Although cardiac resynchronization therapy (CRT) has become a mainstay of therapy for systolic heart failure refractory to medical management for over a decade, more than 30% of CRT recipients do not respond clinically to the intervention. Ideally, cardiologists should be able to predict those who might not respond to CRT in advance and withhold these costly devices in likely nonresponders. However, because of conflicting results and difficulties in mapping the 3-dimensional sequence of left ventricular (LV) electromechanical activation, an effective approach to quantifying dyssynchrony is yet to be established.

The normal electromechanical activation sequence of the LV develops from a close interaction of the specialized conduction system with the myocyte architecture. Nearly the entire LV endocardial layer is directly activated within approximately 40 ms by Purkinje cells (Fig. 1) (1). The epicardial layer, which is void of Purkinje cells, experiences delayed activation through cell-to-cell propagation of electrical activity. Recently, Ramanathan et al. (2) noninvasively studied the normal epicardial activation sequence in intact healthy adults. The endocardial-to-epicardial activation of the LV free wall occurred with a breakthrough seen first over the LV apex. Subsequent apex-to-base spread of activation was associated with the latest activation occurring in the LV posterolateral basal region.

The timing of mechanical activation follows the electrical sequence, but the transmural speed of myofiber shortening (0.25 m/s) lags the speed of electrical conduction (0.49 m/s) (3). This delay is related to the development of a transient stretch in the late-activated epicardial regions of the left ventricle. This stretch of the late-activated regions of the left ventricle is due to shortening of early-activated regions and a steep rise in LV pressure in the absence of a change in LV volume during isovolumic contraction. This stretch (of up to 10%) of the late depolarized myofibers (which also accounts for transient clockwise rotation of the apex during isovolumic contraction) is helpful in generating more shortening during ejection (with subsequent counterclockwise rotation of the apex during ejection). The pre-ejection stretch increases the sarcomeric length in subepicardial myofibers and enhances shortening strains per the Frank-Starling mechanism (4,5). The reciprocal shortening and stretching of the LV wall also alters the LV geometry, which helps preferential streaming of blood flow toward the LV outflow (5).

The specific patterns of delay in LV activation in cardiomyopathic patients who benefit from CRT may also be better understood by considering the sequence of electromechanical coupling and the overall effects on the timing of LV contraction and blood flow. First, electrical activation delays that result from a transmural pattern of block (particularly from the left bundle) may be more amenable to CRT. Recent observations in the Multicenter Automatic Defibrillator Implantation Trial With Cardiac Resynchronization Therapy study suggest that the benefit of CRT in patients with class I and II heart failure was confined to those who had classic complete left bundle branch block (LBBB), whereas those with a non-LBBB configuration did not derive as much benefit (6). Thus, there has been an increase in the importance of separating LBBB from diffuse intraventricular conduction disturbances. Auricchio et al. (7) used 3-dimensional mapping systems to study the sequence of LV activation in patients with heart failure with LBBB QRS configuration during intrinsic rhythm (as also during asynchronous pacing). They demonstrated a U-shaped conduction pattern in the activation sequence of the left ventricle in patients with LBBB. Noncontact mapping showed that the activation wave front could not cross directly to the lateral wall from the anterior region. Instead, this wave front reached the lateral or posterolateral regions by propagating from the site of earliest septal LV breakthrough, inferiorly around the apex and across the inferior wall (Fig. 1). This
U-shaped block, however, was altered on asynchronous pacing. Moreover, the presence of near normal amplitude on unipolar and bipolar electrocardiography excluded the presence of scar tissue, and the presence of fractionated electrocardiographic results suggested that the block was functional and resulted from the nonuniform conduction within the transmural layers of the myocardium.

Interestingly, the study by Sohal et al. (8) in this issue of *JACC* also revealed the presence of a U-shaped mechanical activation block between the septum and lateral wall, and this pattern of block was commonly associated with response to CRT. Just as the transmural electrical activation delay manifests on the surface as a U-shaped block, the observations regarding mechanical activation delay between the septum and the lateral wall may only signify a disruption of LV mechanics between the transmural layers. Normal radial LV wall thickening during ejection requires mechanical interaction of both the early-activated subendocardial and the late-activated subepicardial regions. Activity of both regions needs to be developed in concert for optimal wall thickening; the subendocardial myofibers must further thicken and slide inward, and this inward slippage (shearing) accounts for the larger radial thickening strains (>40%) and segmental volume change (>60%) despite relatively small myocyte contraction developed within the layers (about 15%). Thus, the identification of transmural functional block rather than segmental or regional blocks may better identify patients likely to benefit from CRT.

Transmural mechanical activation delay may also impair diastolic function, because LV systolic and diastolic performances are closely coupled. In normal subjects, the untwisting and recoil of the LV wall in early diastole releases elastic energy stored by the preceding systolic deformation. This creates early diastolic suction with the formation of a vortex ring at the mitral valve tip (9). The vortex rings store part of the kinetic energy of the entering flow into its rotary motion and help redirect the flow toward the outflow tract. A recent study showed that deactivation of CRT results in a delayed onset of LV filling in early diastole, with a delayed onset of blood flow vortex formation (10). A weaker early diastolic vortex further restricted the energy transfer from diastole to systole, impeding the timely onset of LV ejection. Thus, the normal sequence of electromechanical activation can also be valued in synchronizing an optimal transfer of kinetic energy from diastole to systole.

In summary, there are different hierarchical domains for considering the patterns of disruption of cardiac activation and the potential benefits of CRT. We urge investigators to provide a better mechanistic understanding, such that the seemingly complex events in cardiac electrical, muscle, and flow mechanics observed during ventricular dysynchrony are simplified. Identifying potential responders to CRT is an extremely important and vexing question in the present-day care of patients with heart failure and an important piece of the puzzle, which will be solved only by addressing the cascade of activation-contraction-flow sequences.

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