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EDITOR'S PAGE

Cardiac Strain as a Universal Biomarker

Interpreting the Sounds of Uneasy Heart Muscle Cells

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The heart is home to one of the most mechanically dynamic environments in the body. Blood distends the heart chambers (diastole), and a wave of contraction (systole) empties the loaded chamber. At the tissue level, the load stretches the myocytes with subsequent shortening to create cyclic deformations (strain). The overall force generated leads to pulsatile pressure change (stress), with concurrent mechanical, electrical, and molecular feedback and modulation of the contractile machinery of the heart muscle cells. In this issue of *iJACC*, Cordero-Reyes et al. (1) provide significant evidence that myocardial contraction, as defined by noninvasive strain imaging, is correlated with the expression of elements involved in force generation and relaxation at the cellular level in patients with dilated cardiomyopathy. In this page, we propose cardiac strain as a universal biomarker for tracking the changes in the dynamic biological milieu of the functioning cardiomyocytes.

Myocyte Versus Myocardial Strain

Cardiomyocyte deformation can be directly measured using nondestructive and noncontact optical techniques for submicrometer tracking of myocytes using fluorescently labeled molecules or simple fiduciary particles within or over cells (2). A cardiomyocyte in a physiologically loaded state contracts approximately 15% to 20% along its long axis, although the magnitude of shortening can vary for in vitro preparations. Interestingly, myocardial regional strain obtained from the whole heart using echocardiographic and magnetic resonance tissue tracking, although dependent on software algorithms, also ranges between 15% and 25%. Slightly higher strain noted near the apical ends of the left ventricle may be related to tissue shear (longitudinal-circumferential shear or torsion). Although 2-dimensional echocardiography may somewhat overestimate strain because of the presence of through-plane motion (3), it is rather intriguing that strain measurement at the myocyte level and that obtained by myocardial tissue tracking so closely resemble each other in magnitude and temporal pattern. There is a wealth of experimental evidence relating myocardial tissue contraction using in vitro techniques in tissue (Fig. 1) or single-cell preparations for determining the molecular mechanism underlying myocardial function. It would be interesting to compare myocyte shortening as seen on in vitro tracking techniques with that obtained on cardiac imaging–based tissue-tracking techniques for relating cardiac strain with cardiomyocyte functional behavior within a given disease phenotype.

Cellular Processes Related to Myocardial Strain

The sarcomere consists of numerous proteins and an even larger number connect them with the intracellular and extracellular matrix to delicately regulate muscle contraction from beat to beat. At the molecular level, the fulcrum of the contractile process is the changing concentrations of Ca^{2+} ions in the myocardial cytosol. In the failing heart, there are changes in gene expression, including down-regulation of the calcium uptake pump (SERCA2) (4,5). Cordero-Reyes et al. (1) report an association between cardiac strain and SERCA2 and phospholamban (a SERCA modulator) expression. Indeed, attempts to normalize SERCA2 expression by adenoviral gene transfer in experimental models in vivo have been reported to be associated with increased cardiomyocyte-shortening strain (6). Taken together, the existing data suggest that systolic calcium release and diastolic calcium reuptake

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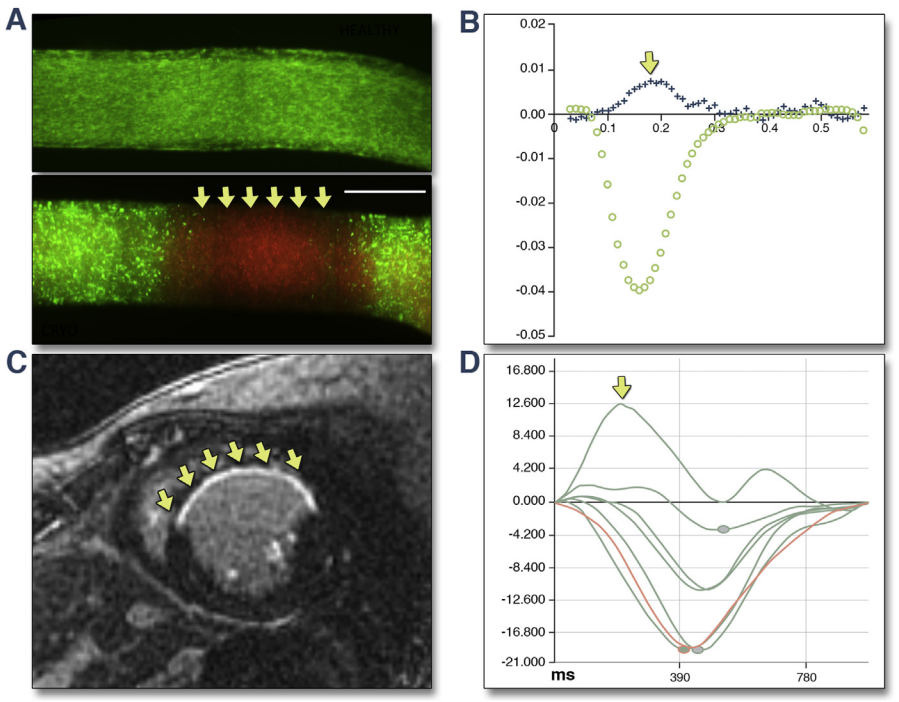

