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Titin Stiffness in Heart Disease

To the Editor:

Hein et al¹ provided an interesting perspective on two articles^{2,3} dealing with the role of titin for myocardial diastolic function. The new concept emerging from these studies is that titin not only contributes significantly to diastolic wall stiffness,⁴ but together with collagen, can be modified in response to chronic heart disease. Titin-based stiffness is tuned by changing the expression ratio of a longer, more compliant N2BA-titin isoform, relative to a shorter, stiffer N2B-titin isoform.

In discussing the paper on human heart,² Hein et al¹ cautioned that patients with coronary artery disease (CAD) represent an extremely variable cohort and that the titin modifications found—from an average N2BA:N2B ratio of 30:70 in normal left ventricles to 47:53 in severely diseased CAD-explant hearts—may not allow definitive conclusions. However, the variability in titin-isoform ratio was no greater among CAD-hearts than among normal donor hearts or nonischemic explants, whereas the ratio change (~0.43 to ~0.89) was statistically highly significant.² In fact, the change was much larger than that observed (in the opposite direction) in the accompanying paper on paced dog hearts.³ Unfortunately, the editorial¹ mistakenly stated, on several occasions, that Neagoe et al² report decreased “total muscle-strip stiffness” in CAD-heart specimens, whereas these hearts were globally stiffened. This is seemingly contradictory. In reality, we found decreased passive stiffness of single cardiac myofibrils or small myofibril bundles—preparations lacking any membranous structures or extracellular material.⁴ This distinction is important, because mechanical measurements on whole muscle strips cannot reveal titin-derived stiffness; nonsarcomeric structures will contribute to measured stiffness. Also, single-myofibril mechanics is technically not trivial and only now is done successfully with human cardiomyofibrils.² A correct description of our results,² then, is that the titin-isoform shift in CAD-explant hearts correlated with lowered stiffness of the myofibrils, whereas the whole myocardium was stiffer than normal. We tentatively proposed that the titin-isoform switch could be a response to elevated preload resulting from increased fibrosis,² but the trigger(s) for the switch still need to be determined beyond doubt. It is quite possible, though, that “discrepancies of results”¹ of the studies on humans² and dogs³ reflect the heterogeneity of cardiac pathology: the direction of the titin-isoform shift in a diseased heart may well depend on the particular signaling pathways involved; higher-than-normal,² unchanged, or lower-than-normal³ N2BA:N2B ratios may be found under different disease conditions. The fact that failing human hearts explanted for reasons other than CAD did not show any titin-isoform shift² supports this hypothesis.

Wolfgang A. Linke, PhD

*Institute of Physiology and Pathophysiology
University of Heidelberg
Heidelberg, Germany*

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Response

In his letter to the Editor, Dr Linke criticized the use of the term “muscle strip” instead of “myofibril” when we described his method of determining passive tension in cardiac preparations in a recent Editorial.^{1,2} Dr Granzier and collaborators, in their report in the same issue of *Circulation*, used the term “muscle strip” for the same type of preparation.³ We employed the latter expression in order to make the nomenclature more homogeneous and we stated in the Editorial that both groups used the same methods as described earlier in their joint publications.^{4,5} We thank Dr Linke for reminding us that precise terminology is important; perhaps we should have avoided a term that he believes is incorrect.

It is correct, however, that the results of the two studies^{2,3} discussed in the Editorial¹ show a significant discrepancy: Neagoe et al in human failing hearts² found a decreased stiffness, and Wu et al³ in a canine model of heart failure reported an increased stiffness. An explanation of this discrepancy is a matter of speculation at the present time. It may be related to the time course of development of heart failure (chronic in humans but short-termed in animals) the species and type of model chosen (left ventricular infarct in rats versus pacing induced cardiac failure in dogs), the fact that human hearts with coronary artery disease show a regionally different pathology (nonuniformity), and probably many other factors.

We sincerely hope that this difference in results will soon be resolved and the role of titin in heart failure more extensively clarified.

Stefan Hein, MD

*Department of Cardiac Surgery
Kerckhoff Clinic
Bad Nauheim, Germany*

William H. Gaasch, MD

*Department of Cardiovascular Medicine
Lahey Clinic
Burlington, Mass*

Jutta Schaper, MD

*Department of Experimental Cardiology
Max Planck Institute
Bad Nauheim, Germany*

1. Hein S, Gaasch WH, Schaper J. Giant molecule titin and myocardial stiffness. *Circulation*. 2002;106:1302–1304.
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Circulation. 2003;107:e73

doi: 10.1161/01.CIR.0000060810.93701.22

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

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Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the
World Wide Web at:

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