Psychiatric disorders and cardiovascular disease: anxiety, depression and hypertension

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Chapter 6

PSYCHIATRIC DISORDERS AND CARDIOVASCULAR DISEASE
ANXIETY, DEPRESSION AND HYPERTENSION

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ABSTRACT

Whereas the association of depression with cardiovascular disease is well established, the literature relating to anxiety disorders and cardiovascular disease is much less developed. There have been several studies which have examined the association of anxiety disorders with cardiovascular diagnoses, in particular with hypertension, an independent risk factor both for myocardial infarction and for stroke.

Here mechanisms proposed for the association of depression and cardiovascular disease based on cytokines, platelets, the autonomic nervous system and illness behaviour are reviewed. The evidence linking anxiety disorders and cardiovascular disease is then examined.

Focussing more specifically on hypertension, data on the associations of abnormal blood pressure with anxiety disorders and with depression are reviewed. While there is considerable evidence for associations of hypertension with panic disorder and some evidence for associations of hypertension with generalized anxiety disorder and depression, associations of low blood pressure with measures of psychological dysfunction have also been reported.

Finally the evidence relating to the aetiology of the association of panic disorder with hypertension is explored, again relating to autonomic nervous system dysfunction, cytokines and platelets. A putative neurobiological model of panic and hypertension
involving autonomic nervous system dysfunction modulated by the neurotransmitter serotonin is presented.

1. INTRODUCTION

The association of depression with cardiovascular disease is now well established in medical literature, having been reported in no fewer than seventeen independent studies (for example [1-6]). Depression is not only an independent risk factor for myocardial infarction [7-10] but also for cardiovascular mortality following a cardiac event [11-13] or following coronary artery bypass surgery [14,15]. Treatment of depression appears to improve cardiovascular outcomes [8,16]. The risk of cardiovascular mortality in the five years following myocardial infarction is linked to the intensity of depression around the time of the cardiac event, suggesting a dose-dependent effect of depressive symptoms even well below the threshold for a diagnosable depressive disorder [17].

The literature relating to anxiety disorders and cardiovascular disease is less developed, but there have been several studies which have examined the association of anxiety disorders with cardiovascular disease and in particular with hypertension, an independent risk factor both for myocardial infarction and for stroke.

In this chapter we will a) revise the mechanisms proposed for the established association of depression and cardiovascular disease b) review the evidence linking anxiety disorders and cardiovascular disease c) examine the data on the association of hypertension with anxiety disorders, in particular panic disorder, and with depression and d) explore the evidence relating to a neurobiological model of the association of panic disorder with hypertension, which may provide useful insights for future research.

2. MECHANISMS UNDERLYING THE ASSOCIATION OF DEPRESSION AND CARDIOVASCULAR DISEASE

Three putative mechanisms which may explain the mechanism underlying the association of depression and cardiovascular disease have been widely discussed and studied in the literature. a) inflammatory mediators and cytokines, b) platelet dysfunction, and c) dysfunction of catecholamines and the autonomic nervous system. A fourth possibility, relating to illness behaviour, such as the functional consequences of depressed mood on adherence to medication regimens for comorbid cardiovascular disease has also been given consideration [18,19]. The rationale for the first three of these mechanisms is discussed here.

2a. Inflammatory Mediators and Cytokines

Major depression is associated with raised inflammatory markers. Most consistently raised are IL-1, IL-2, IL-6, TNFα and CRP [20-22]. For a review of inflammatory markers and the proposal of an immunological aetiology of depression see Schiepers et al [23]. It has
also been proposed that the pro-inflammatory state seen is secondary to psychological stress and sympathetic overactivity seen in depression [24].

Pro-inflammatory cytokines have been suggested to participate in atheroma and thrombus formation [25]. Preclinical studies have shown interleukin-1 (IL-1), interleukin-6 (IL-6) and tumour necrosis factor-alpha (TNFα) induce vascular cell adhesion molecule-1 (VCAM-1) expression on the vascular endothelium [26]. This increases the adhesion of leukocytes to the endothelium and has been proposed to initiate atheromatous plaque formation [27]. Further studies have also shown that TNFα has direct effects upon the myocardium (via TNF receptors 1 and 2); causing decreased contractility and increased apoptosis [28]. This work has been corroborated by clinical studies showing TNFα levels correlate with severity [29] and IL-6 levels predicted future mortality of heart failure [30]. Moreover, increased levels of C-reactive protein (CRP), a further marker of inflammation, predict future risk of coronary disease in healthy controls [31]. From this data it is not possible to determine the direction of this association. It could be that heart failure or impending coronary disease instigates the pro-inflammatory state observed rather than vice versa. However, further research is required to resolve this issue. This notwithstanding, inflammatory markers that are raised in major depression have been implicated in both preclinical and clinical studies as either directly deleterious to the cardiovascular system, or markers of poor cardiac outcome. This suggests an activated immune system could be another potential link between cardiovascular and mood disorders.

