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Psychobiology of depression/distress in congestive heart failure

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Abstract

Heart failure affects millions of Americans and new diagnosis rates are expected to almost triple over the next 30 years as our population ages. Affective disorders including clinical depression and anxiety are common in patients with congestive heart failure. Furthermore, the presence of these disorders significantly impacts quality of life, medical outcomes, and healthcare service utilization. In recent years, the literature has attempted to describe potential pathophysiologic mechanisms relating affective disorders and psychosocial stress to heart failure. Several potential mechanisms have been proposed including autonomic nervous system dysfunction, inflammation, cardiac arrhythmias, and altered platelet function. These mechanisms are reviewed in this article. Additional novel mechanisms such as mental stress-induced myocardial ischemia are also discussed.

Keywords

Heart Failure; Depression; Mental stress; Mechanisms

Overview

Heart failure affects more than 5 million Americans [1] and new diagnosis rates are expected to almost triple over the next 30 years as our population ages [2]. Affective disorders including clinical depression and anxiety are common in patients with congestive heart failure (CHF). Studies suggest that depression occurs in approximately 40% of patients with CHF [3–5]. This greatly exceeds the 2–9% prevalence observed in the normal population [6]. Though fewer studies have evaluated anxiety disorders in the context of heart failure, available reports suggest that anxiety is also common, occurring in 18–45% of

outpatients with heart failure [7,8]. The prevalence of anxiety in this population exceeds the rates observed in the general population [6] and even exceeds the 2–4% prevalence observed in community samples of older adults [9, 10].

Furthermore, the presence of these disorders significantly impacts quality of life, medical outcomes, and healthcare service utilization. Several studies have examined the relationship between depression and outcomes in patients with heart failure [4, 8, 11–14]. These studies show that depression is the strongest predictor of health status in patients with heart failure [12]. In fact, depressed patients exhibited lower observed function (walking distance), increased severity of heart failure symptoms, and impaired health-related quality of life [11, 12]. Decrements in activities of daily living have also been noted [14]. Other studies suggest that heart failure patients with depression are at increased risk for re-hospitalization [4, 13] and death [4, 8, 13, 14] compared to non-depressed heart failure patients.

Weighed against the literature on depression and heart failure, relatively little is known about the relationship between anxiety symptoms and outcomes in heart failure. One study found a univariate association between anxiety and outcomes in patients with heart failure, but failed to show an association after controlling for depression, social isolation, heart failure status, and other potential confounds [15]. However, the results reported are from a medical intervention trial rather than a prospective observational study. A second study by Jiang and colleagues also failed to find an association between anxiety symptoms and mortality in hospitalized patients with heart failure [16]. Due to the inconsistent findings, small number of available reports, and the need for additional research the remainder of this review will focus instead on the relationship between depression, stress, and heart failure.

In recent years, the literature has attempted to describe the pathophysiologic mechanisms relating depression and stress to heart failure. Although this literature is small relative to what is known about the relationship between depression, stress, and other types of heart disease, several potential mechanisms have been proposed including: autonomic nervous system dysfunction, inflammation, cardiac arrhythmias, and altered platelet function. These topics are reviewed in this paper. An additional novel mechanism, mental stress-induced myocardial ischemia, is also discussed.

Autonomic nervous system dysfunction

Autonomic nervous system function in patients with depression

Autonomic nervous system dysfunction appears to be one of the most credible mechanistic explanations for the association between depression and cardiovascular disease. Observation of either decreased parasympathetic activity, increased sympathetic activation, or both would be important as an imbalance between the sympathetic and parasympathetic systems may increase the risk for several types of adverse cardiac events including ventricular fibrillation [17], arrhythmias [18], and sudden death [19].

Autonomic function in individuals without medical disorders—Much of the original work in this area examined changes in norepinephrine (NE) in individuals with major depressive disorder, but no co-morbid medical conditions. Many early studies suggested increased urinary and plasma NE or NE metabolite levels in patients with depression [20–22]. However, due to the assessment techniques used in these studies it was initially unclear whether the observed elevations in circulating NE were due to increased systemic sympathetic activation or decreased NE clearance. Using sophisticated sampling and data analytic techniques, Veith and colleagues [23] were able to demonstrate conclusively that increased circulating NE in patients with depression results from increased systemic sympathetic activation.

Several studies suggest that patients with depression also exhibit increased sympathetic activation in response to acute stressors. Increased circulating NE is observed in response to both physical [24] and psychological stressors [25]. Furthermore, increased norepinephrine levels appear to be correlated with higher resting heart rates [22, 23] and hemodynamic reactivity to stress [26].

Other markers of sympathetic activity also suggest altered autonomic nervous system function in patients with depression. For example, studies suggest that patients with depression have decreased heart rate variability (HRV) [27–29] which is known to predict adverse outcomes in patients with heart disease [30]. Furthermore, a recent study by Carney and colleagues suggests that HRV may partially explain the increased risk of death following myocardial infarction (MI) in coronary artery disease (CAD) patients with co-morbid depression [29]. However, as the HRV contributes to increased risk for arrhythmias, this topic will also be discussed below.

