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## Review

# Psychophysiological biomarkers explaining the association between depression and prognosis in coronary artery patients: A critical review of the literature

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## ABSTRACT

This paper aims to provide an overview of the current state of affairs on psychophysiological factors that may explain the link between depression and adverse outcome in coronary artery disease (CAD) patients. Factors discussed include heart rate variability, inflammation, platelet function, hypothalamus–pituitary–adrenal axis activity, serotonin metabolism and polyunsaturated fatty acids. Evidence suggests the involvement of each of these factors in both depression and CAD, together contributing to the prospective association between depression and cardiac outcome. Unfortunately, the involvement of above factors has been evaluated mostly in isolation, despite their functional interrelations and associations with behavioral factors. Moreover, there may be specific relations between individual symptoms of depression and certain psychophysiological mechanisms, rather than with general depression, further complicating the notion of depression as a cardiotoxic factor. The relatively understudied complexity of the relation between depression and CAD may serve as an explanation for the finding that depression treatment does not or barely affect cardiac outcome. Future studies should focus on the network of psychophysiological (and behavioral) factors to elucidate their precise role and timing in depressed cardiac patients.

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Depression and ischemic heart disease are the two strongest contributors to the global burden of disease (Mathers and Loncar, 2006). Moreover, an intriguing and complex, bidirectional association between psychological factors and heart disease has been observed in which psychological factors act as risk factors for heart disease and vice versa. Most research has focused on the role

of depression, but other psychosocial risk factors of coronary artery disease (CAD) have been studied as well, including stress, anxiety, anger, and specific personality features, such as hostility and Type D personality (Rozanski et al., 2005; Razzini et al., 2008; Suls and Bunde, 2005). As most research has been done on the psychophysiological correlates of depression in the context of CAD, the focus of the current review will be on depression only. Research to date has concentrated on the association between depression following acute coronary syndromes (ACS) and its subsequent association with cardiac disease progression and cardiovascular events, such as myocardial infarction (MI), stroke, chronic heart failure, or cardiac death (Barth et al., 2004; Van Melle et al., 2004a).

The presence of depression following ACS is associated with a twofold increased risk of fatal and nonfatal cardiac events. In individuals without baseline CAD, major depression has been related to the onset of a wide range of cardiovascular diseases (Van der Kooy et al., 2007). In addition, depression following MI has been associated with an average 2.0–2.5 increased risk of poor cardiovascular outcome (Van Melle et al., 2004a). On the other hand, it has become clear that heart disease is a risk factor for depression, evidenced by at least threefold increased prevalence rates (15–20% versus 5% in the general population) of major depression following ACS (Thombs et al., 2006).

These findings warrant further research on the mechanisms behind the association between depression and heart disease (Berkman et al., 2003; Glassman et al., 2002; Lesperance et al., 2007; Van Melle et al., 2007). It is possible that an incorrect or incomplete understanding of the complex nature of the association between heart disease and depression lies at the heart of the failures of recent randomized trials showing only relatively modest improvements of depressive symptoms after antidepressive treatment that did not translate into improved cardiac outcome. Therefore, we set out to provide a review of the evidence on the role of psychophysiological factors in explaining the link between depression and adverse outcome in CAD patients. Earlier, in an authoritative overview, Carney and colleagues have identified lower HRV, reflecting altered cardiac autonomic tone, increased platelet aggregation, and inflammatory activation as possible factors (Carney et al., 2002). In the present review, we will (1) examine the current literature on these three factors, (2) add HPA axis dysregulation, serotonin transmission, and polyunsaturated fatty acids (PUFAs) as additional candidate psychophysiological factors, (3) provide insight in the potential integration of the different psychophysiological factors, and (4) discuss some ways of how to proceed.

