Ventricular Resynchronization: Pathophysiology and Identification of Responders

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Patients with dilated cardiomyopathy and discoordinate wall motion due to intraventricular conduction delay are at increased risk for exacerbated pump failure and arrhythmias and suffer higher mortality rates. Biventricular and left ventricular resynchronization pacing therapies acutely improve systolic ventricular function and energetic efficiency in patients with heart failure and left-bundle–type intraventricular conduction delay. Sustained therapy can further inhibit or reverse chronic chamber dilation and remodeling. As with all therapies for heart failure, individual subject responses are variable; however, the invasive nature and expense of resynchronization therapy has particularly highlighted the need to prospectively identify optimal candidates. Although QRS duration has been principally used to date, increasing evidence shows this to have poor acute and chronic correlations with patient response. In contrast, direct measures of mechanical dyssynchrony based on simple echo imaging and more complex tissue Doppler and magnetic resonance imaging–based approaches appear to afford better predictive accuracy.
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Dilated cardiomyopathy is the consequence of abnormalities in cardiac muscle contraction coupled with pathophysiologic volume and arterial loading and potent activation of the neuroendocrine system. In addition to these changes, abnormal electrical conduction can develop that delays the timing of atrial contraction and generates discoordinate contraction of the left ventricle. The latter is typically observed in persons with a widened QRS complex and intraventricular conduction delay, left bundle pattern being most common. Studies have shown that such conduction delay is an independent

risk factor for dilated cardiomyopathy morbidity and mortality.[1–4] In a recent analysis of more than 5000 patients, the presence of left bundle-branch (LBB) block was associated with a 60%–70% higher risk of all-cause mortality and sudden death and was an independent risk factor after adjusting for age, underlying cardiac disease, the severity of heart failure, and concomitant drug therapies.[5] As detailed in the next section, the unilateral loss of normal His-Purkinje conduction results in the separation of the cardiac chamber into effectively two regions, early- versus late-activated, with the net consequence being compromise of systolic function and reduced chamber energetic inefficiency.

Over the past decade, investigators have established that ventricular stimulation of both the right and left ventricle (biventricular pacing) or even the left ventricular free wall alone can improve the mechanics and energetics of the failing heart with discoordinate contraction. This work has been fully highlighted in several recent reviews (eg, Leclercq and Kass,[6] Trautmann and colleagues,[7] and Abraham[8]). Chronic studies have confirmed enhancement of clinical symptoms, increased exercise capacity, and cessation or reversal of chronic chamber remodeling.[9–12] However, as with all therapies for heart failure, individual patient response to cardiac resynchronization therapy (CRT) varies, with most series reporting an approximate 20%–30% nonresponder rate. Given the complexity of the instrumentation, the need for device implantation, and the medical costs associated with the treatment, investigators are seeking markers that can best prospectively identify the patients who are most likely to respond. This review summarizes our understanding of the pathophysiology of dyssynchronous cardiac contraction, the mechanisms for benefit from resynchronization pacing, and current thinking regarding how to best identify responders.

Pathophysiology of Abnormal Electrical Conduction

To understand factors associated with the clinical efficacy of CRT, it is important to review the primary pathophysiology of altered electrical conduction. The normal cardiac conduction system modulates contraction rate, the mechanical efficacy of atrial systole, and contractile coordination of ventricular chambers. Disease of any one of these components can lead to suboptimal cardiac performance.

Sinus node disease results in chronotropic incompetence that can prove problematic in persons with little preload or contractile reserve. This has become more problematic with the increasing use of adrenergic blockade in heart failure, which can lead to too slow a rate and/or rate response in a heart with limited Frank-Starling reserve. Most commonly, this is treated with a dual-chamber, rate-responsive pacemaker. However, as discussed below, pacing the ventricle itself induces dyssynchrony of contraction and can exacerbate underlying chamber dysfunction.

Ventricular nodal disease delays atrial contraction relative to onset of systole, rendering atrial systole synchronous with early passive filling and effectively removing its value as a booster pump.[13,14] Optimal atrial-ventricular (AV) delay is important to mitral valve competence, as too much delay leaves the mitral leaflets open in the mid-plane position when ventricular systole starts. Closure of the value in this instance is entirely dependent on the developing pressure in the ventricle, and while this is occurring, presystolic mitral regurgitation is more likely. Long AV delays (often 250 msec or longer) also effectively shorten the diastolic filling period, limiting net filling.[15] In persons with this type of conduction abnormality, electronic stimulation with a shortened AV delay time can prove beneficial.

Infranodal conduction delay—most commonly in an LBB pattern—induces discoordinate left ventricular contraction.[16,17] Dilated cardiomyopathy hearts with an LBB-type conduction delay display early activation of the septal wall, typically associated with lateral wall pre-stretch. This is followed by delayed lateral contraction at higher stress and further systolic stretch of the early-activated septum. The septal motion has been termed *paradoxic*, in the sense that it appears to behave as if ischemic despite the absence of such underlying pathophysiology. However, it is not paradoxic, but simply the consequence of a balancing of forces—with the septal myocardium less able to withstand the stresses developed later in systole by the late-activated left ventricle free wall and, therefore, being pushed toward the right heart.