Autonomic nervous system dysfunction in heart failure

Studies suggest that patients with CHF experience alterations in autonomic nervous system function. These studies indicate that CHF is characterized by increased sympathetic outflow to the heart and the peripheral vasculature and decreased parasympathetic activity [31, 32]. Initial reports indicated that CHF patients had decreased NE levels in the left ventricle compared to participants with healthy hearts [33]. However, several other studies point to increased systemic sympathetic activation in patients with CHF as indicated by higher plasma NE concentrations [34–36]. The increase in systemic adrenergic activity in this population is further exacerbated by decreased clearance of NE from the circulation due to low cardiac output [34]. Furthermore, increased plasma NE concentrations appear to predict negative outcomes in patients with CHF [34, 36].

Cardiac arrhythmias and depression—Among other potential effects, altered autonomic nervous system function increases susceptibility to ventricular arrhythmias triggered by inadequately opposed sympathetic stimulation [18]. In fact, about 50% of deaths in the CHF population are due to arrhythmias. As described above, patients with depression exhibit autonomic nervous system changes comparable to the changes observed in patients with heart failure [27, 37–41]. The co-existence of the two conditions in one individual is believed to have an additive effect, putting patients who have both characteristics at increased risk for arrhythmic events and sudden cardiac death.

There are several investigative tools that serve as surrogate markers of vulnerability to arrhythmic events and sudden cardiac death in patients with heart failure and other diseases. Heart rate variability, a widely used method, provides a measurement of the degree of sympathetic–parasympathetic imbalance [42–44]. This simple, non-invasive measurement of the inter-beat variation of RR interval can provide important information regarding autonomic modulation of the sino-atrial node. It may be assessed by time domain, frequency domain, or by nonlinear techniques. In general, reduced HRV indicates excessive cardiac sympathetic modulation, reduced vagal modulation, or both and is a marker for increased susceptibility to arrhythmias in patients with CAD [30, 45–47].

Heart rate variability and depression—There is also a large body of literature suggesting the existence of abnormal patterns of HRV in patients with depressive symptoms. Those abnormal patterns have been shown to occur in depressed patients post-MI as well as stable CAD patients. Carney and colleagues [48] studied 388 acute MI patients with depression and 424 acute MI patients without depression by 24-h ambulatory electrocardiographic monitoring. All but one HRV indices (high-frequency power) were

significantly lower in depressed compared to non-depressed patients. The study concluded that “greater autonomic dysfunction, as reflected by decreased HRV, is a plausible mechanism linking depression to increased cardiac mortality in the post-MI population [48].” In a different study, the same authors found a higher prevalence of ventricular tachycardia among patients with CAD and depression compared to those without depression [49]. In a third study, the same group reported that low HRV partially mediates the effect of depression on survival after acute MI. Similar observations were reported in patients with stable coronary artery disease, where stable CAD patients with moderate to severe depression were found to have markedly lower HRV compared to non-depressed patients [28].

However, the evidence for decreased HRV in depression is not entirely consistent. For example, Gehi and colleagues [50] found no association between depression and HRV in their cross-sectional study of 873 outpatients with stable coronary heart disease. A second report from the same study group later found no association between HRV indices and cognitive symptoms of depression [51]. In contrast, somatic symptoms of depression were associated with decreased HRV. Subsequent analyses revealed that the association between somatic symptoms and decreased HRV was largely attributable to differences in co-morbidities and lifestyle factors.

Other markers of arrhythmic events and depression—Other markers of arrhythmic events include QT-dispersion, heart rate turbulence, and T-wave alternans.

QT dispersion and depression: The QT interval is the electrocardiographic representation of ventricular repolarization time. Variability in the QT interval reflects beat-to-beat fluctuations in myocardial repolarization time, and increased variability is a significant predictor of arrhythmic events and sudden cardiac death. There is also consistent evidence linking depression with indices of QT variability [52, 53].

Heart rate turbulence and depression: HR turbulence is a measure of HR response to Premature Ventricular Contractions (PVCs; [54–56]). Normally, HR first accelerates and then decelerates after a PVC. This response pattern is thought to be regulated by baroreceptor reflexes and the parasympathetic nervous system. Patterns that deviate from this PVC-related response have been found to predict mortality in the post-MI and CHF population [57, 58].

One study has reported a relationship between heart rate turbulence and depression in CAD patients [59]. The study which enrolled 666 post-MI patients found that depressed patients were more likely to have abnormal HR turbulence and worse survival than non-depressed patients. A mediation analysis indicated that the hazard differs over time, with depression posing little risk for mortality in the first year but greater risk in years 2 and 3 of the follow up.

