REVIEW

Heart and mind: (1) relationship between cardiovascular and psychiatric conditions

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The relationship of our emotions and psyche to heart disease is intriguing. In this article we have reviewed the evidence linking cardiovascular and neuropsychiatric disorders and the possible mechanisms and pathophysiology of this association. This review is derived from Medline searches (1966–2002) using the relevant search terms (psychiatric disease, cardiovascular disease, depression, anxiety, and pathophysiology). Finally, the possible role of using mood enhancing therapies (mainly antidepressants) and their safety in patients with cardiovascular disorders is briefly discussed. In a companion paper, the therapeutic aspects of these two conditions is highlighted.

Cardiovascular diseases, such as ischaemic heart disease (IHD), hypertension, chronic heart failure, and arrhythmias are highly prevalent conditions contributing 15.3 million deaths in 1996 and accounting for 30% of the global death toll that year.[1–3] More specifically, they account for almost half of all deaths in developed countries and 25% of deaths in developing countries.

Neuropsychiatric illnesses and the use of psychotropic medications are equally prevalent.[1 4] The two conditions can merely coexist; however, there are now substantial data supporting a strong relationship between these two prevalent conditions. The interaction of heart and psyche is bidirectional. Emotions and stressful experiences affect the heart directly through the autonomic nervous system and indirectly through neuroendocrine pathways. Conversely, cardiac activity and function can reach conscious awareness and may be experienced as symptoms.

However, psychological aspects of organic illnesses are usually ignored or underdiagnosed.[1] Physicians often attribute somatic complaints of fatigue, lethargy, insomnia, and loss of appetite to underlying physical condition and medications. There may also be a lack of confidence by physicians in the use of psychotropic drugs in cardiovascular conditions. Although several psychotropic agents have been shown to be cardiotoxic, there are others that have been shown to be safe in cardiac conditions and might actually improve a patient's morbidity.[4]

This article was written in order to review the extent and coexistence of the two groups of diseases and the relationship between cardiovascular diseases and psychiatric conditions.

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NEUROPSYCHIATRIC FACTORS AFFECTING PATHOGENESIS AND PROGRESSION OF CARDIOVASCULAR DISEASES (BOX 1)

Psychosocial factors

Psychosocial factors may affect behaviours such as smoking, diet, alcohol, or physical activity that in turn can influence the risk of coronary heart disease.[1]

Personality trait and behavioural pattern

A type A personality (a highly ambitious and aggressive individual) has always been considered a prototype for the development of heart disease. One study conducted on initially healthy individuals showed that those with type A behaviour patterns showed a significant risk of developing IHD compared with type B (calm, laid back, and non-aggressive) individuals.[1] However, other studies failed to support this association.[5] These contradictory findings have led to a search for more specific components of type A behaviour that may have a stronger association with IHD. Anger and/or suppressed anger have been suggested to be the pathogenic components of type A personality. Anger, suppressed anger, hostility, antagonistic interactions, cynicism, and mistrust have been associated in long term, prospective studies with an increased incidence of IHD, acute coronary syndromes, and total mortality.[6–10] An angiographic study by Goodman *et al* also reported an association between the degree of hostility and prediction of restenosis after percutaneous transluminal coronary angioplasty.[11]

In general, it appears that hostility and anger may predispose more to the initial cardiac event than adversely influence the course of already established coronary artery disease. It is unclear to what degree hostility's effect may be mediated through its influence on other risk factors, such as lack of social supports, smoking, diet, and alcohol use.

Depression

Major depression is a prevalent and disabling mental illness that is underdiagnosed and undertreated.[1 4] Different degrees of association between depression and IHD have been shown in many epidemiological and observational studies. These studies have shown raised cardiovascular mortality and morbidity rates in patients with diagnosis of depression.[12–19] The evidence that

Abbreviations: HRV, heart rate variability; 5-HT, serotonin; ICD, implantable cardiac defibrillators; IHD, ischaemic heart disease

Box 1: Psychological and social factors implicated in the causation of cardiovascular conditions

Psychosocial factors
- Social class.
- Income.
- Area.
- Type of job.

Type A personality traits
- Anger/suppressed anger.
- Hostility.
- Antagonistic interactions.
- Cynicism.
- Mistrust.

