Cardiovascular Imaging of Biology and Emotion: Considerations Towards a New Paradigm

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Abstract

Central activation in response to emotion and cognitive stress induces perturbations in the heart and the peripheral vasculature that differ in physiology and clinical manifestations when compared to exercise induced changes. While our conventional framework of epicardial coronary artery disease (CAD) is foundational in cardiology, an expanded paradigm is required to address the cardiovascular (CV) response to mental stress (MS) and its associated risks, thus addressing the intersection of the patient's ecologic and psychosocial experience with CV biology. To advance the field of MS in CV health, certain core challenges must be addressed. These include differences in the trigger activation between exercise and emotion, identification and interpretation of imaging cues as measures of pathophysiologic changes, characterization of the vascular response, and identification of central and peripheral treatment targets. Gender and psychosocial determinants of health are important in understanding the emerging overlap of mental stress induced myocardial ischemia (MSIMI) with microvascular dysfunction and symptoms in the absence of obstructive disease. In overcoming these critical knowledge gaps. Integration of the field of MS will require implementation studies to guide use of MS testing, to support diagnosis of MS induced cardiac and vascular pathophysiology, to assess prognosis, and understand the role of endotyping to direct therapy.

Keywords

mental stress provoked ischemia; coronary artery disease; microvascular disease; cardiovascular imaging

Subject Terms:

Cardiovascular Disease; Mental Health; Imaging; Risk Factors; Prognosis; Atherosclerosis

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Introduction

Advanced cardiac imaging serves to assist clinicians in the diagnosis of cardiac conditions, assess prognosis, and guide treatment. With the maturation of this discipline, there has been a concurrent reinforcement of constructs that promote certain understandings and improve efficiencies, which has contributed to a decline in morbidity and mortality. The nature of successful endeavors often are a result of refinements and consolidation that become broadly accepted. The imaging constructs of the past must expand to rally the strengths of new technology and the transformative power inherent in multidisciplinary translational research.

The standard paradigm, epicardial coronary artery disease (CAD) resulting in ischemia, fixates in a locality and a concept: the obstructive epicardial coronary lesion and a binary cue of ischemia. While this framework will remain integral, an 'ischemic phenomenon' due to emotion may fall outside of the this construct. Very often there is clinically meaningful reduction in myocardial blood flow (MBF) in the absence of a localized ischemic signal which may be due to triggers that are not associated with exertion. The effects of emotion and cognitive stress on cardiac physiology may be pervasive, diffuse, and influenced by multiple biologic and environmental inputs.

Thus, the discipline of cardiac imaging is challenged to expand observations and approaches to promote a better understanding of perturbations in cardiac and systemic biology in response to stress experienced in daily life. The stress of daily life has been modeled in the laboratory to study changes in MBF and function. This has resulted in the term mental stress (MS) and its resultant ischemic imaging cue as mental stress induced myocardial ischemia (MSIMI).

The Impact of Stress on Cardiac health

The contribution of stress and emotional factors to incident cardiovascular (CV) disease and mortality has been described through the centuries, from Ovid to Osler to important work that demonstrated emotional stress experienced with anger as a trigger to myocardial infarction (MI).[1] Epidemiologic work from INTERHEART and others demonstrate the important association of cumulative and daily psychosocial stress with CV risk. [2, 3] Responses to emotional stress during the course of daily life can provoke transient changes in myocardial perfusion along with regional and global systolic dysfunction, and is associated with the development of atherosclerosis, hypertension, and heart failure. [4 5 1 6 7] The relationship of life stressors and cardiac physiology has been modeled and standardized through laboratory MS testing, providing affirmation of the association between social determinants of health (socioeconomic status, gender) and psychosocial factors (anger reactivity, depression) with prevalence of MSIMI.

MSIMI is common, occurring in approximately half of patients with stable coronary artery disease (CAD), and has a strong association with increased CV morbidity and mortality. [1] The totality of work has demonstrated that patients who evidence MSIMI are at increased risk for cardiac events and early mortality, above that predicted by exercise provoked ischemia, regardless of the modality used to assess MSIMI. [4, 8, 9] A meta-analysis of 5

studies incorporating outcomes on 555 patients, reported a pooled relative risk of 2.24 (95% CI 1.59-1.35) for cardiac events or total mortality associated with change in LVEF or new RWMA in response to a MS trigger, a finding that has been affirmed in studies using a perfusion cue. [8, 10]

Overcoming obstacles in the field of Mental Stress and Cardiovascular disease

Despite the well-established and accepted concept of MSIMI based upon the relationship between stress and CV pathophysiology, MSIMI is an under-identified disease with a resultant failure of diagnosis and treatment within our standard clinical practice. When we apply the framework of exercise physiology and demand-induced ischemia to that of emotion and cognitive triggers, the imaging cues of locality and threshold bias our observations and understandings.

The two cardinal distinction between triggers of exercise and that of emotion are: a difference in brain/central nervous system (CNS) hyperactivation with attendant neurohormonal stimulation and activation of peripheral vasculature in the opposite vectors. Within the broad and multidisciplinary stress literature,[11] mental stress is recognized as systemic with initiation of central and peripheral processes that are transduced through multiple overlapping and interacting biologic pathways with terminal prominent systemic vascular vasoconstriction. Despite the systemic effects of stress, our measures of MS are often organ-specific, compartment specific, and more so, pathway-specific. The imaging cues must be reconsidered for cognitive triggers to address distinctions in regionality, threshold, target processes, and the interplay of peripheral and cardiac perturbations.

The current approaches in cardiac imaging, informed by a model of coronary obstruction, may not be sufficient to advance an understanding of the effect of emotion/cognitive stress on CV physiology and to promote development of novel treatments. Below we discuss several core challenges to our current approach with respect to MSMI:

1. Differences in ordinate activation of exercise and emotion triggers

2. Imaging cues

3. Characterization of the vascular response

4. Identification of treatment targets

5. Implementation into standard care

1. Differences in Ordinate Activation of Exercise and Emotion Triggers

Brain activation patterns suggest a phenomenological context defined by a cognitive-emotional trigger that is transduced centrally, and communicated to the periphery through both direct innervation of target organs - the myocardium, the vascular system - and through the circulation, by way of release by the adrenals of both catecholamines and cortisol. The autonomic 'fight-flight response' and the hypothalamic-pituitary-adrenal (HPA) axis

response - have implications for provocation of MSIMI and thus provide potential targets for intervention.

