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iVIEW

EDITOR'S PAGE

LV Segmentation and Mechanics in HCM: Twisting the Rubik's Cube Into Perfection!

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". . .Sky knows the reasons and the patterns behind all clouds, and you will know, too, when you lift yourself high enough to see beyond. . ."
—Richard Bach (1)

Two-dimensional echocardiography, nuclear cardiology, and cardiac magnetic resonance have previously developed arbitrary schemes of segmentation based on clinical application and the strengths and limitations of the modalities (2,3). These models of left ventricular (LV) segmentation were primarily developed as an optimally weighted approach to facilitate assessment of regional LV function and/or perfusion as a noninvasive marker of coronary blood supply to myocardial segments. Autopsy studies provided supportive data on the mass and size of the myocardial segments. For example, in a previous autopsy series of adult hearts without cardiac disease, Edwards et al. (4) sectioned the LV into apical, mid-cavity, and the basal thirds perpendicular to the long axis; the myocardial mass for these segments was 21%, 36%, and 42%, respectively. The 17-segment model (Fig. 1), recommended currently for imaging study interpretation corresponds to the mass distribution of 30%, 35%, and 35%, for the apical, mid-cavity, and basal segments, respectively, which is fairly similar to the autopsy data (5). This segmentation system, however, is based on coronary artery distribution and does not take into account the structural anisotropy in cardiac myofiber orientation or its mechanical contributions during the cardiac cycle.

An important goal of a cardiac image segmentation scheme must extract local descriptors of the myocardial structure and its functional organization. The LV mass is a 3-dimensional continuum, with myocardial fibers presenting counter-directional orientation (Fig. 2) from the subendocardium to the subepicardium (6). In general, during a cardiac cycle, the epicardial fibers dominate the endocardial fibers in a way that the full thickness of the LV wall moves with the epicardium; such a twisting deformation is readily identified in a surgically opened chest despite the opposite direction of the endocardial fibers. The twist deformation is associated with fiber sheet sliding (shear) with forced radial reorientation inducing >40% myocardial thickening in systole (7). The untwisting of the fiber sheets results in rapid uncoiling, similar to the opening of a twisted rubber band, allowing the initiation of suction and diastolic restoration. The net systolic and diastolic performance of the LV is dependent on the functional interactions of the counter-directional subendocardial and subepicardial helices that are synergistically coupled.

Characterization of myocardial structure is important for understanding the extent and pattern of its involvement in different disease states. For example, the study by Florian et al. (8) in this issue of *iJACC*, using cardiac magnetic resonance imaging, provides an account of a helical distribution of cardiac hypertrophy in hypertrophic cardiomyopathy (HCM). The hypertrophy began at the basal anteroseptum and descended clockwise toward the apex (as seen from base or counterclockwise if seen from the apex). Although the extent of myocardial disarray in the transmural layers was not clarified in the present study, the segmental hypertrophy direction coincides with the subendocardial fiber direction. These data are consistent with recent experimental observations using diffusion tensor magnetic resonance imaging in homozygous MyBP-C knockout mouse models

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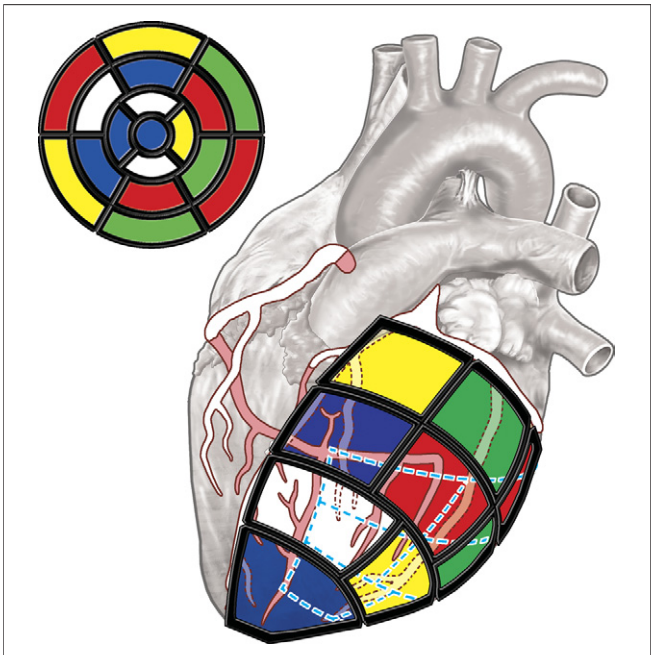

Figure 1. Left Ventricular Segmentation

The cartoon shows the 17 segment model of the left ventricle proposed by the American Heart Association (AHA) writing group on myocardial segmentation and registration for Cardiac Imaging. Segments are colored for a Rubik's Cube analogy. Figure illustration by Craig Skaggs.

of HCM, wherein the maximal myofiber disarray was observed in the subendocardium (9).