Depression

Anxiety
- Phobic anxiety.
- Acute and chronic mental stress.

depression is a risk factor for the development of IHD is less extensive and somewhat less conclusive. Some prospective studies report a modest association between depression and the incidence of IHD, but others fail to find a correlation. In longitudinal studies of initially healthy, community residents without a history of IHD, depression has been associated with a relative risk between 1.5 and 2.0 for the subsequent development of IHD, myocardial infarction, and cardiac death over moderate to longer periods and is largely independent of traditional risk factors (table 1).

On the other hand, depression and depressive symptoms are found to be common in patients with established IHD. Clinically significant depressive symptoms are found in 40%–65% of patients after a myocardial infarction.[20 21] Although most subjects in these studies have been male, there is evidence that the risk of depression in women with IHD may be twice as high as that of men.[1 13 14] The prevalence of depression is also increased in patients with stable IHD and in patients who have undergone coronary artery bypass surgery.[22 23] In patients with implantable cardiac defibrillators (ICDs), while most recipients adjust well to living with the implant, a substantial minority suffer anxiety, depression, and anger that appear to be related to the ICD. A large number of studies have reported on the incidence of psychopathology and common psychosocial problems among patients with ICDs.[24 25]

Major depression and subthreshold depressive symptoms, in patients with IHD, have also been shown to confer an increased risk for subsequent cardiac events.[26 27] In addition, depression exacerbates, prolongs, and amplifies cardiac symptoms.[28] Depression also appears to exert a negative prognostic influence on the course and outcome of IHD. In patients with documented IHD, depression predicted cardiac events and was associated with elevated rates of cardiac mortality.[28 29] After myocardial infarction, depression may increase the risk of future coronary events, both over short and longer periods of time.[30]

The relationship between depression and IHD may be mediated through several different behavioural and physiological mechanisms. Depressed individuals may take poorer care of themselves, pay less attention to diet, drink more alcohol, smoke more, have less motivation and energy to exercise regularly, and be less likely to seek medical care. Depression is also associated with poorer adherence to a medical regimen, cardiac risk factor modification, and a rehabilitation and exercise programme.[31] However, as explained later, depression also has a causal association with the development of IHD explained by various pathophysiological processes.

Anxiety

Chronic anxiety and anxiety disorders such as panic and phobias appear to exert a negative influence on the heart.

Table 1 Prospective studies of the association between depression and ischaemic heart disease (IHD)

Study	Total sample	IHD measure	Follow up (years)	No of non-fatal and fatal events	Relative risk (95% CI)
Anda *et al* (1993)[12]	2832	Non-fatal/ fatal IHD	16	205 non-fatal 189 fatal	1.6 (1.10 to 2.40) 1.5 (1.00 to 2.30)
Ariyo *et al* (2000)[119]	5888 mortality	IHD/all cause	6	606 fatal/non-fatal IHD 270 fatal/non-fatal MI 298 non-fatal angina 614 deaths 122 non-fatal 290 fatal	IHD 1.11 (1.01 to 1.22) MI 1.12 (0.97 to 1.29) Angina 1.13 (1.13 to 1.23) Death 1.13 (1.03 to 1.23)
Ferketich *et al* (2000)[120]	7893	Non-fatal/ fatal IHD	11	Men non-fatal 187 Men fatal 137 Women non-fatal 187 Women fatal 129	Men non-fatal 1.71 (1.14 to 2.56) Men fatal 2.34 (1.54 to 3.56) Women non-fatal 1.73 (1.11 to 2.68) Women fatal 0.74 (0.40 to 1.48)
Ford and Mead (1998)[121]	1190	IHD/MI	40	163 non-fatal	IHD 2.1 (1.24 to 2.63)
Sesso *et al* (1998)[122]	1305	Non-fatal/ fatal	14	30 non-fatal 20 fatal	IHD 1.5 (0.82 to 2.58)

CI, confidence interval; MI, myocardial infarction.

Several studies suggest a relationship between anxiety disorders and increased cardiac outcomes (table 2). High levels of phobic anxiety were associated with an almost fourfold increase in the relative risk for fatal IHD in the Northwick Park study.[32] In a much larger study, in subjects with no prior history of IHD, a dose-response relationship was found between phobic anxiety and coronary heart disease mortality (relative risk 2.5, 95% confidence interval 1.00 to 5.96).[33] Further analysis revealed that this association was caused by an increased risk of sudden death. These findings persisted after adjustment for smoking and other risk factors and in a sample including baseline cases of coronary heart disease. Interestingly, no association was found between phobic anxiety and either non-fatal myocardial infarction or total IHD.