Simultaneous imaging of heart-brain activity in response to MS triggers by positron emmison tomography (PET) in CAD patients has shown specific patterns of CNS hyperactivation in association with MSIMI that are distinct from that observed with demand induced challenge with dobutamine and in non-CAD patients. FIGURE 1[12] Patients with MSIMI demonstrate hyperactivation in frontolimbic circuits associated with neurohormonal and autonomic regulation, emotion, memory, fear, and anxiety. There is deactivation in the prefrontal areas, along with hyperactivation in with the central autonomic network, which is strongly associated with the limbic system and involved in the negative feedback circuit between the limbic system and the prefrontal cortex. This circuit appears essential to the regulation of autonomic responses to stressful stimuli. A situational imbalance in the activity between these areas, or a fixed inability of the prefrontal cortex to attenuate limbic responses, may be linked with autonomic dysregulation which, during MS, can result in a net shift towards increased sympathetic tone and/or withdrawal of parasympathetic tone.[13, 14] In comparison, demand/dobutamine-induced ischemiais associated with brain activation in the peripheral sensorimotor and areas referable to situational awareness.

The results of this transduction is an alteration in sympatho-vagal balance (an increase in sympathetic nervous system activity and a withdrawal of cardiac vagal control), along with additional communication to the periphery as reflected in an increase in downstream inflammatory activity, an increase in both inotrophic and chronotrophic drive, and, likely a consequence of both systemic (e.g., endothelial dysfunction) and local (e.g., altered vasomotor responsivity to autonomic stimulation in the coronary tree) aspects of CAD, a reduction in MBF - MSIMI.[15]

In the current era we have recognized the importance of gender interaction in regard to triggers that culiminate in myocardial ischemia. In regard to MS triggers, female gender is associated with bilateral activation of the anterior cingulate gyrus, which is linked to parasympathetic acetylcholine mediated vasoconstriction, a thought-provoking connection to the gender interaction with INOCA (ischemia and no obstructive coronary artery disease) and microvascular disease.

Understanding the multiple inputs that contribute to the heterogenous response to stress and identifying treatment targets must be informed by the totality of the stress provoked CNS activation, the multiple and overlapping physiologic pathways by which stress is transduced to the periphery, and the terminal effects on vasomotion, arterial compliance, endothelial (dys)function, and clinical CV phenomena. Figure 2. The marked hyperactivation of neurohormonal centers responsible for catecholamine driven responses overlaps with other emotion induced CV dysfunction. Heretofore, MSIMI has been considered to be distinct from Takotsubo cardiomyopathy, however there are similaritines of CNS activation with catecholamine driven terminal vascular changes.[16]

2. Challenges in Using Imaging Cues to Define MSIMI

Numerous studies have demonstrated that MSIMI has distinctions in clinical presentation and prevalence from exercise-induced angina. Early studies using ECG monitoring suggested that physiologic factors perturbed in exercise-induced ischemia differ from that due to emotional triggers, though they have some overlap.[17] In ecological Holter studies, over 75% of the total ischemic episodes in CAD patients occurred during routine activities, without associated anginal symptoms, and at a significantly lower heart rate (HR) than observed during exercise stress.[18] [19, 20]

There has been a consistent and reproducible observations that the cue of ischemia differs in extent, location, degree, and prevalence in response to MS and to demand triggers within and across subjects.[21] [22] [23] In a series of stable CAD patients undergoing echo imaging to stress triggers, more often patients will show ischemia to MS (up to a quarter) without demonstrating ischemia to demand.[24] This finding was affirmed in the REMIT study wherein ischemia to MS was more common than exercise induced ischemia (43.5% vs. 33.8%, p=0.003) and 70.4% of CAD subjects that demonstrated ischemia to exercise also had MSIMI while only half of those with MSIMI demonstrated ischemia to exercise.[25] Sensitive imaging studies using PET evaluated patients with chronic stable angina who underwent sequential arithmetic stress and exercise stress protocols with resulting perfusion heterogeneity to both stressors, though the ischemic distribution did not demonstrate strict concordance of size or location of defects between the two methods of stress.[26] FIGURE 3[27]

Despite MSIMI being common, detection of MSIMI using conventional stress testing imaging tools has resulted in reports of variable prevalence and differences in regional vs. global localization. Work by our group demonstrated a 46% discordance in the detection of MSIMI in patients undergoing both echocardiography and MPI with MS trigger resulting in concordant detection of MSIMI by both modalities in 11%, only perfusion defects on MPI in 32%, and only regional or global LV dysfunction on echo in 21% of subjects.[28] While this may be attributed to differences in test characteristics, it is more likely due to a difference in the physiologic target probed by the imaging cue. First, the regionality of wall motion abnormalities or perfusion is particularly problematic as it suggests a differential effect on epicardial territories or myocardial segments despite a well-based foundation that stress globally affects myocardial physiology, if not also systemic biology. Second, a stress induced drop in LVEF on conventional stress testing is considered a high risk feature indicative of severe diffuse obstructive epicardial disease. As such, global LV systolic function in response to MS would be suggestive of a threshold of ischemia that is out of proportion to what is suggested by a lack of overt symptoms and the mild nature of perfusion defects in MSIMI. Third, discordance of imaging cues may represent individual variability in the relative impact of different biologic pathways, highlighting a role for endotyping.

