The interface of emotion and biology in myocardial ischemia: Can we progress using the traditional paradigm?

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Programmatic research conducted over the past 30 years has consistently found depression to be common in patients with coronary heart disease (CHD), yet it is often unrecognized. Furthermore, depression in this group has been shown to increase risk for recurrent cardiac events and mortality. The threshold of depression severity at which risk is conferred can be quite low and substantially below the threshold associated with a diagnosis of major depression, and the pathway(s) by which depression confers risk may involve physiologic and/or behavioral factors. A higher than expected prevalence of depression is also characteristic of the patient group with diabetes, and similarly is associated with an elevated risk of medical complications and early mortality. Here too, the pathways linking depression to outcomes in this patient group appear to involve both physiologic and behavioral factors.

The current article by Haaf et al.[1] adds to this literature by focusing specifically on incident CHD risk—evidenced by a new myocardial perfusion defect—in diabetic patients with depression. In a sub-study of the BARDOT trial, patients with type 2 diabetes and free from coronary disease manifestations or symptoms at baseline underwent assessment that included myocardial perfusion imaging (MPI) with SPECT and either exercise or pharmacologic stress, along with assessment of psychosocial functioning, including depression. These assessments were repeated 2 years later, and the predictors of new onset MPI defect were tested. Of many variables—including both biologic and psychologic—it was only the psychological measures—depression in particular—that predicted new onset MPI defect. While the sample was not large for a population study, and the number of new 'events' small—in part due perhaps to the length of follow-up—the findings of this paper nonetheless raise important questions regarding risk assessment and surveillance in this high-risk patient group.

DEPRESSION AND CHD

Several large, prospective epidemiological studies of initially healthy individuals have shown that a history of major depression disorder (MDD) carries up to a fourfold elevated risk of incident CHD,[2] with meta-analyses[3] showing depression to carry a relative risk of 1.64 for incident CHD, independent of standard risk factors and markers including poor diet, tobacco use, and lack of physical activity. In patients with CHD, defined as chronic, stable coronary disease, unstable angina, or a history of prior acute coronary syndrome (ACS) event, up to 40% evidence clinically meaningful depression symptomatology, and overall, 15% to 20% meet criteria for MDD,[4] a rate three times greater than in the general population.[5] Hospitalized ACS patients with depression during hospital admission are highly likely to have had depression prior to their cardiac event,[6] which should not be surprising, as depression is a recurring, remitting disorder.

DEPRESSION AND DIABETES

Overall, the comorbidity of depression and CHD mirrors that of depression and diabetes. Approximately 25% of patients with either type 1 or type 2 diabetes report significant depression symptom elevation, while

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10% to 15% meet diagnostic criteria for MDD.[7] The incidence of depression in type 2 diabetics is 24% higher than in non-diabetics,[8] depression in both type 1 and 2 diabetics can be persistent for a great majority, and over 75% of those whose depression remits experience a recurrence over 5 years.[9] As with CHD, the relationship appears bi-directional in those adults with depression, and they are also at up to 37% elevated risk of developing diabetes.[10]

MECHANISMS IN DEPRESSION AND CHD

The mechanisms underlying the link between depression and CHD are many and involve both biological and behavioral components.[11] These include: autonomic dysregulation—e.g., chronically elevated sympathetic nervous system (SNS) activity and reduced cardiac vagal control; chronically elevated activity of the hypothalamic–pituitary–adrenal cortex (HPA) axis; endothelial dysfunction; increased likelihood of experiencing myocardial ischemia during psychological stress; ongoing inflammatory processes; platelet activation; smoking and physical inactivity; and overall health risk behavior and medication non-adherence.

Otherwise healthy individuals with MDD have elevations in circulating catecholamines and cortisol that have been shown to predispose CHD patients to myocardial ischemia, ventricular tachycardia, and fibrillation, thus leading to sudden cardiac death.[11] Depressed patients, both with and without CHD, also have reduced HRV—an indication of reduced cardiac vagal control, and as depression severity increases, the degree of HRV reduction as well increases.[12] Indeed, these patients have a greater degree of HRV decrease than patients with either disease alone, suggesting that the effects of depression and CHD on this indicator of risk are additive.[13] Low HRV has also been found to partially account for the effect of depression on survival after ACS in statistical models.[14] Thus, this dysregulation of autonomic activity that accompanies depression has clear impact on CHD relevant events.

