Optimal cardiac pump function depends on ordered mechanical events that are orchestrated by electrical timing. This electromechanical coupling occurs at multiple anatomic levels: within atria, between atria and ventricles, between ventricles, and especially within the left ventricle (LV). Such disruptions to proper electrical timing result in disordered mechanical events (desynchronization, or “dysynchrony”), can occur spontaneously or be induced in isolation or in various combinations at any level, and degrade cardiac pump function. These disruptions to normal mechanical ordering occur because of fixed or functional conduction blocks and can be generated by myocardial disease or can be induced by cardiac pacing. The adverse effects of disruption of proper electromechanical coupling at all levels with particular attention to the effects of ventricular conduction delays due to conventional (usually right ventricular apical, RVA) pacing and left bundle-branch block (LBBB) are discussed later. Subsequently, remedies for prevention or treatment are discussed along the same lines.

Consequences of Uncoupling at Various Levels

Uncoupling at the Atrial Level

The right atrium and left atrium are activated nearly simultaneously (within 50 to 80 ms) during sinus rhythm. Preferential sites of interatrial conduction exist at the posterior-superior interatrial septum (Bachmann’s bundle region), fossa ovalis, and coronary sinus ostium.1,2 Significant interatrial conduction delays (up to 200 ms or greater) can occur in myopathic atria. Similar conduction delays can be also be induced, or exacerbated, by right atrial pacing. Delayed left atrial contraction can disrupt optimal left-sided atroventricular (AV) coupling. Severe atrial decoupling and delayed left atrial contraction reverses the left-sided AV contraction sequence, resulting in atrial transport block.3 This causes increased left atrial pressures, retrograde flow in the pulmonary veins, and counterphysiological neurohormonal responses termed “pseudopacemaker syndrome.”4–6

Uncoupling at Atrioventricular Level

Optimal AV coupling contributes to ventricular pump function. The normal AV interval results in atrial contraction just before the pre-ejection (isovolumic) period of ventricular contraction that maximizes LV filling (LV end-diastolic pressure, or preload) and cardiac output by the Starling mechanism. This optimal timing relationship maximizes diastolic filling time, reduces diastolic mitral regurgitation (MR), and maintains mean left atrium pressure at low levels. Delayed AV coupling due to conduction delay in the AV node displaces atrial contraction earlier in diastole, which may occur immediately after or even within the preceding ventricular contraction. Atrial contraction before completion of venous return reduces preload and contractile force. A late diastolic LV>left atrium pressure gradient may occur, causing diastolic MR and partial closure of the mitral valve, which shortens diastolic filling time. Delayed AV coupling may be worsened or induced by atrial pacing.7 Atrial fibrillation (AF) disrupts atrial coupling (atrial desynchronization) and eliminates AV coupling (AV uncoupling).

Ventricular Level

Normal LV electrical activation is rapid and homogeneous with minimal temporal dispersion throughout the wall.8 This elicits a synchronous mechanical activation and ventricular contraction.9 The resulting coordinated myocardial segment activation maximizes ventricular pump function. Wiggers10 established the linkage between pacing-induced alterations in ventricular conduction and pump function with 2 seminal observations in 1925: (1) Pacing at virtually any ventricular site disturbs the natural pattern of activation and contraction, because the evoked electrical wavefront propagates slowly through ventricular myocardium rather than through the His-Purkinje system. (2) Altered ventricular activation causes an immediate reduction in pump function, and some sites are worse than others (site selectivity). In general, RV pacing sites appear to be more detrimental than LV pacing sites, and the RVA is among the worst sites within the RV.11

Optimal inter- and intraventricular coupling is more important than AV coupling for maximum ventricular pumping function.12,13 RVA pacing and LBBB both induce delays in transseptal and intraventricular conduction.14 Consequently, the hemodynamic effects of altered ventricular activation during RVA pacing and LBBB are comparable. These effects can be attributed to disturbed interventricular as well as
intraventricular coupling. RVA pacing also disturbs RV activation because of slow intramyocardial conduction.

Interventricular decoupling refers to a sequential RV–LV activation delay. In LBBB, earliest ventricular depolarization is recorded over the anterior surface of the RV and generally latest at the posterior or posterolateral basal LV. Inter-ventricular dys synchrony can be quantified by the time delay between the upslopes of LV and RV systolic pressure as well as time delay between opening of the pulmonic and aortic valves. Similar changes occur during RV pacing. This disruption to ventricular interdependence is a determinant of paradoxical septal motion. Presumably this reduction in ventricular septal contribution to LV ejection is an important factor in the reduction of pump function during LBBB.

