pressure, and modifying lipids could have a large impact on the risk of acute myocardial infarction among Latin Americans.

133. Shah R, Burg MM, Vashist A, Collins D, Liu J, Jadbabaie F, Graeber B, Earley C, Lampert R, Soufer R. C-reactive protein and vulnerability to mental stress-induced myocardial ischemia. Mol Med. 2006 Nov-Dec;12(11-12):269-74. doi: 10.2119/2006–00077.Shah. PMID: 17380191; PMCID: PMC1829194.

Myocardial ischemia provoked in the laboratory during mental stress (MSI) in patients with stable coronary artery disease (CAD) predicts subsequent clinical events. The pathophysiology of MSI differs from that of exercise ischemia, and the mechanisms tying MSI to poor prognosis are not known. C-reactive protein (CRP) is a risk marker for cardiovascular events in patients with CAD, but little is known regarding the relationship of CRP to MSI. The purpose of this study was to examine the association of CRP to risk of MSI in CAD patients. Eighty-three patients with stable CAD underwent simultaneous single-photon emission computed tomography (SPECT) imaging with technetium-99m tetrofosmin myocardial perfusion imaging (MPI) and transthoracic echocardiography (TTE), at rest and during MS induced by laboratory mental stress. Serum CRP levels were measured 24 h after MS. MSI was defined by the presence of a new perfusion defect on SPECT and/or new regional wall motion abnormality on TTE during MS. Of the 83 patients, 30 (36%) developed MSI. There was no difference in gender, sex, BMI, histories of diabetes, hypertension, smoking, lipid profile, medications used (including statins, beta-blockers, ACE inhibitors, and aspirin), or hemodynamic response during MS between those with and without MSI. In univariate logistic regression analysis, each unit (1 mg/L) increase in CRP level was associated with 20% higher risk of MSI (OR 1.2, 95% CI 1.01-1.39, P=.04). This relationship remained in multivariate models. These data suggest that levels of CRP may be a risk marker for MSI in patients with CAD.

134. Peix A, Trápaga A, Asen L, Ponce F, Infante O, Valiente J, Tornés F, Cabrera LO, Guerrero I, García EJ, Carrillo R, García-Barreto D. Mental stress-induced myocardial ischemia in women with angina and normal coronary angiograms. J Nucl Cardiol. 2006 Jul;13(4):507-13. doi: 10.1016/j.nuclcard.2006.03.016. PMID: 16919574.

**Background:** Coronary artery disease is frequent in postmenopausal women. Silent myocardial ischemia has been induced with mental stress testing.

**Methods and results:** To evaluate whether mental stress can induce ischemia in women with typical angina and normal coronary angiography, postmenopausal patients (n = 16) were studied. Each underwent technetium 99m methoxyisobutylisonitrile myocardial scintigraphy (exercise stress/rest/mental stress protocol), brachial artery endothelial function measurement by ultrasonography, and 24-hour ambulatory electrocardiographic recording (Holter). During mental stress testing, 6 patients (group I) had reversible perfusion defects on myocardial scintigraphy whereas the other 10 patients (group II) did not. Group I patients exhibited endothelial dysfunction more frequently than those in group II (83% vs 20%). Myocardial scintigraphy showed anteroapical/septal ischemia in 5 patients and inferoapical ischemia in one other patient, with both types of stress. Among group II patients, none showed a reversible perfusion defect during physical or mental stress. No group I patients had evidence of ischemia by Holter monitoring, whereas 2 of 10 group II patients did.

**Conclusion:** In postmenopausal women with typical angina and normal coronary arteries, mental stress may provoke myocardial ischemia, which can be concordant with ischemia induced by exercise stress, and is associated with endothelial dysfunction.

135. Ramachandruni S, Fillingim RB, McGorray SP, Schmalfuss CM, Cooper GR, Schofield RS, Sheps DS. Mental stress provokes ischemia in coronary artery disease subjects without exercise- or adenosine-induced ischemia. J Am Coll Cardiol. 2006 Mar 7;47(5):987-91. doi: 10.1016/j.jacc.2005.10.051. Epub 2006 Feb 9. PMID: 16516082.

**Objectives:** The purpose of this study was to investigate the possibility that some patients with coronary artery disease (CAD) but negative exercise or chemical stress test results might have mental stress-induced ischemia. The study population consisted solely of those with negative test results.

**Background:** Mental stress-induced ischemia has been reported in 20% to 70% of CAD subjects with exercise-induced ischemia. Because mechanisms of exercise and mental stress-induced ischemia may differ, we studied whether mental stress would produce ischemia in a proportion of subjects with CAD who have no inducible ischemia with exercise or pharmacologic tests.

**Methods:** Twenty-one subjects (14 men, 7 women) with a mean age of 67 years and with a documented history of CAD were studied. All subjects had a recent negative nuclear stress test result (exercise or chemical). Subjects completed a speaking task

involving role playing a difficult interpersonal situation. A total of 30 mCi 99mTc-sestamibi was injected at one minute into the speech, and imaging was started 40 min later. A resting image obtained within one week was compared with the stress image. Images were analyzed for number and severity of perfusion defects. The summed difference score based on the difference between summed stress and rest scores was calculated. Severity was assessed using a semiquantitative scoring method from zero to four.

**Results:** Six of 21 (29%) subjects demonstrated reversible ischemia (summed difference score > or =3) with mental stress. No subject had chest pain or electrocardiographic changes during the stressor. Mean systolic and diastolic blood pressure and heart rate all increased between resting and times of peak stress.

**Conclusions:** Mental stress may produce ischemia in some subjects with CAD and negative exercise or chemical nuclear stress test results.

136. Csef H, Hefner J. Psychosoziale Belastungen als Risiko- und Prognosefaktoren bei KHK und Herzinfarkt [Psychosocial stress as a risk- and prognostic factor in coronary artery disease and myocardial infarction]. Versicherungsmedizin. 2006 Mar 1;58(1):3-8. German. PMID: 16553219.

Cardiovascular diseases (CVD) challenge patients and social systems alike. Epidemiologic and economic data underscores demands for additional knowledge and therapeutic options. As recent data shows, psychosocial stress is underestimated as a risk- and prognostic factor in CVD. Cardiac mortality rises sharply whithin a small time-frame after a catastrophic event. But even common daily hassles, anxiety, depression or personality traits can impair cardiac health. Social networks are thought of being cardio-protective. However, if not perceived as supportive, social networks may influence cardiac health negatively. Therefore new approaches emerge against one of the most relevant disease of our time.