Infranodal conduction abnormalities result in loss of normal coordinated contraction of the ventricles. As summarized in Table 1, this can have protean effects on chamber function that worsen underlying systolic and diastolic performance and increase energy requirements. Prior studies, many performed 15–20 years ago, have revealed the hemodynamic detriments from inhomogeneous temporal activation in the normal heart.[18–20] Figure 1 displays the net effect on early- versus late-activated myocardial stress and strain loops. This type of display (analogous to pressure–volume loops)

shows the simultaneous development of muscle force and deformation during the cardiac cycle. The early-activated territory shortens at low stress (Figure 1A[a]), effectively pre-stretching the opposite territory (Figure 1A[b]). As systole progresses, the late-activated region develops higher load, stretching the early-activated region [c] to limit further shortening in that territory. The net result of this reciprocal *sloshing* of blood from early- to late- to early-activated regions is a decline in ejection and depressed systolic chamber function. This is manifest by a rightward shift of a set of pressure-volume relations (Figure 1B, solid to dashed line) and narrowing of the global pressure-volume loop (ie, stroke volume is reduced), with a rightward shift of the end-systolic pressure-volume point (ie, higher end-systolic stress).[19]

Late-systolic septal stretch worsens function for several reasons. First, it effectively acts as an intracavitary sink for blood volume that would otherwise be ejected, reducing forward output. Second, the late stretch of the contracting muscle can break cross-bridges, diminishing systolic force development, and result in repolarization inhomogeneity and stretch-activated channel stimulation to trigger arrhythmia.[21–23] Inhomogeneous contraction is also a mechanism for delaying muscle relaxation and likely contributes to diastolic dysfunction.[24–27]

There are also important regional and global metabolic/energetic consequences that develop from dyssynchrony. The prematurely activated myocardium develops less overall work (loop area in Figure 1A), consuming less energy.[16,28] The energy it does consume, however, is largely wasted with respect to ejection, because pressure remains low. In fact, recent data suggest that much

Table 1
Mechanisms of Dysfunction Due to Contractile Discoordination

- Reduced ejection volume
  - ❍ Internal *sloshing* from early-activated region to late-activated one
  - ❍ Increased end-systolic volume (stress)
- Mechano-energetic inefficiency
  - ❍ Reduced systolic function despite maintained or increased energetic cost
- Late systolic stretch
  - ❍ Cross-bridge detachment, reduced force
  - ❍ Delayed relaxation
  - ❍ After-contractions/arrhythmias
- Mitral valve dysfunction
  - ❍ Papillary muscle discoordination

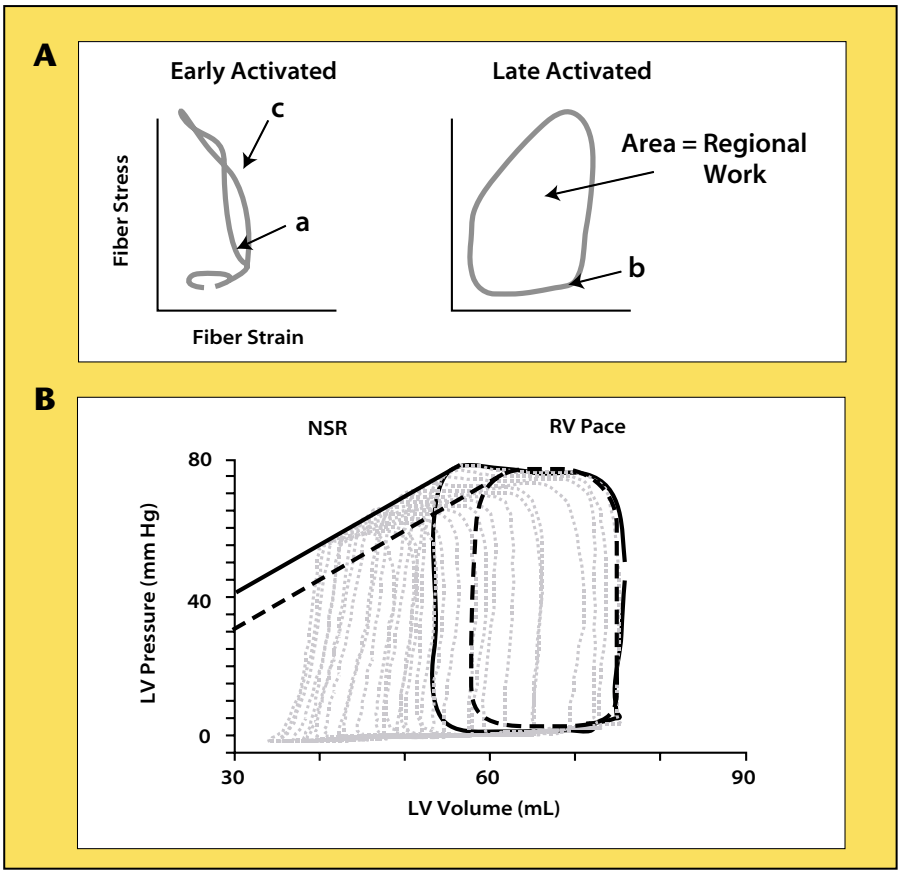

Figure 1. (A) *Stress-strain loops from early- and late-activated territory. In the early stimulated region, there is initial shortening at low stress levels (a), as this motion is principally converted to pre-stretch of the still inactive muscle. Stress then develops, but the region is pushed on by the later-activated myocardium and can stretch toward the right heart (c). The net loop is thin (small area), indicative of reduced regional work. The later-activated territory initiates stress development from a higher pre-stretch (b, increased preload), and the work loop is enlarged, compared with normal.* **(B)** *Pressure-volume loops and relations in synchronous and acutely dyssynchronous heart. With right ventricular (RV) pacing to induce delayed lateral contraction, there is a right shift of the pressure-volume loop, with reduced width (stroke volume) and area, and an increase in end-systolic pressure-volume point. The end-systolic pressure-volume relation shifts rightward. LV, left ventricular.*

