

Nitric oxide: A key player in the relation between cardiovascular disease and major depressive disorder?

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There is now a substantial body of evidence suggesting a strong relation between cardiovascular disease (CVD) and major depressive disorder (MDD). MDD has been shown to be an independent predictor of poorer cardiovascular outcome not only after myocardial infarcts (MI) and in unstable angina but also in patients with heart failure. In turn, physically healthy patients who have MDD have a 2-fold to 4-fold increased risk of developing CVD independent of other known risk factors.¹ The biologic mechanisms underlying the relation between MDD and CVD remain to be identified.

Nitric oxide (NO) is synthesized from L-arginine by a family of isoformic enzymes known as nitric oxide synthase (NOS). The endothelial isoform (eNOS) has been found not only in the endothelium but also in platelets. Numerous CVDs, such as heart failure and coronary artery disease, have been associated with alterations in the NO system. Endothelium-derived NO, through its vasodilator properties, participates in the modulation of vascular tone and inhibits a number of proatherogenic processes. Physiologically, NO inhibits platelet adhesion and aggregation. Plasma concentrations of nitrogen dioxides (NO_x), metabolites of NO, are often used as a marker for vascular NO production. Recent results have revealed that platelet NOS activity and plasma levels of NO_x levels were dramatically lower in patients with MDD compared with healthy controls.²

This apparent decreased NO production by the endothelium and platelets is particularly interesting in the context of the main mechanistic hypotheses of the relation between MDD and cardiovascular risk. Indeed, platelet activation is critical to the development of atherosclerosis and acute coronary syndromes. Both endothelium-derived and platelet-derived NO contribute to preventing platelet adhesion to the vascular wall and platelet aggregation, therefore playing a key role in the prevention of thrombus formation, which is a major trigger of coronary accidents. The decrease in endothelial NO production and platelet eNOS activity suggested by the results reported by our research group² may contribute to the observed increased platelet reactivity found in patients with MDD³ and, therefore, to the increased risk of CVD and acute coronary syndromes described in patients with MDD.

Hyperactivity of the hypothalamic-pituitary-adrenal axis, and more specifically increased cortisol levels, is another of the mechanisms that has been proposed for the increased risk of CVD in patients with MDD. Indeed, cortisol promotes the development of atherosclerosis and accelerates injury to the vascular endothelial cells. Interestingly, injury of endothelial cells is associated with decreased endothelial NO production. It has been shown that cortisol induces a downregulation of eNOS in endothelial cells as well as a decrease in

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plasma NO_x levels.⁴ Cortisol-induced dysregulations of NO production by the endothelium may therefore mediate some of the deleterious cardiovascular effects associated with MDD.

The inflammatory marker C-reactive protein (CRP) is one of the strongest independent predictors of future cardiovascular events both in patients with CVD and in healthy subjects. Several studies^{5,6} have suggested increased CRP in patients with MDD. Interestingly, CRP at concentrations known to predict CVD has been found to downregulate eNOS and destabilize eNOS mRNA, with resultant decreases in both basal and stimulated NO release.⁷

A dysfunctional vascular endothelium promotes atherosclerosis through vasoconstriction, platelet activation, leukocyte adhesion, thrombogenesis, inflammation, smooth-muscle cell proliferation and collagen breakdown. Impaired endothelial function (EDF) has been associated with CVD and major cardiovascular risk factors including smoking, hypertension, diabetes, hypercholesterolemia, physical inactivity and high levels of high-sensitivity CRP. Assessment of EDF with a noninvasive measurement of brachial artery flow-mediated dilatation (FMD) using 2-dimensional Doppler ultrasonography (US) has been developed and is used extensively in cardiovascular research.⁸ A cuff is placed on the arm or forearm of the subject, inflated to suprasystolic pressure and then released, causing reactive hand hyperemia, which in turn leads to increased flow through the observed segment of the brachial artery. This increased flow increases the shear stress at the blood-endothelium interface and stimulates endothelial cells to produce the vasodilator NO. The NO thus produced diffuses to the muscle layer adjacent to the endothelium, inducing relaxation and vessel dilatation that can be measured by US. Assessment of EDF in unmedicated patients with MDD would be a crucial step in providing direct physiological evidence of decreased production of NO by the endothelium in patients with MDD. Because impaired EDF has been shown to precede overt vascular disease and atherosclerosis by many years, patients with MDD who are apparently healthy from a cardiovascular point of view might already display impaired EDF and the associated increased cardiovascular risk. Two investigations have suggested that impaired EDF exists in patients with MDD.^{9,10} Unfortunately, the patients in these studies had received various combinations of

psychotropic treatment, which is a methodological concern because it has been shown that certain antidepressants affect NO production by the endothelium,¹¹ an effect that seems to be independent of the treatment response (unpublished data, 2003).

There have been recent studies that have reported negative findings regarding the impact of MDD on cardiovascular outcomes in patients with MI.¹²⁻¹⁴ The timing of these investigations has coincided with the extensive and growing use of statins after myocardial infarction and, indeed, it has now been demonstrated that statins have cardiovascular benefits beyond the cholesterol-lowering properties for which they were designed. Interestingly, one of the most striking hypotheses constructed to explain the beneficial pleiotropic effect of statins is based on their ability to increase NO bioavailability and endothelium function through multiple mechanisms, including increased activity of eNOS.¹⁵

In summary, research data suggest that decreased NO production from the endothelium and platelets could be a common factor in the main mechanistic hypotheses for the association between MDD and CVD. However, more direct and physiological investigations of the NO system, such as studies of endothelium-dependent FMD of the brachial artery, are needed in patients with MDD. Such information would be extremely valuable not only at baseline but also after antidepressant treatment. Indeed, increased plasma NO_x levels have been reported after treatment with paroxetine (unpublished data, 2003),¹¹ which suggests a beneficial impact of paroxetine on endothelial NO production and, therefore, endothelium function and ultimately a potential beneficial effect on cardiovascular outcomes in patients with MDD. Although speculative at this time, there might be an interest in the future in prophylactic treatment of the cardiovascular risk associated with MDD with statins, especially when patients respond to antidepressants that may not improve the dysregulation of the NO system associated with MDD.

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