Variable Titin-Based Stiffness Adjustment in Heart Disease

To the Editor:

Several issues in a previous letter to the Editor 1 concerning our work on titin in heart disease require clarification. We have studied titin isoform expression in the canine pacing model of heart failure 2 and found that in controls, stiff (N2B) and compliant (N2BA) cardiac titin isoforms are coexpressed at ≈1:1 ratio, whereas after pacing, the stiff isoform is upregulated at the expense of the more compliant one. 2 Using skinned muscle strips dissected from the midwall region of the left ventricle (LV) (note that we did not use myofibrils, as suggested by others 1), we showed that titin-based passive stiffness is elevated in paced animals. The use of muscle strips provides more representative data (we studied ≈5 muscles per heart with each containing ≈10^5 myofibrils) than the use of single myofibrils. Considering the variation in isoform expression ratio (including variation within individual cells 3 ), studying only a few myofibrils (3 to 5 per heart in the Neagoe et al 4 study) has the potential for results that are not representative. Furthermore, gel electrophoresis can be performed with muscle strips but not single myofibrils, allowing the intactness of titin in muscle strip preparations (but not myofibrils) to be verified. 1 Finally, muscle can be studied before and after abolishing titin-based passive stiffness (by extracting titin’s anchors in the sarcomere), providing information about the contribution to passive stiffness of collagen as well as titin. 2 Although each type of preparation (myofibril and muscle) has benefits and drawbacks, muscle is a suitable choice for studying the molecular basis of passive stiffness and its adjustments in disease.

Upregulation of N2B titin in the pacing model is in contrast to the upregulation of N2BA titin reported by Neagoe et al 4 to occur in human transplant hearts with coronary artery disease (CAD). Both canine and human models express similar levels of compliant N2BA and stiff N2B titins in control myocardium, and the titin-based stiffness will therefore be intermediate between that of sarcomeres that express solely N2B or solely N2BA titin. The equal amounts of N2BA and N2B titin and the resulting intermediate stiffness allow for considerable adjustment. Sarcomeres can greatly increase compliance by increasing the N2BA/N2B expression ratio (human transplant hearts with CAD 5 ) or greatly increase stiffness by reducing this ratio (canine rapid pacing model 2 ). Thus, processing of the titin pre-mRNA is subject to subtle regulatory mechanisms that control entry to either the N2B or N2BA splice pathways. We believe that the studies on canine 2 and human 4 models indicate that, depending on the disease state, treatment regimen, and (perhaps) species, a range of adjustments can occur, leading to either increased or decreased passive stiffness.

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