Functional significance of myofilament protein oxidation

Jolanda van der Velden*

Laboratory for Physiology, Institute for Cardiovascular Research, VU University Medical Center, Amsterdam, The Netherlands

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This editorial refers to ‘Oxidative modification of tropomyosin and myocardial dysfunction following coronary microembolization’ by M. Canton et al., on page 875.

During muscle contraction, a molecular interaction takes place between the myofilament proteins actin and myosin, which is triggered by a rise in intracellular calcium and is driven by the energy from ATP hydrolysis. The tropomyosin-troponin complex inhibits the actin–myosin interaction at low intracellular-free calcium. This inhibition is released when intracellular-free calcium increases and calcium binding to troponin C takes place resulting in a conformational change of the troponin–tropomyosin complex. Movement of tropomyosin exposes myosin-binding sites on actin allowing cross-bridge formation and myofilament contraction to take place.1 Myofilament function is determined by the expression levels of multiple isoforms of myofilament proteins, and alterations in cardiac function have been attributed to shifts in isoform composition and protein expression of myofilament proteins. Apart from the translational changes in protein expression, post-translational modifications of myofilament proteins are essential for the regulation of cardiac function both under physiological and pathophysiological conditions. Elucidation of the functional role of post-translational protein modifications is crucial to understand the changes in myocardial performance resulting from myofilament protein alterations during cardiac pathology.

Most research concerning functional effects of post-translational modifications focused on the effects of kinases and phosphatases altering phosphorylation status of myofilament proteins.2 Regulation of myofilament function by phosphorylation is complex and involves cross-talk between phosphatases and kinases and compartmentalization. Alterations in kinase and phosphatase activities have been implicated in impaired myofilament function contributing to reduced pump function in cardiac disease. Recent evidence suggests an important role for oxidative stress in reducing myocardial function via post-translational modifications of the myofilament apparatus. Canton et al.3 demonstrate oxidative damage of myofilament proteins as a likely contributor to reduced cardiac function upon coronary microembolization.

The major reactive oxygen species (ROS) and their derivatives reactive nitrogen species are superoxide radicals (O$_2^-$), hydroperoxyl radicals (HO$_2^-$), nitric oxide (NO), and peroxynitrite (ONOO$^-$). Collectively, these radicals cause a loss of biological function through oxidation of the protein backbone and/or amino acid side chains, which may lead to protein fragmentation and the formation of the protein–protein cross-linkages, respectively.4 Addition of the superoxide anion to isolated rat myofilaments reduced or even completely abolished maximal calcium-activated force.5 In isolated rat ventricular trabeculae6 and in human ventricular myocytes,7 peroxynitrite reduced maximal isometric force in a dose-dependent fashion. Post-translational modification of myofilament proteins due to oxidative stress may be involved in depressed cardiac pump function observed upon ischaemia–reperfusion, in heart failure, and in response to inflammatory cytokines. Reversible and irreversible oxidative alterations of myofilament proteins, in particular actin and tropomyosin, has been found after post-ischaemic reperfusion in isolated rat hearts.8 Proof for a functional role for myofilament oxidation in heart failure was given in a transgenic mouse model of cardiomyopathy, in which inhibition of xanthine oxidase prevented myofibrillar protein oxidation and preserved cardiac function.9 In a previous study, Heusch and co-workers10 showed that contractile dysfunction upon coronary microembolization involved an inflammatory response evidenced by increased levels of tumor necrosis factor-$\alpha$. In the present study, Canton et al.1 have shown that the contractile dysfunction due to coronary microembolization is related to reversible oxidation of the myofilament protein tropomyosin. Oxidative damage of tropomyosin involved the formation of disulphide cross-bridges as illustrated by the mobility shift of tropomyosin on the gels. The antioxidant ascorbic acid largely inhibited disulphide cross-bridge formation and prevented contractile dysfunction, suggesting that tropomyosin oxidation may affect cardiac pump function. It would be interesting to find out whether this tropomyosin modification alters the calcium sensitivity or the maximal force-generating capacity of the myofilaments. As noted by the authors, other post-translational modifications, besides those reported in tropomyosin, cannot be excluded and require further extensive protein analysis. This study links oxidative damage of myofilament proteins to...
cardiac dysfunction and underscores the importance of post-translational myofilament changes due to oxidative stress under pathological conditions. Oxidation of proteins adds to the complex of post-translational signal transduction by directly affecting myofilament function, but also via activation of kinases. Future research on the complex interactions between ROS, cytokines, kinases, and potential target proteins is essential to understand the intricate functional effects of post-translational protein modifications.

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References