CALL FOR PAPERS | Regulation of Cardiac Contraction

Regulation of cardiac muscle contraction: how paramount are the sarcomeres?

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AT THE 2006 EXPERIMENTAL BIOLOGY meeting, the American Physiological Society sponsored a symposium on the Regulation of Cardiac Muscle Contraction, and this same topic received a Call for Papers to the American Journal of Physiology-Regulatory, Integrative and Comparative Physiology. Much of the symposium focused on the perhaps underappreciated role that sarcomeric proteins play in the regulation of heart function. There seems to be a growing body of evidence that processes intrinsic to the sarcomere limit ventricular function (for a brief review, see Ref. 7). While elevation of sarcoplasmic Ca$^{2+}$ concentration ([Ca$^{2+}$]) is a necessary trigger for the onset of contraction, its binding to low-affinity sites on troponin C and the Ca$^{2+}$-induced conformational changes in thin-filament proteins are presumably too rapid to limit force development (3, 13, 15, 16). In addition, there is strong evidence that sarcoplasmic [Ca$^{2+}$] peaks well before maximum force production, and Ca$^{2+}$ is nearly completely removed before the onset of relaxation (2, 9). These findings strongly implicate cooperative signaling and mechanical feedback through the thin and thick filaments as the ultimate determinants of ventricular pressure development, ejection, and relaxation. In this context, there also is a growing body of evidence that suggests altered thin- and thick-filament protein isoforms, posttranslational modifications (including phosphorylations, nitrosylations, and peroxidations) of sarcomeric proteins, and changes in sarcomere length are all important modulators of the kinetics of thin-filament activation levels and cross-bridge cycling rates, both of which likely have a dominant role in dictating ventricular stroke volume.

The symposium examined various aspects of sarcomeric control of cardiac function and, in addition, the role that the Ca$^{2+}$ sensor protein S100A1 plays in modulating cardiac performance in health and disease. The symposium featured Drs. R. John Solaro, Richard L. Moss, Henk Granzier, and Patrick Most. Dr. Solaro presented an overview of thin-filament regulatory proteins and their control of myocardial contraction. Dr. Solaro’s seminar also focused on the novel concept of the multifunctional enzyme P21-activated kinase 1 (Pak1) being involved in the regulation of contraction. An important aspect of Pak1 regulation is through the modulation of phosphatase activity, which is discussed in the accompanying review article (17). Dr. Moss presented aspects of thick-filament regulation of contraction particularly in the context of the cooperative nature of cardiac muscle contraction. Dr. Moss expounded on the potential role of stretch activation in mediating myocardial contraction and control of pressure generation. A series of work have defined a variety of factors, including Ca$^{2+}$ activation levels (20), myosin-binding protein-C (MyBP-C) (19), myosin light-chain phosphorylation (22), protein kinase A phosphorylation (23), and myosin heavy-chain (MyHC) isoform (18), which mediate the magnitude and kinetics of stretch activation. This raises the question of how these potential modulators vary throughout myocytes localized across the ventricular walls, which could have an important role in tuning systolic pressure generation after the onset of and throughout systole. Dr. Granzier presented a seminar that discussed the properties of the sarcomeric protein titin and its potential role in mediating signal transduction and length dependence of activation. Dr. Granzier and colleagues contributed an article to the Call for Papers that discusses how titin splice variations in avians and mammals regulate the structure and biomechanics of the sarcomere (6). Dr. Most presented a seminar that characterized the S100A1 molecule and its multifunctional role in cardiac myocytes. Interestingly, S100A1 seems to play an important role in mediating the Ca$^{2+}$ signal for L-type Ca$^{2+}$ channel conductance, sarcoplasmic reticulum Ca$^{2+}$ channel release, sarcoplasmic reticulum calcium-ATPase (SERCA) activity, and passive mechanical properties induced by titin. Dr. Most and colleagues also provide an outstanding review in this Call for Papers on S100A1 protein and its role in physiological and pathophysiological processes in mammalian hearts (14).

There are three additional articles accompanying this Call for Papers. The first paper tested whether changes in the kinetics in mechanical processes are altered with changes in sarcomere length (5). Ëdes and coworkers (5) found that the rate of force development was similar at long and short sarcomere length in mouse, pig, and human cardiac myocytes; this suggests that length dependence of contraction may be more dependent on overall force production as opposed to kinetics of force development. Interestingly though, when force was matched at long and short sarcomere length, the rate of force development was actually faster at short sarcomere length in their cardiac myocyte preparations (see Fig. 6 of Ref. 5). This finding is consistent with others (1, 11, 21) and suggests faster kinetics at short sarcomere length, which may be important in maintenance of adequate stroke volume at reduced end diastolic loads/volumes. This finding is also consistent with the fact that loaded shortening velocity is actually...
faster at short sarcomere length at loads near optimum for power production in adult rat cardiac myocyte preparations (11). It is unclear what myofibrillar processes mediate the perhaps unexpected faster kinetics of mechanical properties at short sarcomere length but may involve MyBP-C since ablation of this molecule also results in faster rates of force production and loaded shortening velocities, especially at high loads and loads near optimum for power production (12). Interestingly, loaded shortening was found to be slower at short sarcomere lengths in myocytes that contained β-MyHC (induced by hypothyroidism) even at matched force levels (11). This may lend itself to steeper ventricular pressure curves (i.e., Frank-Starling relationships) in mammalian hearts that contain mostly β-MyHC (10), which would help optimize cardiac efficiency. A clear picture, though, has not emerged as to how changes in other sarcomeric protein isoforms, posttranslational modifications, and disease states affect the length dependence of kinetic mechanical properties. Insight into how these factors affect length dependence of myofibrillar mechanics and the underlying mechanisms would be most important toward understanding the molecular basis of the Frank-Starling relationship and how this relationship is depressed in cardiomyopathies.

The second article provides the application of an in situ experimental heart model to test the control point for adequation of energy production by the mitochondria and energy utilization by the myofilaments during ventricular contractions. The results implicate tight coupling between energy utilization by myosin cross bridges and energy production by the mitochondria, which is controlled by sarcoplasmic Ca^{2+} levels (4). The third paper by Hiranandani et al. (8) addresses the role underexpressing the sarco(endo)plasmic reticulum calcium-ATPase. The third paper by Hiranandani et al. (8) addresses the role of altered SERCA activity in mediating depressed myocyte shortening during high frequency activations. Conversely, the downregulation of SERCA2 only increase myocardial force at unphysiologically low frequencies. Insight into how these factors affect length dependence of myofibrillar mechanics and the underlying mechanisms would be most important toward understanding the molecular basis of the Frank-Starling relationship and how this relationship is depressed in cardiomyopathies.

REFERENCES