2b. Platelet Dysfunction

Platelet activation has long been associated with atheroma formation, acute coronary syndromes and myocardial infarction [32]. Platelets are activated by several mechanisms, several of which are associated with major depression. These include: altered serotonin functioning, increased catecholamines and mechanical shear stress, platelet factor 4 and β-thromboglobulin.

Patients with major depression have been found to have increased platelet activity compared to controls by measuring monoclonal antibody binding prothrombinase complexes [33]. This finding is corroborated by using plasma levels of platelet factor 4 and β-thromboglobulin to determine platelet activity. Platelet factor 4 and β-thromboglobulin are stored within platelets. They are released during platelet activation and are potent enhancers of activation [34]. These two factors are only usually detectable in trace amounts in the circulation, therefore any increase in their levels would indicate an increase in platelet activation. It has been found that both platelet factor 4 and β-thromboglobulin are increased in patients with both ischaemic heart disease and depression compared with either ischaemic heart disease only, or healthy controls. Moreover, there were no differences between the ischaemic heart disease only group and healthy controls [35]. This suggests that there is greater platelet activation in depressed patients, therefore producing an increased risk of cardiovascular disease.

Serotonin dysfunction has been proposed as a mechanism of increased platelet activity both in depression and anxiety disorders. Platelets store serotonin in intracellular dense
granules. When activated they release the dense granules (also containing activating substances adenosine diphosphate, calcium ions and thromboxane A2). The released serotonin acts on surrounding platelets via 5HT-2A receptors to activate them in a positive feedback loop. During an acute coronary syndrome serotonin increases thrombus stability and also increases ischaemia due to vasoconstriction [36,37]. Depressed patients have increased platelet 5HT-2A binding [38]. Therefore increased platelet sensitivity to serotonin activation could be one explanation of an increased risk of cardiovascular disease. Selective serotonin reuptake inhibitors (SSRIs) have been associated with reduced recurrent cardiac ischaemia, but increased gastrointestinal bleeding following acute coronary syndromes [39]. This appears counter-intuitive as an increase in available serotonin caused by SSRIs should produce a more thrombotic environ. This can be resolved by the fact that platelets are formed without any intracellular serotonin and so have to collect it by uptake from plasma [40]. SSRIs have high affinity for the membrane serotonin transporter [41]. By blocking this uptake, platelets are left with reduced stores of serotonin which reduces the positive feedback loop when they are activated [42], thus reduction in platelet activity may contribute to the cardio-protective action of SSRIs [41].

Catecholamines also stimulate platelet activation through $\alpha$-2 adrenoceptors. This can be either indirect, though potentiation of other activating factors, or direct when in high concentrations [43]. Patients with depression have been found to have higher plasma levels of noradrenaline than controls [44], as will be discussed in the next section.

2c. Autonomic Nervous System Dysfunction

It has been suggested that cardiovascular disease and depression may be linked through dysfunction of the autonomic nervous system. Evidence uniting mood and cardiovascular disorders comes both from studies of catecholamine concentrations in plasma at rest or in response to stress. For instance, depression has been associated with sympathetic nervous system overactivity evidenced by elevated plasma norepinephrine [45] and excess catecholamine response to orthostatic challenge [46]. By contrast in one study plasma catecholamine concentrations were slightly higher in non-depressed controls than in subjects with depression [47].

Heart rate variability is a marker of autonomic nervous system dysfunction which may be a consequence of sympathetic nervous system overactivity or imbalance between the activity of the sympathetic and parasympathetic nervous systems. This is diminished in depression [48-50]. In cardiovascular disease diminished heart rate variability is associated with a worse prognosis for instance after myocardial infarction [51] or in heart failure [52], although the predictive value of heart rate variability on the prognosis of depression has yet to be established.

Changes in catecholamine concentration and autonomic concentrations reported in depression may represent a target for serotonin promoting treatments. In a healthy volunteer study [53] taking 50mg/day of the Selective Serotonin Reuptake Inhibitor (SSRI) antidepressant Sertraline for two days was associated with lower plasma norepinephrine appearance rates than use of placebo. This is also evidence that SSRI treatment can increase
Both of these lines of evidence point towards a beneficial modulating role for serotonin in the autonomic dysfunction that may link depression and cardiovascular disease. However, cognitive therapy for depression has also been reported to increase heart rate variability [55], so recovery from illness may in itself be protective.

