Potential Risks of Nitric Oxide Inhibition in Spinal Cord Injury

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Orthostatic hypotension is highly prevalent among individuals with spinal cord injury and is primarily due to disruption of peripheral sympathetic pathways (1–3). In addition, we have speculated that prolonged bed rest and the inherent inability to maintain fully upright posture (microgravity) may contribute to orthostatic intolerance in patients with SCI (4). Chronic exposure to microactivity by prolonged space flight or extended bed rest results in adaptive changes, which lead to severe disabling orthostatic hypotension in the returning astronauts and recovering bedridden patients (5–7). In a series of studies utilizing hind-limb unweighed rats (designed to mimic microgravity), we demonstrated marked up-regulations of constitutively expressed inducible nitric oxide (NO) synthase (iNOS) in the heart, kidney and thoracic aorta and of neuronal NO synthase (nNOS) in the kidney and brain of microgravity-adaptive animals (8,9). This was coupled with significant increase in total body NO production, attenuated pressor response *in vivo* and diminished contractile response in artery rings *in vitro* to norepinephrine. These abnormalities were reversed by administration of iNOS inhibitor, aminoguanidine (8,9). Taken together, these observations provided compelling evidence that up-regulations of iNOS and nNOS in the key blood pressure-regulatory tissues contribute to the pathogenesis of the associated cardiovascular instability. Based on these findings in experimental animals, I was tempted to speculate that similar adaptive phenomena may be operative in the pathogenesis of orthostatic hypotension in bedridden patients and those with high-level SCI who are unable to attain and/or maintain upright posture (4).

In this issue, Dr Wecht and associates (10) compared arterial pressure at baseline and after infusion of a nonspecific NOS inhibitor, L-NAME, among a group of patients with tetraplegia and their age-matched able-bodied controls. They found a significantly lower arterial pressure at baseline and a more robust rise in blood pressure after L-NAME administration in the tetraplegic group than in the able-bodied controls. These observa-

tions provided strong evidence for increased basal production of NO in the individuals with SCI. To my knowledge, this is the first study demonstrating indirect evidence for increased NO tone in humans with SCI. Clearly, single infusion of NOS inhibitor, L-NAME, employed in this study under strictly-controlled conditions, has served a valuable purpose of expanding our understanding of the underlying mechanism of orthostatic intolerance in SCI. However, extreme caution should be exercised in therapeutic application of nonspecific NOS inhibitors in general, and in individuals with SCI in particular. This viewpoint is based on the following observations.

Due to the inherent limitation of physical activity, chronic SCI leads to an array of metabolic disorders (including insulin resistance and dyslipidemia) which can cause endothelial dysfunction, atherosclerosis and cardiovascular disease. Endothelium-derived NO plays a crucial role in protection against vascular remodeling and atherosclerosis. Consequently, chronic inhibition of NOS can accelerate the atherogenic process in this and other populations.

Spinal cord injury results in significant alterations of blood coagulation system that lead to a prothrombotic state. This is compounded by the inherent limitations of normal physical activity favoring deep venous thrombosis. Endothelium-derived NO serves as potent inhibitor of platelet activation/adhesion and as such, plays a major role in preservation of normal blood fluidity and prevention of blood coagulation. Thus, chronic inhibition of eNOS can potentially intensify the thrombophilic diathesis in this population.

Instantaneous activation of eNOS (and the consequent rise in endothelial NO production) in response to sudden surges in shear stress and blood pressure (11,12) is indispensable for protection against pressure-mediated injury to brain, kidney, heart, and other tissues. Patients with SCI, particularly those with lesions at or above T6 are highly prone to autonomic dysreflexia, which is marked by abrupt and exuberant activation of sympathetic activity leading to episodes of severe hypertension and occasionally hemorrhagic stroke. These episodes are initiated by a variety of exogenous or endogenous stimuli causing activation of spinal sympathetic circuits which in the absence of inhibitory input from higher centers proceed uncontrollably (13). Given the vital role of endothelium-derived NO in protection against pre-

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capitous surge and/or sustained elevation of arterial pressure, long-term blockade of eNOS can potentially raise the risk of hemorrhagic stroke and other complications in individuals with SCI experiencing autonomic dysreflexia.

For reasons outlined above, I believe that long-term use of nonspecific NOS inhibitors may not be warranted in the SCI population. However, selective inhibitors of iNOS may be safer and more appropriate in this instance.

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