PERSPECTIVES

Nitroxyl effects on myocardium provide new insights into the significance of altered myofilament response to calcium in the regulation of contractility

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The idea that cardiac sarcomeres are not passive slaves to membrane related mechanisms modifying Ca^{2+} fluxes is generally accepted. There is substantial evidence that fundamental regulatory mechanisms including the Frank–Starling mechanism and neuro-humoral control of cardiac dynamics involve alterations in Ca^{2+} binding to troponin C (TnC) or transduction of the Ca–TnC signal to the promotion of ATP hydrolysis, force and shortening (Solaro, 2001; Kobayashi & Solaro 2005). In testimony to the recognition of the relative significance of these potential mechanisms in control of cardiac contractility, there has been a long-standing effort to develop inotropic agents acting directly on the myofilaments to modify their response to Ca^{2+} (Kass & Solaro, 2006).

A paper by Dai *et al.* (2007) in this issue of *The Journal of Physiology* marks a new milestone in this search for ways to modify cardiac myofilament response to Ca^{2+}. They demonstrated that a donor of nitroxyl (HNO) increases maximum tension and Ca^{2+} sensitivity of trabeculae sarcomeres functioning *in situ*. Although HNO also increased the peak amplitude of the Ca^{2+} transient, when compared to controls, the increase in tension was greater than expected from the rise in Ca^{2+}. Except for the implication of thiols for functionally significant Cys residues in the sarcomeric proteins, the molecular mechanism of the effects of HNO remains obscure.

An appealing property of HNO is that the enhancement of myofilament Ca^{2+} response occurs with a concomitant increase in Ca^{2+} flux into and out of the sarcoplasmic reticulum by a mechanism independent of β-adrenergic receptors, cAMP and cGMP. Other agents that increase myofilament response to Ca^{2+} have an associated inhibition of cAMP phospho-diesterases. An increase in cAMP increases the threat of arrythmias. The effects of HNO indicate a novel mechanism of enhancement of contractility without an effect on diastolic function and with a relative increase in the efficiency transduction of the Ca^{2+} binding signal. One aspect of this increase in efficiency is that the increase in myofilament Ca^{2+} response permits an increase in force generation while sparing the energy required in transporting Ca^{2+} to storage depots. There is also the possibility of increased economy in the unit change in ATP hydrolysis required for a unit change in tension (tension cost). Dai *et al.* (2007) reported no effect of HNO on ATPase rate of isolated myofibrils, but these preparations do not generate force. More rigorous tests are required in preparations bearing a load.

The identification of the mechanism of the effect of HNO is necessarily couched in our understanding of the molecular mechanisms of the transitions of sarcomeres from diastolic to systolic states and how this transition is geared into the overt function of the heart to develop pressure, eject against the arterial impedance so as to satisfy metabolic needs of the body, and relax with a time course so as to not compromise filling for the next cycle. The critical parameter with regard to the relative role of the sarcomeres is not the kinetics of free Ca^{2+}, detected by cytoplasmic probes, but the kinetics of Ca bound to TnC during the heart beat. Computations based on best estimates of the kinetics of Ca binding to the myofilaments during a beat of the ejecting ventricle indicate that Ca bound to TnC falls faster than systolic pressure and is near zero during isovolumic relaxation (Peterson *et al.* 1991; Hinken & Solaro, 2007). The mechanism that keeps the myofilaments activated with relatively little Ca bound resides in the ability of strongly bound crossbridges to promote Ca-binding affinity of TnC within a regulatory unit (actin : Tn complex : tropomyosin : myosin in a 7 : 1 : 1 : 1 ratio) and to spread activation longitudinally along the thin filament by near neighbour cooperative mechanisms (Landesberg, 1996; Moss *et al.* 2004).

Future investigation of HNO should include a detailed dissection of potential effects on thin and thick filament proteins as well as determination of effects on TnC–Ca and tension cost. Tropomyosin seems a likely target in view of its functionally significant and reactive Cys as well its key role as a determinant of Ca sensitivity of the number of cross-bridges reacting with the thin filament. It will also be of interest to know the effects of HNO in fast and slow skeletal muscle.

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