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The puzzle of depression and acute coronary syndrome: Reviewing the role of acute inflammation ☆

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ABSTRACT

The relationship between depression and coronary heart disease is well-established, but causal mechanisms are poorly understood. The aim of this review is to stimulate different ways of viewing the relationship between depression and adverse outcomes following acute coronary syndrome (ACS) and coronary artery bypass graft (CABG) surgery patients. We present an argument for depression in ACS and CABG patients being a qualitatively distinct form from that observed in psychiatric populations. This is based on three features: (1) depression developing after cardiac events has been linked in many studies to poorer outcomes than recurrent depression; (2) somatic symptoms of depression following cardiac events are particularly cardiotoxic; (3) depression following an ACS does not respond well to antidepressant treatments. We propose that inflammation is a common causal process responsible in part both for the development of depressive symptoms and for adverse cardiac outcomes, and we draw parallels with inflammation-induced sickness behaviour. Clinical implications of our observations are discussed along with suggestions for further work to advance the field.

Contents

Comorbid depression is commonly observed in patients with coronary heart disease (CHD) [1–3] but has been most widely studied in patients with acute myocardial infarction (MI). A comprehensive literature review of hospitalised post-MI patients estimates the prevalence rate to be nearly 20% for major depression as measured using clinical interviews [4]. Prevalences varied from 7.3% (Hospital and Anxiety Depression Scale score ≥11) to 31.1% (Beck Depression

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Inventory (BDI) score ≥10) when using standardised questionnaires measuring elevated depression symptomatology [4]. Similar estimates have been reported more recently for both major and minor depression, again in post-MI patients [5,6]. The association between depression and cardiovascular morbidity following acute coronary syndrome (ACS) was first identified in the literature more than 15 years ago; Frasure-Smith et al. [7] showed that major depression in patients recently admitted to hospital for MI was an independent risk factor for mortality at 6 months. This association has been replicated in several studies [8] and has been demonstrated in coronary artery bypass graft (CABG) surgery patients as well [9]. The association with recurrent cardiac disease is apparent not only for clinical depression, but also for subclinical dysphoria and elevated symptoms of depression within the normal range [10,11]. Moreover, depression in CHD patients is associated with poorer quality of life after MI [12], longer hospital stays and greater cardiac-related readmissions after MI [13], greater disease progression (e.g., atherosclerosis in CABG patients [14]) and increased use of urgent and unscheduled care [13,15,16]. However, the mechanisms underlying the relationship between depression and CHD have yet to be fully understood.

Depression is associated with traditional cardiac risk factors including smoking, diabetes mellitus and hypertension [17] and of particular salience may be physical inactivity [18]. Covariates have been inconsistently controlled for across studies, making generalisation difficult. However, it seems unlikely that these factors entirely account for the relationship between depression and recurrent cardiac events; for example, Frasure-Smith et al. [7] did not find an association between depression and cardiac risk factors (including smoking, previous MI, Killip class, left ejection fraction, premature ventricular contractions and thrombolysis), while other studies controlled for a comprehensive range of risk factors statistically, finding the relationship between depression and recurrent cardiac events still remained [19]. Behavioural factors such as poor adherence to lifestyle and medical advice may partly mediate the association between depression and health outcomes in cardiac patients [20], but other factors may also be significant. Abnormal platelet function, neuroendocrine dysfunction and disturbances in autonomic cardiac control have all been proposed as mediating processes [21–23]. There are several puzzling features to depression following ACS that suggests a biological model may be useful to our understanding [24–26]. The aim of this article is to outline the main features of depression following ACS that result in future cardiac morbidity and to put forward a model related to inflammation and sickness behaviour that offers a framework for reconciling inconsistencies in the current literature and for guiding future research. While depression is also implicated in CHD onset [27], the focus of this article is on depression following acute cardiac events. Much of this work has been carried out with patients experiencing acute MI, although responses are likely to be similar in other manifestations of ACS. There is also growing evidence for the role of anxiety following ACS in predicting adverse outcomes. A recent meta-analysis concluded that anxiety following MI is associated with a 36% increased risk of adverse cardiac outcomes [28], although few studies have controlled as comprehensively for covariates as in the studies of depression.