A single imaging cue, as a measure of a physiologic response to stress, may not provide a wide enough lens to assess the totality of the CV effects. Cues can be categorized by regionality (change in epicardial caliber, regional wall motion abnormalities (RWMA), regional perfusion defect) vs. global myocardial (change in LV systolic function or size,

global coronary flow reserve (CFR)), coronary macrovascular vs. microvascular vasomotion, and cardiac vs. peripheral vascular effects. Table 1 Given an appreciation of the multiple ways in which MS alters CV measures and imaging cues [29] and the limited applicability of the concept of the ischemic cascade that is anchored in the construct of epicardial CAD, the naming of this phenomenon as MSIMI may not be sufficient to describe the breath of MS-induced perturbations of the CV system. While we will continue to use the MSIMI term in this conversation for familiarity, we recognize that the imaging cues of MSIMI-perfusion heterogeneity and LV function changes- may reflect physiologic alterations that represent both ischemia and non-ischemic phenomenon.

3. Characterization of the vascular response

Studies of MSIMI have focused on cardiac changes using tools interpreted through the framework of demand ischemia in epicardial obstructive CAD, though the systemic effect of stress transduces changes throughout the vascular tree. Unlike patterns seen in conventional stress testing, recent work has affirmed a lack of concordance of MS provoked myocardial perfusion heterogeneity with severity of epicardial obstruction.[8, 30] Angiographic assessment of the epicardial artery demonstrated that MS provocation resulted in dynamic epicardial vasoconstriction in minimally diseased arteries with non-obstructive plaque, as compared to the expected vasodilation in normal epicardial arteries.[31] The vasomotor response of the epicardial arteries correlated with acetylcholine challenge, linking endothelial dysfunction with abnormal vasoconstriction. Perhaps, dynamic changes in the epicardial artery may account for the regionality of the MSIMI signal in certain individuals.

Further work in the invasive laboratory using Doppler measures of intracoronary blood velocity demonstrated that the magnitude of the reduction in coronary flow in the setting of MS was likely secondary to an increase in resistance in the coronary microvascular bed.[32] The differential effects of MS and vasodilator stress on perfusion in coronary distributions subtended by angiographically defined epicardial arteries without obstructive disease was assessed non-invasively using N-13 ammonia (NH_3) PET with measures of absolute MBF, CFR, and derived distal pressures.[33] There was a decrease in MBF at peak MS in regions subtended by arteries with non-obstructive CAD, as compared to an increase in regions subtended by epicardial arteries with a moderate or greater stenosis or normal controls (0.68 ml/min/g vs. 0.75 ml/min/g vs. 0.8, $p<0.05$) and a decrease in CFR at peak MS (1.1 vs. 1.3 vs. 1.5, $p<0.05$). In contrast, there was augmentation in absolute MBF and CFR in response to vasodilator stress in all 3 groups ($p<0.05$). Thus, the role of the microvasculature, likely the pre-arteriolar vessels, was highlighted by an increase in derived distal pressures during MS only in territories subtended by vessels with non-obstructive CAD.

While much of the previous work in MSIMI has used qualitative assessment of flow heterogeneity on MPI, MS-induced changes in sub-endocardial blood flow may be missed due to limited spatial resolution and dependence of partial volume effect.[34] MPI, notably using PET, can be used to measure absolute MBF during MS which may provide increased sensitivity to detect regional and global reductions in flow in response to MS. Alternative techniques such quantitative CT myocardial perfusion, quantitative MR myocardial perfusion, or hybrid nuclear imaging with first pass CT perfusion particularly

with use of particular PET tracers (^{19}F-Flupiridaz or ^{13}N-NH$_3$) may allow measurement of the transmural perfusion gradient (TPG) and ratio (TPGR), to relate sub-endocardial and sub-epicardial perfusion at rest and stress.[35, 36] To understand use of MBF, CFR, TPG, and TPGR, further work needs to be performed to identify normal values and reproducibility of measures under a variety of triggers.

Identification of sub-endocardial hypoperfusion or of systolic dysfunction with MS may not necessarily be indicative of myocardial ischemia due to insufficient MBF, but rather alterations in peripheral vascular tone in response to MS. Work from the PIMI investigators and our group demonstrated that MS was associated with a significant increase in systemic vascular resistance (SVR) - afterload, with a strong inverse correlation between change in SVR and change in LVEF during MS - as SVR increased, LVEF was reduced. [37] Notably, some healthy individuals demonstrated up to 15% decrease in LVEF during MS, with women showing the biggest effect. The drop in LVEF and increase in SVR occurred without discrete regional perfusion deficits, suggesting a global effect on the myocardium notably due to alterations in peripheral vasomotion which is a prominent feature of MS.[37 38]. Even in lessons from conventional stress testing, abnormal rise in blood pressure to an exercise trigger is associated with adverse prognosis, perhaps identifying a marker of abnormal peripheral vasomotion.[39]

Endothelial dysfunction may underlie the systemic vascular response to stress and this peripheral response tracks with myocardial response, thus identifying a peripheral correlate for MS effects on coronary endothelial function and a potential diagnostic target for risk stratification in MSIMI. Initial studies in the periphery demonstrated that MS is associated with flow mediated dilation (FMD) at the brachial artery in healthy vasculature but is blunted in those with hypercholesterolemia and psychosocial features that predispose to MSIMI (hostility, depression in women), suggesting a mediating role of peripheral endothelial function.[40, 41]

Using acetylcholine as a probe of endothelial function in both the coronary and peripheral circulation, investigators in the Mental Stress Ischemia Prognosis study demonstrated that the change in MBF to MS correlates with MBF changes provoked by acetylcholine challenge (r=0.38, P=0.03), while there is a lack of correlation with nitroprusside, a probe of both smooth muscle and nonendothelial dependent vasodilation.[42] This small mechanistic study (n=38) affirms that the predominant global effect of MS is facilitated through endothelial-mediated vasoconstriction in the coronary microvasculature. Additionally, investigators demonstrated a relationship between MS-provoked peripheral vasoconstriction, as assessed by peripheral arterial tonometry, and demand-adjusted measure of coronary microvascular tone (r=−0.60, P=0.004). This peripheral vasoconstriction in response to MS-trigger is associated with a higher risk of adverse CV outcomes (1.77 [95% CI, 1.12-2.80]), a finding that also correlated with norepinephrine, implicating the role of the neurohormonal cascade and sympathetic nervous system.[43] Similarly, peripheral endothelial health is associated with CV events and correlates with epinephrine levels as demonstrated in a cohort of 569 patients with stable CAD in whom brachial artery FMD was assessed before and after MS testing. A MS provoked change in brachial artery FMD was associated with a 78% increase in CV events at 3 years.[44]

