EDITORIAL COMMENT

Exploring Left Ventricular Isovolumic Shortening and Stretch Mechanics*

"The heart has its reasons…"†

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A rifle recoils when fired. This recoil is the result of action-reaction force pairs. Consistent with Newton's third law of motion, as the bullet is propelled, it pushes backward upon the rifle. Similar sequences appear in the heart, nature's most efficient propulsion design. The early activated regions of the left ventricle (LV) shorten, forcing blood to accelerate (1). But an equal and opposite force produces a backward thrust that is felt over the chest wall as

the LV apical impulse. The reshaping of LV geometry during the isovolumic contraction (IVC) period causes simultaneous shortening and stretch of the early and the late activated regions of LV, respectively (2,3). These transient LV reshaping movements during IVC produce rapid biphasic regional velocities that can be recorded with the use of high temporal resolution cardiac imaging techniques (Fig. 1). The study by Ashikaga et al. (4) in this issue *iJACC* provides a comprehensive in vivo analysis of this spatially heterogeneous yet functionally synergistic sequence of transmural deformation that primes the LV for ejection.

The Structural Basis of Functional Asymmetry

Louis Pasteur in 1848 discovered the left-right asymmetry of spin in molecules, a property referred to as "chirality" or "handedness" (Greek, χειρ, *kheir*: "hand"). The property of chirality is not, however, confined to the molecular level alone. In the vertebrate embryo, many key laterality genes are involved in the process of asymmetrical heart looping such that the developing heart emerges as one of the first organs to exhibit a left-right asymmetry (5). Torsion of the embryonic heart transforms the tube into a chiral structure that is wound counterclockwise with myofibers that spiral in the LV wall (5), changing continuously from a right-handed helix in the subendocardium to a left-handed helix in the subepicardium.

The transmural continuum of opposing geometries in the LV creates an anisotropic environment for the spread of electromechanical activation. Durrer's classic study in the 1970s demonstrated that the electrical excitation was initiated in the LV endocardium (6). Subsequent development of electroanatomical imaging further contributed to our understanding of the electrical activation sequence. The His-Purkinje system in mammalian hearts facilitates a rapid conduction of electrical activity from the earliest site of endocardial activation in the septum toward the apex, followed by the rest of the LV (7). In addition to the regional delays, a transmural delay in the onset of electrical activation is also noted. Transmural conduction depends largely on cell-to-cell propagation, and is markedly influenced by intramural anisotropy and the angle formed between myocytes. The delayed mechanical activation of the epicardial region is therefore a consequence of the slow intramural propagation of the excitation wave.

Revised Mechanics of the Pre-Ejection Period

The pre-ejection phase traditionally has been divided into 2 phases (1). The interval from the onset

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of the Q-wave on surface electrocardiography to mitral valve closure is referred to as electromechanical delay, whereas IVC is the period that follows mitral valve closure and is characterized by a rapid increase in LV pressure before opening of the aortic valve. Recent studies (8) have illustrated the onset of subendocardial shortening within the period that was in the past referred to as electromechanical delay. Rather, the phase represents a period of electromechanical dispersion, where both a transmural and axial delay of electromechanical coupling is encountered, paralleling the wave front of electrical activation. The study by Ashikaga et al. (4) provides in-depth observations regarding the transmural component of mechanical dispersion that produces an asynchronous onset of mechanical activity during the IVC period. These features are consistent with our observations in a previous animal experimental study that explored the mechanism of biphasic isovolumic waveforms in tissue Doppler imaging (2). During IVC, shortening of the LV subendocardial fibers that are arranged in the form of a right-handed helix is accompanied with stretching of the nearly orthogonal subepicardial fibers arranged in the form of left-handed helix.

Stretching of LV wall in early systole has been reported previously (3). Pre-ejection stretch may be observed in the late activated region of the subendocardium, particularly near the posterior and lateral segments of the LV base (Fig. 2). However, the components of simultaneous shortening and stretch at varying transmural depths of LV wall were previously unknown. The study by Ashikaga et al. (4) supports the impression that stretch of LV wall during IVC period represents a well-organized feature of the LV wall mechanics that differs from passive lengthening seen during the diastolic filling phases (3). Because of transmural tethering, shortening of the subendocardial fibers maintain tension over the subepicardial surface, forcing it to stretch only along the subepicardial fiber direction.