137. Das S, O'Keefe JH. Behavioral cardiology: recognizing and addressing the profound impact of psychosocial stress on cardiovascular health. Curr Atheroscler Rep. 2006 Mar;8(2):111-8. doi: 10.1007/s11883-006-0048-2. PMID: 16510045.

Psychosocial stress exerts independent adverse effects on cardiovascular health. The recent INTERHEART study reported that psychosocial stress accounted for approximately 30% of the attributable risk of acute myocardial infarction. Prospective

studies consistently indicate that hostility, depression, and anxiety are all related to increased risk of coronary heart disease and cardiovascular death. A sense of hopelessness, in particular, appears to be strongly correlated with adverse cardiovascular outcomes. Time urgency and impatience have not been consistently related to risk of coronary disease, but do increase the likelihood of developing hypertension. Psychosocial stress appears to adversely affect autonomic and hormonal homeostasis, resulting in metabolic abnormalities, inflammation, insulin resistance, and endothelial dysfunction. Additionally, stress is often associated with self-destructive behavior and noncompliance with medications. Psychosocial stress is a highly modifiable risk and many factors have been shown to be protective. These include psychosocial support, regular exercise, stress reduction training, sense of humor, optimism, altruism, faith, and pet ownership. Simple screening questions are available to reliably indicate a patient at risk for psychosocial stress-related health problems.

138. Burg MM, Vashist A, Soufer R. Mental stress ischemia: present status and future goals. J Nucl Cardiol. 2005 Sep-Oct;12(5):523-9. doi: 10.1016/j.nuclcard.2005.06.085. PMID: 16171711.

NO ABSTRACT AVAILABLE

139. Hemdahl AL, Caligiuri G, Hansson GK, Thorén P. Electrocardiographic characterization of stress-induced myocardial infarction in atherosclerotic mice. Acta Physiol Scand. 2005 Jun;184(2):87-94. doi: 10.1111/j.1365-201X.2005.01421.x. PMID: 15916668.

**Aim:** We have previously shown that mental and hypoxic stress can trigger the development of myocardial infarction (MI) in atherosclerotic apoE(-/-) x LDLR(-/-) mice. The purpose of the present study was to characterize the interval between stress and MI and determine whether electrophysiological changes precede the precipitation of an infarct by assessing telemetry recordings of the electrocardiogram.

**Methods:** Isoflurane anaesthetized apoE(-/-) x LDLR(-/-) (n = 16) and C57BL/6J (n = 8) mice were exposed to systemic hypoxia by reducing the inhaled oxygen concentration to 10% for 10 min. Mental stress was induced in eight conscious apoE(-/-) x LDLR(-/-) and eight C57BL/6J mice by blowing air into the cage.

Physiological parameters were recorded every 30 min for 2-6 days by implanted transmitters.

**Results:** During stress all mice developed transient ischaemic STU-area changes, which returned to normal at the end of stress. During the recovery phase (6 days) 50% (4/8) of the mentally stressed apoE(-/-) x LDLR(-/-) mice developed increased STU-area variability ($P < 0.05$) followed by dramatic STU-area elevations and spontaneous death at approximately 12-24 h. In hypoxia-exposed apoE(-/-) x LDLR(-/-) mice 56% (9/16) developed MI as determined by elevated serum levels of the infarction marker troponin T which correlated with increased variability in the STU-area ($P < 0.05$).

**Conclusion:** This is the first mouse model showing that increased STU-area variability is indicative of MI development in atherosclerotic mice following ischaemic stress. Furthermore, our findings suggest a two-phase pathway for the infarction development: an initial phase comprising a transient ischaemic response which triggers a delayed second phase of ischaemia and MI.

## 140. Blumenthal JA, Sherwood A, Babyak MA, Watkins LL, Waugh R, Georgiades A, Bacon SL, Hayano J, Coleman RE, Hinderliter A. Effects of exercise and stress management training on markers of cardiovascular risk in patients with ischemic heart disease: a randomized controlled trial. JAMA. 2005 Apr 6;293(13):1626-34. doi: 10.1001/jama.293.13.1626. PMID: 15811982.

**Context:** Observational studies have shown that psychosocial factors are associated with increased risk for cardiovascular morbidity and mortality, but the effects of behavioral interventions on psychosocial and medical end points remain uncertain.

**Objective:** To determine the effect of 2 behavioral programs, aerobic exercise training and stress management training, with routine medical care on psychosocial functioning and markers of cardiovascular risk.

**Design, setting, and patients:** Randomized controlled trial of 134 patients (92 male and 42 female; aged 40-84 years) with stable ischemic heart disease (IHD) and exercise-induced myocardial ischemia. Conducted from January 1999 to February 2003.

**Interventions:** Routine medical care (usual care); usual care plus supervised aerobic exercise training for 35 minutes 3 times per week for 16 weeks; usual care plus weekly 1.5-hour stress management training for 16 weeks.

**Main outcome measures:** Self-reported measures of general distress (General Health Questionnaire [GHQ]) and depression (Beck Depression Inventory [BDI]); left ventricular ejection fraction (LVEF) and wall motion abnormalities (WMA); flow-mediated dilation; and cardiac autonomic control (heart rate variability during deep breathing and baroreflex sensitivity).

**Results:** Patients in the exercise and stress management groups had lower mean (SE) BDI scores (exercise: 8.2 [0.6]; stress management: 8.2 [0.6]) vs usual care (10.1 [0.6]; P = .02); reduced distress by GHQ scores (exercise: 56.3 [0.9]; stress management: 56.8 [0.9]) vs usual care (53.6 [0.9]; P = .02); and smaller reductions in LVEF during mental stress testing (exercise: -0.54% [0.44%]; stress management: -0.34% [0.45%]) vs usual care (-1.69% [0.46%]; P = .03). Exercise and stress management were associated with lower mean (SE) WMA rating scores (exercise: 0.20 [0.07]; stress management: 0.10 [0.07]) in a subset of patients with significant stress-induced WMA at baseline vs usual care (0.36 [0.07]; P = .02). Patients in the exercise and stress management groups had greater mean (SE) improvements in flow-mediated dilation (exercise: mean [SD], 5.6% [0.45%]; stress management: 5.2% [0.47%]) vs usual care patients (4.1% [0.48%]; P = .03). In a subgroup, those receiving stress management showed improved mean (SE) baroreflex sensitivity (8.2 [0.8] ms/mm Hg) vs usual care (5.1 [0.9] ms/mm Hg; P = .02) and significant increases in heart rate variability (193.7 [19.6] ms) vs usual care (132.1 [21.5] ms; P = .04).