Similar to the extensive work in the area of ischemia with INOCA and microvascular disease, the binary or threshold signal used to interpret standard-of-care MPI studies fails to capture global and more subtle reductions in MBF that may occur along the spectrum of physiologic changes due to MS-a spectrum inclusive of degree, quality, chronicity, and the vascular response. The model of dynamic endothelial-dependent MS–induced microcirculatory dysfunction in MSIMI aligns with the current understanding of symptomatic nonobstructive CAD in women,[45] and there is an emerging intersection between the association of heightened ischemic response to MS triggers in young women with CAD and the presentation and prevalence of INOCA in these patients.[46] Studies such as CorMicA, which stratified patients based on invasive coronary functional testing with acetylcholine and thermodilution for flow reserve/microvascular resistance, have shown that tailoring medical therapy based on specific INOCA endotypes improves symptoms,[47] and hopefully long-term outcomes.[48] As we begin to unravel the overlapping syndromes of MSIMI, INOCA, and microvascular dysfunction, MS testing might be a useful probe of the microvasculature and abnormalities in endothelial function that could further phenotype patients with anginal syndromes. Similarly the identification of specific endotypes in MSIMI may offer a promising construct for personalization of therapies given the presumed heterogeneity in the relative contribution of the multiple biologic pathways.

4. Potential Targets and Treatments

There have been several promising clinical intevention trials to reduce the likelihood of MSIMI under stressful circumstances. This approach using cognitive behavior therapy for stress management has shown promise for reducing the likelihood of MSIMI under controlled laboratory conditions and in the natural environment, and for reducing the risk of major adverse cardiac events that has been found to accompany MSIMI. In a series of studies with moderately sized samples of 100-150 CAD patients, Blumenthal and colleagues have repeatedly shown that augmentation of a standard cardiac rehabilitation-based exercise program with cognitive behavioral stress management training conferred impressive relative risk reduction of events compared to standard cardiac rehabilitation (9.1% x 20.6% at 3 years, RR, 0.26; 95% CI, 0.07-0.90; p=0.03) and stress management training compared to standard cardiac rehabilitation (18% versus 33% at 5 years; hazard ratio=0.49; 95% confidence interval, 0.25–0.95; P=0.035). [49, 50 51] FIGURE 4[51] There was also significantly lower 5-year healthcare utilization and cost associated with the stress management treatment arm. Despite these impressive results, testing of implementation strategies for dissemination of these practices into routine clinical care remains to be accomplished.

The REMIT study demonstrated an alternate, pharmacologic approach that targets central processes in MSIMI. In this study, CAD patients with MSIMI diagnosed by global or regional systolic dysfunction on echocardiography demonstrated that randomization to escitalopram, an SSRI, reduced MSIMI at 6 weeks compared to placebo (OR of not having MSIMI at 6 weeks 2.62 [95% CI, 1.06 to 6.44]; P=.04).[50] The statistical significance of this finding was lost with adjustment for resting systolic dysfunction and gender. Additionally, a number of study participants were re-classified as not meeting the key inclusion criterion of baseline MSIMI when baseline MS-echocardiography was reviewed. In a randomized controlled trial (n=300) of post-ACS patients with depression, 24 weeks of SSRI treatment

was associated with lower risk of events at 8 years as compared to placebo (hazard ratio 0.69; 95% CI, 0.49-0.96; *P* = .03)[52], though more research is needed to demonstrate efficacy and safety in a population without depression and in the context of dual anti-platelet therapy. Use of a serotonin modulating agent highlights the wide and overlapping physiologic changes induced by central processes which may also may produce an effect on a peripheral/terminal processes. Beyond neurons, serotonin reuptake transporter (5-HTT) is active in platelets, a pathway by which serotonin affects platelet aggregation. There have been limited controversial reports of excess bleeding and risks associated with SSRI use, though use of SSRIs are generally shown to be safe for CAD patients.[53, 54]

Potential peripheral targets are also suggested by the *consequences* of the fight-flight autonomic and HPA axis responses to stress. Autoregulation of MBF and microvascular resistance is mediated by the sympathetic nervous system, which directly innervates the coronary arterioles via α-adrenergic receptors, and the myocardium via β-adrenergic receptors.[14] MBF and microvascular resistance are also under the influence of the circulating catecholamines, which in response to MS among patients with known CAD can precipitate coronary vasoconstriction.[55] The effect of MS on peripheral endothelial function are pronounced and prolonged, with impaired brachial artery hyperemic flow being observed for up to 90 minutes.[56, 57] This effect is accompanied by an increase in circulating endothelial microparticles and a decrease in circulating endothelial precursor cells – again, evidence of endothelial cell damage and reduced restorative capacity[58] and appears in part to be mediated by endothelin-1 (ET-1).[59] Overlapping pathophysiologic pathways in MS affect ET-1 through, 1) ET-1 can potentiate vasoconstriction to norepinephrine,[60] and 2) withdrawal of cardiac vagal control may disinhibit the release of ET-1 into the circulation.[61] Additionally, MS is associated with an increase in inflammatory and prothrombotic markers, factors that are associated with endothelial dysfunction and atherosclerotic plaque development.

Despite the broad and varied physiologic processes that connect central activation with peripheral changes, each of which may be a potential therapeutic target, investigation into pharmacotherapeutic interventions directed to the peripheral processes that appear to play a role in MSIMI are required. Small, older cross-sectional studies assessed the effect of metoprolol, atenolol and nifedipine on MS induced RWMA without definitive results.[62, 63] With much of the MSIMI research having been conducted with patients remaining on their optimal medical therapy, and use of standard agents, beta-blockers, ACE inhibitors, statins does not appear to affect the prevalence of this ischemic presentation.

