Nitric Oxide and Viral Cardiomyopathy

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The report by Badorff et al1 in this issue of Circulation provides an opportunity to reflect on the enormous impact that the discovery of nitric oxide (NO) has already had in furthering our understanding of the basic biology of human disease processes. This report also helps to illustrate how basic insights coupled with clinical observations will ultimately lead to redefining previously unrelated clinical conditions along more pathophysiologically relevant lines.

The 1998 Nobel Prize for Medicine or Physiology was awarded to Louis J. Ignarro, Ferid Murad, and Robert Furchgott for the discovery of the role of NO as a signaling molecule in the cardiovascular system.2 Ignarro studied the mechanism of action of nitroglycerin, which was first synthesized by Sobrero more than 150 years ago, and discovered that it mediates its effects through NO. Murad discovered that NO mediates effects through that “other,” less appreciated (ie, not cAMP), cyclic nucleotide, cGMP. Furchgott’s simple experiments with rabbit aortas provided physiological relevance by revealing that vascular endothelium normally produces a relaxing factor, endothelium-derived relaxing factor, which Ignarro showed to be NO. Shortly thereafter, inhibitors were identified, enzyme proteins isolated, and NO synthases (NOS) successively cloned from neurons (type 1), macrophages (type 2), and endothelial cells (type 3).3 It was clear from the beginning that the constitutive, basal production of small quantities of NO by NOS types 1 and 3 played a critical role in normal physiological processes. What has been less obvious, however, is the benefits conferred by the production of much larger quantities of NO by NOS 2 in response to cytokines.

Sepsis has served as the paradigm for cytokine-induced expression of NO.3 Much unsuccessful effort has been invested in regulating the presumed exclusively deleterious effects of cytokine-induced NO production in sepsis. This view of cytokine-induced NO production appears to be too simplistic and avoids a truly important fundamental question: What is the biological advantage to cytokine-induced NO production? Is cytokine-induced NO simply the evil twin of constitutive NO? Evidence has already been provided that cytokine-induced NO production by so-called inducible NO synthase (iNOS) plays an important role in the normal host response to infection.4 This report by Badorff et al helps to shed some additional light on these important questions by providing a potential molecular mechanism for a protective role for NO in viral infection. The authors previously demonstrated that coxsackievirus B3 (CVB3) possesses a protease (2A) that cleaves an integral membrane glycoprotein, dystrophin, in human and mouse cardiac membranes.4 In the present article, they provide evidence that NO donors can S-nitrosylate a cysteine residue that is essential for catalytic activity of protease 2A. Thus, the elaboration of NO by cardiac myocytes may prevent dystrophin cleavage by inactivating viral protease 2A. These data help to explain previous reports that NO inhibits CVB3 replication in vitro and the augmentation of CVB3 infection in iNOS-deficient mice.4 More definitive conclusions must await the demonstration of the same mechanism in human cardiomyopathy specimens and ex vivo experiments in animal models infected with CVB.

This report should have an immediate impact on the way we view viral cardiomyopathy, as well as other causes of heart failure. The rationale for exploring the effects of NO on dystrophin cleavage evolved from previous work by others demonstrating the presence of a dystrophin defect in genetic cardiomyopathy.5 This illustrates the potential for evoking the same molecular mechanism for an acquired as for a genetic defect. A genetic defect in dystrophin alone is sufficient to result in development of a rare cardiomyopathy. A virally acquired defect in a susceptible dystrophin isoform may also be sufficient to develop a relatively more common cardiomyopathy. Yet, both of these are relatively uncommon diseases. Badorff and colleagues provide evidence that cytokine-induced elaboration of NO may have evolved as an important adaptive mechanism in preventing the development of dilated cardiomyopathy after exposure to CVB3. This would further suggest that defects in this NO-mediated host response to viral infection could also contribute to some of the variability in the natural history of idiopathic cardiomyopathy. Too little NO could allow greater viral invasion. Too much NO in response to norepinephrine and/or angiotensin II could depress mitochondrial activity and lead to apoptosis.5

The implications of this study extend beyond CVB3-induced cardiomyopathy to more common clinical problems. The cytokine and NO host response to infection appears to share important features with the host response to other injuries, including ischemia. Historically, and until only recently, the reversible myocardial depression and β-adrenergic desensitization seen experimentally and clinically in ischemia (eg, “stunned myocardium”) were viewed as
unrelated to a similar phenomenon that occurs in sepsis. Basic and clinical investigators and clinicians interested in the effects of ischemia on myocardial function had little interaction with their colleagues who studied the effects of infection and immunity in other systems. However, an interdisciplinary approach that recognized the heart as a target of immune modulation was applied to understand the reversible myocardial depression and β-adrenergic desensitization described in septic patients. The so-called “proinflammatory” cytokines were identified as potential endogenous mediators of myocardial depression in these patients. These cytokines were subsequently demonstrated to directly and reversibly depress myocardial contractility within minutes and over hours through NO-dependent and independent mechanisms in animal models in vitro.