Characteristics of depression after an ACS

Timing of depression and later cardiovascular morbidity

The first unusual feature of the relationship between depression and CHD is that there appears to be a difference between those patients who are depressed before the occurrence of an ACS and those who develop depressive symptoms following the cardiac event. Recent evidence indicates there is a stronger association with mortality and recurrent cardiac events in patients with new-onset depression (post-ACS depressed with no history of depression). For example, in a prospective cohort study of 588 patients admitted to hospital with MI, Dickens et al. [29,30] observed 167 cases of depression, of which 96 had depression before their MI and 71 who developed depression during the 12 months following their MI. Kaplan–Meier survival analysis showed that depression symptomatology from the week preceding MI did not confer risk of cardiac mortality, but new-onset depression did (hazard ratio=2.33, P=.038), even after controlling for a range of risk factors including age, history of angina prior to MI, Killip class, beta-blocker use on discharge, left ventricular fraction, use of antidepressant medication at baseline and serious cardiac events during 12 months follow-up. Similarly, de Jonge et al. [31] compared survival 1 year after acute MI in nondepressed, new-onset depressed and recurrent depressed (i.e., post-ACS depressed but with a history of depression) patients and showed an increased risk of recurrent cardiovascular events only in the new-onset group, even after controlling for age, sex, education, left ventricular ejection fraction and revascularisation. In a longer follow-up study of 750 ACS patients (BDI scores: 515 patients ≤10; 235 patients ≥10), Grace et al. [32] showed that depression symptomatology during hospitalisation after being admitted with an ACS was predictive of 5-year mortality, but history of depression was not. Parker et al. [33] conducted psychiatric interviews on 489 patients admitted to hospital with MI to diagnose patients with a pre-ACS history of depression (observed in 187 participants) and new-onset depression (observed in 57 participants at time of hospital admission and 48 participants at 1 month follow-up). After controlling for covariates including age, sex, left ventricular ejection fraction, diabetes, stroke, smoking and antidepressant use, results showed that cardiovascular outcome was not associated with pre-ACS depression nor with depression at the time of hospital admission; instead, the key risk factor for cardiac related mortality was depression that developed in the month following hospital admission. The small number of depression cases limited the power of this study. The study with the largest number of depression cases (550 recurrent and 370 new-onset cases) by Carney et al. [34] showed that although both new-onset and recurrent episodes of major depression predicted poor survival after acute MI, new-onset major depression episodes were more strongly predictive than recurrent episodes. An early study by Lesperance et al. [35] found that recurrent depression with a new onset following hospitalisation increased the risk of mortality at 18 months follow-up. By contrast, recent findings from the Setraline Antidepressant Heart Attack Randomised Trial (SADHART) found that although major depression following admission predicted mortality over the next 7 years, timing of depression onset and a history of major depression did not [36].

One explanation for this pattern proposed by Spijkerman et al. [37] and later Goodman et al. [38] is that new-onset depression is associated with more severe coronary artery disease than is recurrent depression; however, the studies reported above [30,31,33] all controlled for cardiac risk factors. It has been suggested that new-onset depression has different risk factors to recurrent depression [39], further indicating that it may be a distinct phenomenon. In particular, negative perceptions regarding one's heart condition in the days following an MI [40] or cardiac surgery [41] are associated with increased risk of developing depression. In conclusion, it seems new-onset cases of depression carry at least as much, if not more, risk as chronic, recurrent depression.

Depression symptomatology

The second intriguing feature of the depression–CHD relationship concerns the symptom profile of patients with post-ACS depression who are at risk for future cardiac events. Some types of symptoms appear to be more “cardiotoxic” than others, with somatic symptoms being particularly damaging. Analyses performed on two large data sets comprising more than 2000 patients compared three dimensions