**Conclusion:** For patients with stable IHD, exercise and stress management training reduced emotional distress and improved markers of cardiovascular risk more than usual medical care alone.

### 141. Akinboboye O, Krantz DS, Kop WJ, Schwartz SD, Levine J, Del Negro A, Karasik P, Berman DS, O'Callahan M, Ngai K, Gottdiener JS. Comparison of mental stress-induced myocardial ischemia in coronary artery disease patients with versus without left ventricular dysfunction. Am J Cardiol. 2005 Feb 1;95(3):322-6. doi: 10.1016/j.amjcard.2004.09.027. PMID: 15670538.

To examine the susceptibility to myocardial ischemia with mental stress in patients who have coronary artery disease and normal left ventricular (LV) function versus those who have impaired LV function, we examined 58 patients who had coronary artery disease, including 22 who had normal LV function (ejection fraction >/=50%),

16 who had mild to moderate LV dysfunction (ejection fraction 30% to 50%), and 20 who had severe LV dysfunction (ejection fraction </=30%) and underwent bicycle and mental stress testing with myocardial perfusion scintigraphy on consecutive days in random order. Ischemia was assessed based on summed difference scores in regional rest versus stress myocardial perfusion and defined as a summed difference score >3. At comparable double products across the 3 groups, ischemia was induced with mental stress more frequently in patients who had severe LV dysfunction (50%) than in those who had normal LV function (9%; p <0.01). The frequency of exercise-induced ischemia was different only between those who had mild/moderate LV dysfunction and those who had normal LV function (56% vs 18%, respectively, p <0.05). The pattern of mental stress versus exercise ischemia differed between groups (p <0.02): there was a higher prevalence of mental stress ischemia versus exercise ischemia in patients who had severe LV dysfunction (p = 0.06), a marginally higher prevalence of exercise versus mental stress ischemia in those who had moderate LV dysfunction (p = 0.07), and no difference in mental stress versus exercise ischemia in those who had normal LV function. Thus, at comparable double products during mental stress and similar extent of coronary artery disease, ischemia with mental stress was induced more frequently in patients who had severe LV dysfunction than in those who had normal LV function. These data suggest that mental stress ischemia may be of particular clinical importance in patients who have coronary artery disease and LV dysfunction.

Michael AJ, Krishnaswamy S, Muthusamy TS, Yusuf K, Mohamed J. Anxiety, depression and psychosocial stress in patients with cardiac events. Malays J Med Sci. 2005 Jan;12(1):57-63. PMID: 22605948; PMCID: PMC3349414.

Stress tends to worsen the prognosis of patients with coronary heart disease. The aim of the study is to determine the relationship between stress related psychosocial factors like anxiety, depression and life events and temporally cardiac events specified as acute myocardial infarction and unstable angina 65 subjects with confirmed myocardial infarction or unstable angina were interviewed using 2 sets of questionnaire, the Hospital Anxiety and Depression Scale (HADS) and Life Changes Stress Test, a segment of the Rahe's Stress and Coping Inventory first at time of occurrence of their cardiac event and the second time was 6 months later. Anxiety, depression and life events scores were calculated for both and recurrence of cardiac event for the 6 month duration was also recorded. Patients who had significant levels of depression and or life events were ten times more likely to have recurrence of cardiac events as compared to those without risk for either of these psychological symptoms. Anxiety, depression and stress levels are significantly increased after the

onset of ischemic heart disease and could be contributing or predisposing factors for the recurrence of cardiac events for these patients.

### 142. Gafarov VV, Pak VA, Gagulin IV, Gafarova AV. [Personal anxiety and ischemic heart disease]. Ter Arkh. 2005;77(12):25-9. Russian. PMID: 16514815.

**Aim:** To study correlations between personal anxiety (PA) as one of the leading psychosocial factors and ischemic heart disease (IHD).

**Material and methods:** The third screening (1994) of the program MONICA and subprogram MOPSY-MONICA-psychosocial covered a random representative sample of males at the age of 25-64 years living in Novosibirsk. The response was 82% (657 responders, mean age 44.3 +/- 0.4 years). Statistical analysis was based on the SPSS-10 software package.

**Results:** Prevalence of PA as an indication of social stress in a male population of 25-64-year-olds is very high especially in young age groups. PA is maximal among persons with elementary education and workers. Persons with PA experience strong stress in job and in family settings. An IHD rate is higher among PA patients. High PA is often associated with depression, high hostility, cachexia, sleep problems, low social support. PA patients have a negative opinion of their health but their attempts to improve it are insufficient. The proportion of those who quit smoking, reduce the number of cigarettes, keep diet, restrict physical activity grow in PA persons.

**Conclusion:** PA is prevalent among male population especially in young persons. A PA level correlates with social status. IHD occurs more frequently in PA persons. High PA often associates with other psychosocial factors.

### 143. Denisova TP, Shkoda AS, Malinova LI, Astaf'eva NG. [Social stress as a risk factor for ischemic heart disease]. Ter Arkh. 2005;77(3):52-5. Russian. PMID: 15881100.

**Aim:** To study dynamics of ischemic heart disease in exposure of the population of an industrial city to social-economic stress.

**Material and methods:** Official annual records of Saratov city Health Administration for 1989-1998. In public health evaluation, cardiovascular morbidity is the index rapidly reacting to social-economic changes. Descrete data of myocardial infarction and angina prevalence for the analysed time were approximated by polynomes of high degree. As a result, the first and second derivatives--speed and acceleration--were obtained.

**Results:** A rise in MI morbidity reflected a rise in social tension. The disturbance of the population system of an industrial center (in conditions of a social stress) is accompanied by marked deformation of the profile of cardiovascular diseases in the industrial region: the growth of MI prevalence is associated with lowering of angina pectoris morbidity.

**Conclusion:** A rise in MI incidence rate is proposed as an indicator of social-economic stability or instability. Instability of IHD morbidity in the population allows consideration of social stress as its risk factor.

144. Rosengren A, Hawken S, Ounpuu S, Sliwa K, Zubaid M, Almahmeed WA, Blackett KN, Sitthi-amorn C, Sato H, Yusuf S; INTERHEART investigators. Association of psychosocial risk factors with risk of acute myocardial infarction in 11119 cases and 13648 controls from 52 countries (the INTERHEART study): case-control study. Lancet. 2004 Sep 11-17;364(9438):953-62. doi: 10.1016/S0140-6736(04)17019-0. PMID: 15364186.