Premature ventricular contractions and depression: PVC's may also contribute to increased cardiovascular risk in patients with depression. In a recent study by Frasure-Smith et al. [60], depressed post-MI patients who had 10 or more PVC's per hour after an acute MI were at considerably higher risk for mortality than were depressed patients without PVCs or non-depressed post-acute MI patients with 10 or more PVCs per hour. The authors concluded that depressed patients may be at greater risk for death as a result of arrhythmias.

Autonomic nervous system function and treatment of depression

Authors have also asked whether treating depression may improve heart rate response and HRV indices. Carney and associates measured HRV in 30 depressed CAD patients before and after 16 sessions of cognitive behavioral therapy (CBT). The results of this study suggest that CBT improves one index of HRV (i.e., rMSSD), which reflects mostly parasympathetic activity [61].

Researchers have also examined the effect of antidepressants on autonomic nervous system markers. Ahrens and colleagues [62] found no effect of a single dose sertraline treatment on HRV in healthy young adults. In contrast, Glassman and colleagues [63] observed decreased HRV in depressed patients treated with sertraline vs. placebo following acute coronary syndrome. However, the authors note that the difference between active drug and placebo groups was largely attributable to decreased HRV in the control groups.

Autonomic function, treatment of depression, and heart failure—To the best of our knowledge there has been only one study examining the effect of antidepressant treatments on autonomic nervous system function markers in CHF patients with co-morbid depression. In 2003, Lesperance and colleagues [64] conducted an open label trial of nefazadone in a sample of 28 patients with CHF and major depression. Nineteen patients completed a full 12-week course of treatment. Approximately 74% of study completers demonstrated a 50% reduction in Hamilton Depression Scale scores. Furthermore, patient's who completed the treatment trial also exhibited reductions in heart rate and plasma NE levels, with increased QT intervals. Though this trial provides interesting preliminary data, it is likely that no additional studies were published because sales of nefazadone were discontinued in 2004. Larger, more tightly controlled studies of other related medications are required.

To date, there are no known studies of the efficacy of psychotherapeutic treatments for depression in heart failure patients. Given the rate of depression in this population and its known effects on quality of life and health outcomes, we believe that this is an area which merits additional research.

Autonomic nervous system function and mental stress—There is also a strong anecdotal and case-based history linking mental stress with cardiac arrhythmias and sudden cardiac death. This effect can occur in non-CAD patients with congenital cardiac channelopathies [65]; however, it is potentially more pronounced in patients with pre-existing structural heart disease. Adrenergic stimulation is known to alter electrical properties of the heart muscle, this occurs through the effect of catecholamines on the different cardiac ionic channels with resultant repolarization heterogeneity which serves as a substrate for electrical instability. In a study by Peters and colleagues [66], ventricular tachycardias were found to occur more frequently on Mondays in working patients with implantable-cardioverter defibrillators (ICDs). However, New York Heart Association heart failure status was not available for approximately 20% of the sample, which suggests that a portion of these patients may not have met criteria for a CHF diagnosis.

Lampert et al. [67] conducted an observational study where they gave CAD patients with ICDs diaries to record their levels of defined mood states and physical activity; they found that in the 15 min preceding shock, an anger level ≥ 3 preceded 15% of events compared with 3% of control periods. Other mood states (anxiety, worry, sadness, happiness, challenge, feeling in control, or interest) did not differ. However, heart failure status was not reported for this sample.

In several other studies, markers of susceptibility to ventricular arrhythmias were also found to be exacerbated by mental stress. Kop et al. [68] reported that mental stress can induce changes in T wave alternans indicative of electrical instability, this effect occurred at lower heart rates than with exercise. However, heart failure status was not reported in this study. Pagani and colleagues [69] also studied the effects of mental stress on 16 healthy male volunteers and 9 post-MI patients by subjecting them to a computer-controlled mental task and a stressful interview. Their findings indicate that psychological stress induced marked changes in the sympathovagal balance, which moved toward sympathetic predominance. The low-frequency component of RR variability, a marker of sympathetic activity, increased significantly with the interview. Though again, this sample examined HRV in healthy adults rather than patients with CHF.

Arrhythmias, mental stress, and heart failure—Though the data seem to suggest that emotional experiences may trigger cardiac arrhythmias and sudden death or at least increased risk for these events in some individuals, as described above, there is little direct evidence relating mental stress to cardiac events in patients with heart failure. Given the ubiquity of situational stress in the human experience and the unique stressors and physiology of heart failure in particular, we believe that this is an area of the literature that merits additional research. If patients with heart failure are found to have similar increased risk for arrhythmic events and sudden death in response to emotional stress, it would also be worthwhile to begin to consider potential treatments and their efficacy in this unique patient population.

Inflammation

HPA axis and depression

The association between depression and increased activation of the hypothalamic-pituitary-adrenal axis (HPA) is one of the most consistent findings in this area of the literature. Activation of the HPA axis results in a complex chain of neuroendocrine events including: increased corticotropin releasing hormone activation (CRH; [70]), elevated release of corticotropin (ACTH) from the pituitary and increased release of glucocorticoids [71], increased adrenal but decreased pituitary ACTH response to CRH [72], and decreased dexamethasone suppression [73]. This response chain results in failure of the normal feedback inhibition system.