Delayed intraventricular activation is likely the most important determinant of reduced pump function. In RVA pacing and LBBB, electrical activation starts in the interven- tricular septum, whereas the posterior or posterolateral basal LV wall is activated >100 ms later. Such considerable intraventricular delay during RVA pacing and LBBB pacing is due to slow spread of the depolarization wavefront through the working myocardium rather than through the Purkinje system. Slow intramyocardial conduction during RVA pacing prolongs QRS duration (QRSd) from the normal values of 80 ms to values of 140 ms in otherwise normal hearts to 200 ms in infarcted LVs. Furthermore, the delay in LV activation relative to QRSd during RVA pacing is greater in failing ventricles.

LBBB is a complex electrical disease resulting from LV conduction delay at multiple anatomic levels, which may be anatomically fixed or functional and is exhibited differently according to substrate characterization (ischemic [ICM] versus nonischemic dilated cardiomyopathy [DCM]). Early endo-cardial activation mapping studies of LBBB concluded that conduction delay resided entirely within the ventricular septum and that LV endocardial activation was rapid after septal branches of the His-Purkinje system with basal breakthroughs from the anterior or posterior fascicle and bidirectional wavefront propagation from base to apex and high septum. Breakthrough from both fascicles results in a double wavefront that fuses on the posterolateral wall. Single-site breakthrough from the high septum because of right-to-left muscular conduction (no conduction system present) results in a single wavefront that propagates from base to apex. The pattern of septal activation may affect ventricular mechanics differently. High septal activation may result in simultaneous RV and LV activation in opposite directions, and papillary muscle activation may be influenced by the earliest site of LV activation.

The pattern of LV endocardial and epicardial activation is also influenced by the location and size of lines of fixed or functional conduction block. Fixed conduction block is due to replacement of normal myocardium by interstitial fibrosis. The physiologic basis for functional conduction blocks has not been elucidated but could relate to stretch, heart rate, and spontaneous diastolic depolarization. Anterior locations of the line of functional block are characterized by a U-shaped LV activation pattern, more prolonged QRSd (>150 ms), and greater time to LV breakthrough. Late activation of the posterior or posterolateral basal LV occurred by wavefront propagation around the line of block using the apical or inferior LV walls. Lateral locations of the line of block are characterized by less prolonged QRSd (<150 ms) and shorter time to LV breakthrough. Pacing maneuvers shift either line of block, indicating their functional nature. Noninvasive mapping of epicardial activation using body surface potentials extended these observations and demonstrated that electrical activation patterns in LBBB are highly heterogeneous and unpredictable. Lines of conduction block do not correlate with regions of wall motion abnormality or scarring. Some lines of block arose only during pacing and were site dependent (functional), whereas other lines of block could not be manipulated with pacing maneuvers, indicating these were due to slow or absent conduction (fixed). Latest activation most often occurred in the posterior or posterolateral basal wall but was also observed in the anterior and inferior walls in some patients.

Effects of Asynchrony on LV Mechanics and Structure

Regions that are activated early also start to contract early. Accordingly, in RVA pacing and LBBB, the earliest and latest sites of segmental LV activation correlate well with time to peak systolic velocity by Doppler and strain by tagged magnetic resonance imaging, providing evidence that ventricular conduction delay is responsible for heterogeneous mechanical performance (asynchrony). The mechanical effect of asynchronous electrical activation is dramatic, because the various regions not only differ in the time of onset of contraction but also in the pattern of contraction (Figure 1). Contraction of early activated myocardium is energetically inefficient because LV pressure is low and ejection has not begun. Instead, stretching of not as yet activated remote regions absorbs the energy generated by the early activated regions. This stretching further delays...
shortening of these late activated regions and increases their force of local contraction by virtue of the Frank-Starling mechanism (locally enhanced preload). Vigorous late systolic contraction at delayed sites occurs against high LV cavity pressures (locally enhanced afterload) and imposes loading on the earlier activated regions, which now undergo systolic paradoxical stretch.29 This reciprocated stretching of regions within the LV wall causes a less effective and energetically efficient contraction.30