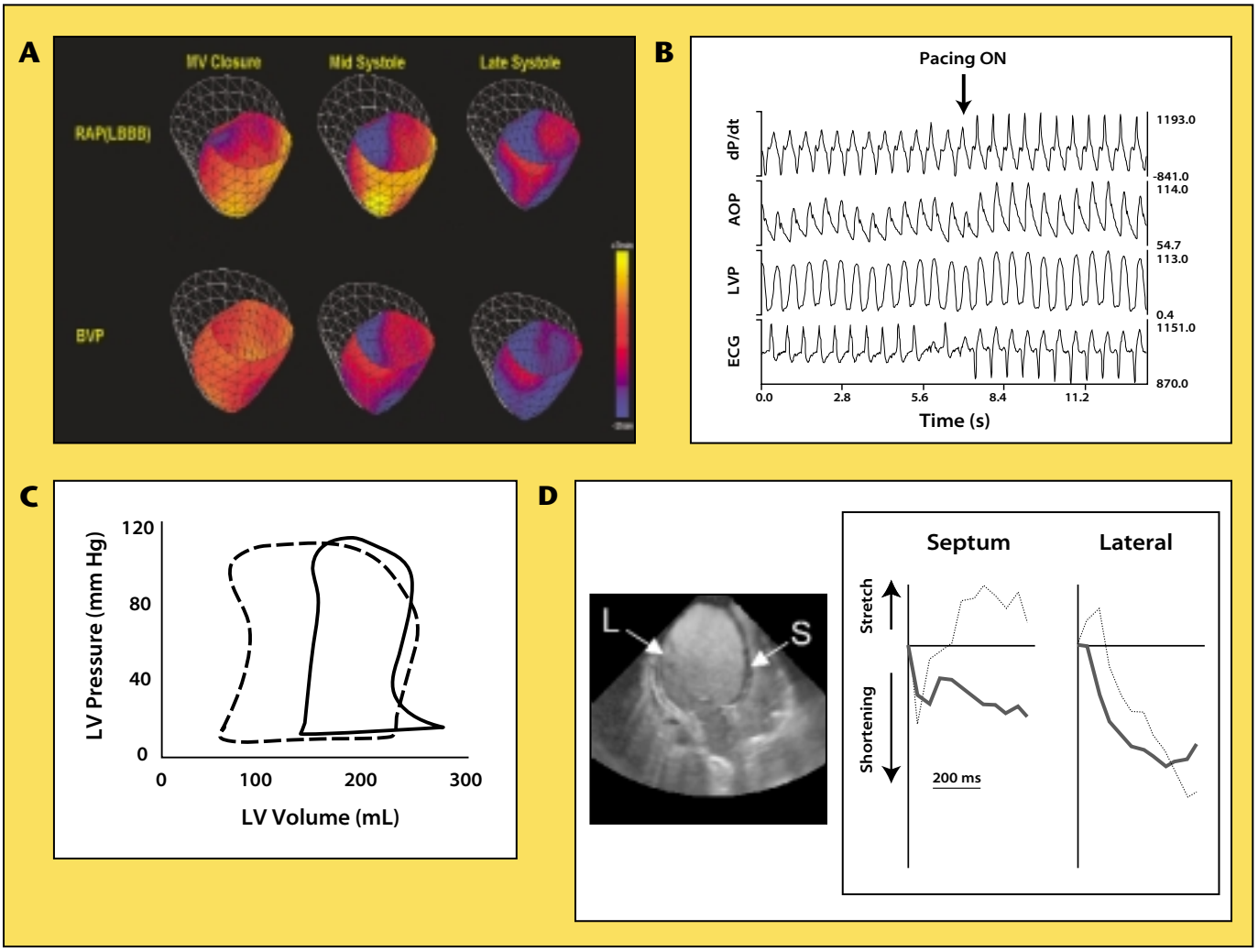

Figure 2. (A) *Tagged magnetic resonance imaging shortening maps of left ventricle with underlying left bundle-branch block (LBB) and cardiac failure (top panels) and the same heart paced using a biventricular stimulator (lower panels). Color coding shows shortening (blue) and stretch (yellow); red is neutral. Reprinted with permission from Leclercq and colleagues.*[37] **(B)** *Acute hemodynamic response in human ventricle with LBB-conduction delay before and after cardiac resynchronization therapy (CRT) pacing. There is an abrupt rise in pressure development and rate of development, and an increase in the arterial pulse pressure indicative of enhanced cardiac output.* **(C)** *Similar data displayed as pressure–volume loops. CRT induces a left shift of the loop, increasing the width and area, and reducing end-systolic volumes.* **(D)** *Regional wall motion improved by CRT. With pacing off, radial septal motion is initially inward but then shifts toward the right ventricle as the lateral wall contracts (so called* paradoxic *motion). CRT converts this to a more consistent inward motion. In the lateral wall, there is initial stretch followed by delayed contraction. CRT influences the phase but not amplitude of motion, stimulating contraction earlier. RAP, right aortic pressure; MV, mitral valve; BVP, biventricular pacing; dP/dt, rate of pressure rise; AOP, aortic pressure; LVP, left ventricular pressure; ECG, electrocardiogram; LV, left ventricular; L, lateral; S, septum.*

of the early septal motion in the typical LBB-pattern conduction delay occurs prior to closure of the mitral valve (*presystolic* shortening)—blurring the definitions of end-diastole and early systole. The late-activated free wall, in contrast, operates under a higher load (larger loop area, Figure 1A), with higher metabolic demand. It too wastes work in stretching the more compliant early-activated territory rather than contributing to ejection, so the net effect is a reduction in chamber efficiency.[28–30]

