Modulation of the adaptive response to myocardial ischemia by coexisting disease

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THE LAST HALF OF THIS CENTURY has been distinguished by vast progress in our understanding of physiological mechanisms that contribute to cellular, tissue, and organ protection against ischemia. Perhaps most notable is the identification of the endothelium-derived vasodilator nitric oxide (6) and ischemic preconditioning (24) as powerful endogenous mechanisms producing cardioprotection. Interestingly, nitric oxide and ischemic preconditioning have been linked in the heart. Nitric oxide serves as a key mediator of the “second window” or late phase of ischemic preconditioning to reduce the extent of myocardial injury following coronary artery occlusion and reperfusion (3, 33). In the May 1999 issue of AJ P: Heart and Circulatory Physiology, the ability of nitric oxide to limit myocardial injury during ischemia was emphasized by the findings of Jones et al. (12), who used endothelial cell nitric oxide synthase (eNOS)-deficient (knockout) mice and by Agullo et al. (2), who used isolated rat hearts subjected to hypoxia and reoxygenation. These studies indicate that nitric oxide and ultimately increases in cGMP activity have a major impact on the extent of myocardial injury occurring during ischemia or hypoxia.

Given the capacity of the heart to robustly respond to ischemic stimuli by preconditioning and the ubiquitous nature of nitric oxide, it would seem logical to assume that the myocardium should be readily adaptable to such untoward events. Yet, worldwide, cardiovascular disease accounts for 12 million deaths each year. The basis for the profound morbidity and mortality associated with myocardial ischemia may be related to the effects of coexisting disease on ischemia and reperfusion injury. In fact, patients with coronary artery disease commonly have concomitant hypertension and diabetes mellitus, two diseases with a high impact on vascular endothelium. Clearly, future research must be directed at the identification of mechanisms by which coexisting disease interferes with endogenous cardioprotection, and several key investigations reported here may provide a direction for future work.

The role of nitric oxide to limit the extent of myocardial ischemia and reperfusion injury has been suggested previously (16, 26, 28), but the availability of pharmacological tools limited earlier investigations. In this May 1999 issue of the Journal, Jones et al. (12) evaluated the role of nitric oxide to mitigate the degree of myocardial infarction in mice genetically deficient in eNOS. Genetically altered mice demonstrated marked increases in infarct size after coronary artery occlusion and reperfusion as compared with wild-type mice. Increases in infarct size occurred concomitant with enhanced expression of the endothelial cell adhesion molecule P-selectin and with pronounced neutrophil infiltration into previously ischemic tissue. These results emphasize the important effects of nitric oxide synthase activity to reduce injury in the myocardium occurring as a result of inflammatory responses mediated by neutrophils and coronary vascular endothelium. Enhanced inflammatory responses to ischemia and reperfusion via adhesion molecules have previously been demonstrated in diabetic animals (29). The similar findings of Jones et al. (12) in eNOS-deficient mice support the contention that impairment of nitric oxide may be partly responsible for maladaptation to ischemia during diabetes mellitus.

Reminiscent of ischemic preconditioning, in the May issue of the Journal, Agullo et al. (2) demonstrated that preanoxic administration of the nitric oxide precursor L-arginine enhanced functional recovery of myocardium and simultaneously increased cGMP release in isolated rat hearts. Only pretreatment was effective, and L-arginine was not cardioprotective if administered solely during the anoxic or reoxygenation periods. Furthermore, a selective antagonist of soluble guanylate cyclase attenuated the benefit afforded by L-arginine. Thus nitric oxide and signal transduction through cGMP are shown again to play critical roles in attenuating the extent of ischemic injury in myocardium. The potential of nitric oxide to act as an effective endogenous cardioprotective substance may be severely limited in patients with coronary artery disease. Changes in nitric oxide signaling pathways may prove to be a critical determinant of insufficient myocardial adaptation to ischemia in hypertension, atherosclerosis, diabetes mellitus, and heart failure, all disease states associated with reduced availability of nitric oxide. For example, it has long been recognized that the prognosis of patients with diabetes mellitus is poor after acute myocardial infarction (1, 11, 17, 22), yet the mechanisms that account for this increased morbidity and mortality are poorly understood. Diabetes, and even hyperglycemia alone, cause vascular endothelial...
dysfunction as a result of decreases in endothelial nitric oxide production and/or activity (7, 15, 19, 31, 37). Experimental acute hyperglycemia also abolishes the protection afforded by ischemic preconditioning (14). Whereas some of the deleterious effects of diabetes and hyperglycemia may be reversed by administration of L-arginine (19, 26, 31), specific therapies to restore the efficacy of cardioprotective pathways altered by these and other diseases remain relatively unexplored.