Cortisol

Cortisol is the primary glucocorticoid in humans. Excess cortisol can contribute to abdominal obesity [74], insulin resistance [75], hypertension [76], altered plasma lipoprotein metabolism and carbohydrate metabolism [77], altered endothelial function [78], oxidative stress [79], vascular tone changes [78], and inflammation [80]. All of these processes are known risk factors for cardiovascular disease and suggest several potential routes by which depression may exert its effects on the heart in patients with known heart disease.

Cortisol and aldosterone in heart failure—Several studies also document increased cortisol levels in patients with CHF [81, 82]. Recent studies suggest that cortisol may also play an important role in the progression of heart failure. In humans, the adrenal cortex produces both cortisol and aldosterone, a mineralocorticoid. The chemical structure of these two steroid hormones is very similar and although both have their own target receptors, the mineralocorticoid receptor may bind either cortisol or aldosterone [83]. Though normally cortisol is prevented from binding with the aldosterone receptor by the insertion of an 11 β -hydroxysteroid dehydrogenase [83], the cardiomyocyte lacks 11 β -hydroxysteroid dehydrogenase type II [84]. In the presence of reactive oxygen species, that occur in instances of tissue damage, cortisol binds with the mineralocorticoid receptor and it

therefore becomes activated [85, 86]. In this way, cortisol appears to imitate the effects of aldosterone in patients with heart failure [86]. However, until recently the prognostic importance of cortisol levels in patients with heart failure was unknown.

In their 2007 study, Güder and colleagues [87] obtained a sample of 300 consecutively enrolled heart failure patients with no current corticosteroid treatment. Serum cortisol and aldosterone levels were collected at enrollment and patients were followed for an average of 2.2 years. Results revealed that both cortisol and aldosterone were independent predictors of death in covariate-adjusted analyses. When patients' cortisol levels were examined by quartile, the hazard ratio for patients with the highest cortisol levels was more than 2 times greater than that of the lowest quartile [87]. Furthermore, the addition of cortisol to the multivariate model resulted in a significant increase in the proportion of variance explained.

HPA function in depression and heart failure

Though we might speculate that depression may exacerbate HPA axis dysregulation in patients with heart failure, such suppositions are merely conjecture. To our knowledge there have been no articles that describe cortisol levels or other markers of HPA axis function in patients with co-morbid heart failure and depression to date.

Cytokines and other inflammatory markers

Overview—In recent years, it has become increasingly clear that depression causes many changes in immune function in addition to its known effects on cortisol. For example, depression is known to alter neutrophil phagocytosis [88], natural killer cell activity [89, 90], lymphocyte proliferation [91], and concentrations of both positive and negative acute phase proteins [92]. However, the effect of depression on cytokine function would seem to have particular importance for understanding the relationship between depression and heart failure as cytokines are implicated in both conditions [93, 94].

Cytokines are small peptides that influence immune function [95]. As a class, they can both increase (proinflammatory) and inhibit inflammation (anti-inflammatory; [95]). Cytokines are also believed to trigger a complex pattern of behaviors including aches in muscles and joints, fatigue, sleep, and appetite disturbances. While these behaviors are non-specific, they are collectively known as “sickness behaviors.” In the case of infection, these sickness behaviors are helpful to the organism in fighting pathogens but can be problematic if the response is particularly intense, occurs out of context or lasts for an unusually long time [96].

Cytokines and mental stress—Cytokines can also be triggered by emotional responses like anxiety or fear. There are many examples of studies documenting increased circulating cytokine levels following mental stress. Maes and colleagues [97] assessed medically healthy medical students at exam time and noted increased production of TNF- α , IL-6, IL-1Ra, IFN- γ , and IL-10. Increased IL-1 β production was also observed in a similar study examining male physicians who were giving a public speech [98]. In controlled laboratory settings, researchers have demonstrated increased circulating IL-1 β , TNF- α , IFN- γ [99], and IL-6 [100] following public speaking tasks. Researchers have also shown significant increases in proinflammatory cytokines following a variety of other mental stress tasks including the Stroop Color-Word and mirror tracing tasks [101–104].

Cytokines and depression—In the context of depression, some studies suggest increased levels of IL-1 β , IL-1Ra, IL-2, soluble IL-2R, IL-6, soluble IL-6R, IL-10, IL-12, TNF- α , and IFN- γ [105–112]. Whereas other studies suggest that the relative balance between Th1- and Th2-derived cytokines is more important [113]. Furthermore, the Th1/

Th2 balance appears to be altered in patients receiving antidepressant treatment [114, 115], with patients on active drug interventions showing a significant increase in Th2-derived anti-inflammatory cytokine circulation [116, 117]. This suggests that the balance between Th1 and Th2 cytokines may be important to the psychological stress responses of patients with pre-existing depression [118].

