Special Report

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.[1] 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[2] is needed. A starting point for discussion at the workshop was the anatomic concept that has been proposed by Torrent-Guasp,[3] 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. The

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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[4] (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[5] 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.[3] 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 of 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,[6] 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[7] and/or optical computed tomography for optical imaging of fiber orientation and mechanics and (2) high field magnetic resonance imaging (MRI) development,[8] particularly using diffusion tensor imaging,[9] tissue tagging, and strain assessment in

2-dimensional and 3-dimensional space. The utility of iron and chelate markers for MRI tracking of cells[10] or even gene activity[11] should be studied. Specifically, chimeric mouse models in which some cells have been tagged in this manner and can be tracked to study the dynamic geometry of fibers might define fiber architecture and how it changes throughout the cycle. Similarly, labeled stem cells might be introduced into remodeled ventricles to assess the factors that determine their eventual orientation. In larger animal and clinical studies, optimization of MRI at existing and expected higher magnetic field strengths has potential to define normal and abnormal structure (fiber orientation via diffusion tensor imaging), systolic and diastolic function (strain or strain rate via tagging or tissue velocity measurement), and perfusion (oxygen saturation using blood-oxygen level-dependent or other methods).

The development and more frequent use of methods that provide long-lasting tagging of myocardium, persisting for months or years, should be encouraged. For example, this method might make use of the implantation of radiopaque or other sensors for high-speed cine imaging or recording to study geometry change and even fiber realignment and systolic/diastolic dimensional change after restoration of appropriate geometry by surgery over extended observation periods.

In the long term, configuration changes in transmembrane proteins following electrical or mechanical events might provide signals that could be detected with noninvasive imaging modalities such as MRI or spectroscopy. Lastly, although ultrasound has limitations for myocardial characterization, new high-resolution methods[12] have recently been introduced. Because it is portable, cardiac ultrasound is ideally suited to use in interventional settings and/or surgery. Therefore, improvement in ultrasound methods for characterization of myocardial function and perfusion would be highly desirable.

Advancing Therapeutics Through Surgery and Devices

- *Advance the surgical techniques of ventricular reconstruction based on new understanding of the role of fiber orientation and shape in heart function.* The centerpiece of several recent techniques in surgical heart failure therapy focuses on the application of Laplace's Law to justify reduction of LV wall tension through the reduction of its radius of curvature. However, a critical dilemma for these surgical treatments is the final form that the LV volume attains. Should we, for example, remodel a dilated sphere-like LV to a smaller sphere or to a smaller volume that has an ellipsoidal shape? Following the latter course will change fiber orientation and produce an anisotropic and thus heterogeneous structure, which might have a crucial impact on restoring the mechanical and hemodynamic functions of the failing spherical heart toward those of a more normal conical heart.

The aforementioned animal models of heart failure should allow assessment of surgical strategies like the surgical ventricular restoration technique,[13] alone and in combination with valve repair or replacement. Improved imaging methods should allow visualization of "reverse remodeling" or "restoration" that might occur after these procedures. New operations may be developed to allow apposition of layers containing different fiber orientations, restoring a more natural scaffold of architectural form. Successful tissue bioengineering using stem cells, which tend to orient along normal fiber directions, might then produce an intact matrix of cardiomyocytes, angiogenesis, fibrous tissue, neural connections, and other focal components.

Human trials of surgical ventricular restoration should be accompanied by in-depth noninvasive studies of changes in geometry (by MRI and 3-dimensional echo) and fiber angle (by diffusion tensor MRI) and invasive (biopsy-derived) studies of changes in neurohormonal and cytokine levels, collagen dynamics (eg, c-propeptide and c-telopeptide assays), and alteration in transmembrane proteins and sarcoplasmic reticulum calcium dynamics.

Guided by advances in the understanding of shape and fiber dynamics, new devices that alter the synchronization of depolarization and repolarization should be developed and tested. In the long term, studies in which cultured Purkinje cells are introduced into hearts with seriously impaired intraventricular activation should be planned.

- *Develop computational models that will integrate all relevant imaging information to allow planning of the proper surgical procedure or device procedure for a given individual patient.* In designing surgical or therapeutic strategies aimed at improving ventricular function, cardiologists and surgeons are forced to deal with a vast number of parameters. Nonlinear interaction of various components from the cell to the fiber level makes intelligent decision making difficult. Fuller recognition of the form/function relationship in normal and failing hearts, coupled with 3-dimensional imaging and measurements of pressure and flow, may yield the ability to have at our disposal realistic computational predictive models of a given patient. What region should be resected? Where are edges to be approximated? What should be done about the mitral valve and mitral regurgitation? What about the papillary muscles? This type of modeling would be dependent on close interaction between theorists and experimentalists, which should be supported and further developed.

The panel agreed that much research has been done in this area, much of which has served to highlight the need for further understanding. Thus, many needs remain to be met. The area of cardiac imaging of structure and function at both the molecular and organ level to study their interaction was considered as a new frontier to be developed with a unique opportunity to use novel tools to study previously unexplored physiological and pathological states. It would also provide a clear benchmark for testing other technologies, now in the developmental stages, that could supplant current techniques in the near future, and will provide a firm foundation for developing new diagnostic and therapeutic strategies in cardiac disease states.

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.

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