## 1. Psychophysiological factors

### 1.1. Heart rate variability

Heart rate variability (HRV), or the healthy beat-to-beat variations in heart rate results from fluctuations in autonomic nervous system (ANS) activity at the sinus node, and is a non-invasive marker of ANS activation of the heart. In CAD, ANS imbalance is observed, indicated by vagal withdrawal and increased sympathetic cardiac drive. This imbalance, favoring sympathetic cardiac drive, is associated with tachycardia and a reduction of total power in the spectral domain of HRV, resulting in lower HRV than non-cardiac patients (Task force ESC and NASPE, 1996). Activation of the sympathetic Nervous System as reflected by decreased HRV is related to the occurrence of life threatening arrhythmias, particularly in patients with a low LVEF (La Rovere et al., 2001). As a consequence, reduced HRV is predictive of future arrhythmic events and sudden death in CAD patients (Grippio and Johnson, 2002).

Studies have suggested that depression may increase the risk for cardiovascular morbidity and mortality through decreased HRV, although mixed findings have been reported. While depression has been associated with reduced HRV in cardiac patients (Carney et al., 2001; Carney and Freedland, 2009; Stein et al., 2000; Van den Berg et al., 2005), studies have also reported on the absence of a relationship between HRV and depression (Gehi et al., 2005; Martens et al., 2008). This contrasting observation may in part be clarified by the presence of different symptoms in depressed, stable CAD and ACS patients. A recent reanalysis of the data from Gehi and colleagues showed that somatic symptoms of depression (such as fatigue and psychomotor changes) were associated with reduced HRV while cognitive symptoms (such as negative self-image) were not (De Jonge et al., 2007a). Another explanation for this discrepancy could lie in the timing of Holter monitoring as stable CAD and ACS patients represent different phases in the continuum of the coronary atherosclerotic process.

The possibility that the ANS might be implicated as a factor underlying the association between depression and poor cardiovascular prognosis, is debated as on the one hand Carney et al. (2005) report a partial mediation of the effect of depression on mortality by low HRV, while on the other hand Kamphuis et al. (2007) report that the increased risk of cardiovascular mortality due to depression in the general population, was not affected by HRV.

### 1.2. Inflammation

Inflammatory processes, such as leukocyte recruitment and expression of pro-inflammatory cytokines, are considered to contribute to the destabilization of atherosclerotic plaques and induce rupture and thrombosis in the later stages of atherosclerosis (Ross, 1999). Inflammatory markers also participate in the pathophysiology of CAD by direct effects on myocardial contractility and apoptosis, as was shown in patients with acute ACS (Tousoulis et al., 2006). Levels of C-reactive protein (CRP), interleukin (IL)-6, and tumor necrosis factor (TNF)-alpha were found to be higher in CAD patients, and these elevations impose an increased risk of major adverse cardiac events and mortality (Sukhija et al., 2007).

Depression is associated with increased levels of inflammation (reflected in increased levels of inflammatory markers like CRP, IL-6) in both CAD patients and psychiatric patients without CAD as shown in a recent meta-analysis (Howren et al., 2009). In psychiatric patients, pro-inflammatory cytokines have been positively related to individual depressive symptoms such as fatigue, cognitive dysfunction, and impaired sleep, as well as to an increased risk of treatment resistance (Miller et al., in press). Several studies have demonstrated that CAD patients with depression, as compared to the non-depressed, are characterized by an increased pro-inflammatory state (see Lett et al., 2004 for a review). It is known that such a pro-inflammatory state may induce 'sickness-behavior' in which somatic, flu-like symptoms of depression such as fatigue, anorexia and psychomotor retardation dominate (Dantzer et al., 2008), potentially explaining (part of) the relation between depression and inflammation.

Only a few studies have examined whether the effects of depression on cardiac prognosis may be mediated by inflammation. Vaccarino et al. (2007) found that depressed women with suspected ACS had an increased chance of adverse cardiac events (i.e. hospital stays for nonfatal MI, stroke, CHF, and CAD-related mortality) compared to their non-depressed counterparts. This increased risk could only for a small part be explained by increased levels of CRP and IL-6. Moreover, in patients with stable CAD, CRP levels explained only a small part of the increased risk of adverse

events (heart failure, MI, stroke, transient ischemic attack, or death) in those with depressive symptoms when considered in concert with a broader range of potentially mediating factors including behavioral ones (Whooley et al., 2008).