of depression symptoms derived from the BDI in relation to cardiovascular risk markers, mortality and readmissions over an average of 2.5 years after ACS [42]. Cox regression analyses found somatic/affective symptoms (e.g., pessimism, fatigue) to predict cardiovascular events and mortality, even after controlling cardiac risk factors (left ventricular ejection fraction, Killip class and previous MI), while cognitive/affective (e.g., social withdrawal, work difficulty) and appetitive symptoms (e.g., loss of appetite, weight loss) did not [42]. Somatic/affective rather than cognitive/affective symptoms were also associated with an increased risk of cardiovascular related mortality and MI severity in a prospective study following 473 patients for an average 2.8 years [43]. Other studies have focused on specific somatic symptoms such as fatigue [44], with evidence that symptoms of fatigue/sadness are associated with increased risk of major cardiac events in patients up to 67 weeks post-ACS [45]. A more recent study of women with suspected myocardial ischemia demonstrated that both somatic/affective and appetitive (but not cognitive/affective) symptoms on the BDI predicted cardiovascular mortality and major events over a median of 5.8 years independently of coronary artery disease severity scores at baseline and self-reported history of cardiovascular-related events and conditions [46].

It should be noted not all evidence supports this association. For example, an early study by Lesperance et al. [35] found that by removing appetite and sleep disturbance symptoms from analyses, depression was better able to predict mortality at 6 months. However, a key limitation of this study is its small sample size, with only 42 depressed patients being followed-up at 6 months. Barefoot et al. [47] administered the Zung Self Rating Depression Scale to patients with stable coronary artery disease, with an average follow-up period of 15.4 years. They found that in a multivariate analysis of 867 patients, only higher negative affect and hopelessness were able to predict mortality and not somatic symptoms. However, this study did not involve MI patients; thus, it does not readily generalise to this population. Another study of stable CHD patients found that while somatic depression symptoms were more predictive of cardiac events than cognitive symptoms, they were also twice as likely to be reported, suggesting that power for detecting associations with cognitive symptoms may be an issue [48]. Davidson et al. [49] and also Leroy et al. [50] have found anhedonia (markedly decreased pleasure in activities) to be a key cardiotoxic symptom.

It is also interesting that somatic symptoms of depression overlap with the concept of vital exhaustion, which is commonly defined as symptoms of excessive tiredness, increased irritability and a sense of demoralisation [51]. Interestingly, vital exhaustion has been shown to be predictive of cardiac prognosis in MI and heart failure patients [52]. Although depression and vital exhaustion are generally understood to be separate constructs [53], more research is needed to delineate their independent effects on the prognosis of ACS patients. Cultural differences and variations in the depression assessment tool used are also likely to impact the findings from these studies.

Limited responsiveness to treatment

A third feature is that depression following ACS responds relatively poorly to standard treatment. The Enhancing Recovery in Coronary Heart Disease (ENRICHD) randomised controlled trial compared cognitive–behavioural treatment to usual case for depressed MI patients [54] but showed only a modest and poorly sustained difference in depression following treatment between the two groups. Although statistically significant, the improvement observed was only between 1.5 and 2.8 points depending on the scale used, which is of questionable clinical significance. Another randomised controlled trial, Canadian Cardiac Randomised Evaluation of Antidepressant and Psychotherapy Efficacy trial (CREATE) [55], used a two-factor factorial design to compare interpersonal psychotherapy vs. clinical management and citalopram vs. placebo pill. Citalopram had only a modest effect on depression scores, and there was no evidence that psychotherapy had a greater effect on depression than clinical management. Subgroup analyses of the CREATE study showed a better effect of citalopram on recurrent rather than first depression, a pattern that was not due to differences in cardiac disease severity or the presence of vascular depression [56]. A multicentre trial in the Netherlands (MIND-IT) compared flexible pharmacotherapy (primarily mirtazapine) with usual care in 331 depressed cardiac patients [57]. There was no significant difference between groups over 18 months either on depression case status or BDI score. A double-blind placebo-controlled study of 369 ACS patients, SADHART [58], reported greater improvements with sertraline (a selective serotonin-reuptake inhibitor (SSRI)) on only one of two primary measures, with the effect of treatment being greatest in those patients with severe and recurrent depression. Similar to ENRICHD, however, the overall difference between the groups was approximately 1 point on the Hamilton Depression Rating Scale or 2.2 points in the subgroup of patients with recurrent depression. Of importance here, a later analysis indicated that episodes of major depression that began after the ACS were less likely to respond to treatment than depression that began before hospitalisation [59]. In a systematic review, Thombs et al. [60] demonstrated only modest benefits to antidepressant treatment in cardiac patients, with effect sizes ranging from .20 to .38. High rates of placebo response as opposed to low treatment responses may, in large part, explain these results.

