

# Depression, anxiety, and platelet reactivity in patients with coronary heart disease

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**This editorial refers to ‘Anxiety is a better predictor of platelet reactivity in coronary artery disease patients than depression’<sup>†</sup>, by M.U. Zafar et al., on page 1573**

There is considerable epidemiological evidence supporting the association between chronic emotional stress and coronary heart disease (CHD). Emotional factors that have been linked to atherosclerosis and adverse cardiac events include primarily negative affective disorders such as depression, anxiety, anger, and hostility.<sup>1,2</sup> It is now well established that depression is related not only to the incidence of CHD but also to the prognosis of patients with established disease. In a meta-analysis concerned with the role of depression in the development of coronary artery disease, Rugulies found that individuals with clinical depression have >2.5 times the risk of a myocardial infarction or coronary death as the general population.<sup>3</sup> In patients with established coronary disease, not only is major depression a significant predictor of mortality following acute myocardial infarction, but the level of depressive symptoms has a dose–response relationship with cardiac mortality over several years of follow-up.<sup>4</sup>

The importance of other affective disorders in the development and progression of CHD is less well established. Large-scale prospective studies have demonstrated a significant link between anxiety and sudden cardiac death,<sup>5</sup> but studies documenting an association between anxiety and the development of coronary artery disease have been inconclusive. In patients with known CHD, Suls and Bunde found a relatively weak association between anxiety and hard cardiac events.<sup>6</sup> More recent studies, however, have demonstrated that anxiety is an independent predictor of major cardiac events in patients with stable coronary disease.<sup>7,8</sup> Hostility and anger are felt to represent the potentially harmful aspects of Type A behaviour, and their relationships to CHD have therefore received considerable attention. While some studies have reported that hostility is an important risk factor for CHD,<sup>6</sup> numerous studies have found no association between hostility and cardiovascular disease after adjusting for confounding factors.<sup>9</sup> Anger can precipitate acute myocardial

infarction, and a dose–response relationship has been found between level of anger and CHD risk.<sup>10</sup> Studies examining the relationship of trait anger and prognosis in patients with established CHD, however, have yielded inconsistent findings.<sup>6</sup>

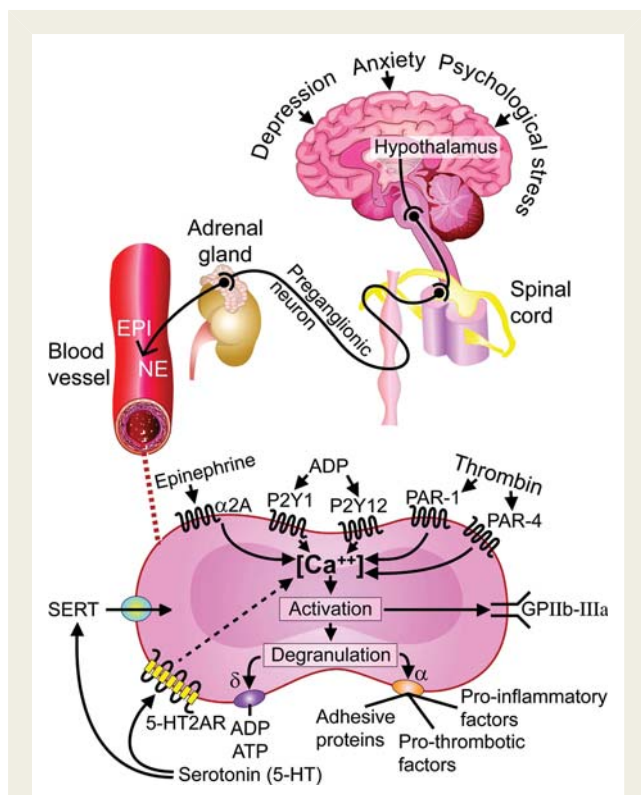
The precise mechanisms by which negative affectivity may influence the development and prognosis of CHD remain unknown. Negative emotions probably adversely affect behavioural factors such as smoking, diet, exercise, and compliance with medical care, thus increasing the risk of cardiovascular morbidity and mortality. Psychological factors also appear to influence directly biological pathways that are important in the development and progression of CHD. Individuals with depression and hostility have evidence of enhanced cortisol secretion, increased sympathetic activation, and elevated plasma catecholamine levels. Depression is also associated with hypertension, endothelial dysfunction, elevated levels of inflammatory cytokines, and increased platelet reactivity.<sup>1</sup> Indeed, the relationship between depression and platelet function has been the focus of considerable attention in recent years.<sup>11</sup> Platelets share many biochemical similarities with central nervous system neuronal monoamine systems, particularly in the uptake, storage, and metabolism of serotonin. There are similarities in the 5-HT<sub>2A</sub> receptors in platelets and brain serotonergic neurons, and the platelet and brain serotonin transporters (SERTs) are encoded by the same gene.<sup>12</sup> Given the central role that platelets play in both acute and chronic coronary syndromes, it is not surprising that serotonin-mediated platelet activation has been proposed to be a key pathogenic link between depression and CHD. Several studies have demonstrated higher levels of platelet factor 4,  $\beta$ -thrombomodulin, and P-selectin in patients with depression.<sup>13</sup> Depressed patients have also been shown to have increased activation of platelet glycoprotein IIb/IIIa receptors and increased serotonin-mediated platelet reactivity.<sup>13</sup> It is important to understand, however, that studies examining the relationship between depression and platelet reactivity have yielded inconsistent results, with some studies showing no difference in platelet reactivity between depressed and non-depressed patients.<sup>11</sup> These conflicting