3. Overview of Depression and Anxiety Disorders

Depression and anxiety disorders are overlapping diagnostic categories, demarcated by pharmacological dissection, expert consensus, and medcopolitical forces over recent decades. Refinement of the standard categorical classification systems (DSM, ICD) continues with the release of DSM-V expected in 2012 (Figure 1). DSM-IV provides definitions of several distinct, but related anxiety disorders, including generalized anxiety disorder, panic disorder, agoraphobia, social phobia (social anxiety disorder), specific phobia, obsessive-compulsive disorder and post-traumatic stress disorder. Comorbidity (i.e.: the simultaneous presence of both depression and anxiety disorders) is common, and usually associated with increased symptoms, impairment and morbidity [56].

In the proposed DSM-V categorization, which is evolving through a consideration of epidemiological, clinical and biological evidence [57], it is expected that these disorders will be categorised differently. If current plans are adopted DSM-V may delineate panic disorder, agoraphobia, social phobia and specific phobias into a sub-category of “fear-based anxiety disorders” with Generalized Anxiety Disorder moving across to the “Distress Disorder” category. Adapted from Watson et al (2005) [56].
disorders” while generalized anxiety disorder and depressive disorders may be classified together occupying a separate sub-category, with both groups being listed together under “distress disorders”. Meanwhile, obsessive-compulsive disorder may be moved away from the anxiety and mood disorders into a new categorization.

Panic Disorder

Of the various clinical anxiety disorders recognised in modern classification systems, Panic Disorder is of particular interest in a cardiovascular context. Panic disorder was first recognised as a discrete clinical entity in 1980 [58] and revised diagnostic criteria were published in the DSM-III-R system of 1987 [59]. Using DSM-III-R criteria, panic attacks are described as discrete episodes of fear or discomfort in which four or more recognised symptoms are experienced. The panic symptoms listed in DSM-III-R are i) shortness of breath (dyspnoea) or smothering sensations, ii) dizziness, unsteady feelings, or faintness, iii) palpitations or accelerated heart rate (tachycardia), iv) trembling or shaking, v) sweating, vi) choking, vii) nausea or abdominal distress, viii) depersonalization or derealization, ix) numbness or tingling sensations (paraesthesias), x) hot flushes or chills, xi) chest pain or discomfort, xii) fear of dying, xiii) fear of going crazy or doing something uncontrolled.

In DSM-III-R, panic disorder is diagnosed in individuals who have spontaneous panic attacks which come on suddenly, reach a peak quickly and are not attributable to any organic cause, and who experience at least four such attacks per month or one attack followed by a month of persistent fear of further attacks. In DSM-IV the criteria were revised slightly [59]. DSM-IV requires recurrent unexpected panic attacks, with at least one of the attacks followed by 1 month or more of either a) persistent concern about having additional attacks, b) worry about the implications of the attack or its consequences (e.g., losing control, having a heart attack, “going crazy”) or c) a significant change in behaviour related to the attacks. As in DSM-III-R, attacks must not be due to any organic cause.

Panic Disorder is common in the general population [60,61] and even more common in hospital outpatient clinics [62,63] but is poorly recognised in medical settings [64]. People with panic attacks may present in the emergency department with chest pain, but recognition rates as low as 2% have been reported in this setting [65], despite the development of brief interview schedules which would allow physicians with no extra training to diagnose panic disorder reliably and initiate effective pharmacological treatment [66].

4. Evidence for Association of Anxiety Disorders with Cardiovascular Disease

Published data on the association of anxiety disorders and cardiovascular disease is less extensive than that for depression. Several previous studies have shown associations of coronary heart disease with panic disorder or related anxiety disorders [67]. Two small studies reported an excess of cardiovascular mortality in patients with panic disorder [68] and its diagnostic fore-runner anxiety neurosis [69]. Using data derived from the Epidemiological
Catchment Area study Weissman [70] reported a significant excess of cardiovascular conditions including history of “heart attack” which had an odds ratio of 4.54 in panic disorder compared to subjects with no psychiatric illness. In this study panic disorder was diagnosed by a structured psychiatric interview but cardiovascular endpoints were identified by self-report and unsupported by physician verification. The authors acknowledged that patients with panic disorder may over-report cardiovascular illness because of hypochondriasis.