Association between other anxiety disorders and cardiovascular mortality was assessed in another work by Kawachi *et al*.[34] Although it showed a significant increase in the relative risk for cardiac mortality, after adjusting for other cardiovascular risk factors, the multivariate odds ratio for fatal coronary heart disease became non-significant. Further analyses of this work also looked at another dimension of anxiety: chronic worrying as a risk factor for coronary heart disease. Overall, worries (particularly about social, financial, and health conditions) were found to be associated with total coronary heart disease including angina and non-fatal and fatal myocardial infarction.

Acute and chronic mental stress

Acute and long standing stress is shown to increase the risk of IHD. Sudden, acute mental stress has negative cardiovascular consequences. Cardiovascular mortality rises in the month immediately after the death of a loved one.[35] The incidence of cardiac events also rises immediately after natural disasters and among civilians subjected to military attack.[36] Such stressors increase heart rate, blood pressure, and myocardial oxygen demands. The effect of acute mental stress on the heart already damaged by pre-existing IHD has been studied extensively. Such stress can precipitate myocardial ischaemia in 30%–60% of IHD patients.[37] Circumstances and situations leading to intense anger and, to a lesser degree, to anxiety are also potent triggers of myocardial ischaemia.[38 39] Thus, there is a twofold increase in the risk of myocardial infarction in the two hours after an episode of intense anger.[40]

Chronic stresses such as job strain and other forms of work related stress have also been shown to have a very strong association with cardiovascular disease. Job strain has been associated with an increased risk of IHD in previously healthy people.[41 42] Cross sectional and longitudinal studies disclose that both male and female workers in jobs high in strain have a higher prevalence of IHD and a higher incidence of myocardial infarction than those with low job strain.[43–45]

In addition to IHD, acute and chronic stress has also been shown to be associated with lethal arrhythmias and sudden cardiac death. A number of studies report increases in life stress in the months preceding sudden cardiac death.[46–53] However, many of these studies lack suitable control groups and are subject to systematic reporting bias or employ problematic measures of life stress.

PATHOPHYSIOLOGY

Psychological stress and conditions such as depression, anxiety, and a specific personality type may cause direct pathophysiological changes (box 2). There is evidence linking neuropsychiatric conditions with hormonal and haematological abnormalities. These include hypothalamic pituitary axis activation, adrenergic hyperactivity, platelet abnormalities leading to increased adhesiveness, raised fibrinogen levels, endothelial dysfunction, raised left ventricular mass, and the progression of carotid atherosclerosis.

Neuroendocrine activation

A stable endocrine system plays an important part in the overall integrity and normal functioning of the cardiovascular system.[54 55] Potentially, many neuroendocrine pathways exist by which acute or chronic psychiatric conditions may contribute to the development of cardiovascular diseases through metabolic and haemostatic actions. Psychological stress results in hypothalamic-adrenocortical and sympathoadrenal hyperactivity.[56–60] This can induce raised corticosteroid and catecholamine concentrations leading to multiple metabolic and autonomic effects. Chronic activation of these pathways has been shown to promote atherosclerosis by causing increases in glucose, cholesterol and free fatty acids, and a blunting of the action of insulin, besides a rise in blood pressure.[61] Sympathoadrenal activation can also contribute to cardiovascular disease through a direct effect of on cardiac function, blood vessels, and platelets.[62–65]

Arrhythmias

Hyperactivity of the hypothalamic-adrenomedullary axis with a resulting increase in circulating catecholamines can cause increased myocardial irritability and a decreased threshold for induction of ventricular fibrillation.[55 66] Sympathetic stimulation of the heart exerts a proarrhythmic effect. It increases ventricular ectopy and lowers the threshold for inducing ventricular arrhythmias especially in the heart with pre-existing ischaemic damage or electrical instability.[67] There is an association between increased mortality after myocardial infarction and depression relating to ventricular ectopic activity. Although ectopic activity is not increased in depressed patients, there is evidence that when

Table 2 Prospective studies of the association between anxiety and ischaemic heart disease (IHD)

Study	Total sample	IHD measure	Follow up (years)	No of non-fatal and fatal events	Relative risk (95% CI)
Haines *et al* (1998)[123]	3500	Non-fatal/fatal IHD	6	57 non-fatal 56 fatal	1.26 (0.62 to 2.54) 3.77 (1.64 to 8.64)
Kawachi *et al* (1994)[33]	51529	Non-fatal/fatal IHD	2	128 non-fatal 140 fatal	0.89 (0.45 to 1.79) 2.45 (1.00 to 5.96)
Kawachi *et al* (1994)[34]	2280	Non-fatal/fatal IHD	32	137 non-fatal 131 fatal	0.71 (0.24 to 2.09) 1.94 (0.70 to 5.41)
Kubzansky *et al* (1997)[124]	2280	Non-fatal/fatal IHD	20	113 non-fatal 86 fatal	2.41 (1.40 to 4.13) 0.81 (0.45 to 1.44)

CI, confidence interval.