The LV Flow-Function Relationship

As illustrated by Ashikaga et al. (4) and others, LV geometric changes during IVC are not isometric. Arguably, distortion of the chamber geometry may have a rheological explanation, because movement of blood would occur as dictated by the law of conservation of mass (1). Interestingly, the net right- and left-handed helical fiber directions in LV face the inflow and outflow regions of the LV, respectively. Shortening of subendocardial fibers
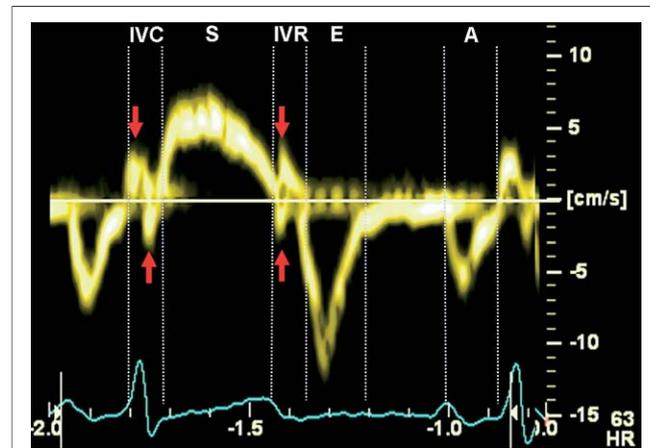

Figure 1. Pulsed Wave Tissue Doppler Velocities Recorded From the Septal Corner of the Mitral Valve Annulus

Note the biphasic tissue Doppler waveforms (**arrows**) during the isovolumic phases. A = late diastole; E = early diastole; IVC = isovolumic contraction; IVR = isovolumic relaxation; S = ejection phase.

and stretch of subepicardial fibers may accompany movement of blood flow from inflow region of the LV toward the outflow. Indeed, recent studies with the use of high-resolution contrast particle imaging velocimetry (Fig. 3A) have shown that, during pre-ejection, flow is redirected toward the LV outflow region, merging with a wake vortex in the submitral region (1). This assists both closure of mitral valve and efficient redirection of blood from inflow toward the LV outflow (Fig. 3B). Flow
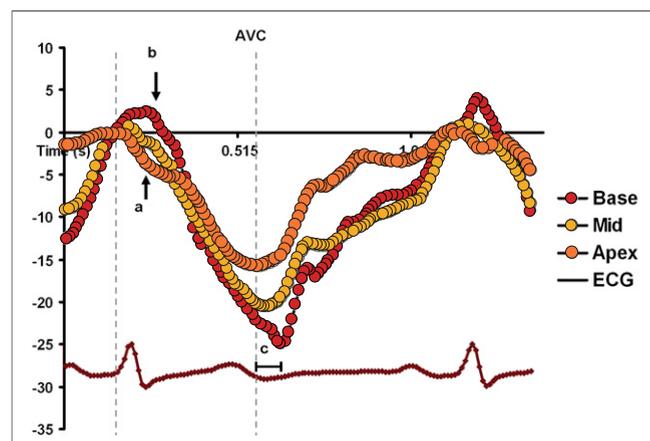

Figure 2. Left Ventricular Shortening and Stretch Kinematics in a Healthy Human Subject

