

Sarcomeric dysfunction in heart failure

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Sarcomeric dysfunction plays a central role in reduced cardiac pump function in heart failure. This review focuses on the alterations in sarcomeric proteins in diseased myocardium that range from altered isoform expression to post-translational protein changes such as proteolysis and phosphorylation. Recent studies in animal models of heart failure and human failing myocardium converge and indicate that sarcomeric dysfunction, including altered maximum force development, Ca²⁺ sensitivity, and increased passive stiffness, largely originates from altered protein phosphorylation, caused by neurohumoral-induced alterations in the kinase–phosphatase balance inside the cardiomyocytes. Novel therapies, which specifically target phosphorylation sites within sarcomeric proteins or the kinases and phosphatases involved, might improve cardiac function in heart failure.

1. Sarcomeric dysfunction

The failing heart is characterized by reduced contractility (systolic dysfunction) and/or impaired filling (diastolic dysfunction). A number of factors, including changes in cardiac structure (dilation and hypertrophy), apoptotic and necrotic cell death, maladaptive remodelling of the extracellular matrix, abnormal energy metabolism, impaired calcium handling, and neurohumoral disturbances have been implicated in the initiation and progression of heart failure.^{1–4} Recent studies revealed that alterations in sarcomeric function play a prominent role in reduced cardiac pump function.

Sarcomeric function is determined by the expression levels of multiple isoforms and by post-translational modifications of sarcomeric proteins. During muscle contraction a molecular interaction takes place between the thin (actin) and thick (myosin) filament of the sarcomeres, which is triggered by a rise in the intracellular calcium and is driven by the energy from ATP hydrolysis.⁵ The tropomyosin–troponin complex inhibits the actin–myosin interaction at low intracellular free calcium (*Figure 1A*). This inhibition is released when intracellular free calcium increases and binds to troponin C (*Figure 1B*). Alterations in sarcomeric protein composition under pathological conditions will influence contractile performance of the heart. Within the first part of this review, we discuss the functional role of individual

sarcomeric protein isoforms and of post-translational protein modifications such as proteolysis and phosphorylation. In the second part, we highlight the major changes in sarcomeric function reported in failing myocardium and discuss the most likely underlying protein modifications.

2. Isoform composition and sarcomeric dysfunction

2.1 Myosin heavy chains

The thick filament is composed of myosin, which consists of two myosin heavy chains (MHC), and two pairs of myosin light chains (MLCs) (*Figure 1*). One of the major isoform changes which has been observed in hypertrophied and failing ventricular myocardium is the shift from the fast α -MHC to the slow β -MHC.^{6–8} The magnitude of the MHC shift largely depends on the amount of endogenous α -MHC present in ventricular tissue, which is species-dependent, being largest in small rodents and smallest in human.^{6–11} Hence, the functional significance of the shift in MHC composition in diseased human ventricles is still a matter of debate.^{8,10,12}

The MHCs carry the site for ATP hydrolysis and are important determinants of the rate of energy consumption and the speed of contraction of the sarcomeres, which are closely related.¹³ *In vitro* studies have shown that the α -MHC isoform has a higher ATPase activity¹⁴ and a higher actin filament sliding velocity compared with the β -MHC isoform.¹⁵

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