With the expansion in our understanding of MS and its broad effects on the CV system, further work is needed to identify possible targets along the physiologic pathways that transduce central stress on the CV system. Candidate therapeutic may target traditional CV risk factors, associated with endothelial dysfunction, catecholamaine responsiveness notably alpha and beta blockers, traditional vasomotion targets (calcium channel blockers, nitrates, phosphodiesterase inhibitors), novel targets of vasomotor tone (ET-1 blockers, rho kinase inhibitors), platelet activation and aggregation, and inflammatory pathways.

As we consider the role of therapeutic interventions, approaches may vary from assessment of single agent to a "kitchen sink" approach to a tailored, personalized approach that targets the specific physiologic pathways that have been demonstrated to be perturbed under MS provocation. In order to move forward to consider therapeutic intervention and assessment of efficacy of the intervention, diagnostic identification of MSIMI must be implemented in our clinical practice despite the well-recognized limitations of our traditional imaging techniques.

5. Implementation into standard care

In order to advance implementation of this science and build the framework for mitigation of CV risk associated with MS, we must develop a better understanding of the relationship between (1) the biologic substrate-the patient, (2) the patient's ecologic experience, and (3) their response to stress in relation to symptoms, underlying CV physiology, and broader systemic biology. Notably, arguments have been put forth that there is little merit in assessment of MSIMI as effective treatments have not been established. Rather, the foundations of conventional stress testing began with its power to diagnose disease and provide prognosis.

And so, a path forward in MSIMI must apply familiar concepts that have shaped conventional stress testing for epicardial obstructive CAD: (1) define the target disorder, (2) apply Bayes Theorem with established models of pretest probability of disease, (4) measure stress trigger, (3) identify imaging cue with established relationship of imaging cue to prognosis, patient-reported outcome, and target disorder, and (4) use of imaging cue to inform management decisions.[64]

Definition of the target disorder should begin with an untangling and recognition of overlaps and differences between syndromes/presentations of MSIMI, atypical angina, microvascular dysfunction, and INOCA. Much of the initial basis of MSIMI studies evaluated cohorts of patients with stable CAD or post-ACS, who have evidence of MSIMI that is often clinically silent. In this population, as described in the CLARIFY study, patient-reported anginal symptoms are associated with worse clinical outcomes regardless of the presence of myocardial ischemia using conventional stress testing, whereas ischemia, as a marker of epicardial obstructive disease, alone was not.[65]

The clinical cohort in whom microvascular dysfunction and/or INOCA is described have been referred for conventional evaluation because of a cardiac symptoms and in whom obstructive epicardial CAD has been excluded. This may have particular relevance in women as over half of women in the WISE study with symptoms suggestive of myocardial ischemia did not have obstructive CAD, thus suggesting alternative mechanisms for symptoms.[66] Additionally, there is a broad and increasing population of patients referred to conventional stress testing with atypical symptoms for whom diagnosis and management remain unclear. A sequential cohort of 39,515 patients undergoing MPI from 1991 to 2009 demonstrated a shift in presenting symptoms with a decline in typical angina (12.7% vs. 1.9%) and an increase in atypical angina (24.8% vs. 59.6%).[67] Gender may be a key factor in these overlapping disorders. In a cohort study of patients undergoing both conventional stress

testing and MS testing, women experiencing angina in the month prior to enrollment demonstrated almost double the probability of MSIMI (19% vs 10%, adjusted prevalence rate ratio, 1.90; 95% confidence interval, 1.04-3.46), as compared to those without anginal symptoms: a finding not seen in men.[68]

The next important steps towards clinical implementation is the development of a model of pretest probability of MSIMI to both identify an at-risk patient and to inform interpretation of imaging cues. Use of previously identified variables and broad collection of triggers, stress exposure, narrative description of symptoms obtained at the time of presentation, along with results of diagnostic imaging and comorbidities should be combined to develop a predictive model. Beyond predicting probability of MSIMI, a useful model will also predict likelihood of an alternative diagnosis. The fitness of the model will need to be assessed in a range of patient cohorts and care settings.

A risk model is intrinsic in the design of studies to compare a MS-informed strategy to standard of care in which this MS-informed strategy incorporates the risk model 'upfront', to inform test selection: MS-testing as initial test vs. conventional stress testing vs. MS-testing in addition to conventional stress testing. As described earlier, the challenge is recognized that there are intrinsic differences in the MS-provoked imaging cues obtained in the variety of diagnostic tests, though the association with outcomes remains consistent. Outcomes of interest beyond prediction of events may include patient-reported outcomes, use of goal-directed medical therapy, and resource utilization.

With demonstration that a MS-informed strategy can be implemented and is prognostically relevant, there is the opportunity to probe the multiple biologic pathways that transduce MS. Phenotypes can be developed through assessment of broad variables incorporated in pretest probability models. Endotyping can be developed through focused cardiac and peripheral physiologic studies in patients with elevated risk for MSIMI which may inform the use of targeted, personalized treatment pathways. The understanding of the relative heterogeneity or homogeneity of MS-induced perturbation will inform therapeutic approaches to risk mitigation. These diagnostic pathways must be built before we can perform studies of therapies for MSIMI.

We expect shared lessons from studies of microvascular disease and MSIMI. While many of the past and the proposed MSIMI studies utilized cardiac imaging, further studies may elucidate less invasive and less expensive diagnostics that can assess likelihood of MS-induced perturbations of CV function and, perhaps, will identify those at risk for microvascular dysfunction.

Education and adoption of a multi-disciplinary scope is integral to the success in implementing constructs derived from our understanding of MSIMI. Medical training, along with primary and secondary CV prevention programs, should incorporate health psychology and public health to address the intersection of biology and psychosocial determinants of health, particularly given evidence supporting stress management training in the cardiac rehabilitation setting.