Endothelial dysfunction is one of the major features of the pathogenesis atherosclerosis. A non-invasive index for Endothelial function is the Flow mediated dilatation (FMD) of the brachial artery. Using FMD endothelial function is found to be an independent predictor of cardiovascular events in CAD patients. Moreover, a lower FMD is found in depressed patients compared to healthy controls. Additionally, in CAD patients depression was independently associated with a lower FMD (Pizzi et al., 2008; Sherwood et al., 2005), suggesting endothelial function to be a mediator in the relation between depression and the risk for cardiovascular events.

### 1.3. Platelet function

Platelets are involved in thrombus formation, a key pathophysiological mechanism in atherosclerosis and MI (Nemeroff and Musselman, 2000), as activated platelets stimulate atherosclerotic plaque progression, and anticoagulation therapy with platelet antagonists has proven to prevent MI.

It has been suggested that depression may also be linked to disturbed platelet function. A recent meta-analysis on the potential role of platelet activity in the depression – CAD link showed that several platelet activity markers are found to be increased in depressed patients as compared to non-depressed controls. In addition, studies that have compared depressed CAD patients with non-depressed CAD patients generally show increased levels of platelet releasing factors in CAD patients with comorbid depression (e.g., Von Känel, 2004). In depression, plasma serotonin (Wulsin et al., 2009) and norepinephrine levels (Wong et al., 2004) are increased. Since serotonin and norepinephrine are platelet agonists (Von Känel, 2004), higher levels of these parameters will result in increased platelet activation through positive feedback loops. It should be noted, however, that the findings in this area of study are very diverse (Von Känel, 2004).

### 1.4. Hypothalamus–pituitary–adrenal axis

The HPA axis plays a pivotal role in the human stress response, and its end product cortisol is heavily involved in the regulation of normal physiology. HPA axis dysregulation is associated with a variety of related CAD risk factors such as abdominal obesity, hypercholesterolemia, hypertriglyceridemia, hypertension, and glucose intolerance (Brown et al., 2004), although not all studies have confirmed these associations (Otte et al., 2004). Dysregulated cortisol secretion has been observed in the context of CAD, and it has been suggested that HPA axis dysfunction is implicated in the pathogenesis of CAD (Nijm and Jonasson, 2009).

In major depression, or after continued exposure to stress, the HPA axis is dysregulated in some cases, resulting either in a chronically excessive secretion of cortisol, due to diminished corticosteroid receptor sensitivity and a continuously increased hypothalamic secretion of corticotrophin releasing hormone, in the melancholic subtype, or in a chronically hypoactive HPA axis, due to corticotrophin releasing hormone deficiency in atypical major depression (Gold and Chrousos, 2002; Holsboer, 2001).

Although not formally tested, research findings hint at a mediatory role for cortisol, as HPA axis dysregulation in depressed patients affects a host of cardiovascular risk factors (Brown et al., 2004) and HPA axis dysregulation has been implicated in the pathogenesis of CAD (Nijm and Jonasson, 2009) and predicted CAD death in depressed male CAD patients (Jokinen and Nordström, 2009). Further evidence comes from a study in which higher levels

of depressive symptoms were significantly associated with an increased prevalence of the metabolic syndrome, partially mediated by HPA axis function, as reflected by urinary cortisol levels (Vogelzangs et al., 2007). Besides its mediating role, cortisol might be a shared risk factor for depression and CAD. Genetic studies indicate that common polymorphisms associated with altered HPA axis function might increase the risk of both depression and CAD (Koeijvoets et al., 2008; Van Rossum et al., 2006).

### 1.5. Serotonin

Serotonin modulates the formation of heart and brain already early in embryogenesis (Nebigil et al., 2000). The cardiovascular effects of serotonin are diverse; amongst them are brady- and tachycardia, vasoconstriction and dilatation. Long-term exposure to serotonin results in proliferative diseases of the endothelium and thickening of the cardiac valves (Watts, 2005).

