

Cardiac Resynchronization Therapy

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Cardiac Resynchronization Therapy. Cardiac resynchronization therapy (CRT) is a recently developed approach to treat dilated heart failure with discoordinate contraction. Such dyssynchrony typically stems from electrical delay that then translates into mechanical delay between the septal and lateral walls. Over the past decade, many studies have examined the pathophysiology of cardiac dyssynchrony, tested the effects of cardiac resynchronization on heart function and energetics, tested the chronic efficacy of this therapy to enhance symptoms and reduce mortality, and better established which patients are most likely to benefit. This brief review discusses these topics. (*J Cardiovasc Electrophysiol*, Vol. 16, pp. S35-S41, Suppl. 1, September 2005)

heart failure, pacing, dyssynchrony, biventricular, tissue

Introduction

In the mid-1990s, investigators working largely in Europe began exploring the possibility that simultaneous electrical stimulation of both right and left ventricles could significantly improve cardiac function and clinical symptoms in patients with heart failure and discoordinate wall motion due to conduction delay. Within a remarkably short period of time, a new therapy known as cardiac resynchronization therapy (CRT) evolved, was tested in clinical trials, and entered into the therapeutic armamentarium for treating heart failure. This story involves several firsts: CRT was the first nonpharmacologic treatment to be tested in large scale clinical trials with placebo controls; the first in which a defined subset of the heart failure population (e.g., wide QRS complex) was targeted from the outset; and arguably the first to be developed and tested largely in humans *first* with animal model data coming later. The goal of this brief presentation is to review some of the more recent data that clarify the mechanisms underlying CRT, its clinical efficacy and optimization, morbidity and mortality benefits, and issues regarding candidate identification.

Mechanisms of CRT

The primary substrate of CRT is a failing heart with discoordinate contraction that is due to electrical timing delay rather than fixed functional defects as with a myocardial infarction. The major property identifying such a heart has been a widened QRS interval—particularly having a LBBB-type morphology. This occurs in about 25% of all heart failure subjects, and is associated with a nearly 1.7-fold higher risk of both worsened failure and sudden cardiac death.¹ Indeed, patients with heart failure and discoordinate contraction have among the worse overall prognosis and underlying LV dysfunction of all CHF patients. However, the QRS duration is an indirect marker of mechanical dyssynchrony, and more recent studies have tested the hypothesis that discoordinate wall motion is itself a predictor of adverse outcome in CHF

patients— independent of QRS duration or indeed any of the other known and accepted risk factors. As shown in Figure 1A, having ventricular dyssynchrony as determined by tissue Doppler imaging confers a significantly worse outcome with a far lower probability of event-free survival.²

To understand how the dyssynchronous heart impacts on cardiac function, it is useful to consider a theoretical model in which large regions of the LV are activated with a phase lag between them (Fig. 1B). This can be viewed from the perspective of cardiac elastance curves (ventricular muscle stiffening versus time), with the early-stimulated territory shown as a solid line and the latter activated region by a dotted line. Differences between these curves (shown by vertical arrows) depict the disparity of activation, and the larger the difference the more one part of the wall effectively stretches the other wasting cardiac work and energy. This occurs first early in systole, and is a major reason that the rapid rate of pressure rise (dP/dt_{max}) is very sensitive to ventricular synchrony, and has been a commonly used measure of this behavior. The difference in stiffnesses becomes more or less constant during the ejection phase, but once again is magnified in early relaxation when the early-stimulated zone shows a rapid decline in muscle stiffness. The still activated late region now can push on this zone (typically seen as septal wall motion toward the RV induced by late LV free wall contraction). The net result (figure to right) is a decline in cardiac stroke volume (PV loop width) and thus cardiac output, and an increase in the end-systolic wall stress (arrow).

In addition to mechanical consequences of discoordinate contraction, the dyssynchronous heart reveals marked local changes in molecular signaling that likely influence calcium handling, electrical coordination between cells, stress responses, and other features of cellular function. Figure 1C shows an example of such molecular changes in a key calcium handling protein, phospholamban (PLB), involved with calcium uptake into the sarcoplasmic reticulum derived from a canine model of heart failure and dyssynchrony (LBBB).³ Phospholamban declines markedly in the late activated endocardium, whereas neighboring epicardium or the early activated septal myocardium does not show similar changes. Reduced PLB could diminish beta-adrenergic reserve, since PLB phosphorylation from adrenergic stimulation normally enhances calcium uptake and release by the sarcoplasmic reticulum to increase both inotropy and lusitropy. Regional disparities in calcium handling could thereby lead