Increased loading in the lateral wall is also accompanied by amplified molecular abnormalities. Using a canine model of heart failure with dyssynchronous contraction, we have found marked reductions in expression of gap junction proteins (connexin 43) and excitation-contraction coupling proteins (SERCA2a and phospholamban), as well as increased stress kinase expression/activation in the late-activated (high-load) lateral endocardium. This is not observed in myocardium that is failing but contracts synchronously.[31]

Acute/Chronic Hemodynamic Effects of Biventricular (or Left Ventricular Free Wall) Pacing

Biventricular pacing or univentricular pacing of the left ventricular lateral free wall can re-coordinate contraction, and both are associated with systolic improvement.[32–36] An example of resynchronization from biventricular stimulation is shown in Figure 2A. These panels display tagged magnetic resonance reconstructions of a failing heart with LBB block before (upper) and after (lower) biventricular stimulation. Early activation (blue) is on the right, and slowly spreads leftward, with evidence of reciprocal stretch (yellow). With biventricular stimulation, shortening is initiated on both sides of the heart more simultaneously, and there is minimal reciprocal stretch. Net ejection is enhanced. Globally, the effect of resynchronization is immediate, as shown in Figure 2B. Hemodynamic parameters, such as the maximal rate of pressure rise (dP/dt_{max}) or arterial pulse pressure, are improved within one beat after initiating pacing, the latter reflecting a rise in cardiac output.[35] From a pressure-volume loop perspective, the effect is the reverse of that shown in Figure 1B. There is a leftward shift of the loop with CRT, lowering the end-systolic wall stress, increasing stroke work and stroke volume and, thus, enhancing systolic performance. Diastolic properties appear little altered, at least acutely.

Recent advances in echo-Doppler imaging methods have provided direct evidence of wall motion resynchronization in persons receiving CRT.[38–40] Figure 2D displays one approach that provides radial displacement tracings for the septal and lateral wall, employing a contrast-echo method.[40] With pacing suspended (native LBB delay), the early inward septal motion followed by rightward displacement is observed. This is converted to more consistent inward motion by biventricular (or left ventricular–only) pacing. In the lateral wall, early stretch is followed by late lateral inward motion under basal conditions. When pacing is initiated, the major effect is to shift the phase of lateral contraction earlier but not to enhance its magnitude.

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Chronic noninvasive studies have reported systolic responses of similar magnitude.[38] For example, dP/dt_{max} acutely increases from 600 mm Hg/s to nearly 800 mm Hg/s. As shown in Figure 3A, similar results are observed 1–12 weeks after chronic CRT. Although acute reduction in end-systolic volume is also observed (ie, Figure 2C), more chronic therapy has been required to observe what most would term reverse remodeling. As demonstrated by Yu and colleagues,[38] after 1 month or more of pacing, both end-systolic and end-diastolic chamber volumes decline (Figure 3B). What was particularly notable in this study was that, when pacing was transiently suspended after 3 months of CRT, there was no change in these volumes, despite an acute reversal of cardiac systolic benefit (ie, dP/dt_{max} declined back toward baseline). This supports a true remodeling effect. When pacing was kept off for the ensuing month, there was evidence of further reversal of the systolic benefits—but also re-initiation of chronic chamber dilation/remodeling. Larger chronic and, importantly, blinded/controlled studies have also reported significant, if not quite as impressive, remodeling effects.[10,12]

In addition to improving function and reversing chamber remodeling, CRT benefits chamber mechanoenergetics. As first reported by Nelson and colleagues,[41] increasing systolic function by CRT is associated with a net decline in myocardial oxygen consumption. More recently, investigators have used positron emission tomography scanning to assess regional metabolism in septal and lateral walls.[42] Net oxidative metabolism was unaltered in this study, although there was an increase in metabolism in the septum consistent with retiming effects that would limit early unloaded shortening. Importantly, when CRT is contrasted with a traditional inotrope, such as dobutamine, the disparity in mechanoenergetics is even more striking (Figure 3C). Whereas CRT enhances systolic function while lowering global myocardial energy demand, the opposite is true of traditional agents that act to increase calcium availability via a cyclic adenosine monophosphate/protein kinase A phosphorylation cascade.

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Although the primary focus has been on biventricular stimulation,

laboratories have shown a similar acute and chronic efficacy with single-site left ventricular free wall pacing alone.[34,35,43] Careful assessment of global function and regional wall motion found similar benefits from both pacing modes, despite large disparities in electric activation pattern and time delay.[37] This suggests that electrical synchrony is not tantamount to mechanical synchrony and, importantly, that the latter is more relevant to a hemodynamic benefit from CRT. This is addressed more fully in the subsequent discussion of how to identify responders. Questions regarding the chronic utility of left ventricular–only pacing are likely to remain, as the large-population clinical trial data have all been based on biventricular pacing.

