Divergent roles of endothelial nitric oxide synthase in cardiac hypertrophy and chamber dilatation?

Ajay M. Shah

Department of Cardiology, GKT School of Medicine, King’s College London, Bessemer Road, London SE5 9PJ, UK

Received and accepted 31 March 2005
Available online 19 April 2005

See also article by Ruetten et al. [11] (pages 444–453) in this issue.

Nitric oxide (NO) influences many aspects of cardiac function including excitation–contraction coupling, myofilament function, oxygen consumption, substrate metabolism, and cell growth and survival [1,2]. All three NO synthase (NOS) isoforms, namely eNOS, nNOS, and iNOS, can be expressed in the heart. An important paradigm with respect to the cardiomyocyte has been the demonstration that eNOS and nNOS are both expressed in this cell type but have distinct effects on contractile function as a result of their specific subcellular localization and distinct interactions with and/or proximity to other signaling molecules and targets such as SR calcium release channels, caveolin, cGMP-specific phosphodiesterases, and others [3,4]. In addition to this complexity at the cardiomyocyte level, individual NOS isoforms may be expressed in several different cell types within the heart. For example, eNOS is expressed at a much higher level in cardiac endothelial and endocardial cells than in cardiomyocytes, and NO released from endothelial cells is capable of exerting paracrine effects on adjacent cardiomyocytes [1].

Although the effects of NO on contractile function initially received more attention than its other actions, it is evident that NO may also influence cardiac hypertrophy and remodeling. NO inhibits agonist-induced hypertrophy of isolated cardiomyocytes and is capable of inducing myocyte apoptosis [5–7]. At least part of the anti-hypertrophic effect of NO appears to be cGMP-mediated, involving the activation of cGMP-dependent protein kinase I (PKG I), and is similar to the anti-hypertrophic effects of atrial natriuretic peptide (ANP) and brain natriuretic peptide (BNP) [8]. In rat neonatal cardiomyocytes, NO inhibits the calcineurin-NFAT signalling pathway and downregulates muscle LIM protein (MLP) through both cGMP-dependent and reactive oxygen species (ROS)-dependent pathways, effects which could account for its anti-hypertrophic actions [6,7]. NO also inhibits cardiac fibroblast proliferation, an effect analogous to the cGMP-mediated actions of ANP and BNP [5,9].

The development of cardiac hypertrophy in vivo in response to chronic pressure overload is a complex process that involves alterations in cardiomyocyte size, structure, and function as well as extracellular matrix remodeling [10]. Chronic hypertrophy usually progresses to left ventricular (LV) dilatation and failure. Different components of the cardiac hypertrophic phenotype, for example hypertrophy, interstitial fibrosis, and contractile dysfunction, are capable of being independently regulated. Translating the actions of NO determined in cultured cells to the intact heart and animal is therefore not straightforward, and it remains unclear what the roles of different NOS isoforms and different cell types are with respect to pressure-overload hypertrophy in vivo.

In the current issue of the Journal, Ruetten and colleagues [11] report the effects of pressure overload induced by abdominal aortic banding in eNOS knockout mice and wild-type controls. Consistent with the aforementioned in vitro studies, these authors found that banded eNOS−/− mice had greater hypertrophy than wild-type mice as assessed by echocardiographic wall thickness or myocyte cross-sectional area. They also found evidence of increased interstitial fibrosis in the banded eNOS−/− animals together with worse systolic and diastolic LV function compared to wild-type banded mice. Interestingly, however, Ruetten et al. [11] found that, in banded eNOS−/− mice, the left ventricle failed to dilate during chronic pressure overload despite greater hypertrophy and contractile dysfunction, whereas banded wild-type mice showed significant increases in both end-diastolic and end-systolic LV dimensions. Thus, banded
eNOS$^{-/-}$ mice developed concentric LV hypertrophy whereas wild-type animals developed eccentric LV remodeling. The authors concluded that banded eNOS$^{-/-}$ mice developed a severe restrictive hypertrophy. A potential limitation of the study was the failure to use littermate controls, since it is clear that non-littermate wild-type mice of the same strain are not perfect controls. Nonetheless, the phenotype reported by Ruetten et al. [11] is reminiscent of that found in rats chronically treated with the non-selective NOS inhibitor N$^\omega$-nitro-L-arginine methyl ester (L-NAME), which also developed eccentric LV remodeling with reduced chamber dimensions [12]. Likewise, Barouch et al. [3] recently reported that double-knockout eNOS$^{-/-}$/nNOS$^{-/-}$ mice developed a restrictive cardiac phenotype with aging. These results suggest a divergence between the (inhibitory) effects of eNOS on cardiomyocyte hypertrophy and interstitial fibrosis versus actions that may promote LV dilatation; i.e., in eNOS$^{-/-}$ mice, hypertrophy is enhanced but LV dilatation is inhibited. In contrast to these results, Ichinose et al. [13] reported that in response to transverse thoracic aortic banding (which induced a greater overload than that induced in the study by Ruetten et al. [11]), eNOS$^{-/-}$ mice developed greater LV dilatation than wild-type bands. The same group also reported that LV remodeling post-MI was greater in eNOS$^{-/-}$ mice than wild-type mice [14]. It is therefore unclear whether the effects of eNOS on chamber remodeling vary depending upon the nature or intensity of the stimulus. However, in the study by Ichinose et al. [13], LV dilatation was prevented by treating eNOS$^{-/-}$ mice with hydralazine to normalize elevated blood pressure, suggesting that the dilatation may have been a secondary effect.

The mechanisms underlying the divergent effects of eNOS deletion on LV hypertrophy versus dilatation after aortic banding were not explored in the current study. The enhancement of LV hypertrophy is consistent with prior in vitro results and could involve mechanisms such as activation of the calcineurin-NFAT pathway. On the other hand, LV dilatation usually involves activation of matrix metalloproteases (MMPs). Whether both of these effects involve eNOS in cardiomyocytes or whether endothelial cell eNOS may also play a role is an interesting question. It is also important to establish whether the differences between eNOS$^{-/-}$ and wild-type mice are indeed due to the loss of eNOS-derived NO in the former group or whether indirect effects, such as altered interaction with ROS or alterations in allosteric regulators or co-factors for the enzyme [4], are involved. The study by Ruetten et al. [11] highlights the potential for divergent regulation of different aspects of the cardiac hypertrophic phenotype as well as raises questions regarding the underlying mechanism(s) of the findings reported. More needs also to be learned about the cell-specific effects of eNOS in cardiac hypertrophy.

Acknowledgements

The author’s work is supported by the British Heart Foundation.

References