Longitudinal strains from the segments of the left ventricular lateral wall have been measured by speckle tracking echocardiography. Shortening in the apical segment (**arrow, a**) is accompanied with stretch of the basal segment (**arrow, b**). Furthermore, shortening of basal segment beyond aortic valve closure (AVC) is associated with post-systolic shortening (interval, **c**). ECG = electrocardiogram.
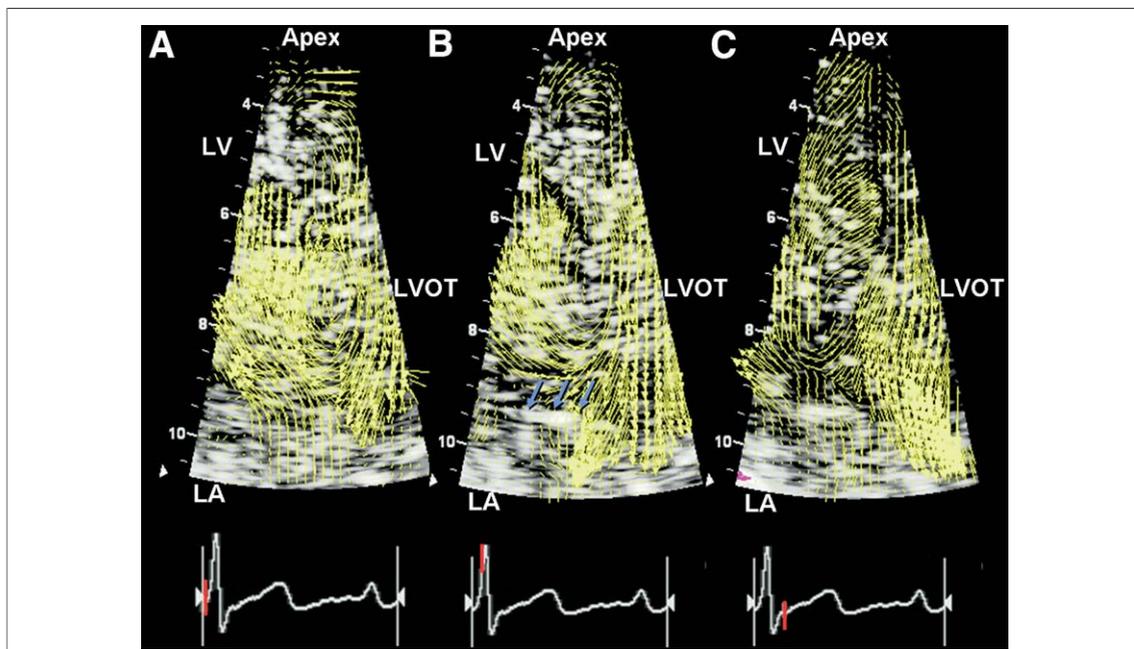
Figure 3. Left Ventricular Intracavitary Flow Sequence During the Pre-Ejection Period by Echo Contrast Particle Imaging Velocimetry

Blood flow is redirected from the left ventricular (LV) apex toward the base **(A)**. Redirected flow streams accentuate the submitral vortex ring and result in closure of the mitral valve leaflets **(arrows, B)**. Continued isovolumic acceleration of blood finally results into the onset of LV ejection **(C)**. LA = left atrium; LV = left ventricle; LVOT = left ventricular outflow tract.

acceleration does not cease with mitral valve closure (Fig. 3C). Rather, continued LV shortening and stretch during the period of isovolumic contraction ensures continued blood flow acceleration toward LV outflow for optimum onset of ejection.

Why Stretch in Pre-Ejection May Be Useful?

Stretching of the flight muscle in an insect allows the contractile features of the flight muscle to be matched to the wing-thorax-aerodynamic load; a role referred to as stretch activation (9). By using skinned myocardial preparations, it has been recently proposed that stretch activation plays an important role in mammalian hearts and provides an intrinsic regulatory mechanism by which cardiac myosin power is adjusted to match the variations in load (9). The exact contribution of stretch activation in vivo, however, remains unclear. Subepicardial stretch in the pre-ejection phase, as demonstrated by Ashikaga et al. (4), may explain some of the unique physiological characteristics of cardiac muscle shortening. For example, the direction of LV torsion is governed by the activity of subepicardial fibers. Stretching of subepicardium during IVC, along with differences in myosin heavy chain isoforms and calcium handling properties may underlie the ability of the subepicardial fibers in driving the global LV torsional deformation during ejection (10). These unique correlates of LV mechanics need more in-depth analysis in future investigations.

Delayed longitudinal shortening of LV segments beyond aortic valve closure is seen physiologically, particularly near the LV base (Fig. 2) and has been previously referred to as post-systolic shortening (10). Interestingly, stretch-activation response in skinned myocardial preparation also results in the development of a delayed tension (9). Thus post-systolic subendocardial shortening observed in vivo and the features of stretch activation described in vitro have close resemblance. The presence of regional shortening-lengthening gradients seen at the onset of isovolumic relaxation may facilitate rapid LV untwisting and global diastolic restoration (Fig. 2). With a little imagination, one can picture how the electromechanical activation sequence and the stretch in early systole may potentially provide a dynamic blueprint for beat-to-beat modulation of myocardial shortening-lengthening cross-over cycles.