The hemodynamic consequences of the asynchronous LV contraction are reductions in contractility and relaxation. These changes occur immediately on initiating RVA pacing in humans and animals11,31 and induction of LBBB in animals.12 The loss of pump function is indicated by decreases in stroke volume, stroke work, and slower rate of rise of LV pressure (Figure 1). Moreover, the LV end-systolic pressure–volume relationship shifts rightward, indicating that the LV operates at a larger volume in order to recruit the Frank-Starling mechanism.11 Premature relaxation in early activated regions and delayed contraction in others also causes abnormal relaxation,11 expressed as slower rate of fall of LV pressure, increase in the relaxation time constant tau, and decrease of E-wave velocity amplitude on Doppler echocardiograms.32 These changes also lead to prolongation of the isovolumic contraction and relaxation times, which are characteristic for asynchronous hearts.33 The prolongation of the isovolumic times occurs mainly at the expense of the diastolic filling time, leading to reduced preload.

The redistribution of the mechanical load within the ventricular wall also leads to reduction of regional myocardial perfusion and oxygen consumption near the RVA pacing site30,34,35 and in the septum during LBBB.36,37 Such perfusion defects and wall motion abnormalities have been demonstrated in up to 70% of patients with angiographically normal coronary arteries exposed to chronic RVA pacing.38–41 These defects are reversible on cessation of RVA pacing39,41 and after biventricular pacing.36,37,42 Accordingly, such perfusion “deficits” do not necessarily indicate coronary heart disease, because they may simply express the regional differences in myocardial workload.

Similar to the situation after myocardial infarction, acute loss of pump function initiates compensatory responses (Figure 2). Some of these responses may, after a certain time and/or certain degree of asynchrony, lead to further impairment of pump function and clinical heart failure. There are various triggers for these “remodeling” processes. As is the case for other conditions of hemodynamic overload, RVA pacing and LBBB lead to stimulation of the sympathetic system resulting in elevated myocardial catecholamine levels43 and activation of the renin–angiotensin–aldosterone system. Regional differences in stretch and mechanical load heterogeneity are most likely important stimuli for remodeling processes. Chronic asynchronous LV activation results in asymmetrical hypertrophy44 and locally different molecular abnormalities including reductions in sarcoplasmic reticulum calcium-ATPase and phospholamban.45 Even stronger regional differences in gene expression are found in failing
hearts with conduction abnormalities. In addition, LV cavity volume increases with longer duration of RVA pacing and LBBB. Dystrophic calcifications, disorganized mitochondria, and myofibrillar cellular disarray have been described with RVA pacing, especially in immature hearts.

Early signs of cellular and molecular adaptation to disturbed ventricular activation are manifest as reduction in ejection fraction (EF) within the first week of RVA pacing. Nahlawi et al showed, in patients with normal EF, an immediate drop in EF of /1015%, followed by another 7% drop during the subsequent week. Suppression of RVA pacing returned EF to baseline values, but only after several days. Also, ventricular repolarization abnormalities have been observed within hours of RVA pacing. Alterations in potassium and calcium channels likely play a role in these phenomena.

Mechanistic Basis for Development of Heart Failure Due to Long-Term RVA Pacing or LBBB

As mentioned above, synchronous activation consistently leads to short- and long-term adverse effects on cardiac pump function, which create a vicious circle of deterioration. Accordingly, the frequency of RVA stimulation has been linked to increased risks of AF, heart failure, ventricular arrhythmias, and death in large randomized clinical trials (RCTs) of pacemakers and implantable cardioverter-defibrillators (ICDs). Similar risks have been reported for LBBB and cardiac morbidity and mortality. Multiple factors may contribute to heart failure associated with RVA pacing and LBBB. At least 4 candidate factors are readily identified: (1) reduced pump function due to asynchronous contraction (dyssynchrony), (2) adverse remodeling due to long-term dyssynchrony, (3) left-sided AV desynchronization, and (4) functional MR (fMR). The first 3 mechanisms have been discussed above. With regard to the fourth mechanism, new onset of mild to moderate fMR and worsening of preexisting MR have been described in 49% and 14% of pacemaker patients, respectively. Functional MR is also found in LBBB patients. The mechanism of such fMR has multiple components. The immediate cause is papillary muscle desynchronization due to ventricular conduction delay, thus increasing time to peak strain between papillary muscle insertion sites. In addition, volumetric remodeling probably contributes to fMR by increasing papillary muscle tethering forces and reducing the transmitral pressure gradient.