We reported that among 390 hypertensive patients attending a hospital clinic, those with a history of panic disorder or panic attacks had a significant excess of coronary heart disease compared with hypertensive patients who had not experienced panic attacks [64]. The odds ratios for coronary heart disease were 2.1 for all panic attacks and 3.0 for panic disorder. There was also an excess of myocardial infarction, with odds ratios of 2.5 for all panic attacks and 10.4 for panic disorder.

However, none of these studies succeeded in combining both a robust method for diagnosing panic disorder and a similarly robust method for diagnosing cardiovascular endpoints. Subsequently, using a managed care database in the US of 78,000 patients, Gomez-Caminero [71] also reported a 2 fold increased risk for cardiovascular disease in patients with panic disorder, independent of the presence of major depressive disorder. This study had the advantage of large numbers and a prospective design. Panic disorder and cardiovascular outcomes were obtained from clinical records, although these were based on the ICD-9 diagnostic system. In a further prospective study, of 3369 postmenopausal women, those reporting one or more panic attacks in the previous 6 months were at increased risk of subsequent cardiovascular events (fatal and nonfatal myocardial infarction and stroke) over the following 5.3 years [72].

The association of cardiovascular conditions and phobic anxiety symptoms has been examined in prospective and cross-sectional studies. In one study, phobic anxiety had relative risk of 3.8 for fatal coronary heart disease in men followed up for an average of 6.7 years [73]. In similar studies [74,75] of men free of coronary heart disease at baseline, phobic anxiety was associated with excess CHD mortality, which was entirely due to excess sudden deaths. A further study by the same authors [76] showed an association between baseline anxiety, and increased risk of sudden cardiac death over 32 years of follow up. In another prospective study, Watkins [77] reported associations of phobic anxiety and depressive symptomatology with ventricular arrhythmias. Fleet’s review [78] concluded these forms of anxiety, which he termed “panic-like anxiety” appeared to be an independent risk factor for cardiovascular death.

In contrast, a number of studies have examined the association of cardiovascular disease with measures of anxiety more closely related to generalized anxiety disorder. A meta analysis of anxiety as a risk factor for cardiovascular disease in studies up to 2003 concluded that the evidence for generalized anxiety as a cardiovascular risk factor was relatively sparse [79], with several studies finding no association. More recently Herbst et al in a population based study of older adults found only a non-significant trend towards an association between lifetime prevalence of an anxiety disorder and coronary heart disease [6].

Positive associations between generalized anxiety and cardiovascular disease have been reported in several studies. In a large prospective study which focussed on worry, a cardinal
symptom of generalized anxiety disorder, total worry score was associated with total coronary heart disease and with angina pectoris but not with non-fatal MI or with coronary heart disease mortality [67]. Using a cross-sectional design, Barger [80] reported that generalized anxiety disorder conferred a five-fold risk of CHD in the general population. Shibeshi [81] reported that a high level of anxiety (measured on Kellner’s Symptoms Questionnaire) which was maintained after diagnosis of coronary artery disease conferred a strong risk of death or myocardial infarction. Most recently both depression and generalized anxiety were predictors of mortality in a cohort of individuals with stable coronary heart disease [82].

It is notable in the light of the proposed DSM-V categorization of anxiety and depressive disorders, that there is a more consistent body of evidence to support associations of cardiovascular disease with the fear based anxiety disorders (panic disorder and the phobias) rather than with generalized anxiety disorder. The proposed categorization, if adopted, may be particularly helpful in signposting further research into the biological and other factors which are characteristic of fear based anxiety disorders and are associated with cardiovascular disease.

5. HYPERTENSION

Hypertension is a common disorder with increasing prevalence through the lifespan. In the United States more than half of those aged 60 to 69 years and three-quarters of those aged 70 years are hypertensive [83]. Despite the continuing development of antihypertensive drug treatments, the prevalence of hypertension in the U.S.A. increased significantly by 10% between data collection conducted between 1999-2004 and an earlier data collection between 1988-94 in adults age over sixty years [84].

The importance of recognizing and treating hypertension lies in it being a strong prognostic factor for myocardial infarction, heart failure and stroke irrespective of other risk factors [85]. From the age of 40 to 89, every 20 mmHg increase in systolic blood pressure or 10 mm Hg in diastolic blood pressure confers a doubling of mortality from both ischemic heart disease and stroke [86]. However, this risk is modifiable since treatment through antihypertensive drugs either alone or in combinations may lower blood pressure below target values [87] and reduce the excess risks of cardiovascular disease in all age groups.