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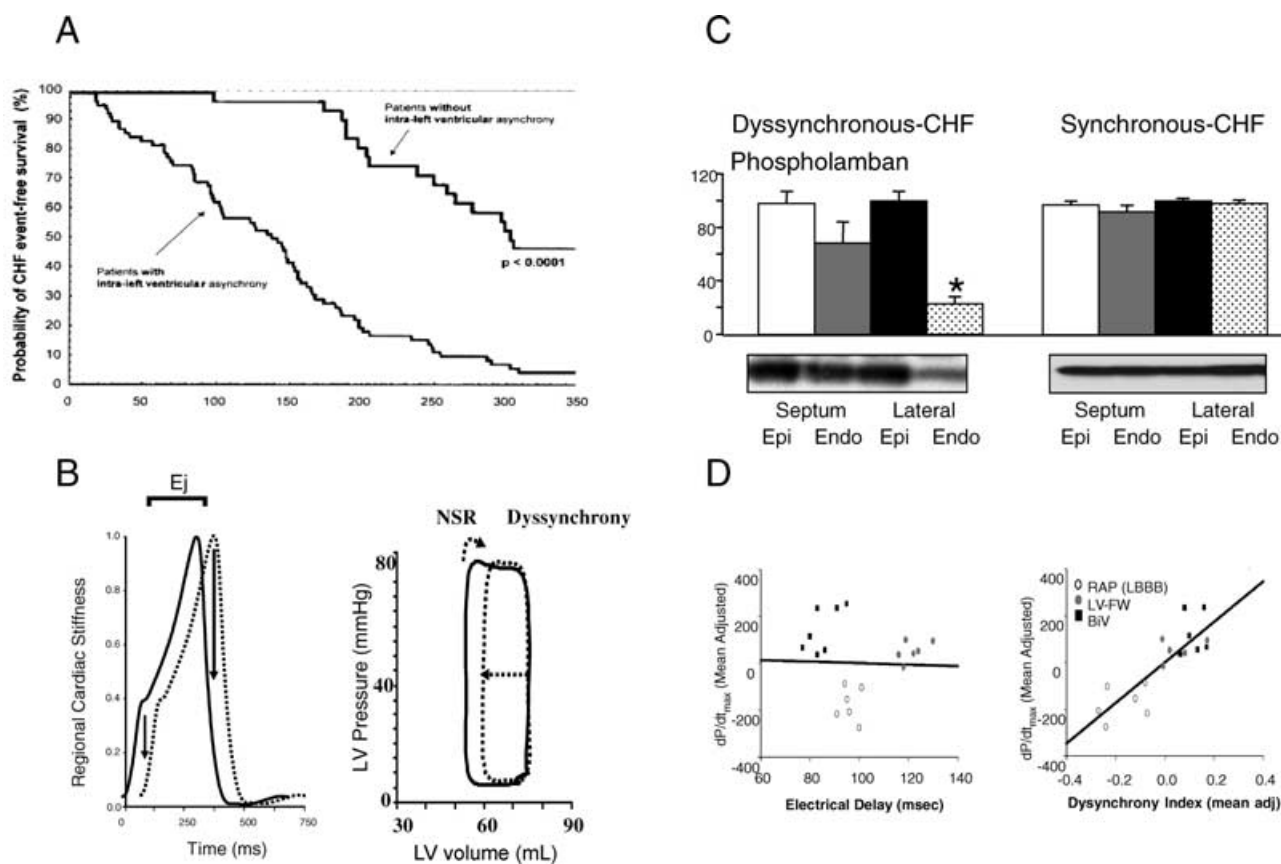


Figure 1. (A) Influence of cardiac mechanical dyssynchrony determined by tissue Doppler imaging on probability of congestive heart failure event-free survival. Patients with dyssynchrony have a markedly worse overall prognosis. From Bader et al.² Reprinted with permission. Copyright © 2004 American College of Cardiology Foundation. (B) Schematic of mechanical impact of dyssynchrony. The early activated region (solid line) muscle activation curve (cardiac stiffening) is shown phase advanced from the late stimulated region (dotted line). Vertical differences between the curves reflects the disparity in stiffening which will mean that one portion of the heart can push on the other stretching the opposing wall. This reduces net function and cardiac efficiency. This disparity is greatest early in contraction (isovolumic pressure rise) and in early diastole. The ejection period (Ej) is shown by the horizontal bracket. The panel to the right shows the net effect on cardiac chamber function. The dyssynchronous beat has a reduced stroke volume (width) and higher end-systolic wall stress; diminished systolic function. (C) Example of molecular polarization in a failing dyssynchronous heart. Phospholamban expression is reduced locally in the lateral (late activated) endocardium in comparison to other territories. This is not observed in failing hearts with synchronous contraction. From Spragg et al.³ Reprinted with permission from the American Heart Association. (D) Basal mechanical dyssynchrony better correlates to global function than does basal electrical delay time. Individual data are shown for seven canine studies using a model of CHF combined with a LBBB. The baseline dyssynchronous condition is right atrial pacing (RAP-LBBB), while two modes of CRT are also shown—LV free-wall pacing (LV-FW) and biventricular (BiV). CRT with both modes results in improved systolic function (y-variable is mean adjusted max-dP/dt). While this did not correlate with electrical delay, it did correlate with mechanical dyssynchrony. Line is least-squares linear regression. From Leclercq et al.⁴ Reprinted with permission from the American Heart Association.