The magnitude of systolic benefit depends in part on the AV timing delay selected.[34,35] Clearly, when atrial and ventricular activation are synchronous, there is a detrimental effect on chamber filling and increased atrial pressures. Increasing the delay time enhances AV mass transfer while still maintaining pre-excitation of the portion of the myocardium with delayed activation. Too long a delay, however, reduces the efficacy of pacing as pre-excitation is lost. The net magnitude of this effect, however, is not large. This is shown in data from a study by Auricchio and coworkers,[34] in which AV delay was varied broadly and in a highly controlled manner (Figure 4A). Although the relation between percent improved dP/dt_{max} and AV delay displays an optimum, falling off at either extreme, there is a broad mid-region (shaded) in which the precise delay makes little difference. Studies have found that

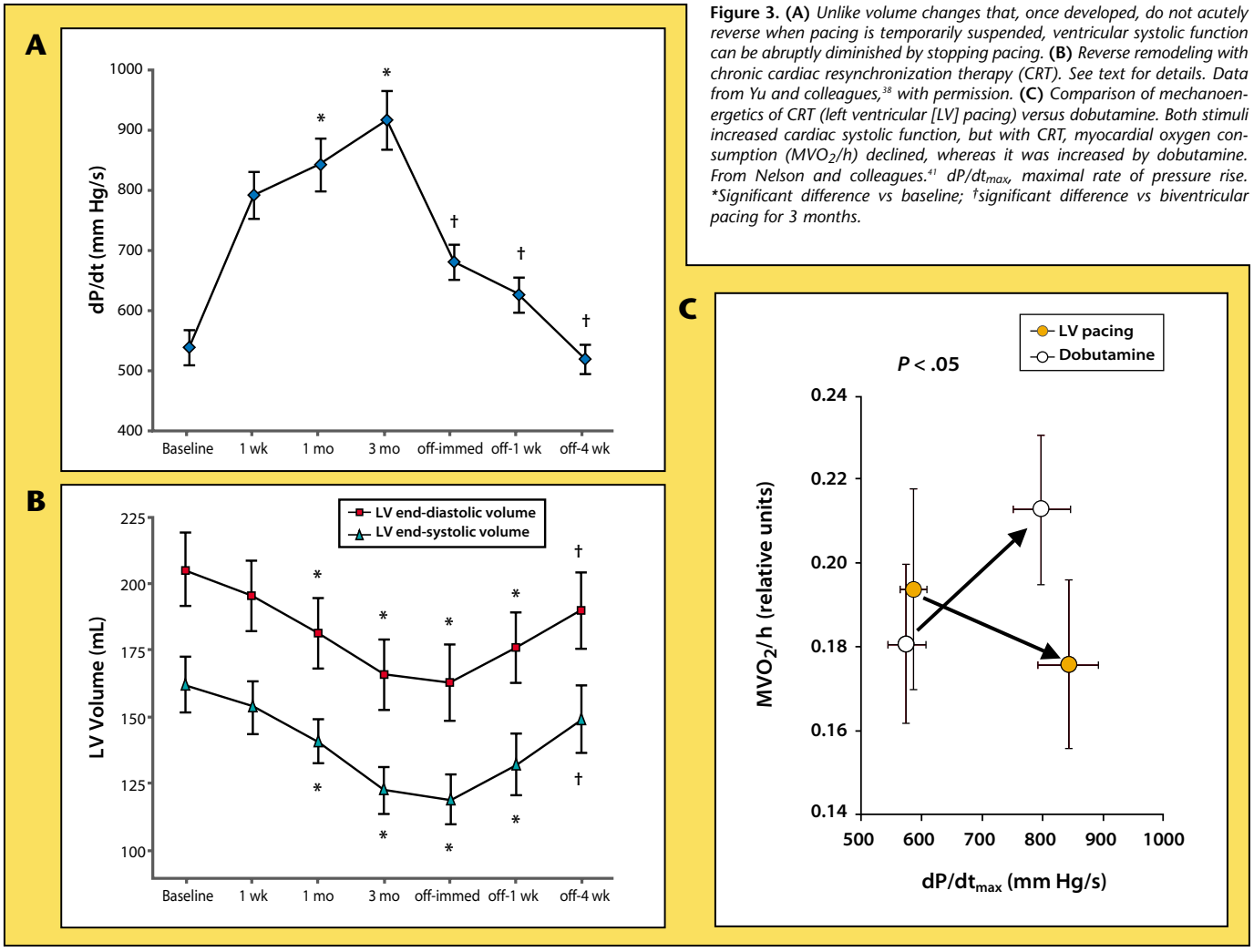

Figure 3. (A) *Unlike volume changes that, once developed, do not acutely reverse when pacing is temporarily suspended, ventricular systolic function can be abruptly diminished by stopping pacing.* **(B)** *Reverse remodeling with chronic cardiac resynchronization therapy (CRT). See text for details. Data from Yu and colleagues,[38] with permission.* **(C)** *Comparison of mechanoenergetics of CRT (left ventricular [LV] pacing) versus dobutamine. Both stimuli increased cardiac systolic function, but with CRT, myocardial oxygen consumption (MVO_2/h) declined, whereas it was increased by dobutamine. From Nelson and colleagues.[41] dP/dt_{max}, maximal rate of pressure rise. *Significant difference vs baseline; †significant difference vs biventricular pacing for 3 months.*