Cytokines and heart disease—Cytokines also effect the progression of coronary artery disease [94, 119]. They are thought to enhance atherosclerosis by increasing molecule adhesion to injured endothelium [120]. Additionally, they promote angiogenesis [121, 122], are found in atheroma mast cells [123], and are implicated in plaque ruptures [124, 125]. Proinflammatory cytokines also appear to be elevated following episodes of myocardial ischemia [126] and unstable angina [127]. Cytokine profiles may also predict risk for cardiac events [128, 129].

Cytokines and heart failure—Although cytokines may not precipitate heart failure, research suggests that damage to the heart due to left ventricular dysfunction results in a cascade of proinflammatory cytokine activation. In fact studies demonstrate elevated levels of TNF- α , IL-1 β , IL-2, IL-6, IL-8 and other proinflammatory cytokines, and soluble cytokine receptors in patients with CHF [130–132]. These cytokine cascades, in conjunction with other neurohormonal processes, are thought to facilitate cardiac remodeling [133], suppress cardiac contractility, and increase apoptosis [134]. Elevated cytokine and soluble cytokine receptor levels also appear to correspond to increased heart failure symptoms [131] and adverse outcomes in patients with heart failure [135, 136].

Cytokines, depression, mental stress, and heart failure—To date there have been only two articles describing in patients with co-morbid depression and heart failure. In the first study, Parissis and colleagues [137] obtained plasma cytokine samples from 35 consecutively enrolled heart failure patients who were followed in an outpatient cardiology clinic. They found that patients with elevated depressive symptomology exhibited higher TNF- α and soluble fas ligand with lower IL-10 compared to non-depressed patients. However, the sample size was quite small and the depressed patients were significantly older than the non-depressed patients in this study.

In the second study, Redwine and colleagues [138] obtained a sample of 18 men with CHF from a Veterans Affairs Medical Center outpatient clinic in the southwest. Heart failure status, depressive symptomology, physical functioning, and immune markers were obtained at baseline and participants were followed for cardiac hospitalizations and death for 2 years. They found that participants with higher depressive scores had lower Th1/Th2 ratios and higher incidence of cardiac hospitalizations or death. The results of this study that it may be the ratio of Th1- to Th2-derived cytokines which is important for predicting risk in this patient population.

In summary, we may hypothesize that heart failure patients who develop depression or experience an emotionally stressful event might also experience an increase in proinflammatory cytokines or an alteration in the relative balance between Th1- and Th2-derived cytokines that could contribute to the development or progression of heart failure. However, as with other important topics in this literature, there is little direct evidence describing cytokine function in heart failure patients with either co-morbid depression or recent emotionally stressful experiences. Additional research in this area will be required.

Inflammation, treatment of depression, and heart failure—To the best of our knowledge there have been no studies examining the effects of either psychotherapeutic or

pharmacological treatments for depression on cortisol, cytokine functioning, or other markers of inflammation in heart failure patients with co-morbid depression.

Platelet function

Physiology of platelet function

Platelets are the smallest cellular element in the blood. They are responsible for maintaining hemostasis and are central to the coagulation process. Exposure to damaged endothelium, shear stress, hypercholesterolemia, and circulating substances, like serotonin, can all initiate platelet activation. The process of platelet activation involves interaction of the platelet membrane glycoproteins with their adhesive proteins. The most functionally critical of these receptors is the glycoprotein IIa/IIIb receptor (GPIIa/IIIb). When activated this receptor becomes a binding site for fibrinogen [139, 140]. GPIIa/IIIb molecule is the target of an anti-platelet pharmacotherapy frequently used in the treatment of acute coronary syndrome. Serotonin can bind platelet 5-HT transporters and 5-HT_{2A} receptors. Stimulation of platelet 5-HT_{2A} receptors leads to a series of post-receptor signals that ultimately can induce calcium mobilization from internal storage sites [141, 142]. Calcium mobilization is required for platelet activation, specifically in the processes of shape change, aggregation, dense granule secretion, and α -granule secretion. Platelet activation is followed by the release of a variety of endogenous cytokines and coagulant factors including platelet factor 4 (PF4), β -thromboglobulin (B-TG), and serotonin. These events consequently promote platelet aggregability, vascular smooth muscle constriction, and activation of clotting factors.

Platelet activation can be assessed using various methods. Quantitative and qualitative analysis of plasma for a number of molecules secreted by activated platelets including platelet factor 4, β -thromboglobulin, soluble P-selectin, thromboxan B₂, and others. Second, platelets themselves could be examined for markers of activation, e.g. the appearance of surface molecules or binding sites, which become detectable after conformational changes of preexisting molecules or the internalization of factors secreted by the platelet or other cells.

Platelet dysfunction in patients in depression

Platelets are frequently thought of as reflective of central nervous system presynaptic nerve terminals, because they possess an identical system for high affinity uptake and storage of serotonin. Serotonin secreted by activated platelets induces both platelet aggregation and coronary vasoconstriction. Therefore the increased platelet reactivity in patients with depressive disorders could be thought of as one of the manifestations of the more widespread serotonin system imbalance characteristic of depressive disorders. Another possible mechanism is related to increased sympathetic stimulation associated with various stressors.