Conclusion:

The spectrum of the scientific enterprise from fundamental physics to various clinical translational scenarios is based upon a similar challenge: a phenomenon is defined by how it is observed and how it is measured.[69] It is an uncommon that the tools to identify, target, and treat the unknown health needs within the population match the calling of a particular professional community. In the absence of that community's involvement, more people suffer. A substantial portion of stable CAD patients do not exhibit ischemia to exercise yet have myocardial ischemia in response to standard laboratory induced MS protocol and have a worse prognosis. The persistence of the framework of exercise induced ischemia applied to the stressful cognitive trigger biases our understanding of expected outcomes and imaging cues. Herein we outlined the consideration from the brain to cardio/peripheral vascular responses to support this needed paradigm change. A recognition of the core differences between emotion and exercise triggers, that of central neurohormonal activation and systemic vascular perturbations require a tailored strategic approach and is supported by emerging studies.[44] Paired with assessment of psychosocial determinants of health, an understanding of gender difference, diagnostic identification and treatment of MS-induced cardiovascular perturbations, a foundation based upon broad empiric evidence will facilitate the integration into standard care to address a pervasive, often subclinical determinant of outcome.

Acknowledgments

Abbreviations:

ACS	acute coronary syndrome
CAD	coronary artery disease
CFR	coronary flow reserve
CNS	central nervous system
CV	cardiovascular
ET-1	endothelin
FMD	flow mediated dilation
HR	heart rate
INOCA	ischemia and no obstructive coronary artery disease
LV	left ventricle
LVEF	left ventricular ejection fraction

MBF	myocardial blood flow
MI	myocardial infarction
MPI	myocardial perfusion imaging
MS	mental stress
MSIMI	mental stress induced myocardial ischemia
^{13}N-NH$_3$	^{13}N-Ammonia
PET	positron emission tomography
RWMA	regional wall motion abnormality
SPECT	single photon emission computed tomography
SVR	systemic vascular resistance
TPG	transmural perfusion gradient
TPGR	transmural perfusion gradient ratio