Traditionally hypertension was categorised as either being “essential”, meaning of unknown aetiology or “secondary” to an identifiable cause such as Renal artery stenosis, Cushing’s disease or phaeochromocytoma. The use of the term “essential” was related to a belief held widely until the 1930s that hypertension was simply a compensatory mechanism to ensure perfusion remained adequate when arteries became sclerosed in other words an “essential” response to maintain the perfusion [88]. The link between hypertension and cardiovascular disease established through the Framingham Heart Study [89] and other cohorts and the evidence that treating hypertension could reduce this risk confirmed that hypertension is not an “essential” homeostatic response but the term “essential hypertension” has persisted to the modern day. In addition, hypertension previously considered “essential” and therefore thought to have no identifiable cause can often now be linked to an associated
pathology. For instance, mechanisms which have been identified in “essential” hypertension are insulin resistance, salt sensitivity, sleep apnoea and dysfunction of the sympathetic nervous system [90,91].

6. ASSOCIATIONS WITH HYPERTENSION

6a. Association of Panic Disorder with Hypertension

Several authors have demonstrated an epidemiological association of hypertension with panic disorder. Hypertension was more common in patients with panic disorder than in controls in two small studies [92,93]. In the first, a retrospective study of patients referred from primary care with panic disorder the prevalence of hypertension, 15%, was reported to be significantly higher than the prevalence of 9% in patients without panic disorder [92]. Patients with panic disorder developed hypertension more commonly than did a control group of surgical patients over five years of follow-up [94]. In an uncontrolled study of African-Americans with hypertension 36% had panic attacks, and 10% fulfilled the diagnostic criteria for panic disorder [95]. Kaplan [96] has described anxiety-related hyperventilation in a prospective but uncontrolled study of patients referred to a tertiary care clinic with hypertension that was difficult to manage. Hyperventilation is a common feature of panic attacks. Of 300 consecutive patients, 35% had symptoms suggestive of hyperventilation, and in 85% of these the symptoms were reproduced by forced hyperventilation. All of these studies, however, were small, or uncontrolled, or both.

Two larger controlled cross-sectional studies have provided evidence for an association of hypertension with panic attacks and panic disorder. The first was derived from the Epidemiological Catchment Area study [70] and the second was performed by our own group in Sheffield, United Kingdom [97]. We studied 891 patients in three groups – hypertensive patients in primary care, matched normotensive controls from the same primary care practice and hypertensive patients attending a hospital clinic. Thirty seven percent of the hypertensives had experienced panic attacks compared with 21% of normotensives, a significant difference (p<0.001). The association was observed for hypertensive patients in both the hospital clinic and primary care settings and could therefore not be attributed to selective referral. Panic disorder, defined by DSM-III-R criteria, was significantly more common in hypertensives studied in primary care than in matched normotensives. There was a similar albeit non-significant excess of panic disorder in hospital clinic hypertensives compared with normotensive controls.

6b. Association of other Anxiety Measures and of Depression with Hypertension

Other studies have examined the association of measures of anxiety and depression with hypertension. In both cases the picture is conflicting.
Anxiety measured by various instruments in both longitudinal [98-103] and cross-sectional designs [101,102] was reported to be associated with hypertension. While some of these studies used measures of “tension-anxiety” [100,102], others employed the Spielberger Anxiety Inventory which describes symptoms most similar to those in generalized anxiety disorder [98,101]. In contrast one large prospective study [104] showed no association of anxiety with the development of hypertension.

For depression, several studies, both those with a longitudinal design [103,105] and cross-sectional studies [106] have reported an association. By contrast large cross-sectional studies [101,104,107] have reported no excess risk of hypertension with depression.

However, further inspection of the literature reveals a separate body of research in large epidemiological cohorts which has focussed on the low blood pressure with psychological endpoints. Low blood pressure was associated with psychological dysfunction measured by the GHQ questionnaire [108,109]. The North Trondelag Health study, a population based cohort study conducted in Norway [110] reported that participants in the lowest 5% centile for systolic blood pressure had significantly lower depression and anxiety scores measured by the HAD scale than those with systolic blood pressures between the 40 and 60% centiles.

In other words, depression and measures of anxiety have been associated both with low and high blood pressure. These two batches of literature have yet to be fully reconciled into one overarching model. One study [111] reported that men with diastolic blood pressure below 75mmHg and those with diastolic blood pressure above 85mmHg both had significantly higher scores on the Beck Depressive Inventory than those in the 75-85 mmHg range. The possibility of a J shaped or U shaped relation between blood pressure and depression and anxiety requires further exploration.