Central serotonin dysfunction is considered as one of the main pathophysiological factors in depression, as serotonin metabolism is disturbed (Bach-Mizrachi et al., 2008), and genetic variations in proteins involved in serotonin processing have been associated to depression (Lopez-Leon et al., 2008). Furthermore, disturbed central serotonin transmission is associated with hypothalamic abnormalities that may contribute to altered appetite, and decreased libido, as well as thalamic and brainstem dysregulations thought to contribute to altered sleep (Ressler and Nemeroff, 2000). These depression-related signs and symptoms may also be observed in the onset of CAD.

Evidence supporting the role of serotonin in the association between depression and CAD comes from genetic studies. A large twin study revealed that shared genetic factors contribute substantially to the co-variation of depression and CAD (McCaffery et al., 2006). In another study, associations were found between specific genetic variants of the serotonin transporter and the presence of post-MI depression (Nakatani et al., 2005). Further support comes from experimental studies reviewed in Van Melle et al. (2006), showing that serotonin reuptake inhibitors, which normalize serotonin transmission in the brain, may reduce activity of platelets, decrease sympathetic nervous system activity, and may induce vasodilatation in vitro. However, above findings are preliminary, and by no means conclusive, as the methodological quality of studies is not optimal, and results should be replicated in vivo.

### 1.6. Polyunsaturated fatty acids

There are several distinct classes of PUFA, which are differentiated by the location of the double bonds in the fatty acid carbon chain. For example, omega-3 PUFAs have the first double bond after the third carbon atom, omega-6 PUFA after the 6th carbon atom. PUFAs play an important role in cellular integrity and intra- and intercellular signal transduction and have been linked to cardiovascular health but also to mental health.

In CAD patients, the use of omega-3 fatty acid supplements has been associated with a reduced risk of cardiac events and a decrease in the progression of atherosclerosis (Kris-Etherton et al., 2002). These protective effects of omega-3 fatty acids are explained by their anti-inflammatory properties, via direct effects on cytokine signal transduction and via control over the expression of pro-inflammatory cytokines (Massaro et al., 2008). In addition, omega-3 PUFAs have the potential to lower serum triglycerides (Weber and Raederstorff, 2000), while the use of relatively high doses of omega-3 PUFA (>3 g/day) has been found to be associated with clinically relevant blood pressure reductions in individuals with untreated hypertension (Appel et al., 1993).

To date, the relation between omega-3 PUFAs and depression is unclear, as there are many inconsistent findings. A meta-analysis on the effects of the consumption of omega-3 PUFAs showed a small beneficial effect in patients diagnosed with major depression, whereas this effect was absent in subclinically depressed populations (Appleton et al., 2006). In several small studies, depression has been associated with a decreased presence of omega-3 PUFA in adipose tissue, marking long-term dietary intake of omega-3 fatty acids (Sarri et al., 2008; Mamalakis et al., 2006). In addition, depression has been linked to lowered levels of omega-3 PUFA in erythrocyte membranes, a more short-term measure of dietary intake of omega-3 PUFA, in case-control studies (Assies et al., 2004; Edwards et al., 1998).

A couple of studies have examined omega-3 PUFA levels in CAD patients with comorbid depression, showing that plasma levels omega-3 PUFA were lower in currently depressed patients who recently suffered an ACS (Frasure-Smith et al., 2004). Amin and coworkers further showed that as compared to non-depressed CAD patients, the depressed patients had lower omega-3 PUFA levels in their erythrocyte membranes (Amin et al., 2008).

## 2. Integrating the psychophysiological factors

Given the fact that both depression and CAD are complex, heterogeneous diseases, it is unlikely that a single psychophysiological factor will explain a substantial proportion of the prospective association between depression and cardiac outcome. Accordingly, a recent review of the neurobiological mechanisms underlying the association between stress, mood disorders and cardiovascular dysregulation concluded that the bidirectional association between mood disorders and heart disease is multifaceted, involving an integration of several central and peripheral processes (Grippe and Johnson, 2009).

