Left Ventricular Form and Function
Scientific Priorities and Strategic Planning for Development of New Views of Disease

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Heart failure continues to be one of the most costly and prevalent medical problems. The increasing age of our population and the increased survival of patients with diseases that lead to heart failure will no doubt further magnify this very serious health problem at a staggering cost, both monetary and human. To address this public health concern, a fuller understanding of what constitutes normal cardiac function is essential to recognize optimal goals for restoration after disease disrupts stability. From micro to macro, our limited understanding of the heart’s function continues to represent an obstacle to our ability to design strategies for effective treatment of heart failure. Thus, there is a critical need to address the existing and emerging issues in this area to develop new safe and effective strategies to address the clinical challenges facing cardiologists and cardiothoracic surgeons. As a result of this need, the National Heart, Lung, and Blood Institute convened a workshop entitled “Form and Function: New Views on Development, Diseases, and Therapies for the Heart” on April 25 to 26, 2002, in Bethesda, Maryland. The objective was an effort to understand the importance of structure/function relationships of the intact ventricles from both the basic science and clinical perspectives, to define where progress is most urgently needed, and to plan research programs that will most effectively integrate understanding of functional geometry into therapy of human heart disease.

There has been a remarkable growth in the understanding of cellular myocardial function at the genetic/molecular level with development of the ability to perform genetic manipulation of cardiac and other cells within the heart. It is critically important to recognize that the complex molecular machinery that enables the heart to fulfill its role in the circulatory system can only function effectively within an architectural design that allows the contractile apparatus to perform with optimal mechanical efficiency, determined by appropriate integration of the vectors of force generated by cardiac sarcomeres. Integration of new genetic techniques and advances in imaging technology must be matched with a new understanding of the importance of shape and fiber architecture to provide insights into disease that can lead to new therapies.

A shift in emphasis from concepts of ventricular function that consider only contractile state and load to those that also incorporate interaction and dynamic rearrangement of myocardial layers is needed. A starting point for discussion at the workshop was the anatomic concept that has been proposed by Torrent-Guasp, in which both ventricles are considered to consist of a single myofiber band extending from the right ventricular muscle just below the pulmonary artery to the left ventricular muscle where it attaches to the aorta, twisted and wrapped into a double helical coil during evolutionary and embryological development. In this construct, sequential activation and contraction beginning in fibers near the pulmonary artery and spreading toward the aortic end of the band might explain the pattern of ejection and suction needed for ventricular output and filling. This model is an example of an emphasis that relates fiber architecture to chamber shape and mechanics and has implications for improved understanding of electrical, electromechanical, and mechanical determinants of cardiac function. Disease resulting from ischemic, non-ischemic, and valvular mechanisms may produce architectural distortion and create a more spherical ventricular shape.

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(Circulation. 2004;110:e333-e336.)

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Circulation is available at http://www.circulationaha.org DOI: 10.1161/01.CIR.0000143625.56882.5C
conceptual underpinning of management may therefore involve restoration of the normal structural scaffold, so that successful interventions can be designed to achieve normalization of fiber orientation.

To advance the understanding of the relationship between form and function of the intact heart and to integrate these findings into therapy, we recommend intensive study along the following pathways.

Understanding Normal and Abnormal Shape and Fiber Mechanics

- **Elucidate signaling pathways by which stress and strain regulate gene expression, myofiber pattern formation, and structural remodeling in vivo.** A comprehensive understanding of the relationship between the nature of the macro-structure of myocardial fiber bands, the optimum shape of the left ventricle (LV), and the state of a heart’s cells does not exist without linking the geometric scaffold with the control mechanisms for filling and emptying. Studies should also investigate the role of cell–matrix interactions in ventricular remodeling. We should differentiate between the effects of structural lesions on the transmission of contractile stress from the myofilaments in the myocyte to the interstitium (inside-out signaling) versus the transduction of external mechanical signals into the myocyte (outside-in signaling). It is now becoming recognized that a diverse family of proteases can influence cell–matrix interactions in a number of disease states. How the regulation, expression, and activation of these proteases can directly affect fiber alignment and orientation, as well as myocardial mechanical performance, warrants critical examination.