**7. MECHANISMS IN THE ASSOCIATION OF HYPERTENSION AND PANIC DISORDER**

Earlier we considered possible mechanisms which may underlie the association between depression and cardiovascular disease. Here we examine the evidence for these mechanisms (autonomic dysfunction, cytokines/inflammatory mediators and platelets) in the association of hypertension and the fear based anxiety disorders most specifically panic disorder. In addition there are a number of further mechanisms such as those involving the respiratory system, illness behaviour, labelling effects and the impact of white coat hypertension which are worthy of consideration.

7a. Autonomic Nervous System Dysfunction

Most interest in the mechanism underlying the association of panic disorder and hypertension to date has focussed on catecholamine function and the autonomic nervous system since central or peripheral catecholamine dysfunction has been described in both disorders. Despite the majority of cases of hypertension being classified as ‘essential hypertension’, implying unknown aetiology, there has been an acknowledgement that in
many cases a dysfunction of the autonomic nervous system may be the underlying pathology [112]. It has been suggested that psychiatric disorders may impair regulation of the autonomic nervous system leading to increased blood pressure variability [113]. Evidence from Esler’s [114] studies of clinical microneurography and measurement of noradrenaline spillover from cardiac nerve terminals suggest sympathetic dysfunction in hypertensives. Using similar techniques excess adrenaline spillover from the heart was reported during panic attacks [115]. There is also evidence of abnormal central catecholamine function in both disorders. Nutt [116] reported altered central alpha 2 adrenergic receptor sensitivity in panic disorder, and excess catecholamine spillover from the brain has been seen in hypertension [117].

In addition, we have explored the role of autonomic dysfunction in the association between hypertension, panic attacks and panic disorder [118]. We analysed 346 questionnaires completed by patients with panic (268 hypertensives and 78 normotensives), examining frequency of different panic symptoms. We performed a factor analysis and examined associations of factors identified with hypertension. Sweating and flushes were significantly more common in hypertensive patients’ attacks. The first factor identified by Factor analysis was dominated by autonomic symptoms, notably sweating, flushes, and also shaking. Only this autonomic dominated factor was associated significantly with hypertension. This suggests that a common autonomic dysfunction may contribute to the association of hypertension with panic.

Serotonin (5-HT) systems may somewhat explain the association among autonomic nervous system dysfunction, hypertension and panic disorder. Serotonin promoting antidepressants are first line treatments in all anxiety disorders, and transient depletion of serotonin by acute tryptophan depletion renders treated patients with a history of panic disorder more vulnerable to panic on stress challenge [119]. Serotonin promoting antidepressants appear to have a cardioprotective effect in patients with depression co-morbid with ischaemic heart disease [120]. Polyak’s intriguing finding that SSRI antidepressants have an antihypertensive effect in hypertensive patients with co-morbid anxiety disorders is worthy of close scrutiny [121]. After three to six months’ drug treatment, patients with co-morbid panic disorder and mild hypertension, experienced more pronounced blood pressure reduction if on treatment with the SSRI drug fluoxetine than those treated with the antihypertensive agent moxonidine. Significant reduction of heart rate and blood pressure variability was only seen in the fluoxetine group.

A role for 5-HT in autonomic nervous system dysfunction is supported by evidence from clinical and pre-clinical sources. Increasing CSF serotonin has been shown to be associated with a marked elevation in ventricular fibrillation threshold in the cat and significant reduction in efferent sympathetic activity from the heart [122,123]. There is substantial literature on reduction in heart rate variability in panic disorder [124,125] which is restored to normal by SSRIs [126].

Thus, lowering 5-HT concentrations using the acute tryptophan depletion technique [127] should alter both cardiovascular and psychological parameters relevant to these conditions. We have previously reported that in treated patients with social anxiety disorder or panic disorder acute tryptophan depletion led to significantly greater blood pressure and psychological responses to stress challenges than that seen under non-depleted conditions.
This suggests that 5HT is having an anti-stress role in both psychological and cardiovascular domains. A lack of correlation of cardiovascular and psychological responses in the difference between tryptophan depleted and non-depleted conditions in this study is suggestive of distinct effects on these two domains.

Our group has constructed a model to illustrate possible neurochemical mechanisms and neuroanatomical pathways that may be involved in the association of panic and hypertension (figure 3). Brainstem-mediated sympathetic activation may lead to hypertension, ischaemia, cardiac arrhythmias and sudden death [130]. Pathologically elevated levels of brainstem-mediated sympathetic activity could result from excess excitatory drive, a deficit in inhibitory control, or a combination of these. Stimulation of the midbrain ventrolateral periaqueductal gray (VLPAG), an integrative centre for autonomic and behavioural responses, induces hypotension and sympathoinhibition. This can be prevented by blockade of 5-HT1A receptors in the rostral ventrolateral medulla (RVLM), a region of critical importance in maintenance of arterial pressure [131]. Thus, serotonergic neurons within the VLPAG may moderate the activity of RVLM neurones. The model also incorporates Richerson's evidence on serotonergic neurones in the medullary raphe [132]. Changes associated with exposure to carbon dioxide or decreases in extracellular pH may be detected in the medullary raphe or the VLPAG, activating these serotonin dependent chemosensors to exert a negative feedback effect on RVLM activation.