**Background:** Psychosocial factors have been reported to be independently associated with coronary heart disease. However, previous studies have been in mainly North American or European populations. The aim of the present analysis was to investigate the relation of psychosocial factors to risk of myocardial infarction in 24767 people from 52 countries.

**Methods:** We used a case-control design with 11119 patients with a first myocardial infarction and 13648 age-matched (up to 5 years older or younger) and sex-matched controls from 262 centres in Asia, Europe, the Middle East, Africa, Australia, and North and South America. Data for demographic factors, education, income, and cardiovascular risk factors were obtained by standardised approaches. Psychosocial stress was assessed by four simple questions about stress at work and at home, financial stress, and major life events in the past year. Additional questions assessed locus of control and presence of depression.

**Findings:** People with myocardial infarction (cases) reported higher prevalence of all four stress factors ($p<0.0001$). Of those cases still working, 23.0% (n=1249) experienced several periods of work stress compared with 17.9% (1324) of controls, and 10.0% (540) experienced permanent work stress during the previous year versus 5.0% (372) of controls. Odds ratios were 1.38 (99% CI 1.19-1.61) for several periods of work stress and 2.14 (1.73-2.64) for permanent stress at work, adjusted for age, sex, geographic region, and smoking. 11.6% (1288) of cases had several periods of stress at home compared with 8.6% (1179) of controls (odds ratio 1.52 [99% CI 1.34-1.72]),

and 3.5% (384) of cases reported permanent stress at home versus 1.9% (253) of controls (2.12 [1.68-2.65]). General stress (work, home, or both) was associated with an odds ratio of 1.45 (99% CI 1.30-1.61) for several periods and 2.17 (1.84-2.55) for permanent stress. Severe financial stress was more typical in cases than controls (14.6% [1622] vs 12.2% [1659]; odds ratio 1.33 [99% CI 1.19-1.48]). Stressful life events in the past year were also more frequent in cases than controls (16.1% [1790] vs 13.0% [1771]; 1.48 [1.33-1.64]), as was depression (24.0% [2673] vs 17.6% [2404]; odds ratio 1.55 [1.42-1.69]). These differences were consistent across regions, in different ethnic groups, and in men and women.

**Interpretation:** Presence of psychosocial stressors is associated with increased risk of acute myocardial infarction, suggesting that approaches aimed at modifying these factors should be developed.

## 145. Goor DA, Sheffy J, Schnall RP, Arditti A, Caspi A, Bragdon EE, Sheps DS. Peripheral arterial tonometry: a diagnostic method for detection of myocardial ischemia induced during mental stress tests: a pilot study. Clin Cardiol. 2004 Mar;27(3):137-41. doi: 10.1002/clc.4960270307. PMID: 15049379; PMCID: PMC6653885.

**Background:** Mental stress testing is considered a reliable method for diagnosing patients with coronary heart disease (CHD) who may be at risk for future events. It has been shown recently that myocardial ischemia induced during mental stress tests is specifically associated with peripheral arterial vasoconstriction.

**Hypothesis:** The study was undertaken to test the diagnostic capability of peripheral arterial tonometry (PAT) to detect peripheral arterial vasomotor changes.

**Methods:** We monitored pulsatile finger blood volume changes using a specially designed finger plethysmograph, PAT that can detect peripheral arterial vasomotor changes. Equilibrium radionuclide angiography (ERNA) was simultaneously performed in 18 male patients at rest and during a mental arithmetic stress test with harassment. All patients had previously diagnosed coronary disease and positive exercise tests. Myocardial ischemia was diagnosed by ERNA when global ejection fraction fell > or = 8% during mental stress or new (or worsened) focal wall motion abnormalities occurred. Peripheral arterial tonometry tracings were considered abnormal when the pulse wave amplitude decreased by > or = 20% from baseline.

**Results:** In 18 patients there were 16 usable studies. In eight patients, both ERNA and PAT were abnormal, and in six patients the tests were negative by both methods.

In two cases, the results were discordant. Therefore, when considering an abnormal PAT tracing as indicative of mental stress-driven myocardial ischemia, concordance of the two methods was 88%.

**Conclusion:** The use of PAT may facilitate both clinical testing and research during mental stress.

### 146. Bilińska M, Tylka E, Tylka J, Piotrowicz R. Test prowokacji stresem psychicznym u chorych ze stabilna choroba wieńcowa [Mental stress test in patients with stable coronary artery disease]. Pol Merkur Lekarski. 2003 Nov;15(89):412-5. Polish. PMID: 14969132.

Myocardial ischemia may be triggered by exercise and non-exercise stimuli.

**The purpose:** Of this study was to determine the usefulness of laboratory mental stress (MS) in inducing myocardial ischemia and/or cardiac arrhythmia in patients (pts) post myocardial infarction, with stable coronary artery disease. Sixty four men, mean age 45 +/- 6 years underwent: 15 min mental stress test during 24 h Holter monitoring and exercise stress testing.

**Results:** Only 8 pts (13%) had positive mental stress test (MS+). Five of them had ST segment depression > 1.0 mm (STD), and the remaining 3 pts had cardiac arrhythmias. All episodes were silent. MS+ pts had higher heart rate (HR) during the mental test than those with negative stress test (MS-) (120/min vs 105/min, $p < 0.05$). In contrast, at least one episode of daily life ischemia (DLI) was recorded in 23 pts (36%) on Holter monitoring. In MS+ pts average duration of DLI (17 min) and mean HR during ischemia (124/min) were greater than in MS-pts (respectively 10.5 min and 94/min, $p < 0.05$). Exercise induced ischemia (STD > 1.0 mm) was observed in 29 of 64 pts (45%). However, in MS+ pts exercise duration (708 +/- 132 s), time to 1 mm STD (432 +/- 108 s) were significantly shorter and double product at 1 mm STD (13,400 +/- 2913 mm Hg/min) was lower than in MS- pts (respectively 924 +/- 174 s, $p < 0.01$; 624 +/- 162 s, $p < 0.01$; 14,800 +/- 3321 mmHg/min, $p < 0.05$).

**Conclusions:** Mental stress test is a weak inducer of ischemia and arrhythmia in patients with stable coronary artery disease. Patients with mental stress-induced ischemia are more likely to display ischemia during daily life and exercise stress testing.