- **Define the extent to which myocyte dysfunction, extracellular matrix remodeling, chamber (shape and fiber architecture) remodeling, and their interactions produce systolic and/or diastolic mechanical dysfunction leading to cardiac failure.** How can this information be integrated into experimentally verifiable computational models that can be used to develop rational, durable therapy? Murine and large animal models in which geometry is altered in the absence of inherent defects in myocyte contractility should be studied to define the structural basis for regional contractile defects. Models of heart failure induced by pacing or the introduction of mitral regurgitation in the dog or pig may be exploited in the sense that abnormalities in myocardial geometry occur in a time-dependent fashion and allow for mapping of muscle fiber pitch and function. The potential reversibility of these models may define how “restoration” of normal fiber alignment can occur during the return toward more normal size and shape. A related question is whether vascular compression during normal systole causes vascular engorgement and influences wall stiffness through an erectile effect, a mechanism that might be lost during the progression of heart disease.

- **Investigate alterations in diastolic deformation that may explain changes in diastolic filling patterns that occur with disease and aging.** Alterations in the rapid filling pattern often occur as the earliest preclinical changes in cardiomyopathy. This occurs in patients with hypertension, patients who have received cardiotoxic chemotherapy, and those with diabetes mellitus, and it may allow early detection of disease. Studies of rapid diastolic recoil of systolic torsion might allow recognition of abnormalities in patients with early disease and elucidation of the etiology of changes that are known to occur in senescent myocardium even in the absence of a pathological stimulus. It has been suggested that in the normal state, these deformations result from a transmural gradient in the onset and duration of activation, which might be altered in disease. Further investigations are required to determine to what extent ventricular suction may be influenced by a sequentially contracting helical band that is responsible for the coordination of a reciprocal twisting as proposed in the Torrent-Guasp model. This model deviates from current concepts of an elastic model in which rapid filling is ascribed to recoil from energy stored during systole, and considers the isovolumic phase during repolarization to be an active phase of systole rather than diastole. These mechanisms would be disturbed in diseases that cause LV remodeling. These hypotheses need testing.

- **Define the relationships between the synchronization of electrical depolarization and repolarization, the coordination of myofiber contraction and relaxation, and changes during the progression of heart failure.** Thorough understanding of electrical coordination is a paramount yet overlooked area. Studies should address how changes in myocardial structure contribute to a loss of normal electrical conduction that causes dyssynergistic contraction and vice versa. Specifically, the role of dilatation in this process must be determined. Large animal model studies should be designed that demonstrate how multiple site pacing can modify electrical and mechanical activation sequences in the failing myocardium, reduce chamber dilatation and regional wall stress, and identify the cellular and extracellular mechanisms for these effects, including potential changes in interstitial proteins. Models such as that of Torrent-Guasp et al., which proposes conduction along fiber orientation in a single muscular band and defies conventional concepts of activation, should be investigated.

Advancing Imaging

- **Develop new approaches to map spatially and temporally heterogeneous 3-dimensional mechanics, electrical activation, and structure, both dynamically and simultaneously.** These methods should improve on current spatial and temporal resolution and in the short term and would involve optimization of current micro-sensors and indicators.

Specific imaging methods with potential for defining fiber orientation and electromechanical sequences in microscopic preparations and small animal models include (1) two photon confocal microscopy and/or optical computed tomography for optical imaging of fiber orientation and mechanics and (2) high field magnetic resonance imaging (MRI) development, particularly using diffusion tensor imaging, tissue tagging, and strain assessment in...
The working group developed these recommendations, which highlight a number of important and new areas for future research, to address these critical issues. Development of new ideas and directions within all 3 of the above areas will feed into and support each of the other 2. Accomplishing these goals will require a multidisciplinary collaboration of physiologists, biomedical engineers, clinicians, radiologists,
and surgeons. In addition, these lines of research are sufficiently complicated to require the cooperation of both theorists and experimentalists; that is, we should encourage the development and validation of new and improved integrative computational models, which provide testable hypotheses concerning myocardial mechanics. Experiments involving genetic and molecular perturbations, or therapeutic interventions including surgery, would then provide tests of model predictions and also develop new parameters to insert into models so that realistic testing can evolve. New funding opportunities should encourage projects with a wide range of scopes, varying from individual grants to multidisciplinary collaborative programs. The highest priority in this endeavor should be to attain a more sophisticated understanding of the contributions of fiber and intracellular architecture to chamber function through the development of improved imaging methods and their creative application, and to investigate the application of these principles to human disease through surgery or other modalities.

Acknowledgments

We thank Aventis for their support.

References

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Circulation. 2004;110:e333-e336
doi: 10.1161/01.CIR.0000143625.56882.5C
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

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