Figure 2. From Davies, Hood, Argyropoulos et al, J Clin Psychopharm 2006. [Ref 130]. Key: Closed triangles = Patients with panic disorder treated by SSRIs, Open Triangles = Patients with panic disorder
Psychiatric Disorders and Cardiovascular Disease

13

treated by Cognitive Behaviour Therapy, Closed Diamonds = Patients with social anxiety disorder treated by SSRIs.

Decreased activity of serotonergic neurons in the VLPAG region could account for the association between hypertension and panic disorder (Figure 3). Serotonergic neurons within the VLPAG are thought to project to both the dorsal periaqueductal gray (DPAG) and the rostral ventrolateral medulla (reviewed by [133]). Activation of 5-HT1A and 5-HT2 receptors within the DPAG are thought to contribute to the inhibition of aversive behavioural responses [134,135], and this effect can be enhanced by chronic treatment with anti-panic medication imipramine [136]. Thus, VLPAG serotonin neurons are in a position to inhibit both the behavioural and autonomic components of panic responses. Neural systems underlying hypertension and behavioural and autonomic components of panic responses may therefore converge at the level of the brainstem. These brainstem structures are under inhibitory control by 5-HT neurons in the VLPAG, which serve as an important sympathomotor control system. If these neurons are compromised there may be vulnerability to both hypertension and the behavioural and autonomic symptoms of panic, which are alleviated by SSRIs and exacerbated by tryptophan depletion.

Figure 3. (From Davies, Lowry and Nutt, J Psychopharm 2007 [Ref 131].)

7b. Cytokines

As noted earlier there is considerable evidence linking depressive disorders to changes in concentrations of inflammatory markers, in particular IL-1, IL-2, IL-6, TNFα and CRP [21,137,138], and these markers are in turn associated with cardiovascular disease. Although increased anxiety symptoms have also been correlated with raised CRP, IL-6 and TNFα levels in one large study of 853 people free of cardiovascular disease [139], evidence for immune activation in specific anxiety disorders is relatively sparse. Focussing on panic disorder, interleukin-1β plasma concentrations were higher in patients with panic disorder
than healthy controls both before and 1 month after treatment with alprazolam [140]. In a further study by the same group, there were no differences in TNFα concentrations between panic disorder patients and healthy controls [141]. Following a preliminary study reporting a modest increase in IL-2 in panic disorder patients compared with controls [142], another small study reported no excess of IL-2 production in patients having panic disorder with or without agoraphobia compared with healthy controls [143], but did note a negative correlation of IL-3 with state anxiety. At present therefore evidence of cytokine derangement in panic disorder is not well established and is insufficient to underpin the association with cardiovascular disease and in particular hypertension.

7c. Platelets

Dysfunction of the serotonin system is central to most current biochemical theories of the mechanisms of panic disorder [144]. Initial research focussed upon the functioning of platelet serotonin functions as a proxy for central nervous system functions. However, contradictory and equivocal evidence emerged with relation to changes in serotonin transporter [145-147], 5HT2 receptors [148,149], platelet monoaminoxidase content [150,151] and platelet serotonin content [152]. More recent work has focussed upon dysfunctional second messenger systems seen in platelets, initial studies have found decreased serotonin receptor coupling [153], decreased platelet cyclic adenosine monophosphate (cAMP) concentrations [154] and altered subunit ratios of protein kinase A [155]. Elevated platelet cAMP concentrations are known to inhibit platelet activation [156]. Therefore, it is possible that platelets are more aggregable in panic disorder - however previous studies have shown that platelets show less aggregation in response to serotonin challenge in panic disorder patients than controls [149]. Overall it remains unclear as to the degree of involvement platelets have in mediating the link between panic disorder and cardiovascular disease.

7d. Respiratory Mechanisms

Hyperventilation is a prominent component of panic attacks, and acute hyperventilation has a significant but short-lived pressor effect averaging 9/8 mmHg in normotensive subjects [157]. In Kaplan’s study [96], anxiety-induced hyperventilation was thought to be present in 35% of patients with hypertension that was difficult to control, and in 85% of these patients symptoms were reproduced by hyperventilation.