147. Spieker L, Noll G. Pathophysiologische Herz-Kreislauf-Veränderungen bei Stress und Depression [Pathophysiologic cardiovascular changes in stress and depression]. Ther Umsch. 2003 Nov;60(11):667-72. German. doi: 10.1024/0040-5930.60.11.667. PMID: 14669704.

Fear, anger, and grief may precipitate myocardial ischemia and infarction. The prognosis of patients with inducible ischemia during mental stress is worse than in those without inducible ischemia. The sympathetic nervous system plays an important role in stress-associated changes in cardiovascular regulation and contributes to cardiovascular morbidity and mortality by inducing vasoconstriction and tachycardia, as well as arrhythmia. Hostility--previously termed type A personality--is often associated with sympathetic hyperreactivity to mental stress and carries an increased risk for atherosclerotic vascular disease. As endothelial dysfunction is an early manifestation of atherosclerosis, the impact of mental stress on endothelial function is also important. Acute mental stress induces prolonged endothelial dysfunction in healthy volunteers, which is prevented by selective endothelin A receptor antagonism. This represents an important link between mental stress and atherosclerotic vascular disease. In addition, patients with depression show hypercortisolemia, and changes in platelet function leading to a prothrombotic state. These findings help to explain the increased cardiovascular risk in patients with depression.

148. Kop WJ. The integration of cardiovascular behavioral medicine and psychoneuroimmunology: new developments based on converging research fields. Brain Behav Immun. 2003 Aug;17(4):233-7. doi: 10.1016/s0889-1591(03)00051-5. PMID: 12831824.

The immune system plays a role in the progression of coronary artery diseases and its clinical manifestations as acute coronary syndromes. It is well established that psychological factors can act as risk factors for acute coronary syndromes. This review describes psychoneuroimmunological pathways involved in coronary disease progression and documents that the stage of coronary disease is a major determinant of pathophysiological mechanisms accounting for the association between psychological risk factors, immune system parameters, and acute coronary syndromes. Chronic psychological risk factors (e.g., hostility and low socioeconomic

status) are important at early disease stages, episodic factors (e.g., depression and exhaustion) are involved in the transition from stable to unstable atherosclerotic plaques, and acute psychological triggers (e.g., mental stress and anger) can promote myocardial ischemia and plaque rupture. The psychoneuroimmunological pathways are described for each of these three types of psychological risk factors for acute coronary syndromes.

149. Chockalingam A, Venkatesan S, Dorairajan S, Moorthy C, Chockalingam V, Subramaniam T. Estimation of subjective stress in acute myocardial infarction. J Postgrad Med. 2003 Jul-Sep;49(3):207-10. PMID: 14597781.

**Background and aims:** Mental stress is considered to be a precipitating factor in acute coronary events. We aimed to assess the association of subjective or 'perceived' mental stress with the occurrence of acute coronary events.

**Settings and design:** Prospective case-control survey was carried out in a referral teaching hospital.

**Subjects & methods:** Consecutive patients with acute myocardial infarction and ST elevation on electrocardiogram who were admitted to the Coronary Care Unit of a referral teaching hospital were enrolled in the study as cases. Controls were unmatched and were enrolled from amongst patients with coronary artery disease who did not have recent acute coronary events. Subjective Stress Functional Classification (SS-FC) for the preceding 2-4 weeks was assessed and assigned four grades from I to IV as follows: I - baseline, II - more than usual but not affecting daily routine, III - significantly high stress affecting daily routine and IV - worst stress in life.

**Statistical analysis:** Proportions of different characteristics were compared using chi-square test with Yates continuity correction. Student's unpaired t test was applied for mean age. 'p' value of < 0.05 was considered statistically significant.

**Results:** SS-FC could be reliably (99%) and easily assessed. Eighty (53%) of the total 150 patients with acute MI reported 'high' levels of stress (stress class III and IV). This is in contrast to only 30 (20%) of 150 healthy controls reporting high stress for the same period (p value < 0.001).

**Conclusion:** Patients with acute myocardial infarction report a higher subjective mental stress during 2 to 4 weeks preceding the acute coronary event.

150. Jiang W, Babyak MA, Rozanski A, Sherwood A, O'Connor CM, Waugh RA, Coleman RE, Hanson MW, Morris JJ, Blumenthal JA. Depression and increased myocardial ischemic activity in patients with ischemic heart disease. Am Heart J. 2003 Jul;146(1):55-61. doi: 10.1016/S0002-8703(03)00152-2. PMID: 12851608.

**Background:** Depression is relatively common in patients with ischemic heart disease (IHD) and is associated with increased risk of mortality and morbidity. However, the mechanisms by which depression adversely affects clinical outcomes of patients with IHD are unknown. This study examined the relationship between depression and myocardial ischemia during mental stress testing and during daily living in patients with stable IHD.Methods and results The Center for Epidemiological Studies-Depression scale (CES-D) was administered to 135 patients with IHD to evaluate depressive symptoms. Radionuclide ventriculography was used to evaluate the occurrence of left ventricular wall motion abnormality (WMA) during mental stress and exercise testing. Forty-eight-hour ambulatory electrocardiography was used to assess myocardial ischemia during daily living. The mean CES-D score was 8.2 (SD 7.4, range 0-47) with a median of 7. Logistic regression models using restricted cubic splines revealed a curvilinear relation among CES-D scores and the probability of ischemia. For patients with CES-D scores <or=19 (81.5% of study population), a 5-point increment in the CES-D score was associated with roughly a 2-fold increase in the likelihood of ischemia during mental stress. For patients with CES-D scores >19, the relation among scores and ischemia during mental stress tended to be inversely related, but the portion of the sample is very small. Similar patterns of results were noted for CES-D scores and ischemia during daily life.

**Conclusions:** Patients with mild to moderate depressive symptoms (CES-D scores <or=19) are more likely to exhibit myocardial ischemia during mental stress testing and during daily living. Myocardial ischemia may be one mechanism by which depression increases the risk of mortality and morbidity in patients with IHD. The observed inverse association between higher level of depressive symptoms and ischemic activity needs to be further assessed in large samples.

151. Arrighi JA, Burg M, Cohen IS, Soufer R. Simultaneous assessment of myocardial perfusion and function during mental stress in patients with chronic coronary artery disease. J Nucl Cardiol. 2003 May-Jun;10(3):267-74. doi: 10.1016/s1071-3581(02)43235-7. PMID: 12794625.