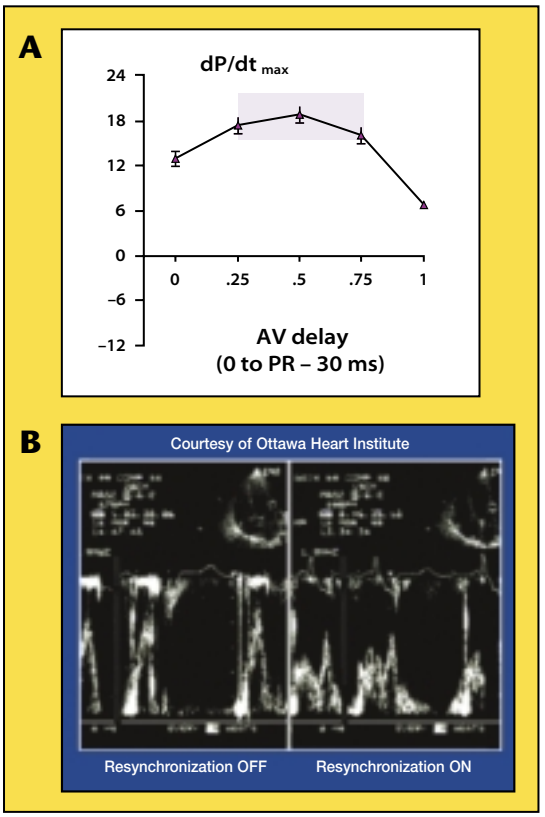

Figure 4. (A) *Influence of atrial-ventricular (AV) interval optimization on systolic response to cardiac resynchronization therapy (CRT). The x-axis shows a normalized AV delay, where 0 represents simultaneous AV stimulation and 1 represents an individual patient's PR interval shortened by 30 ms. There is diminished efficacy at very short or long AV delays, but also a fairly flat maximal response over a broad range of delays in the middle (shaded area). This suggests that AV delay is not a critical parameter, so long as a reasonable (typically in the physiologic range 110 to 140 ms) delay is used. Reproduced with permission from Auricchio et al.*[34] **(B)** *Example of mitral inflow Doppler filling in patient with CRT off (left) and on (right). At baseline there is only an early filling wave with fast E-wave deceleration. With CRT, this is converted to an E and A wave. dP/dt_{max}, maximal rate of pressure rise.*

mechanical responses are similar over a fairly broad range of AV timing intervals (typically ranging from 100 ms to 140 ms). In persons with a very long basal AV delay, shortening the delay can improve the dynamics of filling. This is shown in the Doppler tracings in Figure 4B. With CRT inactive (left), there is a single filling wave (E wave), whereas with CRT activated and shortening of the AV delay (right), there are more clear early (E) and late (A) waves, the normal filling pattern.

Criteria for Identifying Responders

Table 2 summarizes various factors that influence the responsiveness of patients to CRT and/or are used to identify candidates. The most widely used marker to identify patients with cardiac dyssynchrony has been a widened QRS complex on the surface electrocardiogram. To date, all clinical trials have entered subjects based on the presence of systolic dysfunction with dilated cardiomyopathy and a widened QRS duration. The precise amount of QRS widening used for entry has varied from > 120 ms to > 150 ms. The notion that QRS duration should index dyssynchrony seemed logical, in that substantial left ventricular conduction delay should result in widening, in concordance with experimental data.[18] Indeed, many studies have shown that the wider the basal QRS duration, the greater the systolic improvement from biventricular or left ventricular pacing. Figure 5A shows data from two such populations.[34,36] However, the dependence of QRS duration to even this acute mechanical response displays considerable scatter, so that both responsive patients with narrow complexes and less responsive patients with wide complexes exist.

Table 2
Can We Predict Responders?

- QRS complex
- Interventricular dyssynchrony
- Intraventricular dyssynchrony
- Successful lead placement
- Adequate pre-excitation
- Physiologic atrial-ventricular delay

Figure 5B provides further evidence for this correlative and indirect nature of basal QRS width versus response to resynchronization. Despite substantial systolic improvement with left ventricular or biventricular pacing, QRS duration does not consistently narrow, with many subjects displaying no change or even widening of the duration.[36] This may reflect the fact that one is still relying on intramyocardial conduction, and abnormal wall geometry (dilation) as well as gap–junction and ion channel abnormalities can slow this process further. These data highlight the notion that QRS duration is, at best, an indirect correlate but not a direct reflection of mechanical synchrony, which is the real substrate that causes a decline in chamber function.

Recent studies have begun examining the utility of QRS duration in predicting the chronic response to CRT. These data have generally confirmed acute results, showing a general correlation between basal QRS duration with efficacy,[44] but with a poor predictive value for identifying responders versus nonresponders.[45,46] For example, baseline New York Heart Association function class, age, sex, QRS duration, and ejection fraction were no different between responsive and nonresponsive patients in a recent study of 45 subjects.[47] In a larger cohort of 102 consecutive patients, both responders and non-

