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### Nitric Oxide and Arginine Metabolism in Depression: Effect of a Serotonin-Norepinephrine Reuptake Inhibitor

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Depressed mood is known to be an independent risk factor for cardiovascular disease. Nitric oxide (NO)-mediated oxidative stress has been linked to endothelial dysfunction preceding cardiovascular disease (CVD).

In this study, we sought to determine if the metabolic conversion of L-arginine to NO might be altered in the plasma of depressed patients as a possible early-warning sign of future CVD, and whether treating depression might affect this pathway favorably. To do this, the following five plasma biomarkers were measured: (1) asymmetric-dimethylarginine (ADMA; an endogenous inhibitor of the NO synthases), (2) total nitrite (a biomarker of endogenous NO production), (3) agmatine (an alternative metabolite of arginine and putative stress-related transmitter), (4) myeloperoxidase (an enzyme leading to peroxynitrite production), or (5) nitrotyrosine (an index of peroxynitrite levels). No baseline differences were observed for any of these biomarkers between depressed patients (n = 23) and matched healthy controls (n = 17). An ancillary finding was that nitrotyrosine covaried with body mass index ($P$ = .03). Fourteen of the depressed patients were then treated for 8 weeks with venlafaxine, a serotonin-norepinephrine reuptake inhibitor (SNRI). All 14 patients responded by achieving improved Hamilton Depression rating scores < 10. After 8 weeks on venlafaxine, lowered plasma levels of agmatine ($P$ = .02) and myeloperoxidase ($P$ = .02) were observed and there was a trend for elevated nitrite to be correlated with antidepressant drug levels ($P$ = .07). None of the other biomarkers were affected by venlafaxine treatment.

Thus, the L-arginine to NO pathway appeared normal in depressed patients lacking symptoms of CVD, yet the antidepressant venlafaxine appeared to alter certain components of this pathway. The possible long-term clinical consequences of these changes in the L-arginine to NO pathway are unknown but may warrant further study of the cardiovascular effects of venlafaxine and other SNRIs.