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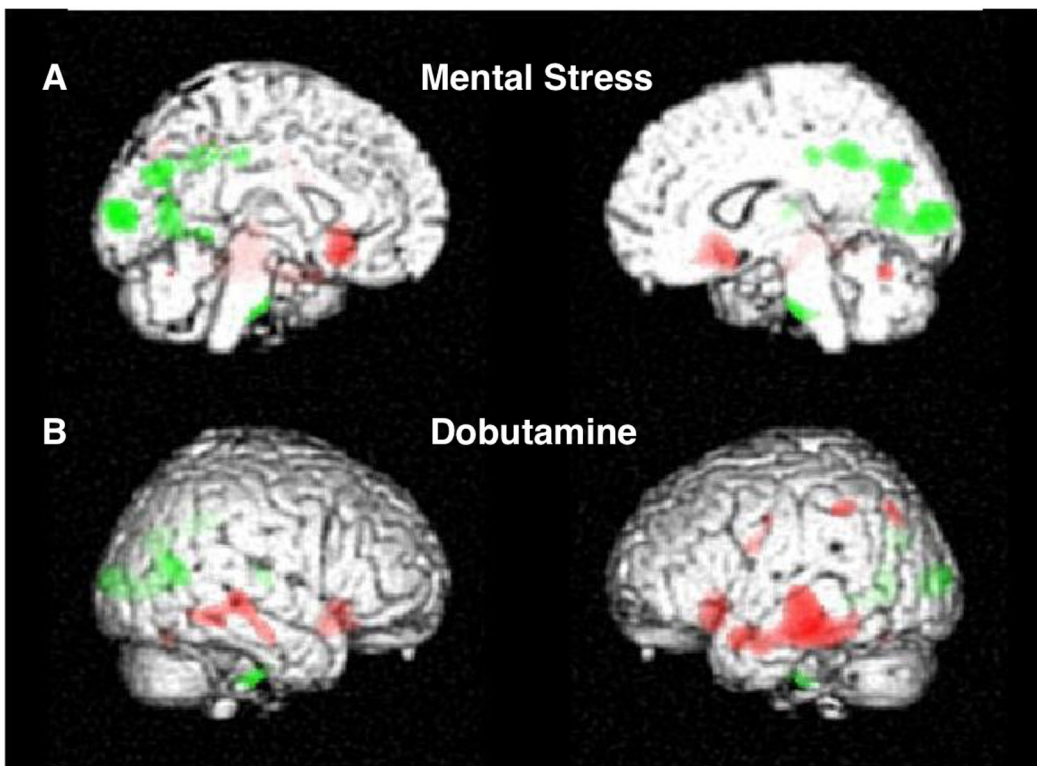**Figure 1:**
Subjects with CAD underwent simultaneous measurement of cerebral blood flow and cardiac function during (**A-top panel)** arithmetic mental stress (MS) and (**B-bottom panel**) dobutamine stress (DS). Cerebral hyperactivation (green) and deactivation (red) in response to MS (**A-top panel**) and DS-demand (**B-bottom panel**).[12] Activation (green) during MS occurs in deep limbic structures, which transduce visceral effectors to the heart and significantly heightens neurohormonal activation. Concurrently, there is deactivation (red) in the frontal lobes. Activation during DS does not occur in deep limbic structures, instead occurs in the somatosensory areas referable to situation and environmental awareness, without activation of areas related to emotion and memory. *Reproduced with permission from Springer Nature and Copyright Clearance Center.*
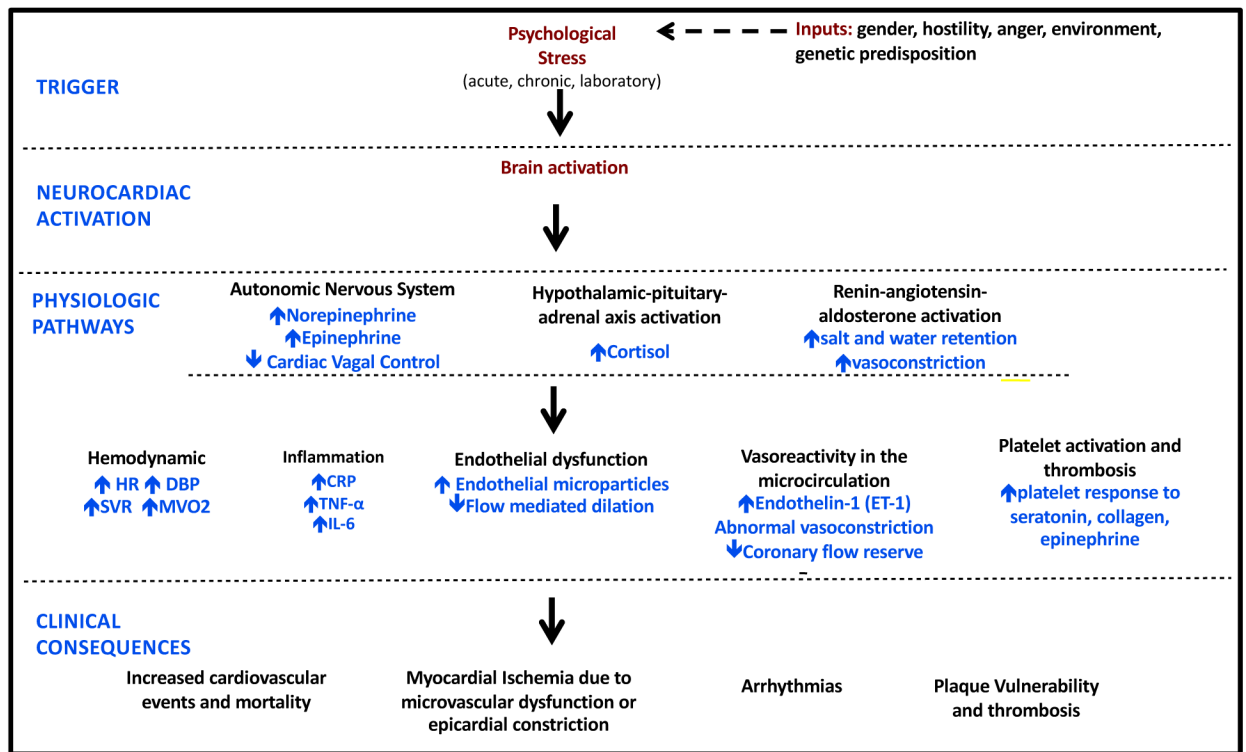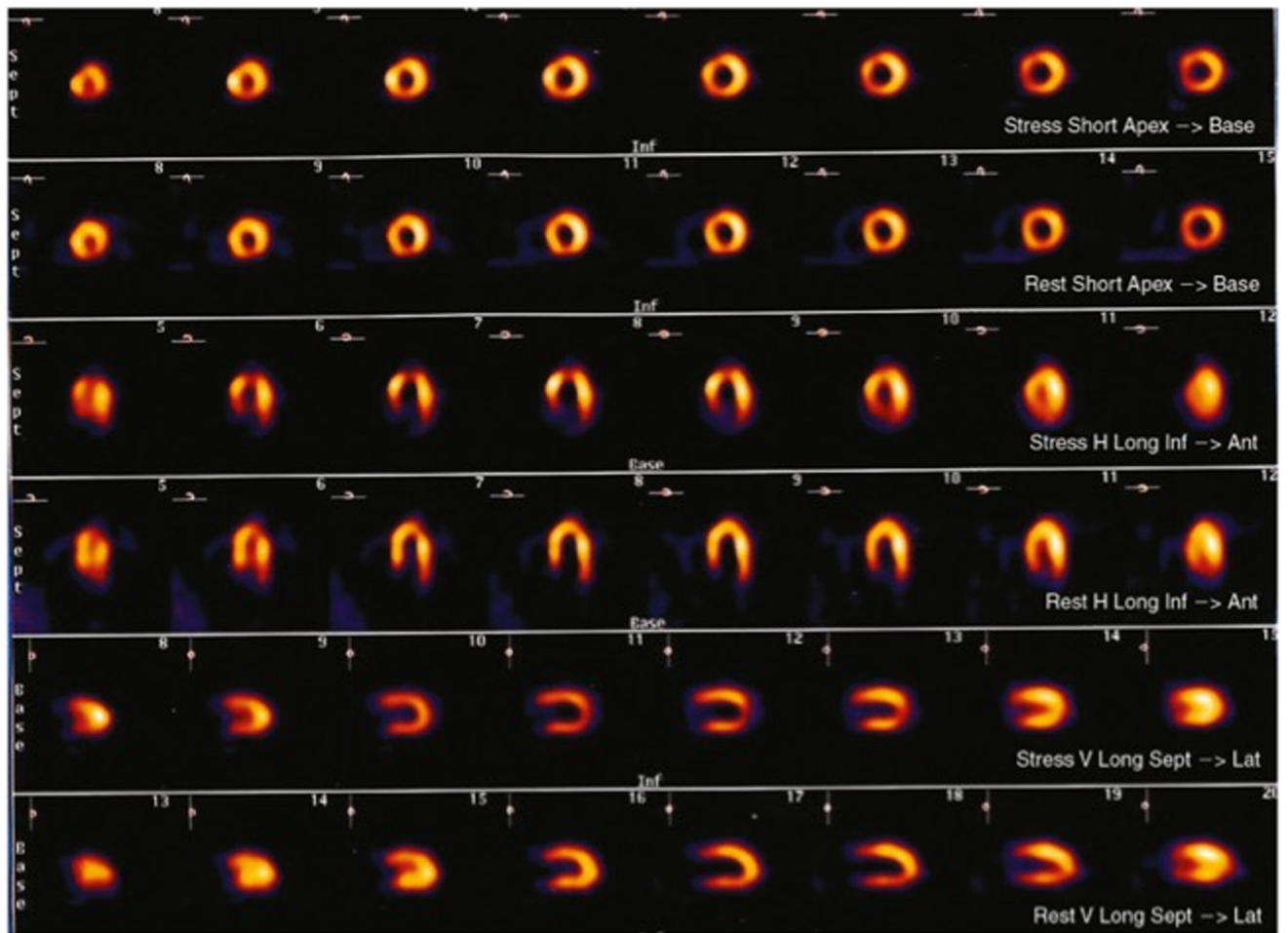
FIGURE 2: Proposed pathophysiologic mechanism of MSIMI.
HR, heart rate, SBP, DBP: diastolic blood pressure, SVR: systemic vascular resistance, CRP: C reactive protein, TNF-α: tumor necrosis factor alpha, IL-6: interleukin-6.