**Background:** Mental stress (MS) is an important provocateur of myocardial ischemia in many patients with chronic coronary artery disease. The majority of laboratory assessments of ischemia in response to MS have included measurements of either myocardial perfusion or function alone. We performed this study to determine the relationship between alterations in perfusion and ventricular function during MS. Methods and results Twenty-eight patients with reversible perfusion defects on exercise or pharmacologic stress myocardial perfusion imaging (MPI) underwent simultaneous technetium 99m sestamibi single photon emission computed tomography (SPECT) MPI and transthoracic echocardiography at rest and during MS according to a mental arithmetic protocol. In all cases the MS study was performed within 4 weeks of the initial exercise or pharmacologic MPI that demonstrated ischemia. SPECT studies were analyzed visually with the use of a 13-segment model and quantitatively by semiautomated circumferential profile analysis. Echocardiograms were graded on a segmental model for regional wall motion on a 4-point scale. Of 28 patients, 18 (64%) had perfusion defects and/or left ventricular dysfunction develop during MS: 9 (32%) had myocardial perfusion defects develop, 6 (21%) had regional or global left ventricular dysfunction develop, and 3 (11%) had both perfusion defects and left ventricular dysfunction develop. The overall concordance between perfusion and function criteria for ischemia during MS was only 46%. Among 9 patients with MS-induced left ventricular dysfunction, 5 had new regional wall motion abnormalities and 4 had a global decrement in function. In patients with MS-induced ischemia by SPECT, the number of reversible perfusion defects was similar during both MS and exercise/pharmacologic stress (2.8 +/- 2.0 vs 3.5 +/- 1.8, P =.41). Hemodynamic changes during MS were similar whether patients were divided on the basis of perfusion defects or left ventricular dysfunction during MS.

**Conclusions:** These data indicate the feasibility of simultaneous assessment of perfusion and function responses during MS. Flow and function responses to MS are frequently not concordant. These data suggest that MS-induced changes in perfusion may represent a different phenomenon than MS-induced changes in left ventricular function (either globally or regionally).

152. Strike PC, Steptoe A. Systematic review of mental stress-induced myocardial ischaemia. Eur Heart J. 2003 Apr;24(8):690-703. doi: 10.1016/s0195-668x(02)00615-2. PMID: 12713764.

NO ABSTRACT AVAILABLE

153. Gafarov VV, Pak VA, Gagulin IV, Gafarova AV. Izuchenie na osnove programmy BOZ monika sviazi psikhosotsial'nykh faktorov riska s ishemicheskoĭ bolez'niu serdtsa u muzhchin v vozraste 25-64 let v Novosibirske [Study based on the WHO Monika program on the connection between psychosocial risk factors and ischemic heart disease in men aged 25-64 in Novosibirsk]. Ter Arkh. 2003;75(4):51-4. Russian. PMID: 12793139.

**Aim:** To study correlations between coronary heart disease (CHD) and psychosocial risk factors.

**Material and methods:** CHD affected more frequently workers engaged in hard physical labour, in poorly educated persons; the least CHD morbidity was recorded in managers and highly educated persons. CHD males think of their health much worse than males free of CHD. The former smoked much more before CHD diagnosis, but when CHD comes they quit and reduce smoking much more frequently. This fact explains why smokers are encountered among CHD patients two times less frequently than in CHD-free males. In spite of stronger motivation for adequate diet, CHD males changed their nutrition pattern only in 3.7%. CHD males sleep worse: good sleep was registered in CHD-free males two times more frequently. Psychological risk factors such as personal anxiety, sleep disorders were reported much more frequently in CHD patients proving the fact of social stress involvement in development of CHD. So-called coronary behavior was observed in both groups of males with the same rate. Thus, the coronary behavior is not associated with CHD.

**Conclusion:** Development of CHD is associated not with the behavior but its components (depression, anxiety, etc.).

154. Schellenbaum GD, Rea TD, Smith NL. Mental stress-induced ischemia and all-cause mortality in patients with coronary artery disease. Circulation. 2002 Nov 26;106(22):e183-4; author reply e183-4. doi: 10.1161/01.cir.0000037296.49324.f8. PMID: 12451019.

NO ABSTRACT AVAILABLE

155. Stalnikowicz R, Tsafrir A. Acute psychosocial stress and cardiovascular events. Am J Emerg Med. 2002 Sep;20(5):488-91. doi: 10.1053/ajem.2002.34788. PMID: 12216051.

Stressful life events can trigger acute myocardial infarction and sudden cardiac death. Victims of natural disasters, such as earthquakes and other conditions of extreme stress should be evaluated for physical injuries as well as for cardiac disease.

156. Blumenthal JA, Babyak M, Wei J, O'Connor C, Waugh R, Eisenstein E, Mark D, Sherwood A, Woodley PS, Irwin RJ, Reed G. Usefulness of psychosocial treatment of mental stress-induced myocardial ischemia in men. Am J Cardiol. 2002 Jan 15;89(2):164-8. doi: 10.1016/s0002-9149(01)02194-4. PMID: 11792336.

This study examined the effects of exercise and stress management training on clinical outcomes and medical expenditures over a 5-year follow-up period in 94 male patients with established coronary artery disease (CAD) and evidence of ambulatory or mental stress-induced myocardial ischemia. Patients were randomly assigned to 4 months of aerobic exercise 3 times per week or to a 1.5-hour weekly class on stress management; patients who lived too far from Duke to participate in the weekly treatments formed the usual care control group. Follow-up was performed at the end of treatment and annually thereafter for 5 years. Stress management was associated with a significant reduction in clinical CAD events relative to usual care over each of the first 2 years of follow-up and after 5 years. Economic analyses revealed that stress management was associated with lower medical costs than usual care and exercise in the first 2 years, and that the cumulative cost over 5 years was also lower for stress management relative to usual care. These results suggest that there may be clinical and economic benefit to offering the type of preventive stress management and exercise interventions

provided to patients with myocardial ischemia. Moreover, these findings suggest that the financial benefits that accrue from an appropriately targeted intervention may be substantial and immediate.

157. Singh RB, Kartik C, Otsuka K, Pella D, Pella J. Brain-heart connection and the risk of heart attack. Biomed Pharmacother. 2002;56 Suppl 2:257s-265s. doi: 10.1016/s0753-3322(02)00300-1. PMID: 12653178.