Box 2: Probable pathological processes triggered/induced by psychological factors involved in the aetiology of cardiovascular system abnormalities

Hypothalamic-adrenocortical and sympathoadrenal effects
- ↑ Cortisol.
- ↑ Blood glucose.
- ↑ Cholesterol.
- ↑ Free fatty acids.
- ↑ Insulin.

Haematological effects
- ↑ Plasma fibrinogen.
- ↑ Platelets aggregation.
- ↑ Platelet factor 4.
- ↑ β-Thromboglobulin.

Cardiac rhythm effects
- Arrhythmias.
- ↓ Heart rate variability.

Cardiac and vascular effects
- ↑ Carotid-intima thickness.
- Endothelial dysfunction.
- ↓ Left ventricular mass.

excessive ectopic activity does occur it has a stronger association with death in patients who are depressed.[68] Patients who were not depressed experienced little increase in risk associated with ventricular ectopic activity even if they had a low ejection fraction.[68] This finding fits in well with animal based models pointing to proarrhythmic factors as the link between psychological disorder and sudden cardiac death.[50 69 70] Experimentally induced psychological stress lowers the ventricular threshold for ventricular fibrillation and increases the frequency of ventricular ectopic beats in animal based models with pre-existing ventricular arrhythmias.[70]

Heart rate variability (HRV) is an important indicator of autonomic nervous system function and stability.[54 55] Blunted or reduced HRV is associated with increased risk of recurrent events in patients with acute coronary syndromes or in survivors of cardiac arrest.[71–73] In patients with depression there is evidence of a low HRV.[74 75] Patients suffering from depression seem to have higher sympathetic tone and blunted inhibitory reflexes. Interestingly, treatment of these patients with antidepressants has been shown to be associated with increase in HRV and thus a possible improvement in mortality.[76 77]

Effect on fibrinogen

Fibrinogen is an acute phase reactant protein, raised levels of which are associated with increased risk of cardiovascular disease.[78 79] Plasma fibrinogen levels have also been found to be associated with several social and psychosocial factors in adulthood, consistent with high rates of IHD in deprived strata of society.[80 81]

Platelet abnormalities

Platelet dysfunction appears to play a fundamental part in the vulnerability of depressed patients to IHD.[82] There is evidence of a baseline elevation in platelet reactivity in depressed patients both with and without co-morbid IHD.[82–85] This heightened activity appears to increase cardiovascular risk and the likelihood of thrombus formation. Increased plasma concentrations of adrenaline and serotonin (5-HT), which have been reported in depressed patients, may contribute to altered platelet function.[86 91] In addition, changes in platelet physiological characteristics that adversely affect platelet function, such as increased intraplatelet calcium mobilisation, upregulation of 5-HT_2 receptors or α_2-adrenoreceptors, downregulation of 5-HT transporter number, altered second messenger signal transduction, or altered intraplatelet concentrations of monoamines or catecholamines, may also be present in patients with depression and contribute to clotting diathesis.[86–91]

5-HT is a neurotransmitter, and has an integral role in the causation of depression.[92] Platelets are richly endowed with 5-HT receptors, and platelet aggregation and coronary vasoconstriction in diseased arteries are partly regulated by activation of these receptors.[86 88 90 93] Platelets from depressed patients have been shown to exhibit increased 5-HT binding density (which normalises on remission of depression) and reduced density of transporter sites.[88–90] Although 5-HT has only a weak thrombogenic effect, it amplifies the response of platelets to other thrombogenic agents. It is therefore possible that 5-HT not only plays a major part in the neurobiology of depression, but probably also influences thrombogenesis.[86] It has been shown that short term treatment with an antidepressant paroxetine reverses platelet abnormalities in depressed patients without cardiac disease and in depressed patients with coronary artery disease.[94]

Platelet factor 4 and β-thromboglobulin are proteins, the levels of which are directly proportional to platelet aggregability. Their levels have been found to be raised in patients suffering from major depression and significantly decrease when they are treated with paroxetine.[95] Increased platelet adhesion has also been shown in circumstances of excessive emotional stress particularly anger and hostility.[33–35 96]

