NO Balance

Regulation of the Cytoskeleton in Congestive Heart Failure by Nitric Oxide

Cornel Badorrh, MD; Stefanie Dimmeler, PhD

Congestive heart failure is a leading cause of cardiovascular mortality in the United States and Europe. Clinically, this syndrome is characterized by water retention and often left ventricular dilatation with poor systolic contractility. Etiologically, congestive heart failure can be of genetic or acquired origin. In 1993, 2 groups independently reported mutations in the cytoskeletal protein dystrophin as the cause of X-linked dilated cardiomyopathy, a rare inheritable disease that leads to enlargement of ventricular dimensions and to congestive heart failure. Over the last decade, the pathophysiological relevance of the cardiac myocyte cytoskeleton for the development of congestive heart failure is being increasingly recognized.

For a coordinated contractile function of the heart, the mechanical forces generated within the sarcomeres of individual cardiac myocytes are transmitted to the extracellular matrix. For this purpose, cardiac myocytes are equipped with a specialized extrasarcomeric cytoskeleton. The cardiac myocyte cytoskeleton acts as a “scaffold” that provides mechanical stability to transmit the periodic shortening of the cytoskeleton possesses important signaling properties. The critical importance of an intact cytoskeleton for normal cardiac function in humans and rodents is highlighted by genetic defects in the cytoskeletal proteins titin, actin, dystrophin, sarcoglycans, and others, all of which cause dilated cardiomyopathy with congestive heart failure in patients. In the cardiomyopathic hamster, a δ-sarcoglycan deletion has been identified as disease-causing, and targeted deletion of the muscle LIM protein (MLP) in mice results in a dilated cardiomyopathy phenotype.

MLP is a muscle-specific, LIM-domain only cytoskeletal adaptor protein that is localized to the Z discs, binds the Z disc protein α-actinin, and binds to telethonin, a component of the titin complex in the sarcolemma. MLP is required for muscle differentiation, and targeted MLP ablation leads to congestive heart failure with cytoskeletal disruption and premature death in a mouse model. Importantly, MLP missense mutations occur in a subset of human dilated cardiomyopathy.

These studies lead to the paradigm that hereditary dilated cardiomyopathy can result from defective transmission of mechanical force from the sarcomere to the extracellular matrix. Similarly, cytoskeletal disruption may pathogenetically contribute to acquired forms of congestive heart failure, such as ischemic cardiomyopathy in humans and enterovirus-induced cardiomyopathy in mice.

Nitric oxide (NO) is a small gaseous molecule that mediates multiple signaling pathways in the heart. NO is generated from L-arginine by 3 different isoforms of nitric oxide synthase (NOS). In contrast to the neuronal (NOSI) and endothelial (NOSII) isoform, the inducible NOS isoform (NOSIII) synthesizes large NO amounts independent of calcium. In addition to acting as a signaling molecule, NO can react with O2 to form peroxynitrite (ONOO−), a cell-toxic reactive nitrogen intermediate that leads to target protein tyrosine residue nitration (NO-Y).

Recent studies have demonstrated that NO can clearly modulate cytoskeletal functions. In high concentrations, NO resulted in a reduction of myofilament responsiveness to calcium in cardiac myocytes via the cGMP-dependent activation of the protein kinase G (PKG). In chick sensory neurons, NO causes microtubule reconfiguration and axonal retraction. NO additionally was shown to directly S-nitrosylate the cytoskeletal proteins actin and tubulin. In glomerular mesangial cells, addition of NO donors results in a change of the cellular shape and a disassembly of filamentous actin (F-actin). Interestingly, in intestinal cells, added ONOO− also leads to disassembly of the F-actin cytoskeleton and actin nitration, both of which could be rescued by radical scavengers. These results show that the adverse effects of NO on the cytoskeleton are mediated, at least in part, by the reactive intermediates O2 and ONOO. Therefore, the balance between NO versus O2− and ONOO−, which in turn is influenced by the availability of NOS cofactors and scavenging mechanisms, seems to be important in the cytoskeletal regulation by NO.

