New and Notable

Mechanisms of the Frank-Starling Law of the Heart: The Beat Goes On

R. John Solaro
Department of Physiology and Biophysics and Center for Cardiovascular Research, University of Illinois at Chicago, Chicago, Illinois 60612

Cellular and molecular mechanisms remain elusive nearly a century after Frank, Starling, and colleagues demonstrated that an increase in ventricular filling (sarcomere length) promotes an increase in developed pressure (tension). Textbooks indicate that changes in filament overlap with stretch of ventricular muscle in the rising phase of the length-tension relation are the main mechanism, but this cannot account for the much steeper dependence of tension on sarcomere length (SL) in heart versus skeletal muscle. Hearts operate at submaximal Ca-activation, and the relatively steep SL-tension relation is likely to be accounted for by so-called length-dependent activation (LDA). LDA is a well-documented dependence of Ca^{2+}-activated tension on SL, which is particularly evident in the heart (1–3).

Thus, a major question to be resolved in the puzzle of Frank-Starling's law is the following: by what mechanism does active force generation become more sensitive to Ca^{2+} as sarcomere length increases? An appealing hypothesis is that increases of length in a constant volume myocyte induce decreases in interfilament spacing, thereby increasing the local concentration of cross-bridges at the thick filament-thin filament interface and promoting force generating cross-bridge reactions without a change in levels of activating Ca^{2+}. The equivalent of the Holy Grail in the quest to understand the mechanisms of Frank-Starling's law is to know the disposition of sarcomeric proteins in an in situ working myocyte. Some measurements have been made in isolated muscle preparations (4), but in this issue, Pearson et al. (5) have advanced this field by employing x-ray diffraction to determine cross-bridge proximity to the thin filament and interfilament spacing in sarcomeres during critical points in pressure-volume relation of the in situ perfused rat heart. The data provide strong evidence for a reduction in interfilament spacing associated with increases in end-diastolic volume, and an increase in the number of cross-bridges reacting with the thin filament in the early phase of isovolumic contraction. Whether these changes are associated with a change in Ca^{2+} delivery to and binding by troponin C remains unclear, but studies with isolated muscle preparations indicate that the Ca^{2+} transient may not change during such a maneuver (1,6). If so, the findings of Pearson et al. would add to extensive data indicating that sarcomeric LDA is the fundamental mechanism in the Frank-Starling relation.

The molecular basis of LDA involves cooperative mechanisms induced by strong cross-bridge reactions with the thin filament that promote an increase in troponin C Ca-affinity and a spread of activation along the thin filament (2,6). Detailed discussions and mathematical models have been presented to relate these cooperative mechanisms to LDA (2,3,7). Importantly, their active involvement in LDA indicates that structural modification of the sarcomeric proteins critical to cooperative activation might affect the Frank-Starling relation. A structural modification of potential significance is the protein kinase A (PKA) dependent phosphorylation occurring in troponin I (cTnI) in the thin filament, myosin-binding protein-C (MyBP-C) in the thick filament, and titin, a giant protein big enough to extend from the Z-disk to the M-line. We (4) reported that treatment of detergent extracted mouse ventricular muscle preparations with PKA induces an increase in diastolic interfilament spacing as determined by x-ray diffraction. Treatment with PKA also induced a decrease in Ca^{2+} sensitivity that was more pronounced at relatively short SL than at long SL, an effect resulting in an enhancement of LDA. These results indicate that interfilament spacing and the Frank-Starling relation vary with inotropic state, making it difficult to separate regulation of cardiac function into intrinsic and extrinsic control mechanisms.

The PKA-dependent alteration in interfilament spacing may be due to altered function of titin. Titin is responsible for nearly all the passive tension of heart muscle and thus a significant sensor of myocardial stretch associated with increases in ventricular volume. Granzier and Labeit (8) have proposed that with increases in ventricular volume in diastole and stretch of the myocardium, there is strain on connections between titin with actin at and near the Z-disk that induce radial and longitudinal forces. The radial forces are proposed to bring thick and thin filaments closer together and thus reduce interfilament spacing. This titin-based mechanism may be modulated by β-adrenergic stimulation as passive stiffness has been demonstrated to be altered by PKA-dependent phosphorylation of titin. However, results of studies with detergent extracted preparations isolated from hearts of transgenic mice in which slow skeletal TnI (ssTnI; the cardiac/embryonic isoform lacking PKA sites) is expressed in place of cardiac TnI demonstrate the complexity of effects of PKA-dependent phosphorylation on LDA (4). LDA was significantly reduced in the ssTnI-containing sarcomeres. Moreover, even though PKA did not affect LDA in preparations expressing ssTnI, there was a significant reduction in diastolic lattice spacing, an effect opposite to that in preparations regulated by cTnI. This

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Address reprint requests to R. John Solaro, PhD, Dept. of Physiology and Biophysics (M/C 901), University of Illinois at Chicago, College of Medicine, 835 South Wolcott Ave., Chicago, IL 60612. Tel.: 312-996-7620; Fax: 312-996-1414; E-mail: solarorj@uic.edu.

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effect may have been due to MyBP-C or titin phosphorylation, which remained intact. Whatever the case, these data stress challenges for the future, which include a lack of correlation of altered interfilament spacing with LDA, and an influence of sarcomeric protein isoforms on LDA. It will be of great interest to extend the approach of Pearson et al. to preparations with altered inotropic state or expressing different sarcomeric protein isoforms or mutant sarcomeric proteins linked to cardiomyopathies.

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