Future Directions

Altered kinetics of the pre-ejection shortening and stretch may adversely impact LV function as the

result of premature or late stretch activation. For example, abnormal dispersion of electrical activation would disrupt regional and transmural stretch mechanics, resulting in global LV dyssynchrony and systolic dysfunction. Similarly, redistribution of stretch activity to regions that normally do not experience stretch during IVC may lead to prolonged LV regional shortening, delaying the onset of relaxation and causing diastolic dysfunction. Optimization of electromechanical activity and improvement in IVC shortening-stretch mechanics may therefore equally influence the global LV systolic and diastolic performance and explain the benefits of cardiac resynchronization therapy. Interestingly, the results from the PROSPECT (Predictors of Response to Cardiac Resynchronization Therapy) trial highlighted the limitations of ejection-phase indexes in characterizing cardiac dyssynchrony in patients undergoing cardiac resynchronization therapy (11). Imaging LV shortening-stretch kinematics during IVC, rather than ejection phase, may therefore impact future algorithms in assessing the effects of cardiac resynchronization therapy.

In summary, the study of Ashikaga et al. (4) provides key insights linking the layer-dependent myofiber mechanics during IVC with the established sequences of LV longitudinal, circumferential, and rotational deformation observed in vivo. This understanding is crucial for deciphering the IVC waveforms and the mechanical sequences observed with the use of cross-sectional imaging techniques. The striking similarities between stretch activation pathway described in skinned myocardial preparations and the IVC shortening-stretch activity recorded in vivo begs further correlation in health and disease. Linking such observations from bench to bedside will support the growing application of noninvasive cardiac imaging techniques in exploring unique mechanisms underlying the suction and ejection performance of a beating heart.

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REFERENCES

1. Sengupta PP, Khandheria BK, Korinek J, et al. Left ventricular isovolumic flow sequence during sinus and paced rhythms: new insights from use of high-resolution Doppler and ultrasonic digital particle imaging velocimetry. J Am Coll Cardiol 2007;49:899–908.
2. Sengupta PP, Khandheria BK, Korinek J, Wang J, Belohlavek M. Biphasic tissue Doppler waveforms during isovolumic phases are associated with asynchronous deformation of subendocardial and subepicardial layers. J Appl Physiol 2005;99:1104–11.
3. Coppola BA, Covell JW, McCulloch AD, Omens JH. Asynchrony of ventricular activation affects magnitude and timing of fiber stretch in late-activated regions of the canine heart. Am J Physiol Heart Circ Physiol 2007;293:H754–61.
4. Ashikaga H, van der Spoel TIG, Coppola BA, Omens JH. Transmural myocardial mechanics during isovolumic contraction. J Am Coll Cardiol Img 2009;2:202–11.
5. Manner J. On rotation, torsion, lateralization, and handedness of the embryonic heart loop: new insights from a simulation model for the heart loop of chick embryos. Anat Rec A Discov Mol Cell Evol Biol 2004;278:481–92.
6. Durrer D, van Dam RT, Freud GE, Janse MJ, Meijler FL, Arzbaecher RC. Total excitation of the isolated human heart. Circulation 1970;41:899–912.
7. Sengupta PP, Tondato F, Khandheria BK, Belohlavek M, Jahangir A. Electromechanical activation sequence in normal heart. Heart Fail Clin 2008;4:303–14.
8. Remme EW, Lyseggen E, Helle-Valle T, et al. Mechanisms of preejection and postejection velocity spikes in left ventricular myocardium: interaction between wall deformation and valve events. Circulation 2008;118:373–80.
9. Campbell KB, Chandra M. Functions of stretch activation in heart muscle. J Gen Physiol 2006;127:89–94.
10. Sengupta PP, Korinek J, Belohlavek M, et al. Left ventricular structure and function: basic science for cardiac imaging. J Am Coll Cardiol 2006;48:1988–2001.
11. Chung ES, Leon AR, Tavazzi L, et al. Results of the Predictors of Response to CRT (PROSPECT) trial. Circulation 2008;117:2608–16.

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