The complex relationship between ventricular conduction delay, due to RVA pacing or LBBB, and heart failure appears to have 3 primary elements: (1) “dose” of asynchrony, (2) substrate, and (3) time. With regard to pacing-induced asynchrony, the risk of heart failure increases with increasing paced QRSd and with high cumulative percentages of RVA pacing. The total burden of ventricular desynchronization can be conceptualized as a function of the paced QRSd, which is a measure of “potency per dose” and the cumulative percent RVA pacing, which is the frequency at which the dose is delivered (Figure 3). The importance of the third element of the desynchronization burden (exposure time) becomes clear when attention is paid to young pacemaker patients. Several studies have shown that some of these patients, exposed to chronic RVA pacing, develop significant LV remodeling in young adulthood that progresses to DCM in about 7% of the population. The importance of the “background substrate” for the development of heart failure is evident from the fact that the standard practice of RVA pacing over the past 40 years has not triggered an epidemic of pacing-induced heart failure. In the Mode Selection Trial, only 10% of patients over a median follow-up of 33 months had heart failure that could be linked to RVA pacing. This is because most typical pacemaker patients are elderly, have normal ventricular function, and no preexisting ventricular conduction delay, heart failure, or myocardial infarction (low risk substrate). Although RVA pacing immediately and increasingly reduces LV EF and reduces diastolic function, such patients tolerate chronic RVA pacing reasonably well, and the 2-year probability of heart failure that can be linked to pacing is approximately 1.4% (Figure 4). This likely explains the relative insensitivity of clinical outcomes to cumulative percent RVA pacing in pacemaker trials. Importantly, approximately 90% of pacemaker recipients are >60 years old, and ≥30% are >80 years old in many nations. Advanced age and a high...
The comorbidity rate in typical pacemaker patients also mean that most will not live long enough to be harmed by their pacemaker (insufficient exposure time). On the other hand, typical patients with implantable cardioverter-defibrillators have most or all of these substrate conditions, and the relative risk of heart failure associated with RVA pacing rises to approximately 52% over 2 years (Figure 4). This provides some explanation for the observation that it took 3 to 5 years before heart failure attributed to RVA pacing became manifest in pacemaker trials, but 1 year in implantable cardioverter-defibrillator trials.

The highest risk of RVA pacing–induced heart failure is observed in patients with reduced EF, prior heart failure, and preexisting ventricular conduction delay (Figure 4). This provides some explanation for the observation that it took 3 to 5 years before heart failure attributed to RVA pacing became manifest in pacemaker trials, but <1 year in implantable cardioverter-defibrillator trials.

The increased risk of heart failure associated with RVA pacing superimposed on LBBB and myocardial infarction (MI) and heart failure hospitalization (HFH) during RVA pacing. Relative risk of HFH (vertical axis) increases with decreasing EF (left horizontal axis) and increasing QRSd (right horizontal axis), and these effects are modified by absence (left) or presence (right) of MI (M.O. Sweeney, MD, A.S. Hellkamp, MS, unpublished data). Each slice is 1 interval on the vertical axis. For each increasing value of QRSd, the relative increased risk of HFH was equivalent regardless of whether the prolongation of QRSd was due to RVA pacing or LBBB. The increased risk of HFH associated with prolonged QRSd was modified by substrate. The incremental increase in risk of HFH per unit increase in QRSd (spontaneously occurring or due to RVA pacing) was higher in patients with low EF or prior MI. The increasing risk of heart failure with QRSd was more rapid among patients with normal EF, suggesting that these patients were initially more vulnerable to the adverse effects of long paced QRSd. The chief effect of this interaction was that at highest values of QRSd (>≈160 ms), normal and low EF patients had equivalent risks of HFH. Thus, the lower baseline risk of HFH conferred by normal versus low EF was canceled out when paced QRSd was very prolonged.61

Bottom, Two-year probabilities of HFH for different patient types and cumulative percent ventricular pacing (Cum%VP) groups. Adapted with permission from Sweeney and Hellkamp.61