Several studies have reported increased platelet reactivity in patients with depressive symptoms [143–146]. Musselman and colleagues measured in vivo platelet activation, secretion, and dose–response aggregation in 12 depressed patients and 8 healthy adults [143]. The depressed patients were found to have enhanced baseline platelet activation and responsiveness in comparison to the normal subjects. Markowitz and colleagues [145] demonstrated increased platelet secretion after in vitro stimulation with collagen along with decreased platelet serotonin receptor density in depressed patients; these latter findings have also been confirmed in several other studies [147–149]. In another study, Laghrissi-Thode and his colleagues demonstrated that the release of chemotactic factors PF4 and B-TG from activated platelets was significantly elevated in elderly depressed patients with CAD [144]. Their study included 17 healthy controls, 8 patients with CAD and 21 patients with major

depression and CAD. They found that plasma levels of PF4 and B-TG were significantly higher in patients with both depression and CAD compared to patients with CAD only or normal controls ($p < 0.0001$). The difference was still striking after controlling for age, gender, ethnicity, medication use, and severity of CAD.

However, there is variability in this literature as well. A 2004 systematic review by Von Kanel [150] identified 11 studies of platelet response to adenosine diphosphate (ADP), 9 studies of platelet response to serotonin (ST), and 5 studies of platelet response to combined ADP and ST showing either decreased or unchanged platelet aggregation. In fact, Von Kanel [150] observed that fewer than half the reviewed studies showed platelet hyperactivity. However, the authors note that recent studies using flow cytometry techniques more consistently support platelet hyperactivity.

Effect of antidepressant treatments on platelet reactivity

Even though serotonin is only a weak platelet agonist itself, it markedly enhances platelet reactions to a variety of other agonists. Several studies have shown that selective serotonin reuptake inhibitors (SSRIs) reduce platelet and whole blood serotonin concentrations after repeated doses, and could therefore exert an inhibitory effect on platelet activation [145, 151]. In fact several studies have reported increased risk of upper gastrointestinal bleeding in patients treated with SSRI's, especially when co-prescribed with non-steroidal anti-inflammatory drugs [152]. This anti-platelet effect appears to be unrelated to the antidepressant effect and occurs both in responders and non-responders. In the SADHART platelet sub-study [153], treatment with sertraline was associated with significant reduction in the release of B-TG, as well as significant reduction in the plasma level of E-selectin, a platelet-derived pro-inflammatory molecule, even in the presence of other anti-platelet agents like aspirin and clopidogrel. In a study comparing paroxetine to nortriptyline in patients with both CAD and depression [152], baseline platelet activity indices were elevated in patients with depression and CAD compared to those with CAD alone or normal controls. Treatment with paroxetine normalized platelet activity. This effect occurred with low doses and was observed early before any antidepressant effects occurred. Nortriptyline in comparison was effective as an antidepressant but did not affect platelet reactivity. Epidemiological studies assessing the risk of MI in patients treated with antidepressants, including SSRI's, are controversial with respect to a potential beneficial effect of SSRI's on CVD risk in depressed patients. However, there is evidence that exposure to SSRI's (compared to tricyclic antidepressants) does not substantially increase the risk of cardiovascular events in patients with CAD [154].

Platelet dysfunction during mental stress

Several studies have suggested a causal link between mental stress and platelet dysfunction [155–159]. This seems to be mediated by increased adrenergic stimulation; both epinephrine and NE are potent stimuli of various platelet functions in vitro. Hemoconcentration through stress-induced decrease in plasma volume with consequent increase in plasma viscosity has also been suggested as an underlying mechanism [160, 161]. Jern et al. collected blood samples before, during, and after 20 min of mental stress from 10 healthy, non-smoking young males [156]. Reactions were compared with those observed during physical exercise and infusion of adrenaline. Both von Willebrand factor antigen and factor VIII coagulant activity increased significantly in response to mental stress. In another study, Grignani et al. showed that mental stress induced a significant increase in platelet aggregation, the formation of circulating platelet aggregates, and an increase in thromboxane B2 levels in plasma and serum [157]. These effects were rapidly reversible. A similar but less evident increase in platelet function by emotional stress were observed in control subjects. The duration of mental stress-induced platelet dysfunction is unknown. Kario and colleagues

studied 42 elderly patients before and after the Hanshin-Awaji earthquake [159]. Their protocol involved testing for fibrinogen, D-dimer, plasmin-alpha2-plasmin inhibitor complex, tissue-type plasminogen activator antigen, and von Willebrand factor before and after the earthquake; their findings suggested that mental stress-induced pro-coagulant effects may last up to 4–6 months.