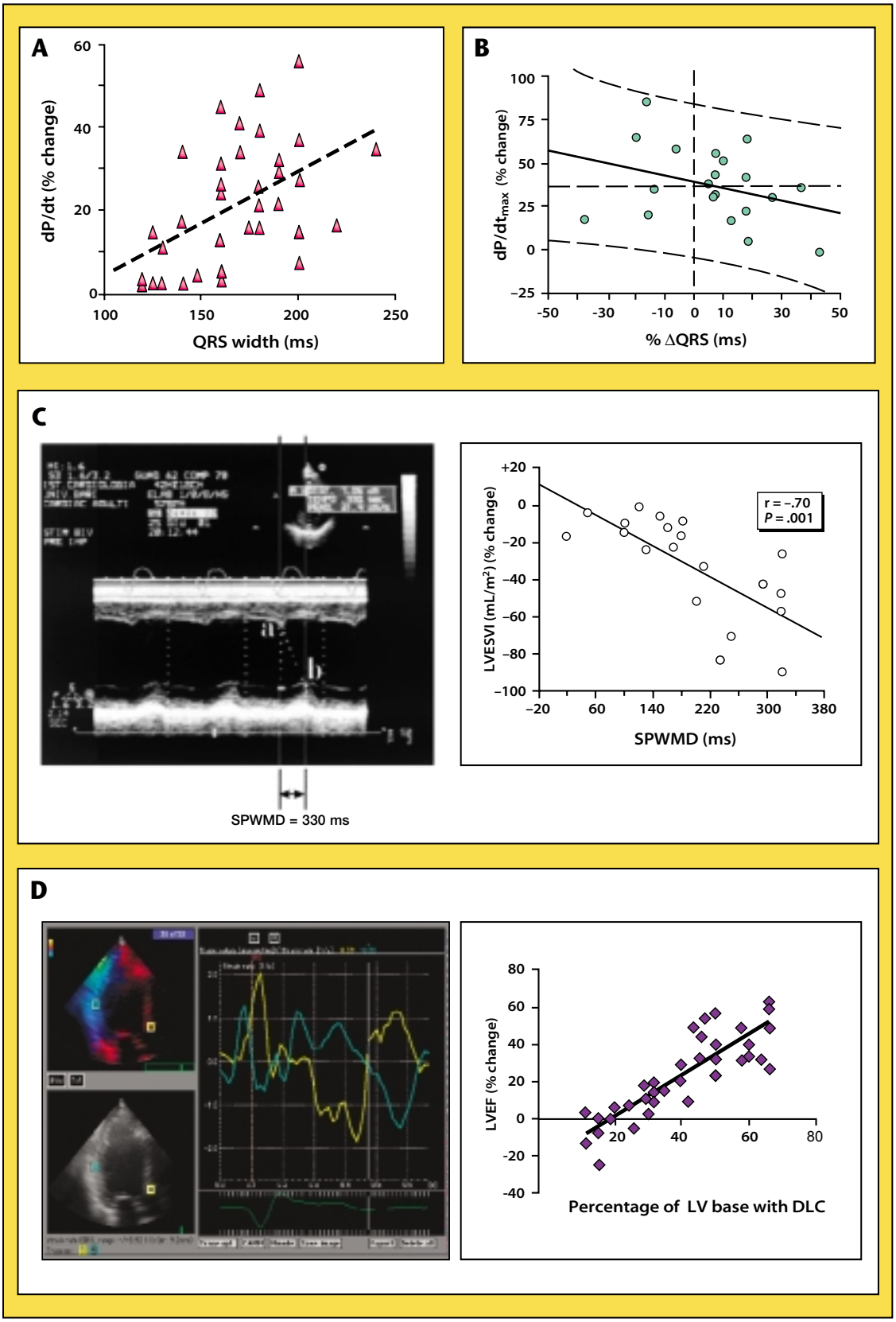

Figure 5. *Predicting responders to cardiac resynchronization therapy (CRT).* **(A)** *QRS duration correlates with the acute mechanical response, although there is considerable scatter in these data, raising questions as to its predictive value.* **(B)** *Correlation between QRS duration change from biventricular or left ventricular–only pacing and mechanical response. Although mechanical changes are substantial, there is no correlation between them and QRS duration change.* **(C)** *M-mode echo assessment of intraventricular dyssynchrony (left panel). The time of initial inward septal motion is identified, and the delay between this time and inferolateral motion assessed. This delay (SPWMD) is then plotted versus the chronic change in ventricular end-systolic volume (LVESVI) (right panel). There is a significant negative correlation, suggesting predictive value of SPWMD in identifying chronic response. From Pitzalis and colleagues,[45] with permission.* **(D)** *Tissue Doppler strain–rate analysis of dyssynchrony. Regional relative longitudinal velocities are determined in the left ventricle (LV), and the delay from septal to lateral wall identified. The percent of LV with delayed contraction (DLC) is determined from multiple samples, and correlates with chronic improvement in LV ejection fraction (LVEF) after CRT therapy. From Sogaard and colleagues,[39] with permission. dP/dt_{max}, maximal rate of pressure rise.*

responders had similar basal QRS duration and displayed near identical shortening of complex duration,[48] a finding mirrored by other recent reports.[49] Patients with reduced dP/dt_{max} that display > 22% acute improvement have been reported to be consistent responders (with few false negatives),[50] concordant with the acute observations of Nelson and colleagues.[36]

Mechanical Dyssynchrony as a Predictor

The use of QRS duration was generally recognized as a surrogate for mechanical discoordination, whose value resided in its clinical simplicity. However, as electrical markers have proved disappointing, recent studies have begun to quantify mechanical dyssynchrony directly and to test this as a prognostic index. Dyssynchrony was first comprehensively examined by means of tagged magnetic resonance imaging.[36] This approach provided full three-dimensional strain measurements throughout the left ventricle and allowed calculation of a variety of synchrony indexes from these maps. Recent animal studies employing this approach have further shown the dissociation that can exist between electrical delay times and mechanical dyssynchrony.[37] The latter appears increasingly to be the primary target for identifying responders and a good candidate parameter for monitoring efficacy.