Autonomic functions, such as increased sympathetic and parasympathetic activity and the brain's suprachiasmatic nucleus, higher nervous centres, depression, hostility and aggression appear to be important determinants of heart rate variability (HRV), which is, itself, an important risk factor of myocardial infarction, arrhythmias, sudden death, heart failure and atherosclerosis. The circadian rhythm of these complications with an increased occurrence in the second quarter of the day may be due to autonomic dysfunction as well as to the presence of excitatory brain and heart tissues. While increased sympathetic activity is associated with increased levels of cortisol, catecholamines, serotonin, renin, aldosterone, angiotensin and free radicals; increased parasympathetic activity may be associated with greater levels of acetylecholine, dopamine, nitric oxide, endorphins, coenzyme Q10, antioxidants and other protective factors. Recent studies indicate that hyperglycemia, diabetes, hyperlipidemia, ambient pollution, insulin resistance and mental stress can increase the risk of low HRV. These risk factors, which are known to favour cardiovascular disease, seem to act by decreasing HRV. There is evidence that regular fasting may modulate HRV and other risk factors of heart attack. While exercise is known to decrease HRV, exercise training may not have any adverse effect on HRV. In a recent study among 202 patients with acute myocardial infarction (AMI), the incidence of onset of chest pain was highest in the second quarter of the day (41.0%), mainly between 4.0-8.0 AM, followed by the fourth quarter, usually after large meals (28.2%). Emotion was the second most common trigger (43.5%). Cold weather was a predisposing factor in 29.2% and hot temperature (> 40 degrees celsius) was common in 24.7% of the patients. Dietary n-3 fatty acids and coenzyme Q10 have been found to prevent the increased circadian occurrence of cardiac events in our randomized controlled trials, possibly by increasing HRV. We have also found that n-3 fatty acids plus CoQ can decrease TNF-alpha and IL-6 in AMI which are pro-inflammatory agents. There is evidence that dietary n-3 fatty acids canenhance hippocampal acetylecholine levels, which may be protective. Similarly, the stimulation of the vagus nerve may inhibit TNF synthesis in the liver and acetylecholine, the

principal vagal neurotransmitter, significantly attenuates the release of pro-inflammatory cytokines TNF-alpha, interleukin 1,6 and 18, but not the anti-inflammatory cytokine IL-10 in experiments. Therefore, any agent which can enhance brain acetylecholine levels, may be used as a therapeutic agent in protecting the suprachiasmatic nucleus, higher nervous centres, vagal activity and sympathetic nerve activity which are known to regulate the body clock and HRV and the risk of SCD and heart attack.

158. Bairey Merz CN, Dwyer J, Nordstrom CK, Walton KG, Salerno JW, Schneider RH. Psychosocial stress and cardiovascular disease: pathophysiological links. Behav Med. 2002 Winter;27(4):141-7. doi: 10.1080/08964280209596039. PMID: 12165968; PMCID: PMC2979339.

The remarkable decline in cardiovascular disease (CVD) experienced in developed countries over the last 40 years appears to have abated. Currently, many CVD patients continue to show cardiac events despite optimal treatment of traditional risk factors. This evidence suggests that additional interventions, particularly those aimed at nontraditional factors, might be useful for continuing the decline. Psychosocial stress is a newly recognized (nontraditional) risk factor that appears to contribute to all recognized mechanisms underlying cardiac events, specifically, (a) clustering of traditional cardiovascular risk factors, (b) endothelial dysfunction, (c) myocardial ischemia, (d) plaque rupture, (e) thrombosis, and (f) malignant arrhythmias. A better understanding of the behavioral and physiologic associations between psychosocial stress and CVD will assist researchers in identifying effective approaches for reducing or reversing the damaging effects of stress and may lead to further reductions of CVD morbidity and mortality.

159. Krantz DS, Quigley JF, O'Callahan M. Mental stress as a trigger of acute cardiac events: the role of laboratory studies. Ital Heart J. 2001 Dec;2(12):895-9. PMID: 11838335.

Mental stress has long been implicated as a potential trigger of myocardial infarction and sudden cardiac death. This article reviews research conducted in the past two decades utilizing laboratory studies to investigate behaviorally-induced pathophysiological effects (including increased cardiac demand, decreased myocardial supply, and impaired dilation of coronary resistance vessels), in patients with coronary artery disease. The clinical significance of mental stress-induced

ischemia is supported by findings of a predictive relationship of mental stress-induced ischemia for ambulatory ischemia and subsequent cardiac events. Mental stress-induced ventricular fibrillation, ventricular tachycardia, and T-wave alternans are also being explored as possible markers of arrhythmic vulnerability in human and animal models. T-wave alternans comparable to exercise can be induced by an anger-like state in an animal model, and with mental stress in patients with implantable cardioverter-defibrillators. Future directions for research on mental stress and cardiac events are suggested, including further studies of mechanisms of mental stress-induced arrhythmia and ischemia, additional studies of the prognostic significance of stress-induced ischemia and T-wave alternans, and use of pharmacological and psychosocial treatments for preventing stress-induced cardiac events.

### 160. Sheps DS, Sheffield D. Depression, anxiety, and the cardiovascular system: the cardiologist's perspective. J Clin Psychiatry. 2001;62 Suppl 8:12-6; discussion 17-8. PMID: 12108816.

Up to one fifth of patients with cardiovascular disease, including those who have experienced a myocardial infarction, may have concomitant major depression. Studies have suggested that the relative risk of major depression with cardiovascular disease ranges from 1.5 to 4.5. Further information is required to establish a dose-response relationship between depression and coronary artery disease (CAD); however, such a relationship has been shown between anxiety and CAD. Development of a conceptual model of the pathophysiologic actions of stress in CAD will assist in the understanding of this relationship. In patients with angiographic evidence of CAD, the presence of major depressive disorder was the best single predictor of cardiac events during the 12 months following diagnosis. Significantly, 6-month cumulative mortality following diagnosis of myocardial infarction has been shown to be higher in depressed patients than in nondepressed patients. A decrease in heart rate variability may mediate the deleterious effect of depression on post-myocardial infarction prognosis. Other factors such as mental stress and altered platelet function may also predispose depressed patients to a heightened risk of cardiac events. With an increased understanding of the relationship between depression and heightened risk of cardiovascular mortality, it is necessary to assess current overall treatment for cardiac patients.

161. Orth-Gomér K, Wamala SP, Horsten M, Schenck-Gustafsson K, Schneiderman N, Mittleman MA. Marital stress worsens prognosis in women with coronary heart disease: The Stockholm Female Coronary Risk Study. JAMA. 2000 Dec 20;284(23):3008-14. doi: 10.1001/jama.284.23.3008. PMID: 11122587.

