The central importance of the cytoskeleton for increased cell stiffness in cardiovascular disease. Focus on “Diabetes increases stiffness of live cardiomyocytes measured by atomic force microscopy nanoindentation”

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ATOMIC FORCE MICROSCOPY (AFM) is proving to be a very useful tool for probing nanoscale and microscale mechanical properties and behavior of cells. A cursory search of the literature reveals that the use of the technique to study various characteristics of myocardial cells dates back to the mid-1990s (2, 7). Perhaps more revealing is its ever-more-frequent application to the study of myocardial contractile function and dysfunction (5, 9, 10). In this issue of *American Journal of Physiology-Cell Physiology*, Benech et al. (1) are, to my knowledge, the first to use AFM to study left ventricular myocardial cells in diabetes mellitus to gain a deeper understanding of the mechanical and functional events that may underlie heart failure in that disease. Importantly, heart failure is a complication that is frequently associated with the diabetic state and is likely to be of increasing importance with the increased prevalence of type 2 diabetes and insulin-resistant states.

Several striking observations were made in the elegant study of Benech et al. (1). First, they observe that, in their streptozotocin model of diabetes, myocytes from the diabetic animals are stiffer than those from control mice. In addition, the increase in stiffness appeared associated with decreased expression of the sarco/endo-sarco/endoplasmic reticulum Ca²⁺-ATPase 2 (SERCA2) and a disordered cytoskeletal organization within the myocytes. The latter changes appeared to strongly influence the actin cytoskeleton. Although the reduced SERCA2 expression would make one suspect that a component of the increased stiffness in the diabetic animals was related to intracellular Ca²⁺, the increase in stiffness was apparent even when intracellular Ca²⁺ was reduced to low levels in a near-Ca²⁺-free buffer. Again, this appears to strongly indicate that normal regulation of the actin cytoskeleton dynamics is fundamentally disturbed. These changes were accompanied by marked changes in the extracellular matrix, as diabetic mice showed increased collagen accumulation between myocytes; in addition, the distribution of myocytes within the myocardium was less orderly than in controls.

The data presented in the study of Benech et al. (1) are, in my opinion, building on an emerging common theme in cardiovascular disease. There appears to be strong evidence accumulating that altered mechanical properties of cardiovascular tissue in disease are not solely attributable to changes in the extracellular matrix protein composition, organization, and posttranslational modification (e.g., glycation, which would be expected in the diabetic model) but also include significant contributions from changes in the intrinsic mechanical properties of the cells. This appears to be true for myocardial cells, as demonstrated here, as well as vascular smooth muscle cells (8, 11) and endothelial cells (3, 4, 6). Furthermore, while a common theme appears to be a fundamental change in the actin cytoskeleton, particularly in the cortical regions of the cell, there is also evidence that cellular interactions with the extracellular matrix are fundamentally altered. An immediate, critical question is what is driving what? What are the respective roles of the extracellular matrix changes, the cytoskeletal changes, and the changes in cell adhesion and in the mechanical environment? Clearly, to function normally, a tissue requires a normally structured and functioning matrix. In addition, the cell and its cytoskeleton must relate properly to the external matrix structure for mechanical force to be sensed and transmitted. Disordered cellular attachment and cytoskeletal properties combined with extracellular matrix changes are a formula for dysfunction (Fig. 1). It will be exciting to watch this area unfold and, in particular, to see what new functional insights and new paradigms emerge in disease.
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DISCLOSURES

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AUTHOR CONTRIBUTIONS

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REFERENCES