In 2006, Strike and colleagues [162] examined hemodynamic and platelet response to acute mental stress in a sample of 34 men with a history of acute cardiac events. They found increased platelet aggregate response to standard behavioral stress protocols (color word and public speaking tasks) and delayed hemodynamic recovery in patients with a history of emotionally triggered acute coronary syndrome. This is particularly noteworthy as it documents an abnormal psychophysiological response in patients with a clinically documented history of psychological stress-evoked cardiac events.

Platelet dysfunction and heart failure

There is ample evidence of alterations in platelet function in patients with CHF. For example, one of the original studies in this area conducted by Mehta and Mehta [163] found evidence of increased platelet aggregates in patients with CHF compared to controls. The increase in platelet aggregation in this sample was correlated with vascular resistance. Other studies describe increased fibrinopeptide A [164], D-dimer [164], von Willebrand factor [164], plasma and blood viscosity [164], sCD40L [165], and soluble and surface-bound p-selectin [166]. Gurbel and colleagues found markers of platelet activation in 22% of their cohort of stable heart failure patients. They also noted a non-significant trend toward increased risk of cardiac events in the year following assessment [167] in patients with increased platelet aggregation. These alterations in platelet functions suggest increased platelet activation and are similar to the markers of increased platelet activation observed in patients with symptoms of depression.

Platelet dysfunction, depression, mental stress, and heart failure

Depression, mental stress, and heart failure are individually associated with increased platelet reactivity. Several mechanisms seem to be operative in mediating these effects including adrenergic stimulation, increased cortisol levels, serotonin dysfunction, and hemoconcentration. Though we may predict that the co-existence of depressive symptoms or acute mental stress might increase platelet reactivity in patients with heart failure, there is no existing literature to verify this assumption. To the best of our knowledge, there are no specific studies describing the effect of depression or mental stress on platelet function in patients with heart failure. Additional research to clarify the relationship between depression, mental stress, and platelet function in patients with heart failure is required.

Mental stress and ischemia

Overview

A long anecdotal tradition links situational stressors to illness and particular attention has been paid to the association between acute psychological stress and cardiovascular disease. For example, studies show that the risk of MI was more than 10 times greater in the hour after an episode of intense anger [168]. Population-based epidemiological studies have also begun to examine the effects of acute psychological stress on patients with preexisting CAD, for example, in the event of natural disasters or terrorist attacks. Research studies also demonstrated increased deaths following the Athens earthquake of 1981 [169].

Epidemiological data

Several research groups have also documented increased cardiac risk following the simultaneous terrorist attacks on the World Trade Center and Pentagon in 2001 [170, 171]. At a New York hospital outpatient clinic, the recorded frequency of tachycardia or ventricular fibrillation more than doubled in patients wearing implantable cardioverterdefibrillators (ICDs). Sixteen patients (8%) showed tachyarrhythmias within 30 days after 9/11, a 2.3-fold increase compared to 7 patients (3.5%) within 30 days before the attack. The first cardiac events were recorded 3 days after 9/11, which the authors speculated may suggest a “suba-cute” stress mechanism [171].

Post-9/11 stress was linked to cardiac events in persons geographically remote from the attacks as well. In a similar observation study of 132 ICD patients in Florida, 14 (11%) had tachyarrhythmias within 30 days after 9/11, a 2.8-fold increase compared to 5 (3.8%) in the 30 days before the attacks [172]. However, not all studies suggest a positive association between situational stressors and increased cardiac risk. Chi and colleagues examined city death records and found no increase in the number of cardiovascular deaths in New York City during the month after the 9/11 attacks [173].

Laboratory data

Epidemiologic evidence, such as that described above, is compelling but insufficient to support definitive conclusions about the effect of mental stress on cardiovascular health. Acute mental stress is easier to model in the laboratory than chronic stress and as a result a growing body of literature started to lay a foundation for understanding pathophysiologic mechanisms underlying this association. Studies suggest that 40–70% of patients with CAD experience transient ischemia in response to acute mental stress [174–176]. The development of myocardial ischemia in this setting has been shown to confer increased risk for fatal and non-fatal cardiac events [177–180].

Mechanisms—Although exercise or pharmacologic stress testing is the most commonly used risk stratification tool in patients with CAD, ischemia during these tests do not completely overlap with mental stress-induced ischemia and there is evidence that exercise or adenosine testing may not adequately assess the propensity of mental stress-related risk in this population [181, 182]. We recently reported that mental stress could provoke ischemia in 29% of CAD patients with negative exercise- or adenosine tests [181]. In another study, Hunziker et al. reported that the addition of mental stress to exercise testing improved the detection of myocardial ischemia [182]. These observations are due to the fact that mental and exercise stress produces different hemodynamic and catecholamine responses and may cause myocardial ischemia via different mechanisms. While mental stress produces pure adrenergic stimulation, exercise produces a combination of parasympathetic and neural and humoral sympathetic responses. With the start of exercise, there is an initial decrease in vagal drive followed by a rebound when the exercise is discontinued; neural sympathetic arousal have the exact opposite pattern of vagal response while adrenergic stimulation of humoral origin increases much more progressively and lasts much longer than the other two factors. As a result of these mechanistic differences, mental stress induces a comparable blood pressure response but a much smaller heart rate response when compared with exercise.