Vascular abnormalities

Carotid intima-media thickness has been shown to be correlated with coronary heart disease.[97 98] Several animal and human studies have shown an association between increased intima-media thickness and psychosocial and socioeconomic factors.[99–103]

Endothelial dysfunction is an early manifestation of developing coronary heart disease. Endothelium plays an important part in determining the vasomotor tone and prothrombotic/antithrombotic and inflammatory processes. Impairment of endothelial function has been shown to be associated with sympathetic over activity and its manifestations in various animal and human studies.[104–105]

Increased left ventricular mass

Left ventricular hypertrophy on electrocardiography has been shown to be strongly associated with clinical cardiovascular end points.[106 107] There are at least two major studies showing the association of psychosocial conditions and left ventricular hypertrophy on electrocardiography.[108–110] However, in another study psychosocial variable or stressors were not found to be significantly associated with increased left ventricular mass on echocardiography.[111]

CONCLUSION

In conclusion, there is quite convincing evidence regarding relationship between diseases of the psyche and conditions affecting the cardiovascular system. This association is particularly strong in patients with depression and phobic anxiety. Depressive symptoms as well as depressive caseness seem to be influential in predicting IHD. It is, however, unclear what the effect of duration of depression is on risk. In case of phobic anxiety, there is a clear association with increased risk of sudden cardiac death. It is probably related

to increased susceptibility to arrhythmias. Like depression, this association with increased myocardial mortality has clinical therapeutic implications. The question whether treating patients with these psychiatric conditions may influence their cardiovascular risk profile needs further exploration and research. Active management of these patients with psychiatric illnesses can potentially reduce the morbidity and mortality associated with coronary heart disease.[112–116] Progress will depend on a greater understanding of the pathophysiological and biochemical links between depression and coronary heart disease and more precise identification of the aspects of depression that confer risk and of the population groups most at risk. The safety of antidepressants is also a factor that should be considered before prescribing these medications in vulnerable patients (unstable symptoms or patients with recent myocardial infarction). More recent work regarding the newer antidepressants in the SADHAT[117] and SADHART[118] trials has shown the safety of at least one selective 5-HT reuptake inhibitor. Hence, in patients with significant depressive symptoms and even recently unstable IHD, this class of medications can be used with greater confidence and safety.

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The rise of troponin

In recent years the use of troponin testing to monitor myocardial damage has become more pervasive and prominent, replacing the old style CK-MB measurement. Troponin elevation is a marker of cardiac injury and high risk, it is also raised in a minority of acute coronary syndrome patients. However, it is important for clinicians to realise that a single rise in troponin levels is of indeterminable significance. An appropriate series of tests over time, fitting in with the right clinical picture, is of most value.

The troponin complex in striated muscle fibres has three distinct subtypes and c-troponin-I is believed to be the one present only in cardiac muscle. Consequently, c-troponin-I is released when there is an assault to the myocardium and this is what laboratory testing picks up (some laboratories may measure the troponin-T subunit; this, however, has been found to be less specific and less sensitive). Interpretation of results can be confusing and there are several caveats to be aware of. A positive c-troponin-I level means that cardiac muscle contents have leaked out of cells. The primary reason why this occurs is in response to injury. There are multiple causes of cardiac muscle injury that includes acute coronary events, but there is also a whole spectrum of disorders that can cause a rise in troponin. The largest study of this subject[1] showed that all of the following were associated with raised c-troponin-I levels. Pulmonary embolism,[2] congestive cardiac failure, cardiomyopathy, myocarditis, rhabdomyolosis, chest contusions, sepsis, mural thrombi, prosthetic heart valves, neoplasms, radiation induced coronary stenosis, homocystinuria, systemic lupus erythematosus, and rheumatoid arthritis. Surprisingly, high troponin levels have also been found in cocaine abusers and marathon runners.

Some of these are obviously significant while others merely represent a normal response to a physiological event; c-troponin-I can therefore be distinctly raised in many ''non-cardiac'' disorders. The rise is evidence of cardiac damage *per se* and the relative importance of this should be determined by the state of the patient.

The troponin test is a valuable and sensitive one but always needs to be assessed in the cold light of the clinical scenario as its specificity to acute coronary syndromes can be questionable, especially on a one-off basis.[3] Perhaps the advancement of this ultimate biochemical test leads us round in full circle when we attempt to clarify its rise. That is, to a thorough clinical history taking.

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