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Review article

The heartbreak of depression: 'Psycho-cardiac' coupling in myocardial infarction

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ABSTRACT

Ample evidence identifies strong links between major depressive disorder (MDD) and both risk of ischemic or coronary heart disease (CHD) and resultant morbidity and mortality. The molecular mechanistic bases of these linkages are poorly defined. Systemic factors linked to MDD, including vascular dysfunction, atherosclerosis, obesity and diabetes, together with associated behavioral changes, all elevate CHD risk. Nonetheless, experimental evidence indicates the myocardium is also directly modified in depression, independently of these factors, impairing infarct tolerance and cardioprotection. It may be that MDD effectively breaks the heart's intrinsic defense mechanisms. Four extrinsic processes are implicated in this psycho-cardiac coupling, presenting potential targets for therapeutic intervention if causally involved: sympathetic over-activity vs. vagal under-activity, together with hypothalamic-pituitary-adrenal (HPA) axis and immuno-inflammatory dysfunctions. However, direct evidence of their involvement remains limited, and whether targeting these upstream mediators is effective (or practical) in limiting the cardiac consequences of MDD is unknown. Detailing *myocardial* phenotype in MDD can also inform approaches to cardioprotection, yet cardiac molecular changes are similarly ill defined. Studies support myocardial sensitization to ischemic insult in models of MDD, including worsened oxidative and nitrosative damage, apoptosis (with altered Bcl-2 family expression) and infarction. Moreover, depression may de-sensitize hearts to protective conditioning stimuli. The mechanistic underpinnings of these changes await delineation. Such information not only advances our fundamental understanding of psychological determinants of health, but also better informs management of the cardiac consequences of MDD and implementing cardioprotection in this cohort.

Contents

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1. Introduction

Major depressive disorder (MDD) shares a reciprocal relationship with coronary heart disease (CHD) (reviewed in [1–3]). This behavioral disorder places healthy individuals at increased risk of CHD [4–7], is strongly linked to CHD in those with or without existing cardiac disease [6,8–10], is an independent risk factor for cardiovascular mortality and morbidity [11–13], and is more prevalent in those who have suffered AMI [12,14]. As a CHD risk factor, MDD exerts an impact similar to conventional determinants (eg. smoking, elevated cholesterol, hypertension, diabetes) [15,16], and increases the risk of recurrent cardiac events and death in those with CHD by up to 4-fold [11,17,18]. The magnitude of CHD risk is also related to the severity of MDD, ranging from a 2-fold increase to up to 5-fold with more severe depression [7]. Depression thus appears as powerful a determinant of CHD risk and outcomes as more traditional risk factors, and its occurrence is significant: recent analyses indicate a lifetime prevalence of ~16% in the US [19], with varying estimates from other populations (and diagnostic criteria), for example ~11% in Canada [20], 4–7% in Singapore [21], 12% in a Scottish cohort [22], 18% in urban Ethiopians [23], and 5% in rural-to-urban Chinese workers [24]. Whether overall incidence is on the rise is questionable, with a perceived growing epidemic of MDD and anxiety disorders potentially reflecting population growth, among other factors [25]. Whether more extensive 'sub-threshold' depression influences CHD risk and outcomes is also unclear.

As opposed to most major CHD risk factors, the biological mechanisms linking depressive disorders and heart disease remain to be detailed. From a holistic perspective [reviewed in 2,26], depressive and chronic heart disorders share the same physiological network of mechanisms (thus risk factors). This Psycho-Immune-Neuroendocrine (PINE) network is predicated on key regulatory systems [26], including the autonomic nervous, immune and endocrine systems, and components of the central nervous system (Figs. 1 and 2). Perturbation of the regulatory PINE network may predispose an individual to both MDD and CHD, with onset of either disease (and manifestation of one ahead of the other) influenced by hereditary and environmental factors [26] (Fig. 1). Highlighted in Fig. 1, there is a high degree of bidirectional interconnectedness between CHD and MDD – common mechanistic elements are implicated in both scenarios, and pathologic outcomes of each exert positive feedbacks on the other. For example, MDD may promote cardiac dysfunction via intermediate pathological and physiological mechanisms: behavioral changes with MDD contribute to inactivity, in turn promoting obesity, dyslipidemia, type 2 diabetes and hypertension, while associated social isolation additionally worsens CHD risk and mortality. There is also evidence that disruption of the PINE network can physiologically promote risk of dyslipidemia, type 2 diabetes and hypertension, and thus CHD [26]. The same intermediary pathologies can equally contribute to MDD.