Data supporting a myocardial depressant effect of cytokine-induced NO production in patients with sepsis have also been reported. It is now clear that cytokines and NO are elaborated locally and systemically during a variety of stresses, including ischemia and infection. This has led to the proposal that cytokines and NO are common mediators of reversible myocardial depression and β-adrenergic desensitization in such disparate clinical and experimental conditions as Sepsis, Trauma, Ischemia, Transplant rejection, myoCarditis, and Heart failure (“STITCH syndrome”). This report by Badorff et al may provide a rationale in support of the hypothesis that cytokines and NO are mediators of the myocardial response to ischemia and infection. This brings us to the next question: Just how similar are the molecular mechanisms involved in the host responses to ischemia and infection? An answer to this question may be provided from insights derived from elegant parallel studies into the mechanisms responsible for lipopolysaccharide (LPS) tolerance and ischemic preconditioning.

Murry et al described “ischemic preconditioning” as the phenomenon of myocardial protection that occurs after brief periods of ischemia with intermittent reperfusion. From the results of clinical trials, astute clinicians appreciated that patients who presented with a stuttering course of intermittent chest pain before their myocardial infarction fared better than those who did not. It is reasonable to infer that patients with recurrent, brief episodes of chest pain before a myocardial infarction with intermittent reperfusion are undergoing the clinical correlate of the experimental condition involving brief periods of coronary ligation followed by complete occlusion, ie, ischemic preconditioning. This potentially clinically relevant protective effect has been reproduced and studied in a variety of animal models as an unexpected and unique means of myocardial protection from subsequent ischemia. The molecular mechanisms responsible for the early and delayed protective effects are not fully understood. The early benefits that occur within minutes appear to be related to adenosine-mediated potassium channel regulation. Presumably, the opening of ATP-sensitive potassium channels (K<sub>ATP</sub>) causes a repolarizing current that reduces the duration of the cardiac action potential, which results in reduction in calcium entry and thereby, myocardial injury.

Experimental data suggest that activation of protein kinase C (PKC) via an inhibitory GTP regulatory protein (G<sub>i</sub> protein) might be a crucial step in the mediation of late preconditioning that occurs over hours. This is supported by studies that show that activation of PKC elicits protection against ischemia, whereas inhibition of PKC activation results in the loss of the late/delayed protection conferred by preconditioning. PKC-induced preconditioning could be due to the phosphorylation of other proteins, such as the mitogen-activated protein kinase cascade, and the subsequent phosphorylation of gene transcription factors. More recently, Ping et al reported that the NO donor SNAP induces preconditioning via activation of PKC in the rabbit heart. NO donors have also been shown to induce late preconditioning by generation of the oxidant species ONOO− and/or ·OH.

Pretreatments with LPS and with monophosphoryl lipid A (MLA; a nontoxic analogue of endotoxin) have each been reported to induce a cardioprotective effect against subsequent ischemia. Of particular interest to this discussion, NO appears to play an important role in LPS- and MLA-induced cardioprotection. Cytokines are well known to induce NO production after LPS exposure in vivo. The sources of cytokines have been attributed largely to noncardiac origins. Growing evidence now suggests that the heart itself is also a cytokine-producing organ. Thus, LPS and/or ischemia can each trigger a cytokine-mediated response to injury by cardiomyocytes or other resident intramyocardial cells to produce NO to protect the heart from subsequent potential insults such as ischemia or reinfarction. It is interesting to note that both tumor necrosis factor-α and interleukin-1β have been identified in postischemic, reperfused myocardium. These same cytokines can stimulate NO production by cardiomyocytes. Taken together, these clinical and experimental studies raise the intriguing possibility that ischemic preconditioning and LPS tolerance share common molecular mechanisms involving cytokines and NO.

A role for NO in the programmed host response to a variety of injuries conforms with the principles of simplicity and redundancy in evolutionary biology. The host responses to infection and ischemia are clearly essential for survival. The adaptations to these stresses would be expected to share common phenotypic features and signaling pathways. Elucidating the molecular mechanisms that regulate these responses has the potential to enhance our basic understanding and management of patients with seemingly unrelated cardiac conditions. Considerably more work needs to be done before we can draw definitive and clinically applicable conclusions. However, the report by Badorff et al in this issue of Circulation does help us to appreciate that “big” NO is not “little” NO’s evil twin.

References

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