to heterogeneity of myocyte contraction strength and timing, that may worsen net wall function and stimulate arrhythmia due to local forces and action potential duration. Importantly, if the same level of cardiac failure is induced synchronously, this regional disparity is not observed. This indicates that such molecular heterogeneity is not due to heart failure itself, but is more specific to the presence of dyssynchrony in this setting.

Recent research has demonstrated that mechanical dyssynchrony rather than electrical delay per se is most directly linked to CRT effects.⁴ Figure 1D shows data from a canine model of CHF combined with a LBBB in which CRT was implemented by either biventricular or LV only pacing. The y-axis reflects the global CRT response, measured by the relative change in dP/dt_{max} (normalized to the mean for each animal, $n = 7$). The electrical conduction delay based on epicardial electrograms did not correlate with global systolic function among the three conditions, particularly as LV only pacing improved function despite increasing

this electrical delay. In contrast, there was a strong correlation between mechanical dyssynchrony and function (right panel)—showing that LV pacing did indeed result in mechanical resynchronization, and that this most directed related to net chamber function. For this analysis, a dyssynchrony index was used that ranges from 0—perfectly dyssynchronous to 1—synchronous, and is shown normalized to each animal's respective mean value.⁴ Such data were among the first to reveal the more complex linkage between the electrical delay that often initiates dyssynchronous contraction, the actual discoordinate wall motion that ensues, and the functional decline that ultimately results. This is an important issue, since the mechanical changes from delayed activation are the likely triggers for local molecular and cellular abnormalities, and centrally determine the impact of this delay on global heart function.

Coupling of underlying electrical delay to mechanical dyssynchrony is simple enough in a normal homogeneous ventricle, but becomes considerably more complex when

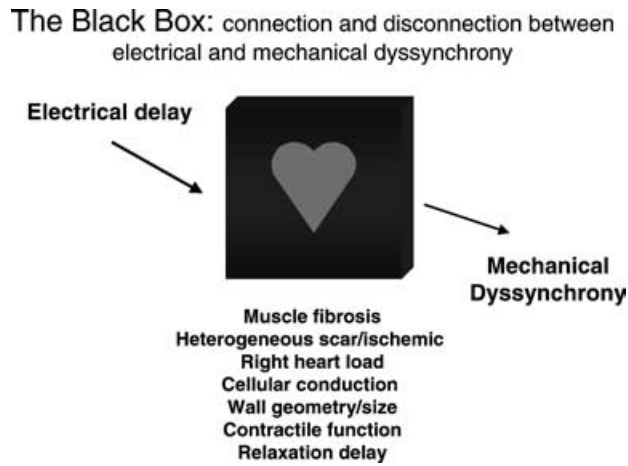


Figure 2. Potential mechanisms coupling electrical conduction delay within the heart-to-net mechanical dyssynchrony. Abnormalities in the underlying myocardium, regional geometry and chamber size, right heart load, etc. all can influence how one behavior results in the other. Each may be an important component of determining the net efficacy of CRT therapy in a given patient.

considered within the context of underlying heart failure pathophysiology. Currently, this linkage remains somewhat of a black box (Fig. 2), but there is growing appreciation for the various factors that may well influence it. For example, myocardial fibrosis and heterogeneously dispersed scar and/or ischemia can modify how electrical delay translates into contractile dysfunction. Elevation of right heart loading is common in heart failure and may also impact on mechanical dyssynchrony. The late systolic rightward shift of the septum due to late lateral wall contraction is likely to be far less prominent if right heart pressures are greatly elevated from pulmonary hypertension. Changes in the behavior of failing myocytes involving calcium cycling, contractile function, chamber and myocyte geometry, and prolonged relaxation may all further impact on this process.