Although obstructive HCM had been recognized as a distinct disease by the mid-20th century (10), one wonders why the helical nature of asymmetric hypertrophy was not previously recognized. In general, helical structures are one of the most difficult patterns to classify, particularly in 2 dimensions. Therefore, although echocardiographic imaging was introduced to image HCM as early as 1969 (11) and demonstrated the characteristic asymmetric pattern of LV hypertrophy, the helical nature of the asymmetric hypertrophy did not become evident in the 2-dimensional images. Similarly, observations from cross sections of the cardiac specimens may have undermined the recognition of the helical nature of the muscle involvement in HCM in autopsies and surgical studies. The currently used LV segmental scheme is also adapted for cross-sectional imaging and confines the LV in cross-sectional segments that may not correspond to the actual morphological boundaries of a helical system. Although the existing models of LV segmentation are appealing for their ease of communication and corroboration with vascular distribution, the existing approach may risk improper phenotypic recognition of common cardiac diseases.

Muscle Mechanics and Adaptive Changes in Cardiac Architecture

In a normal heart, cardiac myofiber orientation plays a role in the uniform transmural distribution of mechanical stress and strain (12). Regional hypertrophy with myofiber disaaray may occur as an adaptive mechanism for restoring the uniformity of stress when local mechanics deviate from normal (13,14). The onset of relaxation is the most vulnerable period in myofiber mechanics (15) and patients with HCM show reduction in longitudinal relaxation velocities even before the appearance of regional hypertrophy (16,17,18). Thus, one can postulate that the development of segmental hypertrophy and myocardial disarray may occur in segments with maximal reduction in myocardial mechanics, and this change may help reduce subendocardial stress and preserve the global left ventricular ejection fraction in the face of ongoing subclinical myocardial dysfunction (19,20). Since myocardial hypertrophy and disarray occur in response to maladapted stress-strain relationships in the subendocardium, it is logical to expect that regional hypertrophy should follow the helical distribution of subendocardial region. Although stress-strain relationships may serve as a stimulus for progressive hypertrophy, the reason this change is more pronounced in some segments versus another, however, remains unclear.

Blood Flow Dynamics and Adaptive Changes in Cardiac Architecture

A potential reason for asymmetric distribution of hemodynamic load may be related to the asymmetric structure of blood flow transiting through the LV cavity. Recent investigations have shown that blood flowing into the cardiac chambers results in the formation of an asymmetric vortex ring during ventricular filling (21). The flow interacts with the left ventricular (LV) wall and turns preferentially into a larger anterior vortex at the end of diastole that is directed toward the aorta. Furthermore, the trabeculae over the endocardial region are helically arranged, and these structures have been further suggested to provide a helical spin to the asymmetric toroidal-shaped

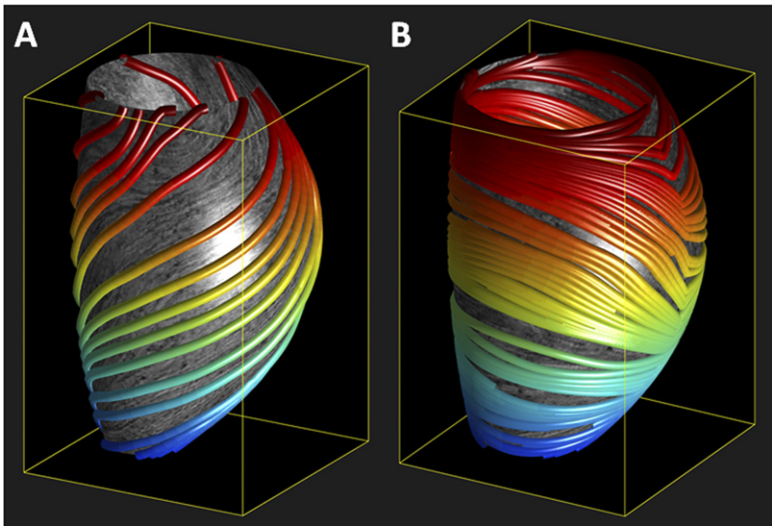

Figure 2. Counterdirectional Helical Architecture of Myofibers in the Left Ventricle