Klein (1993) suggested that there are two main sub-types of panic attacks, the first due to “false suffocation alarms” and characterised by panics with a predominance of respiratory symptoms and the second group attributable to sympathetic nervous system or HPA axis deficits and not characterized by respiratory symptoms. In the factor analysis of panic attack symptoms in hypertensive and normotensive patients described earlier [128] we reported that the factor significantly associated with hypertension was the one comprising symptoms typical of sympathetic nervous system dysfunction. In fact, respiratory panic symptoms were
no more common in hypertensives than normotensives and the factor dominated by respiratory symptoms had no association with hypertension.

7e. Illness Behaviour

Psychological symptoms may impair the ability of patients both to tolerate or adhere to medication regimes and to follow interventions that reduce cardiovascular risk after myocardial infarction. Panic attacks, anxiety and depression are associated with episodes of intolerance to antihypertensive agents [158]. When reported side effects were subdivided into those which would be considered as typical of the drugs implicated (drug-specific intolerance) and those which were not (non-specific intolerance), only intolerances due to non-drug specific side-effects were associated significantly with panic attacks and symptoms of depression and anxiety (figure 4). The number of episodes of non-specific intolerance was significantly associated with poor outcome in blood pressure control [158].

![Graphs showing the relationship between panic attacks and depression to non-specific and drug-specific intolerance episodes.](attachment:image.png)

Figure 4. Relations of panic attacks and depression (HAD depression score >7) to non-specific intolerance episodes (upper panels) and to drug-specific intolerance episodes (lower panels). Note the significant relations of psychiatric morbidity to non-specific drug intolerance but not to drug-specific drug intolerance. (From Davies et al, Arch Int Med 2001 [ref 160].)

Depressed patients were less able to adhere to behaviour and lifestyle changes recommended after myocardial infarction [159]. Meta-analysis of anxiety and depression as a risk factor for non-compliance to medication across a range of medical disorders yields a clear effect for depression but a more complex picture for anxiety [160]. In most studies,
however, the anxiety endpoint was measured using scales most related to the symptoms of generalized anxiety disorder. One study conducted in asthmatics which used a scale specifically measuring panic and fear reported an association between this endpoint and non-compliance [161].

7f. White Coat Hypertension & Labelling Effect

A simple explanation for reported associations of hypertension and panic disorder may be
that patients with panic disorder appear artefactually to have higher blood pressures due to a greater ‘white coat’ (anxiety-induced hypertension) response compared with patients without panic disorder. Patients who are prone to panic attacks may perceive a primary care facility or hospital clinic as threatening, and could have a pressor effect as a conditioned response to these situations [162]. In an earlier clinical study we found no excess ‘white coat effect’ in patients with panic disorder and panic attacks making this explanation unlikely [163], (Figure 5).

One further possibility which cannot be excluded is that the association of panic disorder and hypertension might be due at least in part to a ‘labelling effect’. Patients’ awareness of a diagnosis of hypertension may lead to subsequent adverse effects on psychological well being [164] and to vulnerability to the development of panic disorder. Indeed, in the one study which examined the temporal relationship of the onset of panic attacks and hypertension [97], the diagnosis of hypertension preceded panic attacks significantly more often than vice versa (p<0.01).

**8. Future Research**

An association between anxiety (especially panic disorder) and cardiovascular disease (especially hypertension) is intuitive and is well supported by existing scientific literature. Although our group and others have explored this relationship and posited autonomic dysfunction as an explanation, there are a number of additional areas worthy of research focus.

Firstly, the refinement of practical psychological and physiological tests that measure autonomic responses to stress, validated in both normal subjects and hypertensives would be a useful prerequisite to studies exploring neurobiological links between hypetension and panic disorder. Secondly, manipulation of serotonergic function via the acute tryptophan depletion technique in combination with the validated autonomic stress challenge platform would allow investigation of the ability of central serotonin to buffer the autonomic stress response in hypertensive patients and others. Exploration of adjunctive SSRI treatment in clinically hypertensive subjects, especially those with panic attacks featuring autonomic symptoms may be a therapeutic strategy worthy of further consideration.

Therefore, the development of reproducible and reliable tests that aid identification of a subset of hypertensive patients who may have co-morbid anxiety and autonomic dysfunction amenable to treatment with 5HT-promoting drugs such as SSRIs may be an ultimate goal of research in this area, broadening and refining the range of antihypertensive therapies available. Such outcomes would be of manifest benefit in the overall reduction of cardiovascular risk.
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