**Endothelial nitric oxide synthase and cardiac remodelling: location, location, location?**

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This editorial refers to ‘Endothelial nitric oxide synthase of the bone marrow regulates myocardial hypertrophy, fibrosis, and angiogenesis’ by A. Kazakov et al., pp. 397–405, this issue.

Left ventricular hypertrophy (LVH) in response to an increased systolic load is a compensatory mechanism that aims to restore LV pump function to normal levels. Clinically, chronic systolic LV overload most commonly results from myocardial infarction (MI), or chronic pressure overload, including hypertension and aortic stenosis. Despite the apparent appropriateness of the hypertrophy process, LVH in response to these pathological processes constitutes an independent risk factor for developing angina pectoris and congestive heart failure. The mechanisms underlying the progressive deterioration in LV function remain incompletely understood but include myocardial blood flow abnormalities, as the coronary vascular tree fails to grow commensurate with the degree of LVH. The resulting impaired myocardial O2 delivery contributes to cardiac contractile dysfunction, apoptosis, and fibrosis. In contrast to LVH produced by MI or pressure overload, LVH produced by regular dynamic physical exercise is associated with a decreased risk for coronary artery disease and congestive heart failure. Indeed, exercise-induced LVH is associated with an increased myocardial perfusion capacity and normal to increased LV contractile function, which is at least partially mediated by endothelial nitric oxide synthase (eNOS)-derived NO.

Experimental and clinical studies suggest that eNOS not only contributes to the myocardial and coronary vascular adaptations to exercise, but also modulates LV and vascular remodelling in pathological LVH (Figure 1). Thus, eNOS has been shown to ameliorate many of the perturbations observed in cardiac remodelling after MI, including cardiac dysfunction, pulmonary congestion, and interstitial fibrosis, as well as to mediate the beneficial effects of exercise training on these perturbations after MI. In contrast, the evidence of a beneficial influence of endogenous levels of eNOS on cardiac hypertrophy and dysfunction in pressure overload LVH is presently unclear. While some studies suggest a protective effect, other studies demonstrated uncoupling of eNOS-elevated oxidative stress thereby aggravating LVH and dysfunction. An explanation for these discrepant findings is not readily found but might be due to the relatively mild degree of LVH in the former studies compared with the latter studies. Importantly, however, eNOS is not only expressed in resident coronary vascular endothelial cells but also in cardiomyocytes and EPCs. Hence, the aforementioned studies, employing global knockout or transgenic eNOS mouse models do not allow delineation between the contributions of eNOS in each of the various cell types in the heart. This is important, as angiogenesis in the heart not only depends on NO bioavailability but may also involve EPC recruitment from bone marrow (BM).

Kazakov et al. therefore assessed the role of eNOS in EPCs in ameliorating pressure overload-induced LVH and dysfunction produced by transverse aortic constriction (TAC). To address this question, the authors used strain-mismatched BM transplantations into wild-type (WT) mice (WT/eNOS−/−-BM) and WT-BM in eNOS−/− mice (eNOS−/−/WT-BM) as well as strain-matched controls (WT/WT-BM and eNOS−/−/eNOS−/−-BM). Notwithstanding the elegance of this experimental approach, the procedures of radiation and subsequent restoration of BM (i.e. WT/WT-BM and eNOS−/−/eNOS−/−-BM) appeared to blunt TAC-induced LVH and dysfunction when compared with the TAC-induced responses in WT and eNOS−/− mice. As discussed by the authors, these differences were possibly related to ionizing radiation-induced accelerated ageing of cardiac tissue, but this observation certainly warrants further investigation in future studies.

The study by Kazakov et al. demonstrates that the absence of eNOS in BM cells of WT mice aggravated cardiac hypertrophy and fibrosis post-TAC and reduced myocardial capillarization. Moreover, eNOS−/−-BM reduced the production and mobilization of EPCs, as well as their migratory capacity, compared with WT/WT-BM TAC mice. Conversely, eNOS−/− mice transplanted with WT-BM displayed less cardiac fibrosis, improved myocardial capillarization, increased levels of EPCs in the peripheral blood, and enhanced migratory capacity. This elegant study clearly demonstrates the importance of eNOS activity in medullary tissue in limiting LVH and dysfunction in a murine model of LV pressure overload.
An important consequence of this study is that it forces us to consider EPCs as part of the mechanism of the beneficial effect of eNOS in many earlier studies investigating the effects of systemic eNOS knockout or overexpression on cardiovascular disease or on the effects of exercise training. Furthermore, the study demonstrates the two faces of eNOS in cardiovascular disease. Thus, in agreement with more recent studies of TAC-induced severe LVH, the degree of LVH and pulmonary congestion produced by TAC were blunted in global eNOS knockout compared with WT mice, suggesting that, overall, eNOS exerted a detrimental influence on the pressure-overloaded heart. Similarly, TAC-induced LVH, capillary rarefaction, fibrosis, and pulmonary congestion were aggravated in WT/eNOS knockout compared with WT/WT-BM mice. The beneficial influence of eNOS in BM-derived EPCs implies that the overall detrimental influence of eNOS must originate from non-medullary eNOS. Earlier observations that cardiomyocyte-restricted restoration of eNOS activity blunted LVH and dysfunction by TAC in eNOS knockout mice could be interpreted to suggest that eNOS uncoupling may occur preferentially in residential coronary endothelial cells. However, the degree of LVH was only moderate in the latter study, which may have prevented uncoupling of cardiomyocyte eNOS. Thus, future studies are required to further elucidate where eNOS (i.e. in which cell type) is susceptible to uncoupling and in which form of LVH (Figure 1). This way, targeted therapy to prevent eNOS uncoupling at its specific location could then be applied, although one might argue that systemic 'eNOS-coupling therapy' with co-factor tetrahydrobiopterin will likely target eNOS at all its locations.

In conclusion, the study by Kazakov et al. highlights the importance of investigating the role of eNOS in cardiac and extra-cardiac cell types in LVH in order to fully appreciate the two faces of eNOS in modulating cardiac hypertrophy and dysfunction. Furthermore, this elegant study illustrates how, more than 25 years after the discovery of NO, the story of the many ways in which NO contributes to cardiovascular homeostasis continues to unfold.

Conflict of interest: none declared.

References

Figure 1 eNOS in cardiac function and remodelling. Adverse cardiac remodelling and dysfunction are inhibited by nitric oxide (NO) from coupled eNOS but aggravated by superoxide (O2) formed by uncoupled eNOS. EPC, endothelial precursor cell; ONOO–, peroxynitrite; sGC, soluble guanylyl cyclase; PKG, protein kinase G; SR, sarcoplasmic reticulum; RYR, ryanodine receptor; SERCA, sarcoplasmic reticulum Ca2+ ATPase; PLB, phospholamban.