The myofiber orientations of the subendocardial **(A)** and subepicardium **(B)** was reconstructed by tracking the magnetic resonance imaging short-axis slices of a rat's heart video (Online Video 1). Image analysis and reconstruction was performed in MatLab 7.11 (Mathworks, Inc., Natick, Massachusetts) using optical flow algorithm. Image courtesy of Professor Gianni Pedrizzetti, Mount Sinai School of Medicine, New York, New York.

filling vortex (22). Vortex rings not only help to conserve energy from diastole into systole but also are energy-efficient structures that provide a loading mechanism for favorably stretching the LV for optimal force generation during ejection. Finally, the spinning mass of fluid is ejected into the aorta such that the blood flow spirals like a bullet over the threads of a rifle barrel to obtain better directional stability (23,24). Since the LV vortex has an asymmetric shape, the LV wall may also be stretched asymmetrically and this may potentially explain the asymmetric distribution of stress-strain relationship and segmental hypertrophy in HCM.

Blood flow is an important epigenetic factor that modulates embryonic patterning, morphogenesis, and function (25,26). Biomechanical forces exerted by blood flow are registered by endocardial cells that differentially respond to these functional cues. For example, the direction of initial heart looping is mediated through ciliated endodermal cells (27). The clockwise rotation of motile cilia causes a leftward fluid flow that is sensed by adjacent cells with primary cilia through mechanoreception (28). This results in an increase in intracellular Ca^{2+} and activation of the asymmetric cardiac looping steps. Whether myocardial segmental hypertrophy and disarray in HCM is also influenced by stretch forces is not yet clear. Such interactions may continue throughout life, and it is tempting to hypothesize that forces experienced by cardiac cells (mechanoduction) may stimulate them to hypertrophy, secreting matrix and changing the overall shape and thickness of the LV wall, explaining the phenotypic expression of a genetic disease with a high diversity in degree and pattern (asymmetric, concentric, and apical), penetrance, age of onset, and clinical course. The helical course of hypertrophy observed by Florian et al. (8) raises several such interesting questions that will require careful evaluation in future investigations.

The scientific quest for understanding the structure of the LV in health and disease is almost like solving a Rubik's Cube, the 3-dimensional mechanical puzzle in which all of the colors need to finally align. Make the wrong move, and the puzzle appears even more confusing. Make the right one, and the puzzle becomes easier to complete. The flow-redirecting behavior of LV may be intimately related to the helical LV architectural surface. With little imagination, one could therefore reason that the regions of interest and segmentation schemes should contain oblique and curvilinear paths, which are more aligned to the actual myofiber and flow directions. In this regard, newer techniques, such as diffusion

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magnetic resonance imaging described in this issue of *iJACC* by Poveda et al. (29), which display in vivo myofiber orientation may help resolve LV muscle and fluid mechanics and develop robust segmentation schemes for functional cardiac imaging.