Figure 4. Top, Surface plots of interaction between EF, ventricular conduction (QRSd), myocardial infarction (MI), and heart failure hospitalization (HFH) during RVA pacing. Relative risk of HFH (vertical axis) increases with decreasing EF (left horizontal axis) and increasing QRSd (right horizontal axis), and these effects are modified by absence (left) or presence (right) of MI (M.O. Sweeney, MD, A.S. Hellkamp, MS, unpublished data). Each slice is 1 interval on the vertical axis. For each increasing value of QRSd, the relative increased risk of HFH was equivalent regardless of whether the prolongation of QRSd was due to RVA pacing or LBBB. The increased risk of HFH associated with prolonged QRSd was modified by substrate. The incremental increase in risk of HFH per unit increase in QRSd (spontaneously occurring or due to RVA pacing) was higher in patients with low EF or prior MI. The increasing risk of heart failure with QRSd was more rapid among patients with normal EF, suggesting that these patients were initially more vulnerable to the adverse effects of long paced QRSd. The chief effect of this interaction was that at highest values of QRSd (>≈160 ms), normal and low EF patients had equivalent risks of HFH. Thus, the lower baseline risk of HFH conferred by normal versus low EF was canceled out when paced QRSd was very prolonged.61
enlargement after the emergence of LBBB unaccompanied by any other explanation has been documented in case series. Furthermore, complete recovery of ventricular function shortly after initiation of biventricular pacing in so-called hyper-responders suggests that LBBB may be a primary and reversible trigger of DCM in some patients.

Several studies also showed that LBBB is associated with increased mortality, the impact being higher the sicker the patient population was. The relative risk associated with the presence of LBBB in these studies varies roughly between 1.5 and 2.0, even after adjustment for covariates (reviewed in Ref. 57). The only study rejecting the idea that LBBB is associated with increased mortality drew this conclusion after adjustments for LV EF as a covariable. However, the conclusion that LBBB is not an independent predictor of mortality after the adjustment for EF can be understood because LBBB directly reduces EF because of its acute and chronic effect on LV pump function (see above).

**Strategies to Reduce the Adverse Effects of Ventricular Conduction Delay on Pump Function**

**Dual-Chamber Minimal Ventricular Pacing**

In patients with symptomatic bradycardia due to sinus node disease and heart failure patients requiring rate support, the primary strategy is to preserve normal ventricular conduction by minimizing ventricular pacing using new dual-chamber enhanced AAI/R pacing algorithms. These algorithms have been recently demonstrated to be highly effective and safe. One such algorithm reduced the relative risk of persistent AF by 40% compared with conventional dual-chamber RVA pacing, a decrease that was accompanied by fewer heart failure hospitalizations and interventions for AF.

**Alternative Ventricular Pacing Strategies**

Whether alternative ventricular pacing strategies could mitigate the adverse effects of ventricular desynchronization during obligatory pacing remains an open area of clinical investigation. Because pacing leads are usually implanted along the transvenous route, alternative sites within the RV have been studied intensively. Acute hemodynamic studies generally, although not consistently, show an advantage of RVA pacing over LV apex pacing. However, small enrollment and inconsistent methods and definition of the “break-out” site hinder the interpretation of these studies. Two longer-term studies have shown that pacing at the inferoapical LV septum and the epicardium yields LV pumping function that closely approximates function during normal ventricular conduction.

Pacing the His bundle preserves native ventricular activation and yields QRSd, electrical axis, and activation sequence identical to normal ventricular conduction. Studies in the electrophysiology laboratory have shown favorable effects of His bundle pacing on cardiac performance compared with RVA pacing. Permanent His bundle pacing has been achieved in humans by only a few specialists. Development of new tools may facilitate this otherwise complicated procedure.

A few publications indicate that LV pacing may improve hemodynamics, even beyond that during His bundle pacing, suggesting that in patients with LV systolic dysfunction, maintenance of natural ventricular conduction may not be the ultimate goal, even in the presence of a relatively narrow QRS complex. In hearts with normal ventricular conduction, LV pumping function is less adversely affected by pacing from most LV sites than by RVA pacing. Within the LV, some sites are better than others. Importantly, the better sites for normally conducting ventricles are different from those in ventricles with LBBB-like conduction abnormalities. Studies in animals and children showed that pacing at the inferoapical LV septum and the epicardium of the LV apex yields LV pumping function that closely approximates function during normal ventricular conduction. These results may be explained by rapid engagement of the specialized conduction systems in the LV wall near its “break-out” site. Switching from RV to LV apex pacing dramatically improved cardiac function in a child with congenital AV block.

Because the activation pattern during RVA pacing is similar to that during LBBB, it is not surprising that biventricular pacing has been used to reduce ventricular desynchronization during obligatory pacing. Although biventricular pacing reduces regional mechanical activation heterogeneity compared with RVA pacing, dyssynchrony persists compared with normal ventricular activation.