These clinical trials have also analysed the effect of treatment on survival. The ENRICHD study failed to find a difference between the groups on event-free survival at 29 months follow-up [54], although more recent analyses have suggested a benefit of group therapy plus individual therapy on mortality as compared with usual care [61]. Likewise, the MIND-IT trial failed to find an effect of treatment on cardiac events at 18 months follow-up [57]. In SADHART [58], a trend towards fewer cardiac events was observed in the setraline group, but this needs to be interpreted with caution because of the relatively short follow-up period of only 6 months. A more recent publication from this trial [36] showed that the severity of depression at baseline and poor treatment responsivity were predictive of mortality at 7 years follow-up, which is in line with evidence that treatment-resistant depression is linked to cardiac mortality [62,63].

The randomised trials described here have generally shown limited depression treatment efficacy in ACS patients. However, this should be interpreted in light of evidence from noncardiac populations. Turner et al. [64] conducted a literature search of both published and unpublished data on antidepressant efficacy in psychiatric populations, finding effect sizes that are comparable to the ENRICHD and SADHART results. This suggests both noncardiac and cardiac patients alike often respond poorly to standard treatment. One of the difficulties in determining whether cardiac patients respond less well to treatment is that many cases of depression resolve in the weeks following the event, making a treatment effect hard to demonstrate. The literature is suggestive of a reduced response to pharmacological and cognitive behavioural treatment following ACS, but further systematic studies are required fully to resolve this issue.

Summary

It can be argued that the form of depression in ACS that is particularly cardiotoxic is a distinct disorder from psychiatric depression. It is comprised of three elements, namely, new onset, somatic symptoms and limited responsiveness to treatment. The model we have described presents one way in which we can interpret the differences in presentation of depression in ACS patients compared with their psychiatric counterparts. An alternative explanation is that the depression/future cardiac morbidity link is an epiphenomenon and that the apparent association with recurrent cardiac events is due to underlying coronary artery disease severity.

Recurrent cardiac events and mortality are predicted by the extent of coronary stenosis and by features of the ACS such as impaired left ventricular function. A number of composite measures of risk have been developed such as the Global Registry of Acute Events (GRACE) index, which uses nine variables to predict survival, namely older age, history of MI, history of heart failure, increased pulse rate at presentation, lower systolic blood pressure at presentation, elevated initial serum creatinine level, elevated initial serum cardiac biomarker levels, ST-segment depression on presenting electrocardiogram and not having a percutaneous coronary intervention performed in hospital [65]. The predictive value of the index for short- and longer-term morbidity has been confirmed in independent studies [66,67]. Other risk measures include the Simple Risk Index, the EMMACE index and the PURSUIT index [68]. However, Lett et al. [69] found no relationship between depression and disease severity in a sample of over 1000 outpatients with stable CHD. A more recent study of 457 patients with ACS showed that that even after adjusting for GRACE scores, the relationship between depression and cardiac morbidity remained significant [70]. Nevertheless, other biological processes might be involved. For example, one possibility is that of the so-called vascular depression hypothesis [71], which posits that cerebrovascular disease can cause or perpetuate depression in elderly individuals. While there is some evidence in support of this view in ACS patients [72], recent analyses have not identified greater risk of vascular depression in new-onset patients [56]. For example, a 6-year prospective study of 3564 older adults found no association between measures of atherosclerosis and new-onset depression [73]. An alternative process that has received little attention to date is the very large inflammatory response that occurs during acute cardiac events.

An acute inflammation model of depression after major cardiac events (ACS or CABG)

Inflammation and depression

Depression is associated with an innate inflammatory response [74], and a meta-analysis by Howren et al. [75] has shown depressive symptoms to be positively associated with C-reactive protein (CRP), interleukin (IL) 1 and IL-6 in both clinical and community samples. Epidemiological evidence for the directionality of the depression–inflammation relationship is mixed, with some studies suggesting that depression precedes inflammation [76], while others showing that inflammation precedes depression [77].