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**Figure 1** Illustration of a potential pathway linking serotonin to enhanced platelet activation in patients with anxiety. Anxiety and other forms of psychological stress are perceived in the cerebral cortex, and activating signals are sent via the hypothalamus to sympathetic preganglionic neurons in the spinal cord. Preganglionic sympathetic stimulation of chromaffin cells in the adrenal medulla results in release of catecholamines, primarily epinephrine (EPI), into the circulation. Epinephrine binds to the  $\alpha_{2A}$  receptor on circulating platelets and stimulates other platelet agonists such as ADP. These platelet agonists result in the mobilization of intracellular calcium ( $[Ca^{2+}]$ ) which causes conformational shape change of the platelet and expression of the glycoprotein IIb/IIIa receptor (GPIIb-IIIa). Increased intracellular calcium also leads to degranulation of alpha ( $\alpha$ ) and dense ( $\delta$ ) granules. The  $\alpha$  granules release a variety of adhesive proteins and prothrombotic and inflammatory factors. The  $\delta$  granules store serotonin (5-HT) and release it along with other platelet agonists such as ADP and ATP. Once released, serotonin can be taken back up by the serotonin transporter (SERT) to be stored once again in  $\delta$  granules, or it can bind to the serotonin receptor (5-HT $_2$ AR). Binding of serotonin to its receptor results in further calcium mobilization and degranulation, thus enhancing the activation of neighbouring platelets in an evolving thrombus.

findings may simply be the result of methodological differences, or alternatively may reflect true physiological differences among varying patient populations.

While platelet function in patients with depression has been studied extensively, relatively little information exists regarding platelet reactivity in other negative affective disorders. The recent study by Zafar *et al.*<sup>14</sup> is, therefore, particularly welcome since it examines the effects of both depression and anxiety on

