EDITORIAL COMMENT

Inducible Nitric Oxide Synthase in Severe Human Heart Failure*

Impact of Mechanical Unloading

Randall C. Starling, MD, MPH, FACC
Cleveland, Ohio

In this issue of the Journal, Patten et al. (1) report the impact of unloading therapy in humans with advanced stage D heart failure who were supported with a left ventricular-assist device (VAD). The authors hypothesized that the hemodynamic improvements that accompany VAD support would decrease the expression of myocardial inducible nitric oxide synthase (iNOS) and cardiomyocyte apoptosis in failing hearts. The work of Patten et al. (1) extends our knowledge of iNOS in human heart failure by presenting serial data and showing the relationship to cell death (apoptosis) and the impact of mechanical stress (and subsequent unloading), which may be an independent stimulus for iNOS activity, regardless of the inflammatory milieu.

See page 1419

Nitric oxide (NO) remains the topic of considerable interest for this work. NO is present in all tissues and cells of the body and can be synthesized by three isozymes: neuronal NO synthase (nNOS) or type I, expressed in the brain and the peripheral nervous system; endothelial NO synthase (eNOS) or type III, present in the vascular endothelium and cardiac myocytes; and inducible NO synthase (iNOS), induced in response to a variety of stimuli such as inflammation, endotoxins, and cytokines. The complexity of this topic has been attributed to the fact that nitric oxide synthase III plays a central role in NO production and that also up-regulate oxidase and, therefore, upsetting the balance between NO and superoxide production. Hence, the overexpression of iNOS can ironically lead to cellular damage (9). Cardiomyocyte overexpression of iNOS in mice results in peroxynitrite generation associated with fibrosis, hypertrophy, and chamber dilation, a cardiomyopathic phenotype (10). Hence, a scenario evolves in which the overexpression of iNOS can lead to the deleterious consequences, presumably by the simultaneous up-regulation of oxidase and, therefore, up-regulating the balance between NO and superoxide production. The observation of elevated iNOS in human heart failure that is attenuated by mechanical unloading with a VAD provides additional insight into the deleterious consequences of elevated wall stress in perpetuating progressive left ventricular dysfunction and myocardial failure.

Triggers for iNOS expression include inflammatory cytokines (interleukin-6, tumor necrosis factor-alpha, interferon-gamma) and lipopolysaccharides; hence, catecholamine-resistant hypotension associated with septic shock has been attributed to enhanced iNOS activity. Known triggers of the iNOS isoform include acute ischemia, sepsis, myocarditis, cardiac allograft rejection, and mechanical stress. The interaction between NO and superoxide is delicate because deficiencies of NO and an overabundance of superoxide can impair the balance between physiologic and pathologic pathways. Cellular damage that occurs in the setting of elevated iNOS is a consequence of common stimuli that result in the formation of NO and that also up-regulate oxidase, hence resulting in tissue elevations in both NO and superoxide, which leads to the formation of peroxynitrite (8). Peroxynitrite and superoxide are toxic species capable of causing cellular damage (9). Cardiomyocyte overexpression of iNOS in mice results in peroxynitrite generation associated with fibrosis, hypertrophy, and chamber dilation, a cardiomyopathic phenotype (10). Hence, a scenario evolves in which the overexpression of iNOS can lead to pathologic consequences, presumably by the simultaneous up-regulation of oxidase and, therefore, up-regulating the balance between NO and superoxide production. The observation of elevated iNOS in human heart failure that is attenuated by mechanical unloading with a VAD provides additional insight into the deleterious consequences of elevated wall stress in perpetuating progressive left ventricular dysfunction and myocardial failure.

The role of iNOS in heart failure pathogenesis is contentious. The complexity of this topic has been attributed to the...
differing physiologic effects of leukocyte-derived iNOS versus myocyte-derived iNOS and the impact of the cellular microenvironment (2). Previous work in humans has shown an elevation of iNOS gene expression in humans with heart failure, but the extent was greater in New York Heart Association functional class II versus class IV patients (11). However, as noted earlier, common stimuli that increase iNOS/NO can be deleterious by facilitating superoxide and peroxynitrite production. It appears unclear whether indeed wall stress or cytokine activation is the predominant stimulus for iNOS. Mechanical strain suppresses iNOS in cardiac myocytes in contrast to NOS III, which is up-regulated, hence the concept that NOS in the failing human heart is a “double-edged sword” (12). The hemodynamics in these New York Heart Association functional class IV patients were very abnormal at the time of VAD implantation and improved with VAD unloading, suggesting that iNOS expression is correlated positively with an increasing severity of heart failure. A reduction in wall stress is inferred based on LaPlace’s law because both a pressure and radius decrease after VAD unloading and a concomitant reduction in iNOS expression were observed. Perhaps this theory explains why better outcomes have been observed with unloading therapies versus inotropic therapies in human studies (13).

The etiology of heart failure did not appear to influence the results; however, the limited samples were confined to ischemic and nonischemic myocardial failure and did not include inflammatory heart disease. The results in previous human studies have differed with respect to the relationship between etiology of heart failure and iNOS expression (7,14). The authors did not attempt to determine whether iNOS expression was related to myocyte or leukocyte production, but this distinction does not seem relevant to their observations, albeit mechanistically of interest (2,14). Similarly, an examination of inflammatory cytokines and the relationship to iNOS expression may have yielded further mechanistic insights (15).

The major conclusions of this study provide new insights and unanswered questions. Inducible nitric oxide synthase protein expression was increased in the hearts of patients with refractory heart failure before heart transplantation. Mechanical unloading with VAD therapy decreases iNOS protein abundance in association with a decrease in the rate of cardiomyocyte apoptosis. A significant correlation between iNOS protein abundance and cardiomyocyte apoptosis was demonstrated. These observations suggest that severe heart failure is associated with up-regulation of iNOS, which correlates with the extent of cell damage and is attenuated by unloading with VAD therapy. It is intriguing to speculate that medical unloading with vasodilators and, specifically, NO enhancers might lead to analogous salutary effects in less severe heart failure.

This work adds to the wealth of information that has amassed in humans supported with VADs showing that the cardiac phenotype can change with mechanical unloading. The authors speculate that nuclear factor kappa B, the ubiquitous and putative regulator of genes associated with apoptosis, may be the mediator of “reverse remodeling.” Perhaps iNOS is a marker of the dynamic myocardial events that take place as mechanical stress develops and is alleviated? Many steps in the pathway to failed myocardium have been described by other investigators, including atrial natriuretic peptide, brain natriuretic peptide, interleukin-6, tumor necrosis factor-alpha, and transforming growth factor-beta, to name a few, and shown to “reverse” with mechanical unloading. However, despite the restoration of health with VAD therapies, rarely does the native heart recover to sustain long-term and event-free survival, except in an extremely small percentage of patients and especially those with relatively acute onset of heart failure (16). Future studies using paired tissue samples are important to elucidate the mechanisms of human heart failure. Consortiums that pool resources of clinical information and tissue banks will facilitate and enable future discoveries to unravel the complex and vexing process of myocardial failure.

Reprint requests and correspondence: Dr. Randall C. Starling, Head, Section of Heart Failure and Cardiac Transplant Medicine, Cleveland Clinic Foundation, Department of Cardiovascular Medicine, 9500 Euclid Avenue, Desk F-25, Cleveland, Ohio 44195. E-mail: starlir@ccf.org.

REFERENCES


