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Psychological Stress and Induced Ischemic Syndromes

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Introduction

Early observations suggested that intense emotions could be a powerful trigger of angina pectoris, and indeed, myocardial infarction, as described in the early 20th century by Osler[1]. Case reports and clinical research further indicated that ECG changes indicative of impaired cardiac function could be provoked by psychological stress in patients with coronary artery disease (CAD)[2]. Testing the effects of *physical* stress – e.g., exercise – on cardiac function is a hallmark diagnostic approach for identifying obstructive coronary atherosclerosis, and mirroring this approach, researchers have over the past 3 decades sought to assess the effects of *psychological* stress in much the same way. In this paper we will first provide a concise review of research on the phenomenon of myocardial ischemia provoked by *psychological* stress, following this with a review of research that has emerged over the past year, and concluding with a discussion of outstanding questions that are important to clinical cardiology.

Background

In an early study using Positron Emission Tomography Deanfield et al.[3] demonstrated that a significant decrement in myocardial blood flow could be induced by the performance of a demanding mental arithmetic task in 12 of 16 patients with stable angina. Of note, only 6 of these 12 evidenced an ECG change during arithmetic stress, and only 4 reported their typical angina symptoms, yet all evidenced both during exercise stress. While showing that mental stress could provoke a decrement in myocardial blood flow, the absence of other characteristics of ischemia – ECG changes and chest pain – provided a signal that the pathophysiology underlying mental stress provoked ischemia likely differed from that underlying exercise provoked ischemia. Indeed, most studies since then have also shown that mental stress induced ischemia (MSI) - regardless of how it is indexed - also occurs at a lower double product than exercise induced ischemia, hence at a lower myocardial oxygen demand[4]. Thus, many questions remained regarding how best to index MSI, along with questions of pathophysiology, clinical significance, whether it could be reduced by pharmacologic and/or behavioral interventions, and the physiological and psychological characteristics of patients most susceptible to MSI.

Human and Animal Rights and Informed Consent
This article does not contain any studies with human or animal subjects performed by the author.

Conflict of Interest
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As the field developed, it continued to mirror clinical cardiology in methodology. Thus despite the more precise demonstration of ischemia by myocardial blood flow decrement shown by Deanfield et al[3], researchers moved to the assessment of ventricular performance as the index of ischemia, as this was more widely used in cardiology practice, and when using ultrasound – cardiac ECHO - allowed for repeat testing using several mental stress tasks sequentially. A paradigm for MSI research was established involving: (1) use of left ventricular performance in response to mental stress as the marker of ischemia; (2) examining responses to a series of standardized laboratory stressors such as public speaking or mental arithmetic; and (3) defining a study population consisting of patients with known coronary artery disease (e.g., ischemia on exercise or pharmacologic stress testing, previous ACS, and/or previous revascularization). What followed was a series of studies by various research groups, including the NHLBI funded PIMI multi-site series[5], each of which demonstrated that mental stress could induce decreases in left ventricular ejection fraction and/or a new wall motion abnormality in patients with known coronary disease, with these effects evident in between 30–60% of stable patients[4]. The results of these studies also pointed to aspects of pathophysiology and risk, highlighting to various degrees the poorer prognosis associated with MSI[6–8], and the risk imparted by hostility and anger as trait characteristics[9], among other things. Key question remain concerning this ischemic syndrome, including issues of assessment, pathophysiology, risk, and treatment.

Recent Findings

The past year has seen the publication of important papers on MSI that are directed to underlying pathophysiology, and to novel treatment approaches. These are reviewed below.

The REMIT Trial

The baseline description[10] and primary findings[11] from the largest single study of MSI to date (N=310), the Responses of Myocardial Ischemia to Escitalopram Treatment (REMIT) Trial were published this year. The REMIT placebo controlled randomized trial was designed to investigate whether treatment with escitalopram, a selective serotonin reuptake inhibitor (SSRI), can improve MSI[12]. The REMIT trial utilized myocardial performance (wall motion abnormality, left ventricular ejection fraction) assessed by echocardiography as the index of ischemia, and sequential administration of 3 mental stress tasks.