platelet reactivity in a patient population with stable coronary artery disease. In this cross-sectional study, symptom severity of both depression and anxiety was assessed in 83 subjects following an acute coronary syndrome using the Beck Depression Inventory (BDI) and the anxiety subscale of the Hospital Anxiety and Depression Scale (HADS-A), respectively. All subjects underwent assessment of platelet reactivity 3 months after the acute coronary presentation, and all were taking aspirin and clopidogrel at the time of testing. Platelets were activated with epinephrine and varying concentrations of serotonin. Platelet reactivity was assessed using optical aggregometry to measure platelet aggregation and flow cytometry to measure platelet surface receptor activation. Several important observations were reported in this study. In an unadjusted analysis, subjects who were both depressed and anxious had significantly higher serotonin-mediated platelet aggregation compared with depressed-only subjects and subjects without affective symptoms. No significant difference in serotonin-mediated platelet reactivity was seen between the depressed-only group and the symptom-free group. While anxiety symptom severity correlated significantly with serotonin-mediated platelet aggregation and activation, a similar correlation was not observed with depression symptom severity, which displayed a weak and inconsistent relationship with platelet reactivity measures. In a multivariate analysis, only anxiety symptom severity remained a significant predictor of serotonin-mediated platelet reactivity. Finally, no difference in platelet reactivity was seen between groups when epinephrine alone was used as the platelet agonist, suggesting that the mechanism of platelet activation in subjects with anxiety is serotonin mediated.

Based on these observations, the authors have suggested that anxiety may be a better predictor of platelet reactivity than depression in patients with CHD. Several issues need to be carefully considered, however, before arriving at this conclusion. First, it is important to remember that in studies where structured clinical interviews are not performed, the validity of the findings is completely dependent on the ability of the chosen self-report measures to discriminate accurately between various affective dimensions. While the BDI and HADS have been used extensively in patients with CHD, the ability of HADS to distinguish anxiety from depression reliably has been challenged.<sup>15</sup> The potential contamination of study groups due to the inherent limitations of self-report inventories must certainly be considered when evaluating the strength of the study findings. Secondly, this was a small study with a total of 83 subjects, and only two subjects comprising the anxiety-only group. While this may reflect the clinical reality that depression and anxiety frequently co-exist, the small sample size makes it difficult to compare the effects of these two dispositions on platelet reactivity directly. The primary observation in this study was that the combination of depression and anxiety resulted in greater serotonin-mediated platelet reactivity than depression alone. This may say less about how anxiety compares with depression and more about the potential additive effects of these disorders on platelet reactivity, possibly due to activation of both serotonergic and adrenergic signalling pathways. While a primarily serotonin-mediated effect was observed in the current study, others have reported increased platelet reactivity due to prolonged sympathetic activation in patients with both anxiety

and depression.<sup>16</sup> Similarly, sympathetic nervous activity in patients with manic depressive disorder appears to be highest in patients with co-morbid panic disorder.<sup>17</sup> Clearly, larger studies are necessary to determine whether depression and anxiety have independent and additive effects on platelet reactivity and to clarify the specific signalling pathways involved (Figure 1).

An inherent difficulty in studying the relationship of emotional factors with CHD risk is the tendency for various affective dispositions to cluster. The overlap of negative dispositions makes it difficult to study the true impact of an individual emotional factor on CHD risk, and very few studies have attempted to examine the simultaneous influence of multiple negative affects in patients with existing CHD. Similarly, the effect of a particular affective disorder on platelet reactivity and other physiological responses may also be confounded by overlapping affective dispositions, possibly explaining in part why platelet reactivity studies in patients with depression have yielded inconsistencies.<sup>11</sup> The study by Zafar *et al.* is novel in its attempt to compare directly the influence of two separate negative dispositions on platelet reactivity in patients with CHD. The observation that anxiety may be a more potent predictor of platelet reactivity than depression serves as an important reminder that while various dimensions of negative affectivity frequently co-exist, the mechanisms by which they impact biological pathways and ultimately cardiovascular risk may be different. Designing additional studies to elucidate further the mechanistic links between emotional factors and cardiac disease will be an exciting challenge for the future, and will hopefully lead to targeted therapeutic interventions that reduce cardiovascular risk in patients with affective disorders.

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