REFERENCES

1. Bach R. Available at: http://en.wikiquote.org/wiki/Richard_Bach. Accessed June 7, 2012.
2. Schiller NB, Shah PM, Crawford M, et al. Recommendations for quantitation of the left ventricle by two-dimensional echocardiography. American Society of Echocardiography Committee on Standards, Subcommittee on Quantitation of Two-Dimensional Echocardiograms. J Am Soc Echocardiogr 1989;2:358–67.
3. Imaging guidelines for nuclear cardiology procedures, part 2. American Society of Nuclear Cardiology. J Nucl Cardiol 1999;6:G47–84.
4. Edwards WD, Tajik AJ, Seward JB. Standardized nomenclature and anatomic basis for regional tomographic analysis of the heart. Mayo Clin Proc 1989;56:479–97.
5. Cerqueira MD, Weissman NJ, Dilsizian V, et al., for the American Heart Association Writing Group on Myocardial Segmentation and Registration for Cardiac Imaging. Standardized myocardial segmentation and nomenclature for tomographic imaging of the heart: a statement for healthcare professionals from the Cardiac Imaging Committee of the Council on Clinical Cardiology of the American Heart Association. Circulation 2002; 105:539–42.
6. Sengupta PP, Tajik AJ, Chandrasekaran K, Khandheria BK. Twist mechanics of the left ventricle: principles and application. J Am Coll Cardiol Img 2008;1:366–76.
7. Sengupta PP. Exploring left ventricular isovolumic shortening and stretch mechanics: "the heart has its reasons. . ." J Am Coll Cardiol Img 2009; 2:212–5.
8. Florian A, Masci PG, De Buck S, et al. Geometric assessment of asymmetric septal hypertrophic cardiomyopathy by CMR. J Am Coll Cardiol Img 2012;5: 702–11.
9. Wang TT, Kwon HS, Dai G, et al. Resolving myoarchitectural disarray in the mouse ventricular wall with diffusion spectrum magnetic resonance imaging. Ann Biomed Eng 2010;38: 2841–50.
10. Brock RC. Functional obstruction of the left ventricle (acquired aortic subvalvar stenosis). Guys Hosp Rep 1957; 106:221.
11. Shah PM, Gramiak R, Kramer DH. Ultrasound localization of left ventricular outflow obstruction in hypertrophic obstructive cardiomyopathy. Circulation 1969;40:3–11.
12. Tea BS, Dam TV, Moreau P, et al. Apoptosis during regression of cardiac hypertrophy in spontaneously hypertensive rats: temporal regulation and spatial heterogeneity. Hypertension 1999;34:229–35.
13. Vendelin M, Bovendeerd PH, Engelbrecht J, Arts T. Optimizing ventricular fibers: uniform strain or stress, but not ATP consumption, leads to high efficiency. Am J Physiol Heart Circ Physiol 283;2002:H1072–81.
14. Karpawich PP, Justice CD, Cavitt DL, Chang CH. Developmental sequelae of fixed-rate ventricular pacing in the immature canine heart: an electrophysiologic, hemodynamic, and histopathologic evaluation. Am Heart J 1990;119: 1077–83.
15. Pouleur H. Diastolic dysfunction and myocardial energetics. Eur Heart J 1990;11 Suppl C:30–4.
16. De S, Borowski AG, Wang H, et al. Subclinical echocardiographic abnormalities in phenotype-negative carriers of myosin-binding protein C3 gene mutation for hypertrophic cardiomyopathy. Am Heart J 2011;162: 262–7.e3.
17. Ho CY, Carlsen C, Thune JJ, et al. Echocardiographic strain imaging to assess early and late consequences of sarcomere mutations in hypertrophic cardiomyopathy. Circ Cardiovasc Genet 2009;2:314–21.
18. Vinereanu D, Nicolaides E, Tweddel AC, et al. "Pure" diastolic dysfunction is associated with long-axis systolic dysfunction: implications for the diagnosis and classification of heart failure. Eur J Heart Fail 2005;7:820–8.
19. Zhang J. Myocardial energetics in cardiac hypertrophy. Clin Exp Pharmacol Physiol 2002;29:351–9.
20. Carasso S, Yang H, Woo A, et al. Systolic myocardial mechanics in hypertrophic cardiomyopathy: novel concepts and implications for clinical status. J Am Soc Echocardiogr 2008; 21:675–83.
21. Sengupta PP, Pedrizzetti G, Kilner PJ, et al. Emerging trends in CV flow visualization. J Am Coll Cardiol Img 2012;5:305–16.
22. Gorodkov A, Dobrova NB, Dubernard J-PH, et al. Anatomical structures determining blood flow in the heart left ventricle. J Mater Sci Mater Med 1996;3:153–60.
23. Houston JG, Gandy SJ, Sheppard DG, Dick JB, Belch JJ, Stonebridge PA. Two-dimensional flow quantitative MRI of aortic arch blood flow patterns: effect of age, sex, and presence of carotid atheromatous disease on prevalence of spiral blood flow. J Magn Reson Imaging 2003;18:169–74.
24. Stonebridge PA, Brophy CM. Spiral laminar flow in arteries? Lancet 1991; 338:1360–1.
25. Santhanakrishnan A, Miller LA. Fluid dynamics of heart development. Cell Biochem Biophys 2011;61:1–22.
26. Hove JR, Köster RW, Forouhar AS, Acevedo-Bolton G, Fraser SE, Gharib M. Intracardiac fluid forces are an essential epigenetic factor for embryonic cardiogenesis. Nature 2003;421:172–7.
27. Yost HJ. Left-right asymmetry: nodal cilia make and catch a wave. Curr Biol 2003;13:R808–9.
28. McGrath J, Brueckner M. Cilia are at the heart of vertebrate left-right asymmetry. Curr Opin Genet Dev 2003; 13:385–92.
29. Poveda F, Martí E, Gil D, Carreras F, Ballester M. Helical structure of cardiac ventricular anatomy by diffusion tensor cardiac MR tractography. J Am Coll Cardiol Img 2012;5:754–5.

APPENDIX

For a supplementary video and its legend, please see the online version of this article.