While the lack of dramatic HR response during mental stress is mostly due to the absence of parasympathetic withdrawal, the marked BP response during this stress modality is due to peripheral vascular responses with increase in peripheral vascular resistance. Goldberg and colleagues [183] studied the pathophysiologic mechanisms underlying mental stress-induced ischemia; mental stress was found to induce a rapid rise in systemic vascular resistance.

Peak catecholamine responses occurred within 1 min of starting the mentally stressful task. Furthermore, ischemia induced by mental stress was found to occur at a much lower rate/pressure product threshold compared to exercise-induced ischemia. This observation is the basis for the prevailing belief that other vascular mechanisms are involved in the development of mental stress ischemia. Transient epicardial coronary vasoconstriction has been shown to occur during mental stress in patients with CAD [181, 182, 184–188]. This seems to occur via an endothelium-dependant mechanism [187]. Dakak and associates reported that, the coronary microcirculation fails to dilate during mental stress [188]. In another study, Arrighi and colleagues [189] observed that mental stress blunts the augmentation of myocardial blood flow in regions without significant epicardial stenosis, suggesting a prominent role for microvascular dysfunction in this setting.

Another mechanistic difference between mental and exercise stress relates to the presentation of the stressor, while response to exercise is gradual; a mentally challenging task provides a sudden stressor without a warm-up period. In fact even healthy individuals have been shown to develop myocardial ischemia if exercised to a high work load without a warm up period [190].

The majority of patients report no anginal symptoms during mental stress; in addition, the electrocardiographic changes typically associated with exercise or pharmacologic stress-induced ischemia are not usually observed with mental stress ischemia [191]. Nonetheless, evidence of mental stress-induced ischemia is observed in both laboratory and daily life settings. In fact, ambulatory electrocardiogram (ECG) studies suggest that there may be as much as a three-fold increase in the relative risk of ischemia in the hour following highly negative emotional states [192]. Furthermore, studies suggest that ischemia during daily life follows a circadian pattern [193]. In a study by Krantz and associates, a circadian variation in ischemia was observed with a peak at 6 AM. A significant increase in ischemia occurred immediately after awakening, but activity-adjusted increases in morning ischemia persisted for 2 h afterwards. Furthermore, exogenous factors (including mental activities) were found to be the most potent triggers of ischemia during the morning hours [193].

Mental stress ischemia in patients with heart failure

The prevalence of mental stress-induced myocardial ischemia in patients with heart failure was the subject of two recent studies [194, 195]. Our group recently conducted a study in which 182 participants with a documented history of broadly defined CAD were submitted to a mental stress induction via a public speaking task. We found that patients with left ventricular dysfunction were equally susceptible to mental stress-induced myocardial ischemia relative to patients with normal left ventricular function (LVF; [194]). Akinboboye and colleagues also examined susceptibility to mental stress ischemia in CAD patients with versus without left ventricular dysfunction. Participants in this study underwent both bicycle-induced exercise and mental stress testing on alternate days. Participants were stratified based on left ventricular ejection fraction into normal, mild to moderate, and severe LVEF dysfunction groups. They found that MSI occurred more frequently in patients with severely reduced LVF (LVEF < 20%) compared to patients with normal LVF [190]. However, due to the relatively small number of studies in this area and the conflicting nature of these results, additional research will be required.

Conclusions

In summary, a large body of literature has attempted to describe the pathophysiologic mechanisms relating affective disorders such as clinical depression and psychosocial stress to heart failure. Several potential mechanisms have been proposed including HPA Axis dysregulation, autonomic nervous system dysfunction, inflammation, cardiac arrhythmias,

and altered platelet function. Mental stress may also be an important link between psychological and biologic functioning in this patient population, either through unique mechanisms such as myocardial ischemia or through its effect on other known mechanisms.

However, there are several limitations to this literature. First, current thinking about the mechanisms underlying the association between affective disorders and heart failure is based largely on evidence of parallel alterations in autonomic nervous system and neuroendocrine function. Although it appears that there are many similar processes occurring in both disorders few studies have examined affective disorders and CHF simultaneously. Second, it is difficult to interpret findings in studies that appear to be addressing heart failure populations as they often do not provide information about heart failure diagnosis or disease severity. Furthermore, though there is a fairly extensive literature detailing the common pathways between depression and heart failure, relatively little is known about other affective disorders or novel psychosocial risk factors such as mental stress.

In conclusion, the proposed psychobiological mechanisms that link depression and acute mental stress with CHF are in no way satisfactory and, in many instances, do not explain common clinical observations. For example, many CHF patients who exhibit the proposed autonomic, inflammatory, or platelet disturbances do not develop clinical depression. It is possible that there are other environmental or genetic factors that determine susceptibility to co-morbid depression and distress in these populations. Further research needs to be done in this area.

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