Magnetic resonance imaging analysis is complex and has limited clinical use; thus, simpler echo-based methods have been developed. The simplest is M-mode imaging used to assess timing delays. Both an interventricular and intraventricular delay time can be assessed. This can be examined by plotting instantaneous right ventricular and left ventricular pressure tracings, but this requires collecting data invasively. It can also be determined from the delay between two time intervals: $T_2 - T_1$; with T_1 the time from QRS to the onset of pulmonary artery flow, and T_2 the QRS to aortic flow time. A delay of greater than 40 ms is considered compatible with significant dyssynchrony. Recent studies have raised questions as to the predictive utility of such an interventricular delay for defining responders and, instead, support analysis of intraventricular delay.[45,46]

Recent studies have begun to quantify mechanical dyssynchrony directly and to test this as a prognostic index.

Intraventricular delay is the mechanical dispersion of motion between septal and lateral walls. This can be assessed in various ways. Echocontrast imaging indexes regional inward wall motion, from which one can calculate a dissynchrony index.[40] M-mode echo imaging has been used to determine the delay between initial septal inward motion and inferolateral motion.[45] An example is shown in Figure 5C. Intriguingly, Pitzalis and colleagues[45] found that this delay time correlated

Main Points

- The normal cardiac conduction system modulates contraction rate, the mechanical efficacy of atrial systole, and contractile coordination of ventricular chambers; disease of each of these components can lead to suboptimal cardiac performance.
- In addition to improving function and reversing chamber remodeling, CRT benefits chamber mechanoenergetics.
- Ventricular nodal disease delays atrial contraction relative to onset of systole, rendering atrial systole synchronous with early passive filling and effectively removing its value as a booster pump. In persons with this type of conduction abnormality, electronic stimulation with a shortened AV delay time can prove beneficial.
- Infranodal conduction abnormalities result in loss of normal coordinated contraction of the ventricles; this can have protean effects on chamber function that worsen underlying systolic and diastolic performance and increase energy requirements.
- Over the past decade, investigators have established that ventricular stimulation of both the right and left ventricle (biventricular pacing) or even the left ventricular free wall alone can improve the mechanics and energetics of the failing heart with discoordinate contraction.
- Optimal identification of cardiac resynchronization therapy (CRT) candidates remains a high priority. Although initially focusing on electrical markers, recent data has highlighted the value of more direct assessment of mechanical discoordination by means of tissue Doppler, echo Doppler, or magnetic resonance imaging. Other factors that could play an important role in patient response to CRT are lead placement, atrial–ventricular delay time, and tissue viability.

with chronic improvement in left ventricular end-systolic volume (reverse remodeling) in patients receiving CRT. In contrast, there was little to no significant correlation with QRS duration. Other investigators have applied tissue Doppler imaging to assess absolute or relative wall velocities (the latter termed *strain* rate imaging) and thereby determine timing delays between opposing portions of the left ventricle. This imaging is commonly applied in long-axis views and thus quantifies longitudinal motion. An example of such analysis is shown in Figure 5D (from Sogaard and colleagues[50]). As with other measures of dyssynchrony, the delay lateral contraction parameter (DLC in figure) has been shown to correlate with chronic improvement in ejection fraction (Figure 5D, right panel) as well as with reduced cardiac volumes. These and other investigators are prospectively evaluating the utility of dyssynchrony measures for predicting responders to CRT. All existing chronic controlled trial data are based solely on QRS duration as an entry criterion and, yet, have demonstrated substantial improvements. However, the abovecited and ongoing trials support mechanical synchrony assessment, and it is likely that such an approach will be strongly recommended in the near future to better stratify patients and identify the most likely responders.

Finally, a few other factors that could play an important role in patient response to CRT should be noted. One is whether or not the lead in the left ventricle has been optimally positioned. The closer the lead is to the already early-activated septum/ anterior wall, the less the mechanical effect on resynchronization and hemodynamic benefit. Pacing the anterior wall can actually worsen function in some patients, as demonstrated in a study by Butter and colleagues[51] in which anterior wall placement yielded less than 50% of the systolic benefit of lateral free wall placement. Another factor is the AV delay time, which if too long will not provide sufficient preexcitation of the lateral wall, and if too short will compromise function by adverse AV timing. Tissue viability is also a factor, as the paced region must be excitable and cannot be diffusely infiltrated by scar tissue. These latter factors should be particularly considered when a candidate is unresponsive to CRT despite evidence of dyssynchrony and QRS widening.

Summary

CRT based on biventricular and/or left ventricular pre-excitation to resynchronize the discoordinate heart has been recently established as a novel method to enhance systolic function in a subset of patients with dilated cardiomyopathy. Optimal identification of candidates remains a high priority. Although initially focusing on electrical markers, recent data have highlighted the value of more direct assessment of mechanical discoordination by means of tissue Doppler, echo Doppler, or magnetic resonance imaging. Ongoing efforts to prospectively test the utility of these measures to predict responders will likely provide a major advance in targeting this therapy to those most likely to benefit. ■

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