The REMIT Baseline report confirmed earlier research by showing the lack of complete concordance between ischemia provoked by exercise vs. mental stress, with 24% showing ischemia to both, 20% to mental stress alone, and 10% to exercise alone; of those with exercise ischemia, 70% had MSI, while 55% with MSI also had exercise ischemia. In addition, lower hemodynamic responses were observed during ischemia induced by mental vs. exercise stress. This study also provided new insights regarding the apparent greater risk of MSI among women, and among single men.

The REMIT Outcome paper[11] reported that of the 335 patients who underwent mental stress testing, only 132 were identified as having MSI, and 127 randomized, with 112 completing the trial; all 127 however were included in the intention to treat analysis. At the end of the 6-week treatment window 82.5% of those on placebo and 65.8% of those on escitalopram

demonstrated MSI on repeat testing. While significant in unadjusted multiple imputation models (p=0.04), the results were only marginally significant in models adjusting for sex and baseline ventricular function (p=0.06). While there was an overall significant reduction in the hemodynamic response to mental stress for patients on SSRI at 6-weeks, there were no significant group differences in ventricular function at rest or during mental stress.

Psychological factors were also a focus of the REMIT Trial, including depression, which has repeatedly been strongly linked to recurrent-ACS and mortality risk[14–15]. Boyle et al[13] reported that in REMIT, depression assessed by the Beck Depression Inventory (BDI) version II - but not the Centers for Disease Control Depression Scale - was marginally associated with probability of MSI, after adjustments for age, sex, resting LVEF, and resting wall motion (p = .053). By linking depression to the occurrence of MSI, these investigators expanded the psychological factors that increase risk of MSI beyond anger as previously reported[9], while also providing evidence consistent with the hypothesis that at least part of the risk of ACS recurrence/ mortality associated with depression may be attributable to risk for MSI.

Despite the baseline finding of a link between depression and risk for MSI – and the fact that escitalopram is an SSRI antidepressant medication, there was no effect of treatment in the REMIT trial reported for depression, or for measures of anxiety, perceived stress, or hostility. Patients in the escitalopram group felt significantly more in control and calmer than those in the placebo group during mental stress testing at 6-weeks, though there were no differences in the negative emotional responses to mental stress.

The REMIT Trial was an important step in promoting an understanding of MSI as an ischemic phenomenon, with regard to pathophysiology, markers of risk, and potential promising treatments. That being said, there were 2 critical aspects of the overall methodology – the use of myocardial performance vs. perfusion as the marker of ischemia, and the use of 3 sequential mental stressors with merely 6 minutes of rest between them – that raise important tissues and temper enthusiasm. We discuss these issues and their implications below.

MSI Pathophysiology

In previous research[15], the peripheral vascular response to emotional stress was better able to predict a myocardial perfusion defect during this stress among patients taking vs not taking angiotensin converting enzyme (ACE) inhibitors, with 90% accuracy in predicting the patients who *did not* demonstrate this flow defect. Following upon this finding, Ramadan et al[16] examined whether ACE inhibition “protected” patients from a myocardial perfusion defect during mental stress. In a retrospective analysis of data from a sample of 218 patients with clinically stable CAD, these investigators found that a perfusion defect during mental stress was less likely to occur in patients taking ACE inhibitors (13% vs. 24%; p = .030), but that there were no differences in perfusion defect during physical stress between those taking and not taking ACE inhibitors (39% vs. 35%, respectively). It is important to note however, that only 40 patients (18%) overall demonstrated a myocardial perfusion defect during mental stress, (37% demonstrated a perfusion defect during exercise stress) and this prevalence of MSI is very low, being only approximately one-third of what is typically

reported in the literature. Also of note, those taking vs. not taking ACE inhibitors showed a significantly greater diastolic blood pressure (DBP) response to mental stress, with no other hemodynamic indices differing. In addition, there was no correlation during mental stress between the sum myocardial perfusion defect score (SDS) and any hemodynamic indices for those taking ACE inhibitors however, there was a significant correlation between DBP and SDS for those not taking ACE inhibitors. In their discussion, the authors note that ACE inhibition may protect against MSI because of effects on endothelial function[17], and epicardial and/or coronary microvascular vasomotion, each of which can become compromised during mental stress[18].

It is also interesting to consider that in REMIT, patients with MSI were *more* likely to be taking ACE inhibitors[13]. This disparate finding compared to that by Ramadan et al[16] may reflect the difference in using ventricular function vs. myocardial perfusion as the index of ischemia. While ACE inhibition may directly affect myocardial blood flow under conditions that influence coronary vasomotor tone as is the case during mental stress, other factors not directly related to ischemia per se may still actively influence ventricular performance.