The relationship has also been studied experimentally or quasi-experimentally, testing the depressive responses to acute inflammatory stimuli.

Vaccination studies

Inflammatory responses can be stimulated by administration of endotoxin or by inoculation with attenuated vaccines. Reichenberg et al. [78] used a cross-over design to test the effects of *Salmonella abortus equi* endotoxin or saline on sickness symptoms and mood. Blood was collected at baseline and at hourly intervals for up to 10 h postinjection. Results showed that healthy participants showed a transient significant increase in their levels of depressive and anxiety symptoms in response to the endotoxin together with increases in IL-6, IL-1 receptor antagonist (IL-1Ra) and tumour necrosis factor (TNF) α. No differences in sickness were reported after the endotoxin as compared with placebo. These results were confirmed in a similar study using *S. typhi* vaccine or placebo, reporting negative changes in mood following injection with vaccine that were significantly correlated with increases in IL-6 production [79]. Notably, no significant symptoms of nausea were reported, so it cannot be argued that negative moods arose because the participants were feeling ill. Brain imaging studies indicate that the cytokine-induced mood response to typhoid vaccination is correlated with activity within the subgenual anterior cingulate gyrus (sACC) and with reduced connectivity between the sACC and amygdala, medial prefrontal cortex, nucleus accumbens and superior temporal sulcus [80]. Interestingly, the inflammation induced by typhoid vaccination impairs endothelial-dependent vascular dilatation, implicating transient endothelial dysfunction [81]. This may be the mechanism underlying the transient increased risk of ACS in patients following acute infections such as influenza [82]. In summary, vaccination studies have shown that experimentally induced inflammation is capable of triggering negative mood responses.

Immunotherapy-induced depression

A second set of literature that is relevant concerns clinical studies investigating the effects of treatment with cytokine-based therapy on mood. These studies were stimulated by the observation of depression in some patients with cancer treated with immunotherapy [83]. Capuron et al. [84] systematically investigated the association between different immunotherapies (IL-2, IL-2 plus interferon (IFN) α, subcutaneous IFN-α or intravenous IFN-α) and the development of depressive symptoms in 33 patients with cancer. Patients treated with IL-2 or IL-2 plus IFN-α showed concomitant increases in depression symptoms and increased levels of the anti-inflammatory cytokine IL-10 during treatment. Patients who are susceptible to inflammation-induced depression are more likely to show higher depression symptom scores prior to treatment [85] and a heightened pituitary–adrenal response following the first IFN-α injection [86]. Another study showed that around one third of patients who were free of depression before therapy developed major depression during treatment with IFN-α [87]. Interestingly, Musselman et al. [88] studied the effects of treatment with an antidepressant on depression induced by IFN-α treatment in a randomised placebo-controlled trial of 40 malignant melanoma patients. The intervention (paroxetine or placebo) began 2 weeks before initiation of IFN-α therapy and continued for 12 weeks. Results showed that there was a fourfold reduction in risk of developing major depression by pretreatment with paroxetine (an SSRI). To summarise, cytokine-based immunotherapy induces depressive symptomatology, and these effects can be attenuated by pretreatment with antidepressant medication.

Animal work

Animal studies have also investigated the mechanisms linking inflammatory responses with depression-like syndromes. A comprehensive review is provided by Dantzer et al. [89], who present two lines of argument in support of the role of inflammation in the development of depression.

First, inflammatory stimuli induce depression-like symptoms. Frenois et al. [90] conducted an experiment using two measures considered to be indicative of depressive state in animal models: immobility and decreased preference for sweet solutions. They showed that mice treated with a proinflammatory cytokine stimulant (lipopolysaccharide) displayed increased immobility 24 h after two stress tasks aimed to elicit a depressive response (tail suspension and forced swim), even though motor activity had returned to normal. In addition, preference for sweetened water was also reduced even after food intake and drinking had returned to baseline levels. These effects are more prominent in genetically vulnerable species. For example, fawn-hooded rats, which exhibit many of the symptoms thought to align with depression, are more sensitive to IL-1β-induced immobility in the forced-swim test compared with controls [91].

