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EDITORIAL COMMENT

A Microvascular-Myocardial Diastolic Dysfunctional State and Risk for Mental Stress Ischemia

A Revised Concept of Ischemia During Daily Life*

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To improve our understanding of pathophysiological responses to stress in "triggering" adverse events, stressors have been used in the laboratory to evoke "mental stress–induced ischemia" (MSIMI). Our studies found that patients with MSIMI had increased risk for death (1), and their hemodynamic and neurohormonal changes differed from those observed with exercise (2). Mental stress increased heart rate, systolic blood pressure, cardiac output, and systemic vascular resistance, which correlated with plasma epinephrine increases, whereas during exercise-induced ischemia, systemic resistance declined, with no relationship to epinephrine levels. Interestingly, depression of left ventricular (LV) ejection fraction (EF) was greater with MSIMI than with exercise and was inversely correlated with systemic resistance. Greater increases in epinephrine and norepinephrine occurred during exercise, whereas greater increases in systemic resistance occurred with MSIMI. Thus, arteriolar constriction and minor increases in myocardial oxygen demand occur with MSIMI compared with exercise as adrenal epinephrine secretion mediates, in part, these different responses. Our findings provide a framework for the underlying pathophysiological processes involved in responses to mental stress.

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Hypothetical Mechanistic Construct for Mental Stress Ischemia

The prevailing model suggests that MSIMI results from coronary microcirculatory dysfunction (limited dilation and/or constriction) in the setting of endothelial and/or vascular smooth muscle dysfunction (Fig. 1). Atherosclerosis risk conditions (hypertension, dysglycemia, etc.), via oxidant stress and inflammation, and dysregulation of the central nervous system and hypothalamic-pituitary-adrenal axis likely contribute. The pathophysiological mechanisms of MSIMI are also important in understanding daily-life ischemia, elucidating links with adverse outcomes, and providing direction for appropriate management.

In this issue, Ersbøll et al. (3) report that patients with MSIMI have LV dysfunction in the absence of the mental stress test. This finding suggests that a more chronic form of asymptomatic ischemia is present during their daily lives, extending concepts of the "silent" ambulatory electrocardiographic and LV perfusion abnormalities that we described several decades ago (4,5).

Some Thoughts on the Left Ventricular Dysfunction Observed in Subjects With Mental Stress–Induced Ischemia

It is suspected that stress over time leads to a microvascular-myocardial diastolic dysfunctional state. The pattern of LV dysfunction from microvascular dysregulation is different from that observed with obstructive epicardial coronary disease. The latter initially leads to impaired regional LV relaxation reflected in global relaxation measures and later impaired contraction. Our cardiac magnetic resonance studies indicated that ischemia resulting from

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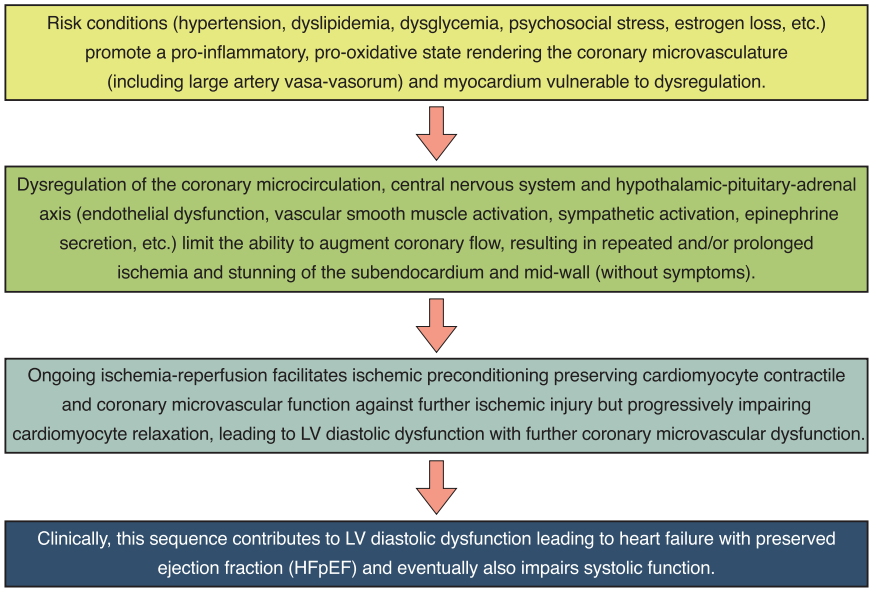

Figure 1. Microvascular Ischemia Hypothesis With or Without Obstructive Atherosclerosis

The prevailing model suggests that mental stress ischemia results from coronary microcirculatory dysfunction (limited dilation and/or constriction) in the setting of endothelial and/or vascular smooth muscle dysfunction. LV = left ventricular.

microvascular dysregulation appears more diffuse but limited to the subendocardium and midwall, with less profound functional alterations.

LV diastolic dysfunction is prevalent in patients with endothelial dysfunction, related to microvascular inflammation or dysregulation, and this likely contributes to heart failure with preserved EF (HFpEF) (6). Although patients with HFpEF have relatively normal EFs, mild systolic dysfunction is not readily detectable with global EF. Parameters used to evaluate LV function in patients with MSIMI and microvascular dysregulation may require constructs derived from measures of diastolic and systolic LV function.

Ersbøll et al. (3) used a composite LV function score, the eas index ($e'/a' \times s'$), which includes both diastolic and systolic measures of mitral annular longitudinal motion. This index incorporates information about systolic dysfunction with increased preload (e'/s') and increased LV stiffness (e'/a'), and a high eas index indicates increased preload with systolic dysfunction, diastolic dysfunction, or both (7). Patients in the present study had MSIMI but also had increased eas indexes at baseline without the mental stressor, suggesting mild diastolic dysfunction. With advanced diastolic dysfunction, e' would continue to decrease and may become out of proportion to the decrease in a' or s', which could lead to reduction in the eas index (8). Although consideration of systolic and diastolic LV function in MSIMI and microvascular dysregulation is important, correlation of eas index with clinical outcomes in patients with MSIMI with more severe LV diastolic dysfunction remains warranted.

Importantly, the eas index evaluates both systolic and diastolic longitudinal LV motion, a critical aspect of efficient contraction (9). Longitudinal motion depends primarily on subendocardial fiber contraction, and deficits in longitudinal contraction are an early marker of damage related to ischemia and/or subendocardial fibrosis in pressure overload (10). Longitudinal contractility is reduced in patients with HFpEF (11). Longitudinal contractility appears to be an appropriate measure of LV function in patients with MSIMI.

Considerations on Need to Revise the Prevailing Microvascular Ischemia Model

First, these patients had ischemia at other times in response to a mental stressor, and their microvasculature and myocardium were likely "vulnerable" to stressors in daily life. One such stressor may be the baseline echocardiographic procedure per se.

Second, such vulnerable patients likely have similar ischemia-related LV functional changes off and on or persisting chronically. If proved, this would require a