The situation is less clear when RVA and biventricular pacing are compared in AF patients immediately after AV junction ablation presumably because the benefits of rate control in AF conceal the effect of asynchronous activation.

It is therefore important to recognize that biventricular pacing in hearts without conduction abnormalities at best reduces the amount of desynchronization when compared with RVA pacing, whereas biventricular pacing in hearts with ventricular conduction block can correct asynchronous contraction patterns, as will be discussed in the following paragraphs.

**Mechanisms of Cardiac Resynchronization Therapy**

Fixed and functional disruptions to normal electromechanical ordering due to conduction delay serve as potential targets for electromechanical reconstitution of pump function. The basis of this therapeutic strategy is to restore coordinated contraction by minimizing the conduction delay, thereby restoring interventricular and intraventricular coupling. A second-order effect is the reduction of left-sided AV uncoupling, which may improve diastolic performance and thereby LV pumping function. As part of this effect, fMR may be reduced. These acute beneficial hemodynamic effects may lead to even more beneficial long-term effects, because many adverse molecular and cellular derangements, elicited by chronic RVA pacing or LBBB (Figure 2), appear to be reversible. This property of cardiac resynchronization therapy (CRT) is remarkable, because many (pharmacological) therapies tend to lose their effectiveness over time, whereas the beneficial effects of
CRT are maintained for many years. The best explanation of the lasting benefit of CRT is that it largely restores the normal electromechanical coupling of the heart with LBBB. This idea is supported by studies in the canine models where CRT abolished all adverse effects of LBBB. Thus, CRT may be “curative” of LBBB-induced ventricular desynchronization in some situations.

**Improved Ventricular Mechanics Due to Reduction in Ventricular Conduction Delay**

Reduction of intraventricular delay during atrial-synchronous LV or biventricular pacing has an immediate positive effect on ventricular mechanics. Instantaneous improvement in pump function is indicated by increases in LV dP/dt\text{max}, stroke volume, stroke work, arterial pulse pressure and peak systolic pressure, and reduced end-systolic volume (Figure 5). Moreover, unlike the inotropic effects of dobutamine, systolic augmentation with ventricular resynchronization increases efficiency of conversion of myocardial oxygen consumption to mechanical work. This positive contractile response demonstrates a modestly positive correlation with increasing baseline QRSd and is strongly correlated with baseline mechanical dyssynchrony. Conversely, improved contractility does not require QRS narrowing during LV or biventricular pacing.

Early acute hemodynamic studies demonstrated that the relationship between AV delay and LV dP/dt\text{max} among patients with an acute improvement in contractile response to simultaneous biventricular pacing is positive and unimodal with a peak effect at approximately 50% of the native PR interval (Figure 6), resulting in complete replacement of native ventricular conduction with paced activation. LV dP/dt\text{max} increased 15% to 45% across a narrow range of AV delays and declined at very short AV delays (truncated filling times) or very long AV delays (inadequate correction of LV conduction delay). The maximum improvement in pump function occurs at minimal intraventricular asynchrony and unchanged LV end-diastolic pressure (preload). This indicates that the acute contractile response is explained by ventricular resynchronization, not by better filling.

The AV delay and the interventricular (VV) interval have an interactive relationship. The effect of AV delay on acute hemodynamic response to CRT is best understood in terms of the effect on ventricular resynchronization during biventricular or left univentricular pacing (Figure 7). During LBBB, the RV is activated by RBB conduction (RBBc) before the LV, and the time difference between RV and LV activation is the interventricular conduction delay. Biventricular pacing at short AV delays results in complete replacement of intrinsic activation, thereby allowing complete control of chamber timing with sequential ventricular stimulation. Intermediate AV delays result in “pure” fusion between RBBc and LV paced activation because LV preexcitation is still possible because of interventricular conduction delay. Modification of the AV delay alone can therefore achieve (1) biventricular paced fusion, (2) biventricular paced fusion with sequential ventricular stimulation (LV first), and (3) “pure” RBBc-LV pacing fusion.