MSI, CAD Burden, & Microvascular Function

Myocardial ischemia is defined by insufficient myocardial oxygen supply for a given demand, with the insufficiency usually caused by a static, flow limiting/obstructive atherosclerotic plaque in a large coronary vessel. This model of CAD guides disease management – e.g., the identification and "opening" of the obstructive plaque, either by percutaneous or surgical revascularization. In contrast to this traditional model, two small studies[18–19] have previously provided evidence that MSI can – and perhaps often - occurs in coronary distributions *without* a flow limiting atherosclerotic plaque. Another paper by Ramadan et al[20] published in the past year expands upon this finding, providing further evidence that MSI represents a phenomenon of *dynamic* coronary obstruction. In this study, the investigators used prior coronary angiography to assess the extent/severity of atherosclerosis, while also performing myocardial perfusion assessment under conditions of rest, and both physical and mental stress. The authors also assessed the peripheral vascular response to stress using the EndoPAT™ (Itamar, Israel). This device measures beat-to-beat pulse wave amplitude (PWA) and generates a ratio of PWA during stress and rest that has previously been correlated with coronary vascular performance[21]. A lower ratio corresponds to vasoconstriction and predicts a myocardial perfusion defect during mental stress[15]. In pooled analysis of data from 384 patients, the extent and severity of coronary stenosis correlated significantly with myocardial perfusion defect at rest and during exercise stress (all p=0.001), as expected. In contrast, the correlation of extent and severity of coronary stenosis with perfusion defects provoked by mental stress – MSI – was not significant. Indeed, in multivariate analysis, the authors found that the PWA ratio was the only significant predictor of a myocardial perfusion defect during mental stress (p=0.009). This finding highlights that MSI is likely a distinct phenomenon of coronary vasomotion in the presence of atherosclerosis, rather than consequent to threshold CAD severity. It further highlights issues of best approaches to understanding the nature of MSI and has important implications for future research and clinical efforts that we discuss below.

Moving Forward

Indexing MSI

As mentioned above, the current model of CAD that guides patient management focuses on the identification and dilation of obstructive atherosclerotic plaque. Acknowledging the poor prognostic impact of this care model, leaders in Cardiology have recently articulated a new model that shifts the focus from a simple obstructive epicardial plaque to a complex multifactorial process that includes inflammation, coronary microvascular dysfunction, and endothelial dysfunction[22]. This new thinking includes the notion that rather than a single "smoking gun", ischemic syndromes result from a confluence of factors that provoke coronary vascular dysfunction and the consequent mobilization of platelet, vasoactive, and inflammatory pathways[23], with psychosocial factors – including acute stress – contributing to what we call a "perfect storm"[24].

This new "perfect storm" model has important implications for research on MSI moving forward. Throughout the history of research into this phenomenon, there has been a tension surrounding the technique(s) used to index its occurrence. Many studies of MSI have relied upon ventricular performance as the index of ischemia, including REMIT. Given the growing understanding that vascular (dys)function is the nexus of ischemia, and that an increase in coronary vasomotion can create a *dynamic* obstruction and consequent perfusion abnormality (in contrast to the flow heterogeneity that results from a fixed obstruction under demand conditions), the continued use of ventricular function to index MSI creates issues of sensitivity and specificity, as previously reported in the literature[20,25]. The lack of concordance between the two approaches to the assessment of ischemia[25] should not be surprising, since mental stress also induces an increase in peripheral vascular resistance[5] and thus a decrease in ventricular performance may merely reflect an increase in afterload, rather than any decrement in myocardial perfusion. Furthermore with *mental* stress, aspects of the 'ischemic cascade' occur at a comparatively lower myocardial oxygen demand[4], and studies have shown that during mental stress, there is a significant decrement in myocardial blood flow in coronary distributions without flow limiting atherosclerotic plaques[18], and significant coronary vaso-constriction in diseased coronary segments, even those with minor obstructions[19]. These factors highlight that the use of ventricular performance as the index of ischemia represents one significant limitation of findings from the REMIT trial. This is not the first time that a 'standard' marker of ischemia has been found wanting in this area of research. For example, the use of ST-segment change on the ECG was dropped early on, as researchers found that ischemia during mental stress was not only asymptomatic, but rarely accompanied by any ECG change[4]. It is our assertion that moving forward, research on MSI must utilize indices of myocardial perfusion to index the phenomenon, and indeed, emerging methods that utilize cardiac MR may provide new insights because it allows visualization and quantification of differential perfusion at the transmural and subendocardial level, thus greater spatial resolution.