Although now a well-recognized and clinically important manifestation of psycho-cardiac coupling, and while the PINE network model provides a framework for understanding depression-dependent changes in CHD risk and outcomes [26], relatively few studies have investigated the molecular mechanistic basis of these interactions. In particular, *how the heart itself is intrinsically modified by depression remains to be fully detailed*. Certainly, co-morbidities associated with or promoted by MDD, including obesity, diabetes and aging, are known to negatively impact myocardial stress-resistance and cardioprotection [27–30]. However, experimental evidence reveals that chronic stress and MDD *directly impair myocardial capacity to withstand injury/infarction independently of these systemic factors*. This review focuses on these direct myocardial impacts of depression, specifically the heart's capacity to withstand damage with infarction and respond to protective intervention. Not only contributing to worsened CHD risk and outcomes, depression may simultaneously render the heart resistant to cardioprotective interventions. While Tako-Tsubo cardiomyopathy exemplifies the notion of a 'broken heart', evidence suggests depression may effectively break the heart's intrinsic defense mechanisms, thus ability to withstand cellular injury and death. Beyond accumulating epidemiological evidence, and development of frameworks with which to test and unravel these interactions [2,26] (Fig. 1), the molecular bases of these myocardial changes await more detailed investigation (Fig. 2).

2. Impacts of depression on myocardial infarction

2.1. Pre-ischemic depression

It is only relatively recently that studies have examined the detrimental impacts of stress and MDD on the heart's response to ischemic insult or infarction. Data generated in the landmark Whitehall study revealed strong relationships between social stress and metabolic and cardiovascular health outcomes [31–33]. In terms of those at risk of AMI, the prevalence of depression is significant with approximately 1-in-5 patients referred for diagnostic catheterization and angiography suffering pre-existing MDD [8,34], confirming significant prevalence of the disorder in those at risk of AMI. Early investigations revealed that depression impairs heart rate variability and autonomic control in humans [35], and that chronic stress (inducing depressive symptoms) increases heart rate, sympathetic tone, and cardiovascular reactivity to stress in animals [36,37], suggesting enhanced cardiac vulnerability to arrhythmia and injury. Further investigations over the last 3 decades have largely relied on chronic stress models (eg. subjecting animals to physical restraint, social isolation, predation stress, forced swimming, environmental instability, and randomized series of such stressors), which exhibit symptoms of depression that may include anhedonia and decreases in sexual drive, aggression, investigative behavior and locomotion, together with circadian disruption, disordered sleep and weight loss [38,39] (models discussed below in section 4). These studies identify both ultrastructural disruption in otherwise healthy hearts [40,41] and substantial changes in myocardial injury responses [40,42–47]. However, they have not yet developed a mechanistic understanding of these cardiac outcomes. Most research to date has focused on key end-points, including cell death, infarction, arrhythmogenesis and stunning, with few delving into underlying molecular mechanisms.

Scheuer and Mifflin showed that experimental infarction in rats is significantly worsened by daily restraint stress [42]. These investigators had previously identified worsened infarction in response to chronically elevated corticosterone [43]. Subsequent work indicates that chronic emotional stress exaggerates infarction in rats in association with increases in markers of oxidative and nitrosative damage [44]. Ravingerova et al. found chronic stress also increases contractile dysfunction and risk of post-ischemic arrhythmias in normotensive rats, though stress somewhat paradoxically improved these parameters in hypertensive animals [45]. While emulating post-traumatic stress