Second, pharmacological corroboration for the role of inflammation has been provided by studies showing that depression-like symptoms induced by exogenously administered inflammatory stimuli can be attenuated with antidepressant drugs. For example, pretreatment with the antidepressant drugs imipramine or fluoxetine blocked the reduced intake of sweetened solution and reduced social

exploration in rats treated with lipopolysaccharide [92,93]. In another study, pretreatment with fluoxetine abolished the impaired performance of IL-1β-treated rats in a task designed to test reactivity to reward (anhedonia) [94].

These findings indicate that animal models corroborate the human literature with evidence that depression-like symptoms can be experimentally induced by inflammatory stimuli and are likewise responsive to pretreatment with antidepressant drugs.

Depression and low-grade inflammation in CHD patients

Depression has also been linked to inflammation in persons with CHD, although the literature is somewhat inconsistent. Some evidence shows depressed cardiac patients to have heightened inflammation; for example, Bankier et al. [95] studied 72 CHD outpatients of whom 30 were classified as having major depressive disorder. Stepwise multiple regression analyses revealed a significant positive relationship between depression and levels of CRP. Mixed findings were found in a much larger study by Lesperance et al. [96] who assessed 481 outpatients 2 months after hospitalisation for ACS with diagnostic psychiatric interviews. Depressed participants had higher levels of soluble intracellular adhesion molecule 1, but there was no association with IL-6. Frasure-Smith et al. [97,98] found patients with elevated depression symptoms to have higher levels of CRP, but not IL-6, as compared with nondepressed cardiac patients.

However, other studies have not supported this observation. Schins et al. [99] conducted a case-controlled study of depressed (n=57) and nondepressed (n=46) MI patients and found no differences between the groups in levels of IL-6, TNF-α or CRP. Frasure-Smith et al. [97] followed-up 741 patients for 2 years after ACS for major adverse cardiac events and showed that elevated CRP and BDI score 2 months after the cardiac event were both associated with increased risk to a similar extent. In other studies, Empana et al. [100] and, more recently, Davidson et al. [101] did not find that inflammation mediated the association between depression and cardiac outcome.

One difficulty in the interpretation of this literature is the impact of medications such as statins. In addition to their effects on cholesterol synthesis, statins have marked immunomodulatory and anti-inflammatory properties and modulate vascular endothelial function [102]. Other cardiovascular medications are also anti-inflammatory and have not been consistently taken into account. The relevance of this literature is also called into question by the controversy concerning the relevance of inflammation to prognosis in patients with stable coronary artery disease. Contrary to guidelines issued by the American Heart Association, some authors [103,104] have recently demonstrated that the literature relating elevated CRP with poor prognosis is seriously flawed, with poor control for confounders, poor methodology and publication bias. The significance of any associations between inflammatory markers and future CHD risk in patients with established disease is therefore uncertain.

Inflammation during ACS

An ACS is associated with a massive acute inflammatory response [105,106]. The magnitude of the acute inflammatory response during ACS is predictive of poor cardiac outcome. For example, Biasucci et al. [107] showed in unstable angina patients that increases in IL-1Ra and IL-6 measured 48 h after hospital admission were associated with greater risk of in-hospital cardiac events, while elevated CRP predicts 14-day mortality in unstable angina and non-Q-wave MI independently of troponin responses [108]. Further studies have confirmed this positive association in non-ST-segment elevation ACS patients [109] and acute MI patients [106,109–113]. A recent meta-analysis of 20 cohort and randomised controlled trials showed that CRP levels >10 mg/L measured within 72 h of ACS onset were associated with a relative risk of 2.18 (95% confidence interval 1.77–2.68) for recurrent cardiovascular events or death compared with values ≤3 mg/L [114]. Most of these studies controlled for age, sex, cardiac enzyme levels, ejection fraction, heart failure and other markers of risk, suggesting that the impact of acute inflammation is independent of multiple risk indicators. The association between these large acute inflammatory responses and subsequent depression has not been tested.