Reproducibility of MSI

For MSI to move from the laboratory setting to the clinical domain where prognostic algorithms can be applied to the care of patients, a reliable and reproducible test must be

developed. Reproducibility of MSI was the focus of two early studies[26–27], and approaches that have the patient describe a previously emotionally upsetting event have demonstrated 90% reproducibility[26].

More recently, others have utilized serially presented stressors (e.g., mental arithmetic, public speaking, emotion recall) with short recovery periods in between[28]. This approach was taken by the REMIT investigators, and represents a second important shortcoming of the REMIT findings. Specifically, research has consistently shown that mental stress provokes significant endothelial dysfunction that can persist for more than 90 minutes after the stressor has ended[29–30]. Thus, when using multiple stressors with short rest periods in between there may be a cumulative effect on myocardial perfusion and, the extent to which this is so reflected, on ventricular function as well. Furthermore, since the experience of psychological stress is highly personal, some individuals may experience each of multiple stressors as "sufficiently" psychologically stressful to affect coronary vasomotor tone and thus myocardial blood flow, while others may find only one such task to have this effect, and still others, neither. It is thus easy to see that when using multiple stressors, interpretation of the data becomes fraught with difficulties. While researchers – like the REMIT investigators – justify this approach by asserting that the use of multiple stressors increases the likelihood that the mental stress protocol will have at least one task that is of sufficient "strength" to provoke ischemia in each of the patients who are so vulnerable, these researchers will often grade the severity of ischemia during mental stress according to how many of the multiple stressor tasks provoke a defect. Thus, if a wall motion abnormality is observed in response to only one task, the severity score is less than if the wall motion abnormality is observed in response to two tasks, and so on. We believe that since psychological stress is personal, the best approach may to have the patient engage in a task that is personally relevant – for example, describing an incident that provoked a strong negative emotional response.

Population heterogeneity and MSI

The populations studied in research on MSI have largely been noted for their heterogeneity, being broadly defined as having "stable coronary disease". The populations include patients who have had previous ACS and/or percutaneous/surgical revascularization, and/or a positive exercise stress test. The time since revascularization has varied considerably, and for the most part a deficit in myocardial perfusion or ventricular function with mental stress has not been accounted for regionally – e.g., in relation to the underlying coronary anatomy. Furthermore, representation by women and minorities in studies has been variable. There is a recognized need to address these issues moving forward. At the same time, the study by Ramadan et al[20] published this year would seem to indicate that the underlying coronary anatomy *does not* account for mental stress provoked perfusion defects, and again, this is consistent with earlier literature[18–19]. It is also intriguing to consider the clinical presentation of chest pain syndrome with non-obstructive atherosclerosis and whether this represents *clinical* MSI, a phenomenon noted previously, particularly among women[31]. With the growing recognition that the standard model of CAD does not lead to sufficient improvement in clinical outcomes and the associated articulation of newer models[22–25], more attention as to the role that emotional factors may play in chest pain syndromes among

patients without obstructive CAD should be a focus of the research on MSI in the coming years.

Summary

There is an ever growing appreciation of the importance that psychological events play in the provocation of ischemic syndromes, whether catastrophic as in the case of ACS, or transient, as in the case of MSI. The past year has seen the publication of several important papers that while illuminating and serving to move the research and clinical agenda forward, also highlight critical issues concerning methods for assessing ischemia, underlying pathophysiology, and the integration of MSI as an ischemic phenomenon into the larger understanding of coronary atherosclerosis. Throughout this paper we have made a number of key recommendations for addressing these issues, while also describing areas – such as non-occlusive coronary disease – where we believe approaches that utilize psychological stress hold great promise as contributing to an understanding of the clinical presentation. We look forward to the work that remains to be accomplished, and the integration of psychologically provoked ischemic syndromes into the clinical domain and the care of patients.

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