In human dilated cardiomyopathy and congestive heart failure, increased systemic NO production and enhanced myocardial NOSII mRNA and NOSII enzymatic activity have been reported. However, the pathophysiological role of NO in this context remains controversial, and NO has been referred to as a “double-edged sword.” Heger et al reported that increased cardiac iNOS expression did not alter cardiac structure and function. In contrast, Mungrue et al recently described that conditional cardiac overexpression of NOSII in

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From Molecular Cardiology, Department of Internal Medicine IV, University of Frankfurt, Frankfurt, Germany.

Correspondence to Stefanie Dimmeler, Dept. of Molecular Cardiology, University of Frankfurt, Theodor Stern-Kai 7, 60590 Frankfurt, Germany. E-mail Dimmeler@em.uni-frankfurt.de

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transgenic mice leads to an increased cardiac ONOO⁻ production and NO-Y formation in the animals' hearts. This was associated with a mild inflammatory infiltrate, cardiac fibrosis, hypertrophy, chamber dilatation, and, albeit infrequently, congestive heart failure.¹⁸ Although the cytoskeleton of these transgenic mice were not directly assessed, the development of cardiac fibrosis suggests some degree of cytoskeletal reorganization.¹⁸ The different phenotypes of the transgenic mice might be explained by the experimental setting. One may speculate that the non-conditional approach used by Heger et al¹⁷ may have allowed for the upregulation of compensatory mechanisms, which may shift the balance between NO and ONOO⁻. Indeed, in the conditional iNOS transgenic animals, where a phenotype was observed, drastic increases in ONOO⁻ were demonstrated.¹⁸

In the current issue of Circulation, Heineke et al¹⁹ report that addition of the NO donor S-Nitro-N-Acetyl-Penicillamine to rat neonatal ventricular cardiac myocytes reduced the endothelin-1–induced MLP upregulation by approximately 50%. Similarly, induction of NOSII in cardiac myocytes also significantly reduced the endothelin-1–induced MLP upregulation. The effects were partially rescued by radical scavenging superoxide dismutase and were reproduced by the addition of ONOO⁻. This suggests that NO suppressed MLP expression in part through ONOO⁻ formation. However, cGMP-dependent activation of PKG also contributed to the phenotype, as demonstrated by the use of cardiac myocytes adenosinorally transduced with a dominant-negative PKG mutant.¹⁹ Importantly, the expression levels of NOSII and MLP displayed an inverse correlation in human hearts with congestive heart failure due to ischemic or dilated cardiomyopathy. Finally, antisense MLP downregulation suppressed cardiac myocyte hypertrophy and, in turn, MLP overexpression was sufficient for some aspects of cardiomyocyte hypertrophy.¹⁹

These data provide the first molecular link between NO/ONOO⁻ and a component of the cardiac myocyte cytoskeleton crucial for a normal function of the heart. Together with in vivo results,¹⁸ these data support the concept that the adverse effects of ONOO⁻ on cardiac myocytes are, at least in part, mediated through the cardiac myocyte cytoskeleton. This represents further evidence for the “final common pathway hypothesis” postulating that cytoskeletal abnormalities underlie or contribute to many forms of congestive heart failure.¹ In this regard, it is important to note that a 50% reduction of MLP expression in human heart failure has been independently described.²⁰ It is tempting to speculate that downregulation of MLP is functionally important in the setting of human heart failure, although MLP⁻/⁻ mice with 50% MLP expression levels do not display a dilated cardiomyopathy phenotype at baseline.⁵ Further experiments are required to determine the effects of partial MLP deficiency in various pathological conditions, such as myocardial infarction or pressure overload. Nevertheless, the study by Heineke et al¹⁹ provides an important molecular insight how NO/ONOO⁻ regulates the cardiac myocyte cytoskeleton, a critical player in congestive heart failure.

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References


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