Quenching of nitric oxide by the superoxide anion (O$_2^-$) is increasingly being recognized as an important pathophysiological consequence of many diseases, including hypertension (34, 36), atherosclerosis (21, 32), and diabetes (4, 30, 37). Provision of substrate (i.e., L-arginine) alone as a means to restore nitric oxide activity may prove to be ineffective because of interactions between nitric oxide and O$_2^-$ (9). The findings of Gupta et al. (10) in the May issue of the Journal provide additional evidence of a provocative link between cellular redox state and nitric oxide activity. These investigators demonstrate that increased intracellular concentrations of lactate cause a reduction in nitrovasodilator-induced relaxation of pulmonary arteries and reduced activation of guanylate cyclase when endogenous superoxide dismutase activity is inhibited. Metabolism of lactate by the lactate dehydrogenase enzyme increases intracellular NADH, a substrate for NADH oxidase. The latter is an important source of O$_2^-$ in the pulmonary vasculature, and changes in cellular redox state lead to increases in O$_2^-$ production. Normally, increases in O$_2^-$ are mitigated by superoxide dismutase; however, in the absence of sufficient SOD activity, nitric oxide-mediated signaling is dramatically diminished. These results suggest that, if endogenous SOD activity is decreased by disease, alterations in the cellular redox state that occur during ischemia may be met by an attenuated nitric oxide response. Diminished nitric oxide action in such a case represents an example of how coexisting disease may affect the adaptive response to an ischemic event. This process is clearly demonstrated by the increases in oxidant stress that occur during diabetes and hyperglycemia and contribute to vascular endothelial dysfunction that may be reversible on administration of free radical scavengers (4, 8, 18, 30). It is unknown if treatment with antioxidants will ultimately enhance the efficacy of endogenous cardioprotective mechanisms during disease states associated with absolute or relative overproduction of O$_2^-$. This represents an important area for future investigation.

Nitric oxide mediates adaptive responses to ischemia not only through direct effects but also indirectly via the coronary vasculature. For example, nitric oxide has been shown to be responsible for tonic vasodilation of the coronary collateral circulation (5), and diabetes (13, 25, 27) or atherosclerosis (21) impairs coronary vasodilator responses to physiological and pharmacological stimuli. Recently, Metais et al. (20) evaluated human coronary microvascular responses to vascular endothelial growth factor in vitro. Vascular endothelial growth factor caused dose-dependent relaxation of microvessels obtained from patients without coronary artery disease. The vasodilator responses were blocked by inhibition of nitric oxide synthase and were absent in microvessels harvested from patients with coronary artery disease. These results provide strong evidence that coexisting disease may influence the adaptation to myocardial ischemia. Such maladaptation to ischemia may also extend to an impairment of angiogenesis and vasculogenesis. Angiogenesis was significantly impaired in the ischemic hindlimb of ecNOS-deficient mice as compared with mice possessing the wild-type gene (23) and was impaired by diabetes in a similar model (35). Whereas coronary collateral development was not specifically evaluated in these models, capillary density was decreased in infarcted myocardium of diabetic patients (38). An important goal of future research will be to determine whether alterations in nitric oxide signaling or other mechanisms are responsible for insufficient coronary collateral development in some patients, whereas others may adapt to chronic myocardial ischemia by new vessel growth. It is clear that coexisting disease states markedly modify adaptive responses to myocardial ischemia. Determination of the responsible mechanisms will present new challenges and may suggest new treatment modalities, allowing the full potential of endogenous cardioprotective mechanisms to be achieved.

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