Coronary artery bypass graft surgery is also associated with an acute inflammatory response. The contact with the surfaces of the extracorporeal circuit inherent in cardiopulmonary bypass surgery (on-pump) triggers a systemic inflammatory response that, in severe cases, can lead to systemic inflammatory response syndrome; this is a serious disorder capable of causing major organ dysfunction and death [115]. Clinical management of the perioperative inflammatory response is therefore critical to patient outcomes. An observational study of 29 cardiopulmonary bypass patients by Holmes et al. [116] used a median split to compare outcomes between those patients who showed a heightened inflammatory response to those who did not. Findings showed that hyperresponders in IL-8, IL-6 and CR3 (an anaphylatoxin) had increased risk of adverse clinical outcomes. However, the small sample size limits the generalisability of these findings. Other work has shown an acute inflammatory response not only in on-pump but also off-pump surgery [117]. The extent of the inflammatory response is thought largely to reflect the amount of trauma derived from the surgical procedure itself and is associated with a host of clinical outcomes, both cardiac and noncardiac in scope [117,118]. However, there is a lack of studies in which perioperative variables have been adjusted for, limiting the conclusions to be drawn from these findings.

In summary, both ACS and CABG surgery are associated with an acute inflammatory response. In ACS patients, this inflammation is linked to prognosis; although the literature points towards this being true in CABG populations as well, more high quality research is needed.

Inflammation and depressive symptoms in patients with advanced CHD (in ACS patients and following CABG)

Depression and poor outcomes in patients who experience ACS or CABG appear to share a common inflammatory pathology. One way of understanding the association among depression, acute coronary events and inflammation is to draw on the literature on sickness behaviour. Sickness behaviour refers to a cluster of symptoms affecting both behavioural and affective state, triggered by the release of proinflammatory cytokines commonly observed in response to a systemic infection. In animals, sickness behaviour is reflected in social withdrawal, decreased locomotion and exploratory activity and reduced food and water intake. In humans, these are accompanied by malaise, increased negative mood, fatigue and listlessness. Parallels can be drawn between sickness behaviour and the symptoms of depression, including lassitude, fatigue and dysphoric mood, and this similarity forms the basis for a sickness behaviour model of depression in patients experiencing ACS or CABG. Sickness behaviour is thought to be adaptive in organising bodily responses that fight infection, promoting cellular (T-helper 1) immunity, targeting intracellular organisms through activation of macrophages, cytotoxic T lymphocytes and natural killer cells [119]. However, in the case of ACS and CABG, the extent of tissue trauma invokes a large inflammatory response, capable of triggering a series of sickness behaviours. In these vulnerable individuals, where the immune response is exacerbated in duration and intensity, decompensation (i.e., functional deterioration) occurs causing a shift in balance between proinflammatory and anti-inflammatory cytokines towards one of inflammation [89]. We hypothesise that under these conditions sickness behaviours are no longer benign but instead can take on the form of depression.

In this review, we presented the case that depression in ACS and CABG patients is distinct from that experienced in psychiatric populations based on three features in which timing, symptom profile and treatment responsiveness are key. The model of inflammation proposed would help to explain these differences by distinguishing the pathogenesis of depression in ACS and CABG patients from that of psychiatric patients. In ACS and CABG patients, the extent of the inflammatory response is such that it may promote not only worse cardiac outcomes but also depression. This depression is characterised by more somatic symptoms that we have hypothesised are caused by the activation of the sickness behaviour syndrome. In addition, depression in acute cardiac patients shows a reduced treatment response, possibly resulting from inflammation causing more physical, as opposed to affective, depression symptoms. Both these factors, in turn, can be linked to poorer outcomes for these patients, since there is substantial evidence that depression with concomitant physical symptoms is associated with a longer depressive episode, less response to treatment and less adherence to treatment [120].