The best ventricular resynchronization occurs when the wavefronts from the RV pacing site (or originating from RBBc) and the LV pacing site collide halfway (fusion). Experimental evidence suggests that optimal hemodynamic

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**Figure 5.** Pressure–volume loops during LBBB and LV pacing. Correction of regional mechanical delay results in immediate increases in stroke work (larger loop), stroke volume (width of loop) (data derived from Verbeek et al).
effect can be achieved using LV pacing at certain AV delays as well as using simultaneous and sequential biventricular pacing because fusion of electrical wavefronts can be achieved by either approach.\(^{13,107}\)

Although this and other experimental studies show a clear mechanism of action for optimizing the interaction between AV and VV timing, confusion in this area is large, and a clinical advantage of patient-specific timing optimization has not been convincingly demonstrated in clinical trials.\(^{108–110}\)

Reverse Volumetric LV Remodeling

Sustained improvement in ventricular mechanics results in regression of adverse LV remodeling, termed reverse remodeling. This results in reductions in LV volumes and mass, reduced mitral orifice size, regression of asymmetrical hypertrophy, and increased ejection fraction.\(^{111–119}\) The magnitude of the reduction in end-systolic volume ranges between 10% and 30%,\(^{111,115,120,121}\) which is equivalent to or greater than the effects of β-blockers and angiotensin-converting enzyme inhibitors. These hemodynamic effects are chronically sustained assuming LV pacing is continuously maintained.\(^{118}\)

Although improvement in New York Heart Association class, quality of life, and 6-minute walk tests may be confounded by placebo effects and reporting bias, reverse remodeling is a completely objective measure. More importantly, it appears to be related to better survival.\(^{121}\)

Evidence of baseline mechanical dyssynchrony and acute mechanical resynchronization appears to be necessary for reverse remodeling to occur, and the greater the reduction in dyssynchrony, the higher the probability of remodeling.\(^{119,122}\) Likewise, absence of mechanical resynchronization acutely eliminates the possibility of chronic reverse remodeling.\(^{119}\) In canine hearts with induced LBBB, it was shown that 8 weeks of CRT was sufficient to almost completely reverse the \(\approx 25\%\) LV cavity dilation and asymmetrical LV hypertrophy induced by dysynchrony to pre-LBBB baseline values.\(^{42}\)

This observation has been replicated in clinical studies where in some cases, reverse remodeling results in complete normalization of LV volumes and ejection fraction.\(^{76}\) This suggests the intriguing possibility that ventricular conduction delay may be the primary cause of DCM in some pa-
Reduction in Functional Mitral Regurgitation

In many patients CRT reduces fMR. This can be attributed to 3 mechanisms: (1) Improved contractility reduces fMR instantaneously and is quantitatively related to an increase in LV $\frac{dP}{dt\text{max}}$ and transmitral pressure; (2) ventricular resynchronization shortens interpapillary muscle delay, which instantaneously reduces fMR because of more coordinated papillary muscle activation; and (3) reverse volumetric LV remodeling reduces fMR chronically by reducing LV volumes and sphericity, which reduces tethering forces on the mitral valve. In an acute study in patients selected for the presence of fMR, Breithardt et al. estimated that CRT reduced regurgitant flow from 32 to 19 mL/beat. It is not well understood what part of the benefit of CRT is due to reduction in fMR versus resynchronization of contraction directly, because few studies quantitatively measure regurgitant flow.

Clinical Experience With CRT

CRT pacing is an effective adjunctive treatment for moderately severely symptomatic heart failure associated with DCM and ventricular conduction delay. RCTs involving >5000 patients have demonstrated modest, concordant improvements in functional class, exercise tolerance, and quality of life. Heart failure hospitalizations are reduced by 29% to 52%, heart failure death by 51%, sudden cardiac death by 46%, and total mortality by 40%; LV stimulation at these sites improves acute electrical resynchronization measured at the pacing sites (Figure 8). Both situations may contribute to nonresponse.

Ventricular asynchrony has been shown to predict acute and chronic response (including remodeling) to CRT. Although QRSd correlates only modestly with ventricular asynchrony, more severe baseline conduction delay (QRS >150 ms) is predictive of acute improvement in contractile response, short-term improvements in exercise tolerance and quality of life, and long-term reductions in mortality and heart failure hospitalization, whereas none of these benefits were consistently observed among patients with less severe conduction delay (QRS 120 to 150 ms). In this situation, CRT may induce dysynchrony and worsen pump function. Furthermore, CRT does not benefit patients with ventricular conduction delay due to right bundle-branch block because significant LV asynchrony is generally absent.

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References


34. Spragg DD, Leclercq C, Loghmanis M, Faris OP, Tunin RS, DiSilvestre D, McVeigh ER, Tomaseilli GF, Kass DA. Regional alterations in


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Ventricular Pump Function and Pacing


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