Endothelial dysfunction, among the earliest markers of CHD risk, is common among otherwise healthy individuals with MDD or elevated depression symptom severity.[15,16] Depression treatment with selective serotonin reuptake inhibitors (SSRIs) improves endothelial function in patients with stable CHD, supporting a role for endothelial dysfunction as a key factor linking between depression and cardiac outcomes.[17] Burg et al.[18] found that among patients with stable CHD, depression symptom severity predicted level of endothelin-1 (ET-1), which is an endogenous vasoconstricting protein, and a biomarker involved in both endothelial dysfunction and plaque rupture. They also found that CHD patients with depression were more likely to evidence dynamic impairment in myocardial blood flow during acute psychological stress.[19] Each of these findings points to vascular dysfunction in the coronary arteries—down to the microvascular bed—in patients with both depression and CHD.

MECHANISMS IN DEPRESSION AND DIABETES

Here as well, the mechanisms underlying comorbidity are similar. The propensity toward an unhealthy life-style associated with depression—lack of physical activity, diets rich in saturated fats, and refined sugars—and overall non-adherence regarding the necessary self-care behaviors that accompany a diagnosis of diabetes, leave the non-diabetic person at risk for developing this metabolic disease and the diabetic person at risk for complications and poor outcomes.[20,21] Meta-analysis that has shown depression is associated with missed medical appointments, and non-adherence to diet, exercise, medication use, glucose monitoring, and foot care,[22] while elsewhere it was reported that as depression symptom severity increased there was a dose response increase in the degree of non-adherence to these key elements of diabetic self-care.[23]

Pathways involving both autonomic and HPA-axis elements along with inflammation also appear relevant.[22] Along with depression, diabetes is associated with dysregulation in HPA-axis function characterized by subclinical hypercortisolemia and altered diurnal cortisol rhythm. In addition, diabetes is accompanied by a chronic inflammatory state, as evidenced by elevations in the level of circulating inflammatory markers.

DEPRESSION, DIABETES, AND VASCULAR DYSFUNCTION

While it should be clear that the consequences of depression and the pathways involved are very similar whether we are considering CHD or diabetes, it is perhaps the dysregulation of vascular processes—as evidenced by endothelial dysfunction—that provides a common pathway touched on by the Haaf et al. paper. Endothelial dysfunction—the earliest indicator of a vascular dysregulation in CHD—has been described as the main etiology for death and the majority of morbidity in patients with diabetes.[24] In particular, microvascular disease underlies the complications of retinopathy, neuropathy, and nephropathy, while large vessel disease is seen in the accelerated atherosclerosis that accompanies diabetes. The findings of Haaf and colleagues confirm the end result of this vascular process, showing that comorbid depression and diabetes is associated with incident—yet asymptomatic—MPI

defect on exercise or pharmacologic stress test. The asymptomatic nature of the finding could be attributable to the neuropathy that accompanies diabetes, yet that assumption may oversimplify the pathophysiology, which in the case here may involve coronary microvascular disease rather than frank and significant epicardial disease. Furthermore, left unaddressed is the effect that psychological stress may be having as a contributor to incident and transient—yet prognostically relevant—myocardial perfusion deficits. Prior research has shown that during psychological stress, patients with depression are more likely to show new myocardial perfusion deficits on SPECT myocardial perfusion imaging (MPI) than their non-depressed counterparts.[19] These patients also demonstrate resting elevations in ET-1 commonly seen in the immediate post-ACS period and predictive of recurrent ACS events.[18] Of note,[25] the pathophysiology underlying this mental stress-provoked myocardial ischemia (MSIMI) appears to predominantly involve the coronary microvascular bed, and regardless of depression status, it is universally asymptomatic. In addition, MSIMI has been observed in a substantial percent of patients who do not demonstrate myocardial ischemia during exercise or pharmacologic stress.[26] Thus, while the findings of Haaf et al.—even with the small event rate—may be seen as a wakeup call, the approach taken in the research methods with the reliance on exercise and pharmacologic stress may be just the tip of the iceberg insofar as what might be expected as a higher event rate if mental stress testing was also included.