The model of inflammation we propose is not exclusive, and other pathways are certainly relevant. Indeed, there may be several forms of depression within the ACS patient population, with only a subset experiencing the inflammation-related syndrome described here. For example, it is generally assumed that depression in the physically ill results from illness burden (i.e., ongoing symptoms), role limitation and associated loss events in people who are vulnerable, such as through genetic vulnerability to depression or poor coping strategies. The sickness behaviour model suggests there may be a direct biological element to the development of depression, although there is something still missing from this argument—inflammation elicits a behavioural syndrome that resembles depression, yet it is not quite depression. One explanation could be that these sickness behaviours act as an additional burden among people who are already vulnerable. Alternatively, it might be that there are neurocognitive changes associated with inflammation that account for the behaviours and possibly result in mood changes. Underlying this could be the effects of inflammatory mediators on neurotransmitters such as serotonin [121] or even minor damage to the central nervous system [122]. More research is needed to delineate these mechanisms in greater detail.

Implications

This review is intended to stimulate different ways of viewing the relationship between depression and adverse outcomes following ACS and CABG, describing the ways in which depression manifests itself in ACS patients and proposing an inflammatory model to account for this presentation. This is unlikely to be the only mechanism, and other pathways and processes are undoubtedly at work. Nevertheless, if an inflammatory pathway is relevant, it would have several implications. First, we would expect the magnitude of the acute inflammatory response to predict the development of depression following acute cardiac events or CABG and that ongoing inflammation might help sustain depressive symptoms. Second, the size of acute inflammatory responses might be associated with the biological mechanisms related to future cardiac morbidity that are associated with depression, including reduced heart rate variability, hypothalamic–pituitary–adrenal axis dysregulation and impaired platelet function. Third, it can be inferred that the association between depression after ACS or CABG and adverse cardiac outcomes would be reduced if inflammation was included in the model. Finally, interventions that reduce acute inflammation during cardiac events might reduce the magnitude of depressive responses. Current trials are evaluating techniques for limiting acute inflammatory responses, for example, the MRC-ILA-HEART study [123]. If these trials are successful, they would provide the opportunity to test links between inflammation and the development of depression in ACS patients.

There are also important clinical implications of this hypothesis. There has been a recent drive to effectively screen and manage depression in ACS patients, an approach advocated by the American Heart Association Prevention Committee [124]. The methods recommended include routine screening of all cardiac patients for depression using two short instruments—the Patient Health Questionnaire 2 and 9. This approach has been reviewed by Sowden et al. [125], who found them to be feasible, well-accepted and not resource-intensive. However, effective treatment for these patients continues to pose a challenge. The lack of response to treatment of depression following ACS is itself something of an anomaly, because inflammation-induced depression in melanoma patients [87] and depression-like behaviour in animal models [92–94] are responsive to treatment. While there is some evidence in favour of using an enhanced care approach to alleviate depression symptoms, improve patient satisfaction and reduce cardiac mortality in ACS patients [126], other novel attempts to improve treatment efficacy have not been so effective [127]. There is some evidence that psychological therapies with a behavioural component may be useful in reducing all-cause mortality [128]. However, more work is still needed, and exploring the mechanisms underpinning the relationship between depression and ACS may provide an opportunity for developing more targeted and selective therapeutic strategies. Other areas for future research include elucidating the trajectory of inflammation over time and understanding the processes by which acute inflammatory responses during an ACS or CABG relate to subsequent elevations in inflammatory markers 2 to 8 weeks after the event. In addition, more research is needed to extend our knowledge of depression following an ACS to the CABG surgery population; for example, does depression following CABG have similar characteristics to those observed in ACS, with somatic symptoms being particularly hazardous?

Conclusion

We have presented an argument for depression in ACS patients and in patients following CABG being a qualitatively distinct form from that observed in psychiatric populations. This is based on three features: (1) depression developing after cardiac events is linked to equally if not poorer outcomes as recurrent depression; (2) somatic symptoms of depression following cardiac events are particularly cardiotoxic; (3) depression following an ACS does not respond well to antidepressant treatments. We have proposed that inflammation is a common causal process responsible, in part, both for the development of depressive symptoms and for adverse cardiac outcomes and have drawn parallels with inflammation-induced sickness behaviour. Future work is needed to test this pathway empirically and to elucidate the complex interactions occurring between psychology and physiology.

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