Nitric Oxide Modulation as a Therapeutic Strategy in Heart Failure

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KEYWORDS

• Nitric oxide • Heart failure • Oxidant stress

Nitric Oxide (NO) is recognized as one of the most important cardiovascular signaling molecules, with multiple regulatory effects on myocardial and vascular tissue as well as on other tissues and organ systems. Furchgott and Zawandski[1] first identified a substance secreted by endothelial cells that induced relaxation of vascular smooth muscle, which was initially called endothelium-derived relaxing factor (EDRF). EDRF was subsequently definitively identified as NO.[1–3] Though first recognized as a substance originating from endothelial cells that regulated vascular function and thrombogenicity, NO is also known to be expressed by cardiomyocytes as well as vascular endothelium, and to have multiple, complex regulatory roles on myocardial function including myocardial metabolism, mitochondrial respiration, autonomic function, contractility, relaxation, cell growth, ion channel behavior, and responsiveness to β-adrenergic stimulation, among others.[4–10] NO effects on the cardiovascular system and in heart failure may be positive or deleterious depending on the source of NO, the stimulus for NO release, the subcellular site of NO release, and the magnitude of NO release.[11–13]

In a wide range of cardiovascular diseases including systemic and pulmonary hypertension, coronary and peripheral atherosclerosis, ventricular hypertrophy, and right and left ventricular failure, there are significant alterations in NO bioavailability and signaling capacity.[6,14–24] With the growth in understanding of the range and mechanisms of NO effects on the cardiovascular system, it is now possible to consider pharmaceutical interventions that directly target either NO or key steps in NO effector pathways. This article briefly reviews some aspects of the cardiovascular effects of NO and abnormalities in NO regulation in heart failure, followed by a review of clinical trials of drugs that target specific aspects of NO signaling pathways.

GENERATION OF NITRIC OXIDE AND NITRIC OXIDE EFFECTOR PATHWAYS

NO is formed in tissues by the enzyme nitric oxide synthase (NOS), which converts L-arginine to L-citrulline and NO, and exists in myocardium in 3 different isoforms: neuronal NOS (nNOS or NOS1), endothelial NOS (eNOS or NOS3), and inducible NOS (iNOS or NOS2).[4–6,12,23] Nitric oxide synthases produce NO in response to different stimuli; for example, NOS1 and NOS3 require calcium for activation, whereas NOS2 does not. NOS2 is induced by proinflammatory cytokines and can release large quantities of NO, which can have direct toxic effects or increase the production of reactive oxygen species (ROS).[5,22,23] Quantities of NOS produced by each isoform may be quite

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different, and finally, NO produced by NOS may at times have quite different effects on myocardial function.[11,22,23] NOS isoforms are distributed within different cell compartments[12,13,22,23] and NO effects are determined in part by the specific subcellular target organelle, by the concentrations achieved within these cell compartments, and by the duration of time it is present.[5] The fact that NOS isoforms are located in different subcellular compartments and respond to different stimuli allows a heterogeneity of responses to a single molecule, NO, based on the specific cellular site of NO release, the isoform activated, and the stimulus for release, as well as the effector pathway activated.[6,12,22] **Table 1** summarizes some effects of activation of different NOS isoforms.

Two effector pathways for NO signaling are illustrated in **Fig. 1**. In endothelial cells, NOS converts L-arginine to L-citrulline and NO. NO then may bind to the heme moiety of soluble guanylyl cyclase (sGC), which catalyzes production of cyclic guanosine-3′,5′-monophosphate (cGMP) to activate protein kinases, ion channels, and cGMP-dependent phosphodiesterases.[4,5,23,25] cGMP effects are further regulated by degradation of GMP by phosphodiesterase type 5 (PDE-5). A second effector pathway for NO is cGMP independent and is the result of nitrosylation of cysteine residues (*S*-nitrosylation) of proteins.[25–29] Although the NO/cGMP signaling pathway was the first identified, *S*-nitrosylation is emerging as a widespread NO signaling mechanism with effects on cardiac excitation-contraction coupling, response to β-adrenergic stimulation, and arrhythmogenesis, to name a few.[25–29] Inactivation of the cGMP-derived NO effects occurs by degradation of cGMP by PDE-5, whereas the *S*-nitrosylation–dependent effects are regulated by protein denitrosylation.[22,29] Thus, biological effects of NO can occur by cGMP-dependent or cGMP-independent mechanisms, another variable that may contribute to the large number and heterogeneity of NO effects.

While NO is critical to the regulation of a large number of cellular functions, it can also be toxic

Table 1
Properties of NOS isoform activity in the normal and diseased heart

	NOS1 nNOS Neuronal NOS	NOS2 iNOS Inducible NOS	NOS3 eNOS Endothelial NOS
In Normal Hearts			
Antihypertrophic effect	✓		✓
Prohypertrophic effect		✓ or –	
Inhibition of L-type Ca^{2+} current	✓	–	✓
Net negative inotropic effect	✓	–	✓
Attenuate the β-adrenergic receptor-stimulated increase in myocardial contractility	✓		✓
Proapoptotic effect		✓ or –	
Profibrotic effect		✓ or –	
Induces left ventricular remodeling and failure		✓ or –	
During Hypertrophy/Failing/ Coronary Artery Occlusion			
Upregulated expression	✓	✓	
Downregulated expression			✓
Protects against remodeling	✓		✓
Protects against calcium overload	✓		
Limits infarct size		✓	
Improves contractile recovery after ischemia/reperfusion		✓	

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