FIGURE 3:

Mental stress technetium-99m tetrofosmin single-photon emmision tomography (low-dose rest, high-dose stress) images from a patient who had an apical perfusion defect, consistent with mental stress-induced ischemia (*top*) compared with resst images (*bottom*). Ant, anterior; Inf, inferior; Lat, lateral; Sept, septum. [27] *Reproduced with permission from Elsevier and Copyright Clearance Center.*
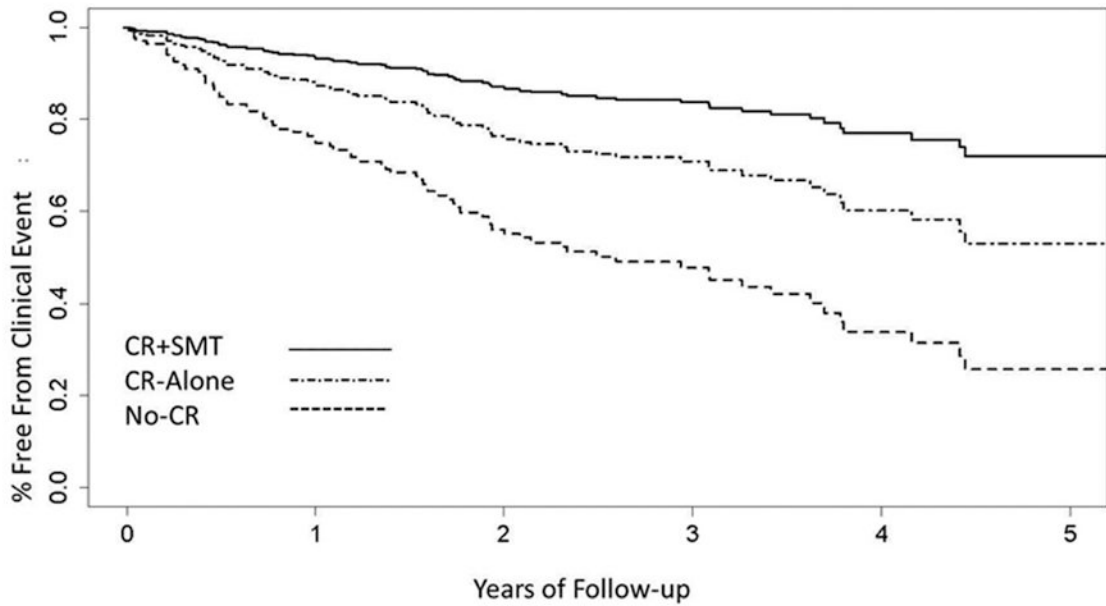
FIGURE 4: Association of cardiac rehabilitation and stress management with cardiovascular outcomes in patients following acute coronary syndrome.

Cumulative time-to-event curves for clinical events in the CR+SMT, CR-alone, and No-CR groups. Clinical events included all-cause mortality, myocardial infarction, cardiac or peripheral vascular intervention, stroke/TIA, or unstable angina requiring hospitalization. Participants in the CR+SMT were at significantly lower risk of clinical events compared with the CR-alone group (HR= 0.47 [0.24, 0.91], P = 0.025). Both CR groups had lower event rates compared with a non-randomized, matched No-CR control group (HR = 0.35 [0.22, 0.56], P < .001). Number at risk represents participants with follow-up data for clinical events who had not yet had an event at years 0, 2, and 4.[51] *Reproduced with permission from Wolters Kluwer Health, Inc. and Copyright Clearance Center.*

Table 1:

Characteristics of Imaging Cues of MSIMI and Associated Physiologic Target

Measure of MSIMI	Diagnostic technique	Probable target	Vascular compartment	Regionality	Setting
ST segment depression	Holter monitoring ECG Wearable devices	Cardiac ischemia	Cardiac • Epicardial • Cardiac microvasculature	Regional or Global Non-transmural	Ecologic Laboratory Non-invasive
Fall in LVEF >5%	Nuclear VEST ERNA Echocardiography	Systolic dysfunction Due to: (1) Global Ischemia (epicardial or microvascular) (2) Peripheral vascular tone and SVR	Cardiac • Epicardial • Microvasculature Systemic • Peripheral macro-vasculature	Global Transmural or non-transmural	Ecologic Laboratory Non-invasive
New regional wall motion abnormality	Echocardiography	Regional ischemia	Cardiac • Epicardial	Regional Transmural or non-transmural	Laboratory Non-invasive
Reversible segmental hypoperfusion	Nuclear perfusion imaging (SPECT, PET), qualitative	Segmental ischemia or segmental heterogeneity in vasomotor response	Cardiac • Epicardial • Microvasculature	Regional Likely non-transmural	Laboratory Non-invasive
Dynamic epicardial vasoconstriction	Coronary angiography	Epicardial artery reactivity/spasm	Cardiac • Epicardial artery • Endothelial vs. non-endothelial mechanism	Regional	Laboratory Invasive
Coronary flow at peak stress and reserve	Quantitative PET (MRI perfusion, CT perfusion) Invasive measure of intracoronary blood velocity	Global or segmental ischemia or alteration in vasomotor response Segmental or global abnormal change in flow	Cardiac • Epicardial • Microvasculature (with epicardial disease excluded by angiography) *Exclude systemic effect by adjustment by RPP*	Regional and Global	Laboratory Non-invasive or invasive
Coronary microvascular resistance	Index of Microcirculatory Resistance (IMR)	Coronary microvascular tone	Cardiac • Resistance vessels or microcirculation	Regional	Laboratory Invasive
Systemic vascular tone	Calculated SVR Peripheral arterial tonometry	Peripheral macrovascular and microvascular tone	Systemic • Macrovasculature • Microvasculature		Laboratory Ecologic?
Endothelial Function	Brachial artery reactivity Peripheral arterial tonometry	Endothelium	Systemic • Macrovasculature • Microvasculature		Laboratory