Arginase: a modulator of myocardial function

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When nitric oxide (NO) donors were first administered to isolated, normal cardiomyocytes, a negative, cGMP-dependent inotropic effect was observed, whereas inhibitors of NO synthases (NOS) had no effect. Further studies then demonstrated a biphasic contractile response to exogenous NO and cGMP, explained by dose-dependent inhibition or activation of phosphodiesterases modulating cAMP. Also, exogenous NO can, via cGMP, activation of protein kinase G, and phosphorylation of troponin I, decrease myofilamental calcium responsiveness and exert cGMP-independent positive inotropic effects by nitrosylation. These in part contradictory findings are not surprising given the multiple mechanisms (via cGMP, nitrosylation, antioxidation), sites of production (cardiomyocytes, endothelial cells, nerve endings), and targets (mitochondrial respiration, glucose transport, cAMP turnover, L-type calcium channels, sarcoplasmic reticulum Cu²⁺-ATPase, ryanodine receptor, myofilaments) of myocardial NO signaling known to date [11].

Large animal studies demonstrated that there is a net positive inotropic effect of constitutive myocardial NO synthesis during normoperfusion and ischemia [6] and that basal NO release supports myocardial efficiency, i.e., the amount of myocardial work produced at a given level of oxygen consumption, during normoperfusion, ischemia [6], exercise [2], and pacing-induced heart failure [15]. This was ascribed to a counterbalance of xanthine oxidase-derived oxygen radical production by NO, whereas in the exercised heart, basal NO release is increased by shear stress and pacing-induced heart failure [15]. Importantly, heart failure represents a NO-deficient state of xanthine oxidase-derived oxygen radical production by NO, whereas in the exercised heart, basal NO release is increased by shear stress and pacing-induced heart failure [15].

In line with that, upregulation of NO synthesis by statins [9] and angiotensin-converting enzyme antagonism [10] supports cardiac function after myocardial infarction or during tachycardic pacing in dogs [20]. In the current issue of the American Journal of Physiology-Heart and Circulatory Physiology, Jung et al. [7] demonstrate in a clear and straightforward study that arginase I is constitutively expressed in normal feline cardiomyocytes and impacts on cardiomyocyte NO signaling. Inhibition of arginase with boronoethyl chloride increased normal cardiomyocyte cGMP threefold, decreased the calcium transient, and exerted a pronounced negative inotropic effect mediated by cGMP. Although direct NOS inhibition was not applied, these data strongly imply that in isolated normal cardiomyocytes, NO production is regulated by L-arginine availability toward NOS, such that the term L-arginine paradox could from now also comprise cardiomyocytes.

Given the numerous studies that did not find an effect of endogenous NO synthesis on cardiac function in vitro (as in contrast to in vivo), the question arises whether there might have been not enough fuel for NOS in vitro. In the perfused, beating heart, basal NO release is increased by shear stress and stretch, which might inhibit arginase activity by N-hydroxy-L-arginine, thus shifting more L-arginine toward NOS. Such a mechanism would not be active in nonperfused cardiac preparations. Clearly, experiments in integrated models are needed to assess whether constitutive arginase activity indeed limits cardiomyocyte NO production in vivo and in which direction it may shift cardiac function in normal and diseased states.

Jung et al. [7] also report that in compensated hypertrophy, arginase expression is decreased, thus facilitating NO signaling. It is tempting to hypothesize that in decompensated failure, cardiomyocyte arginase activity might be upregulated and, by attenuating NOS signaling, could worsen cardiac disease. Such
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a mechanism has been proposed to promote asthmatic disease (12); however, the first clinical data about dietary L-arginine supplementation in patients after myocardial infarction showed no benefit (18). Thus cardiomyocyte arginase has now been introduced as a new modulator of myocardial function via limiting substrate supply to NOS, but many more studies are needed before its beneficial or harmful role can be assessed.

REFERENCES