Figure 1. Direct Strain Analysis in Human Cardiomyocytes Versus Noninvasive Strain Assessments From Cardiac Imaging

(A) Fluorescent images of living cardiomyocytes **(green)** and injured cells **(red, arrows)** in a healthy engineered cardiac tissue **(top)** and 10 min after local cryoinjury **(bottom)** (scale bar, 1 mm). **(B)** Regional finite strains along the ECT axis (E_{11}) versus time (seconds), indicating a change from normal systolic shortening **(open circles)** to local paradoxical stretching **(arrow)** in the cryoinjury zone. In comparison, delayed gadolinium enhanced cardiac magnetic resonance **(C)** shows a scarred interventricular septum in a patient with an old myocardial infarction **(arrows)**. Circumferential strain (percent) versus time (milliseconds) derived by speckle-tracking echocardiography **(D)** shows paradoxical stretch **(arrow)** in the areas of scarred myocardium. Panels **A** and **B** are courtesy of Kevin Costa, PhD, Cardiovascular Research Center, Icahn School of Medicine at Mount Sinai, New York, New York.

are key determinants of cardiac deformation. Strain imaging as a quantitative tool may have a potential role in guiding and interpreting cardiac deformation after therapies aimed at enhancing calcium reuptake mechanisms, and therefore, merits further investigation.

Consistent with previous observations (7), Cordero-Reyes et al. (1) also note that myocardial stiffness and diastolic relaxation were closely related to isoforms of titin, the giant endosarcomeric protein that contributes to diastolic restoration forces. Overall, these data suggest that the changes seen in cardiac strain imaging primarily track cardiomyocyte deformation rather than passive alterations in the material properties of myocardium. Further studies are needed to validate these relationships in other phenotypic presentations and important molecular targets for gene therapy, such as protein phosphatase-1 and inhibitor protein 1, beta-adrenergic receptors, the G protein–coupled receptor kinase 2 system, renin-angiotensin-aldosterone receptors, and adenylyl cyclase activity, to name a few (8).

Cardiac Strain and Subclinical Cardiac Dysfunction

In recent years, there has been growing interest in using cardiac strain as a marker of subclinical cardiac disease. For example, myocardial strain is attenuated in asymptomatic patients with diabetes mellitus, hypertension, smoking, obesity, and subclinical atherosclerosis (9). Similarly, patients with endocrine abnormalities, renal disease, cerebral white matter disease, and inflammatory arthritis may show reductions in myocardial strain despite no evidence of myocardial involvement. These observations become more relevant because of the emerging epidemic of noncommunicable diseases, particularly obesity, which is associated with a clustering of risk factors such as hyperlipidemia, hyperleptinemia, hyperinsulinemia, insulin resistance, elevated circulating cytokines, hypertension, and type 2 diabetes. Cardiac strain is reduced in all these milieus and

may result from impaired activity of calcium reuptake mechanisms. Experimental data suggest that insulin resistance and related metabolic disorders are associated with elevated oxidative stress and increased SERCA2 oxidation, resulting in prolonged Ca^{2+} transients (10). The higher oxidative stress also triggers inflammation and downregulation of mitochondrial energetics, which further reduce myocyte function. Moreover, increased insulin stimulates the renin-angiotensin signaling pathway and consequently cardiomyocyte hypertrophy and cardiac fibrosis. Maladapted hypertrophy may trigger cardiomyocyte death through heightened apoptosis and autophagy, causing progressive cardiac remodeling and heart failure (11). Currently, interventions to address cardiomyocyte distress and cell death and survival pathways remain an exciting area of translational research (12). In particular, modulation of insulin-like growth factor 1 has been shown have a unique role in the upregulation of prosurvival mechanisms, with defense offered simultaneously against diabetes, cancer, and cardiovascular diseases (13). With the emergence of such novel targets, cardiac strain therefore may find a role in identifying subclinical myocyte dysfunction that results from increased oxidative stress amid a milieu of risk factors and subclinical diseases.

Recently, the emphasis has been placed on addressing the growth of cost-effective, high-throughput genomic and epigenomic analytics that can underpin common molecular pathways. In particular, there is a need to focus on developing system-based approaches in cardiovascular diseases that correlate cardiomyocyte gene expression and molecular pathways with phenotypic and functional imaging of pathology (14). With the burgeoning field of nanotechnology and cell-based therapy (15), the standardization of cardiac strain may aid in the early recognition of disease, clusters of risk factors, and comorbidities that result in cardiomyocyte contractile dysfunction. We believe that strain may be subclinical sign of uneasy heart muscle cells.

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