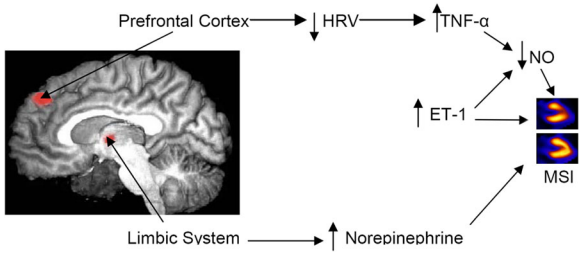

Figure 1. The neurocardiovascular axis during cognitive stress. Regional PET CNS activation during an arithmetic laboratory mental stress with simultaneous SPECT/MPI imaging. Regional brain activations during stress include the Prefrontal cortex, which has a general role in emotional/evaluative processing and self-regulation and the Limbic system, a complex that includes the Amygdala—critical to fear-related processing and Hippocampus—appropriate contextual processing. These areas when activated are multidimensional, and cognition is associated with attendant biological processes. The prefrontal activations promote parasympathetic withdrawal (↓HRV) and generate an inflammatory response (parasympathetic inflammatory reflex), while simultaneous activation of the Limbic system promotes sympathetic nervous system activation with increased levels of catecholamines. Many of these factors work synergistically resulting in this example, anteroapical ischemia.

MOVING FORWARD

Despite the absence of an evidence base, analysis of cost-effectiveness, or implementation of clinical resources, a number of professional organizations have recommended that CHD patients be screened for depression, and those with depression be referred for appropriate treatment.[27] What about comorbid depression and diabetes? Clearly, for quality of life purposes alone, one can easily see that a cost-effective screening algorithm for depression among patients with diabetes is needed. How best is to screen for incident CHD in asymptomatic diabetic patients with depression who have no prior history?

The costs and exposures associated with SPECT MPI do not warrant the large scale implementation of imaging in this patient group. It is deductive that, to the extent that cognition is a fundamental brain function, psychological triggers that result in myocardial ischemia are shaped by the CNS.[28] Patients with ischemia in response to this type of stress have brain activation patterns that exacerbate the fundamental processes common to depression and diabetes, which promote CAD. These activations overlap with PTSD, which is associated with early CAD[29]: Specifically, autonomic dysregulation, which promotes an inflammatory response, endothelial microvascular dysfunction, and dynamic impairment of MBF (Figure 1). From the end-organ perspective, the pathophysiology and indeed the vascular territory vulnerable to emotion- and psychological stress-provoked perfusion deficits on MPI differ from that provoked by exercise or pharmacologic stress. Forty percent of patients who demonstrate no new MPI defect with exercise or pharmacologic stress nonetheless demonstrate new MPI defects with psychological/mental stress, which employs the same single day, rest-stress protocol as with standard stress MPI, substituting a cognitively provocative task for exercise or pharmacologic intervention. These new MPI defects in response to emotional provocation often occur in vascular beds without significant coronary obstruction, and thus are likely subendocardial in nature,[30] whereas exercise-induced defects occur in obstructed vascular territories. Thus, new and emerging imaging modalities may be needed to identify important flow perturbations that are associated with emotional provocation and related factors. Furthermore, the inclusion of ‘‘mental stress MPI’’ in the study by Haaf et al. might have enriched the dataset and provided additional and potentially critical information concerning incidence and degree of ischemia, and vascular targets. Given that depression and

related affective disorders (e.g., post-traumatic stress) have an impact on cardiovascular biology in such a way as to affect microvasculature function—independent of obstructive disease, the manifestation of this effect in terms of unrecognized and asymptomatic myocardial ischemia may not be most accurately identified by traditional exercise/vasodilator imaging.

What then are the options? If one wants to alter the extant tools to detect the response to mental/emotional stress, quantitative myocardial blood flow may provide the territory affected and guide surveillance and attendant therapies. Alternative strategies may be available for cost-effective assessment of associated risk markers. Peripheral tonometric approaches have been developed for assessment of endothelial function and vascular health, and thresholds have been identified that provide acceptable sensitivity and specificity for myocardial ischemia.[31] The utilization of these technologies could be considered for the high risk, depressed, and diabetic patient group. Additional data to be included in risk stratification for the depressed patient with diabetes prior to MPI with mental stress could include thresholds of inflammation, ET-1, and body mass index, each of which has been implicated in the ischemia provoked under these conditions.[18,32,33] In addition to replication of the Haaf et al. findings and further follow-up with the study cohort, it will be critical to develop and test the risk stratification and both CHD prevention and mitigation efforts for patients with comorbid depression and diabetes. Clinical trials testing depression treatment vs focused risk factor management (e.g., with a focus on adherence to life-style recommendations and/or medication) will also be necessary to determine the most cost-effective methods for addressing the medical consequences of this comorbidity.

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