**Context:** Psychosocial stress has been associated with incidence of coronary heart disease (CHD) in men, but the prognostic impact of such stress rarely has been studied in women.

**Objective:** To investigate the prognostic impact of psychosocial work stress and marital stress among women with CHD.

**Design and setting:** Population-based, prospective follow-up study conducted in the city of Stockholm, Sweden.

**Participants:** A total of 292 consecutive female patients aged 30 to 65 years (n = 279 working or cohabiting with a male partner) who were hospitalized for acute myocardial infarction or unstable angina pectoris between February 1991 and February 1994. Patients were followed up from the date of clinical examination until August 1997 (median, 4.8 years).

**Main outcome measures:** Recurrent coronary events, including cardiac death, acute myocardial infarction, and revascularization procedures, by marital stress (assessed using the Stockholm Marital Stress Scale, a structured interview) and by work stress (assessed using the ratio of work demand to work control).

**Results:** Among women who were married or cohabiting with a male partner (n = 187), marital stress was associated with a 2.9-fold (95% confidence interval [CI], 1.3-6.5) increased risk of recurrent events after adjustment for age, estrogen status, education level, smoking, diagnosis at index event, diabetes mellitus, systolic blood pressure, smoking, triglyceride level, high-density lipoprotein cholesterol level, and left ventricular dysfunction. Among working women (n = 200), work stress did not significantly predict recurrent coronary events (hazard ratio, 1.6; 95% CI, 0.8-3.3).

**Conclusions:** Our results indicate that marital stress but not work stress predicts poor prognosis in women aged 30 to 65 years with CHD. These findings differ from previous findings in men and suggest that specific preventive measures be tailored to the needs of women with CHD.

## 162. O'connor CM, Gurbel PA, Serebruany VL. Depression and ischemic heart disease. Am Heart J. 2000 Oct;140(4 Suppl):63-9. doi: 10.1067/mhj.2000.109979. PMID: 11011350.

Major depression is a common comorbidity associated with ischemic heart disease (IHD). There is growing evidence that psychological stress in general and depression in particular predispose to cardiovascular disease. Persons who have mental stress during daily life are at twice the risk of myocardial ischemia, and patients with post-myocardial infarction depression have higher mortality rates than nondepressed controls. These data suggest a psychophysiologic mechanism underlying the vulnerability of depressed patients to IHD. Clinical studies have demonstrated that depression is associated with a much higher risk of both cardiovascular morbidity and mortality, which could be caused by platelet activation. Physicians should maintain a heightened level of clinical suspicion for depression and depressive disorders in persons with IHD, particularly those individuals who are recovering from an acute ischemic event, such as myocardial infarction. Furthermore, depression may complicate the recovery of IHD, but in most cases depression can be effectively treated with antidepressant agents.

## 163. Krantz DS, Sheps DS, Carney RM, Natelson BH. Effects of mental stress in patients with coronary artery disease: evidence and clinical implications. JAMA. 2000 Apr 12;283(14):1800-2. doi: 10.1001/jama.283.14.1800. PMID: 10770129.

NO ABSTRACT AVAILABLE

Ketterer MW, Freedland KE, Krantz DS, Kaufmann P, Forman S, Greene A, Raczynski J, Knatterud G, Light K, Carney RM, Stone P, Becker L, Sheps D. Psychological Correlates of Mental Stress-induced Ischemia in the Laboratory: The Psychophysiological Investigation of Myocardial Ischemia (PIMI) Study. J Health Psychol. 2000 Jan;5(1):75-85. doi: 10.1177/135910530000500112. PMID: 22048826.

Participants consisted of 184 patients (160 males, 24 females) with positive angiograms or prior myocardial infarctions who displayed at least 1 mm of ST segment depression on a standardized treadmill test. Mean scores on the Reward Dependence subscale of the Tridimensional Personality Questionnaire were higher in patients displaying ischemia during mental stress. Patients who reported higher levels of irritability/anger in response to the Speech stressor were also more likely to display ischemia. However, this result was primarily a result of the females in the

sample whose ratings of interest and irritability were associated with ischemia during the Speech task. Psychometric measures previously found in prospective studies to predict acute cardiac events were unrelated to mental stress-induced ischemia in the laboratory.

164. Schöder H, Silverman DH, Campisi R, Karpman H, Phelps ME, Schelbert HR, Czernin J. Effect of mental stress on myocardial blood flow and vasomotion in patients with coronary artery disease. J Nucl Med. 2000 Jan;41(1):11-6. PMID: 10647599.

In patients with coronary artery disease (CAD), mental stress may provoke ischemic electrocardiograph changes and abnormalities in regional and global left ventricular function. However, little is known about the underlying myocardial blood flow response (MBF) in these patients.

**Methods:** We investigated the hemodynamic, neurohumoral, and myocardial blood flow responses to mental stress in 17 patients with CAD and 17 healthy volunteers of similar age. Mental stress was induced by asking individuals to solve mathematic subtractions in a progressively challenging sequence; MBF was quantified at rest and during mental stress using 13N ammonia PET.

**Results:** Mental stress induced significant ($P < 0.01$) and comparable increases in rate-pressure product, measured in beats per minute x mm Hg, in both patients (from 7826 +/- 2006 to 10586 +/- 2800) and healthy volunteers (from 8227 +/- 1272 to 10618 +/- 2468). Comparable increases also occurred in serum epinephrine (58% in patients versus 52% in healthy volunteers) and norepinephrine (22% in patients versus 27% in healthy volunteers). Although MBF increased in patients (from 0.67 +/- 0.15 to 0.77 +/- 0.18 mL/min/g, $P < 0.05$) and healthy volunteers (from 0.73 +/- 0.13 to 0.95 +/- 0.22 mL/min/g, $P < 0.001$), the magnitude of flow increase was smaller in patients (14% +/- 17%) than in healthy volunteers (29% +/- 14%) ($P = 0.01$). The increase in MBF during mental stress correlated significantly with changes in cardiac work in healthy volunteers ($r = 0.77$; $P < 0.001$) but not in patients.

**Conclusion:** Despite similar increases in cardiac work and comparable sympathetic stimulation in CAD patients and healthy volunteers, CAD patients exhibit an attenuated blood flow response to mental stress that may contribute to mental stress-induced ischemic episodes in daily life.