Multiple lines of evidence support the presence of a network of effects, of which serotonergic projection may be of specific importance. Central serotonergic projections are involved in the central regulation of cardiovascular reflexes and control both parasympathetic and sympathetic cardiovascular drives (Ramage and Villalon, 2008). These projections also modulate relevant endocrine axes, including the HPA axis (Fuller, 1996). Peripheral serotonin plays an established role in platelet aggregation and activation, facilitating plaque and thrombus formation, and in the regulation of vascular tone, hereby inducing hypertension, and facilitating damage to the vascular walls (Jonakuty and Gragnoli, 2008). Further, HPA axis hyperactivity inducing prolonged exposure to high levels of cortisol results in several changes in the immune system, such as the down-regulation of glucocorticoid receptors on leukocytes, thereby nullifying cortisol's natural immunosuppressant effects, and contributing to the pro-inflammatory state that promotes atherosclerosis (Miller et al., 2002). Atherosclerosis itself, due to its inflammatory properties, promotes the catabolism of tryptophan, leading to a decrease in central serotonin (Russo et al., 2003), as well as increased immune and platelet activation. In addition, desensitisation of central glucocorticoid receptors induces disturbances in central norepinephrine and serotonin transmission (Leonard and Myint, 2009). Influence of the HPA axis hyperactivity on serotonin also follows from research showing that SSRI treatment for depression is less effective in patients with a hyperactive HPA axis (Porter et al., 2004). Associations between PUFAs and serotonin and inflammation have also been suggested, as omega-3 and omega-6 PUFAs increase membrane fluidity and influence serotonergic neurotransmission (Chalon, 2006). Further, omega-3 PUFAs inhibit the production of pro-inflammatory cytokines by reducing the production of pro-inflammatory prostaglandins (Calder, 2006). Recent pre-clinical experimental evidence shows a complex

bidirectional relation between the sympathetic nervous system and inflammatory pathways. Peripheral pro-inflammatory cytokines induce activation of afferent neurons of the vagus nerve and central areas activating this nerve. The other way round the cholinergic-anti-inflammatory pathway was found to influence cytokine production of macrophages (Rosas-Ballina et al., 2009). Moreover, in a clinical study HVR was inversely correlated with inflammatory markers in both healthy individuals and CAD patients (Haensel et al., 2008) suggesting a role of the cholinergic-anti-inflammatory pathway in the pathophysiology of CAD.

Although tempting to represent all these interrelations in a single model, in our opinion, any attempt to develop such a model would fail, as it would be a priori incomplete, too succinct or too complex and losing its illustrative meaning. The relation between depression and CAD is best described as a complex system, consisting of many distinct but interrelated and interdependent components linked through multiple interconnections and feedback loops. We can only observe properties in cardiac patients with depression that emerge from the interaction of these components, and cannot be predicted from the properties of these individual components, as they are too much intertwined (Whooley et al., 2008). Instead of the presently prevailing reductionist approach in medical research, the entirety of processes involved in the relation between depression and CAD prognosis are better examined holistically, using advanced computational models from system biology instead of regular medical statistics. At the present, the inability of researchers to address the interrelatedness of the psychophysiological factors (using regular statistics) prevents the drawing of firm conclusions on how the mediating mechanisms between depression and cardiac events may operate.

In addition, although a thorough discussion of behavioral mechanisms underlying the association is beyond the scope of this review, recent evidence suggests that non-compliance to cardiac aftercare and access to cardiac aftercare may be important mediators which have been relatively understudied. Skala et al. (2006) noted that physiological pathways have received far greater attention than behavioral ones of which non-optimal CAD treatment (Druss et al., 2000), non-adherence to cardiac treatment (Ziegelstein et al., 2000) and aftercare programs (Grace et al., 2005), and poor lifestyle including smoking, poor diet, and limited physical activity (Whooley et al., 2008) are the most plausible ones. Druss and colleagues (Druss et al., 2000), comparing the health care utilization of post-ACS patients with and without mental disorders, found that patients with documented mood disorder were significantly less likely to undergo cardiovascular procedures. This finding suggests that physician decision making process or physician-patient interactions may result in suboptimal care for depressed ACS patients. In addition, higher rates of non-adherence and drop-out from CAD treatment regimens and aftercare programs have been reported in depressed (post-ACS) patients (Grace et al., 2005). Separate lines of research have indicated that depression is associated with an increased risk of displaying behavior patterns considered to be risk factors for CAD and its progression, including smoking (Manley et al., 2009), lack of physical exercise (Babyak et al., 2000) and being overweight (Lavie et al., 2009).

