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iVIEW

EDITOR'S PAGE


The New Wave of Cardiovascular Biomechanics

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I welcome new words, or old words used in new ways, provided the result is more precision, added color or greater expressiveness."

—William Safire (1)

The heart has a unique architectural design that allows the cardiac chambers to empty and fill with optimal mechanical efficiency. The forces are actively generated by myocytes that shorten within an extracellular scaffold of collagen matrix. Together, both the active and passive constructs of the myocardium maintain overall muscle tension, alignment, ventricular size, and shape while the heart deforms. The advent of newer cardiac imaging techniques as illustrated in the study by Villemain et al. (2) and the accompanying editorial by Jens-Uwe Voigt (3) highlight exciting opportunities for increasing our understanding of the biomechanical interactions between the active (functioning) and passive (structural) units of the myocardium (2,3). These new insights are expected to reshape 2 emerging fields of cardiovascular practice: precision cardiac imaging (cardiac shape, motion, deformation, and material properties); and patient-specific computational models that can be constructed from cardiac imaging data.

From an engineering perspective, biological processes such as ischemia, inflammation, and fibrosis can be thought to reduce cardiac biomaterial and biomechanical performances. However, the quantification of cardiac biomaterial properties is not a straightforward task. Basic science researchers have traditionally performed direct mechanical testing on small, excised pieces of cardiac tissue for assessing cardiac material properties. Such mechanical testing has also been performed on individual myocytes. However, the data obtained from ex vivo studies cannot be directly translated to in vivo studies. Clinical in vivo studies have typically used the assessment of pressure-volume (P-V) loops using high-fidelity catheters for estimating myocardial stiffness. However, the P-V loop approach has its own limitations; for example, it is unable to distinguish between the myocyte and matrix-related contributions to left ventricular stiffness. Thus, progress will be contingent upon developing new noninvasive methods, often imaging, to study discrete elements of a complex pathophysiology (e.g., diastolic dysfunction).

Fortunately, the technological advances in cardiac imaging have provided newer opportunities for applying the engineering toolbox in clinical practice, and *iJACC* has had the opportunity to showcase some of these important developments. One of the most exciting is ultrafast echocardiography, which images with high temporal resolution (many thousands of frames per second) and offers unique opportunities in measuring cardiac material properties (e.g., stiffness), as well as functional data such as electromechanical activation mapping and temporally enhanced blood flow imaging (4-9). These techniques are specifically overcoming the uncertainties of assessments using echo-Doppler techniques that have traditionally relied on a combination of parameters or their interactions for "reverse engineering" the knowledge regarding myocardial material properties. For example, the study by Villemain et al. (2) not only

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provided an estimate of age-related changes in myocardial stiffness in a healthy population, but also showed a robust diagnostic value (95% sensitivity and 100% specificity) in differentiating normal age-related changes from other phenotypes, such as heart failure with preserved ejection fraction (HFpEF) and hypertrophic cardiomyopathy. Moreover, the investigators provided comprehensive correlation with conventional parameters of diastolic dysfunction and myocardial fibrosis observed using delayed gadolinium enhancement. This work extended other bodies of evidence regarding the use of myocardial shear wave propagation velocity for differentiating diastolic dysfunction severity in an infiltrative disease (e.g., cardiac amyloidosis) (10).

Despite continuous enhancements in the accuracy of cardiac imaging techniques, more work is still required to enable the translation of cardiac structure–function relationships to mainstream clinical practice. One of the major limitations has been the inability to directly image the myocardial fiber architecture, which is a key determinant of cardiac function. The fibers wind along the left-handed helix on the epicardium and change progressively through the wall thickness to wind along the right-handed helix on the endocardium (11). From an anatomical perspective, the complete characterization of myocardial mechanical properties therefore needs 2 independent perspectives, the along-fiber and across-fiber directions. Diffusion tensor magnetic resonance imaging (12) and recent reports of fiber geometry direction extraction using echocardiography speckle data have been recently reported (13,14). There is little doubt that more work will be needed to decipher the link between myofiber function and multiscale, organ-level, whole-heart biomechanics.

Significant advances have been made in past years in engineering functional cardiac tissues for developing personalized healthy and diseased "heart-on-a-chip" systems (15–17). These technologies provide more controlled microphysiological systems that are expected to not only better forecast the efficacy and toxicity of potential therapies, but also provide a more in-depth understanding of human cardiac disease in complex and heterogeneous microenvironments. An ideal in vitro cardiac model should precisely reiterate the physiological or pathological conditions of the human heart. This leads to a natural question: whether the myocardial biomechanical properties seen in cardiac images could be mimicked on individualized models. For example, studies have suggested passive stiffness in HFpEF is higher than that in normal populations; however, this may vary individually based on the relative contribution of changes in the extracellular matrix and the intracellular elements (e.g., giant sarcomeric protein titin). Previous studies have shown that the myocytes may be fairly normal in contractility despite alteration in whole heart function and have attributed to the restriction in deformation imposed by the stiffness of the interstitium (18–20). Therefore, patient-specific biophysical parameters governing myocardial stiffness and contractility in these models could be optimally matched to real-life data from medical imaging for improved precision.

The combination of cardiac model-based interpretation with machine learning techniques is another exciting front with unprecedented opportunities in developing insights into disease mechanisms and therapeutic pathways (21). For example, atlas-based shape analysis was used in the MESA (Multi-Ethnic Study of Atherosclerosis) cohort and shown to be more sensitive than traditional remodeling indexes such as mass and volumes (22). Furthermore, principal component analysis was found to be useful to quantify the major determinants of shape variation in MESA participants. The applications of tissue-specific parameters, which are ideally independent of chamber geometry and loading conditions, could be of paramount importance to improve the yield of such an analysis.

Finally, it is worth considering the applications of noninvasive biomechanical assessments for the field of cardiac tissue engineering that offers the potential of biologically based repair of injured and damaged cardiac tissue (23). This would be particularly important for designing scaffold materials that should match the mechanical properties of the myocardium and heart valves. The careful selection of the material properties for an engineered tissue may allow uniform distribution of stress and strain consistent with body's physiological limits. Furthermore, noninvasive assessment of the implanted scaffold would allow longitudinal monitoring of the stages of repair and regrowth. There have been recent interests in injecting a variety of cellular and acellular materials into a damaged myocardium to prevent or reverse remodeling. For example, numerous injectable hydrogels have been developed, and many of them have been tried for application in cardiac repair after myocardial infarction. In preclinical studies, acellular injectable hydrogels have been found to thicken the myocardial wall, thereby reducing abnormal stresses when injected directly after a myocardial infarction (24). In experimental studies, cardiac function after hydrogel injection with or without stem cells or gene delivery has been monitored using echocardiographic approaches. One can foresee that use of advanced

biomechanical imaging techniques (e.g., stiffness, and stress and strain imaging) could be useful for monitoring new tissue engineered solutions to repair or replace damaged cardiac tissues.

In summary, the combination of clinical cardiac imaging techniques, biomechanical imaging, computational modeling and machine learning are creating unprecedented opportunities in positioning cardiac imagers at the heart of precision medicine. In future data from electronic health records, administrative, clinical registries, and cardiac imaging, techniques could be merged with biometrics, genomics, proteomics, radiomics, computational modeling, and other sources, including experimental studies and social media, to successfully combine population-based cardiac image modeling with biophysical parameter identification for the prediction of personalized risks. Finally, the ability to customize cardiac biomechanical performance targets for treating individual patients with novel therapies could significantly transform clinical care.

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