Strong recent evidence for the statement that lifestyle represents an important pathway between depression and CAD prognosis comes from the Heart and Soul study (Whooley et al., 2008), in which lifestyle factors accounted for almost 50% of the association between depression and new cardiac events. Physical activity alone accounted for >30% of the effects. Interestingly, physiological factors, including heart rate variability, inflammatory markers and serotonin levels only mildly attenuated the association between depression and cardiovascular events,

confirming that lifestyle is a promising venue to follow in future research on the depression–heart disease association.

### 3. Clinical implications

It is yet not clear whether progress in the understanding of the possible psychophysiological mechanisms will result in treatment options that will lead to both depression benefits and improved cardiac outcome. Apparently, the effects of antidepressants impacting on serotonin metabolism in CAD patients are comparable to the effects in persons in the general population (Thombs et al., 2008), in which a substantial proportion of depressive symptoms disappear also in response to placebo treatment or even in the absence of treatment. From a theoretical point of view, SSRIs may have the potential to improve cardiovascular prognosis (Van Melle et al., 2006). Depression is associated with enhanced platelet reactivity. Interestingly, SSRIs have shown pleiotropic effects. For example based on the level of platelet and endothelium derived biomarkers sertraline exhibited antiplatelet and endothelium protective properties (Serebruany et al., 2005). Animal studies pointed to vasoactive properties of sertraline (Van Melle et al., 2004a,b). It could therefore be hypothesized that in CAD patients SSRIs have beneficial effects independent from their CNS antidepressant effect. Effects of SSRIs on platelet hyperactivity seem quite consistent but may relate to an intrinsic pharmacologic effect of SSRIs on platelet function independent of depression (Galan et al., 2009). This is an important example to show that there might be underlying third factors contributing to both depression and CAD without the two necessarily being linked causally with each other.

However, in practice the effects of SSRIs on psychophysiological parameters are rather conflicting at best: the available studies are small, contradictory and difficult to compare due to differences in inclusion criteria. The effects of SSRIs on HRV have been studied, yet remain unclear: while some have found positive effects on HRV (Balogh et al., 1993; Khaykin et al., 1998), others have found negative effects (Volkers et al., 2004). No beneficial effects of antidepressant treatment on cardiac outcomes have been reported, except for indirect evidence from non-randomised comparisons (Taylor et al., 2005; De Jonge et al., 2007b). More, larger and carefully designed studies are therefore warranted, that in addition to hard medical outcomes also examine the response of multiple physiological characteristics to antidepressant therapy.

The extent to which depression can be regarded as a single disease entity in the presence of a severe physical illness such as CAD has been debated in the literature in recent years (e.g. De Jonge and Ormel, 2008). While the diagnosis of depression is determined on the basis of the presence of nine different symptoms, consistent support for the observation that some symptoms may be more strongly related to cardiac outcomes than other can be found. Specifically, the distinction between somatic-affective versus cognitive-affective has proved to be of interest, in which the first is consistently found to be associated with a worsened prognosis than the latter (e.g. De Jonge et al., 2006; Martens et al., 2009; Linke et al., 2009). Since it may be expected that these different symptom dimensions may warrant different therapeutical approaches, this distinction may be relevant for optimising antidepressant treatments in the future.

### 4. Concluding remarks

Although the bidirectional association between depression and cardiovascular disease is well documented, much of the role of psychophysiological factors explaining this association remains unclear due to the complexity of the network of systems involved. More attention should be directed to integrating the variety of

factors and assuming a more interdisciplinary approach, in which an amalgamation is sought between psychophysiological and behavioral factors.

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