Effects of CRT

Many studies have demonstrated that CRT can abruptly enhance cardiac systolic function. An example from a human subject is shown in Figure 3A.^{5,6} With the initiation of CRT, there is a near immediate increase in maximal dP/dt (top tracing), along with a rise in systolic arterial pressure and widening of the arterial pulse pressure. The latter correlates with increased cardiac output. Other studies revealed that this effect occurs with no increase in metabolic demand by the heart, but rather an improvement in chamber efficiency.⁷ There is remarkably little data examining effects of CRT on cardiac function during exercise, although some recent studies show further enhancement under stress conditions.^{8,9} For example, in patients with atrial fibrillation and high degree AV nodal block (or an ablated node), pacing at the RV apex generating a LBB-type conduction delay results in significantly lower systolic function compared to LV pacing (RBB-type) or biventricular pacing. However, these disparities become substantially amplified at higher heart rates (Fig. 3B).⁹

Diastolic function and end-diastolic volumes are little influenced by acute CRT.⁵ However, chronic CRT leads to a decline in both end-diastolic and end-systolic volumes compatible with reversal of cardiac failure remodeling.¹⁰⁻¹³

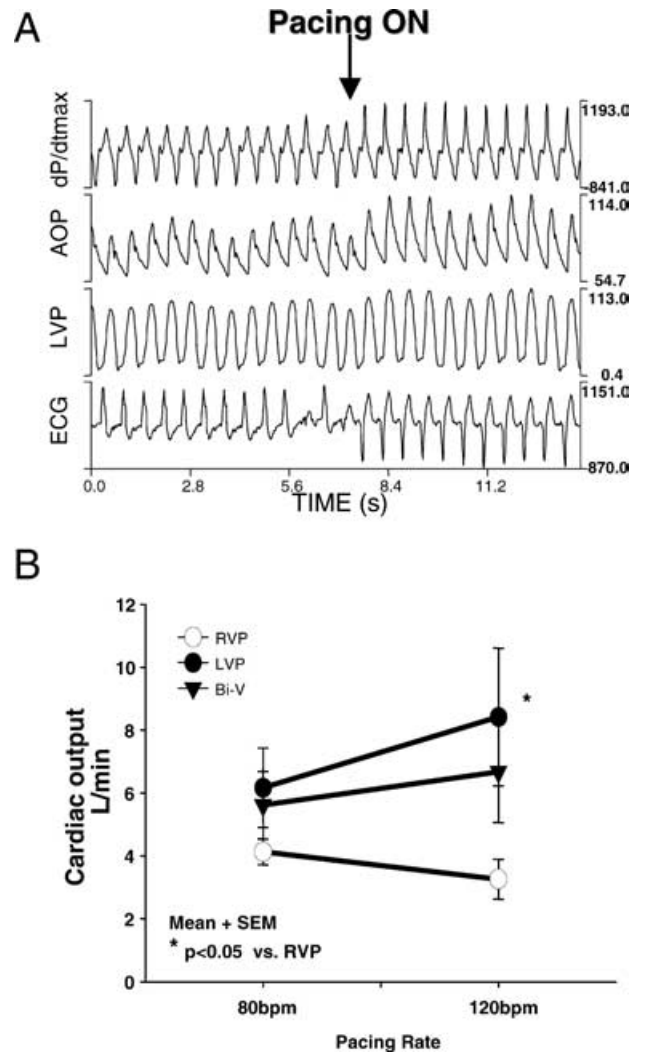


Figure 3. (A) Example of acute impact of CRT on left ventricular function in a patient with dilated heart failure and LBB-type conduction delay. Improvement in systolic function is observed nearly immediately with the institution of CRT (pacing on). (B) Increased disparity between dyssynchronous (LBB-type) and synchronous (biventricular or LV only pacing; BiV, LVP) with cardiac stress induced by rapid pacing. At the faster mean heart rate, the hearts with LV or BiV pacing show increases in cardiac output whereas RV paced (LBB-type) contractions display worsened output. From Hay et al.⁹ Reprinted with permission from the American Heart Association.

Table 1 summarizes recent trials in which remodeling of the heart was studied. The largest was performed in the echosubstudy of the MIRACLE trial. In general, chronic CRT (3–6 months) results in approximately a 10% decline in both volumes. Importantly, if pacing is abruptly suspended, these volume changes do not immediately reverse, consistent with this effect being a remodeling change and not directly related to beat-by-beat CRT-mediated effects on contractile or diastolic function.

Recent Chronic Clinical Data: Mortality

Early clinical trials including randomized studies with and without therapy crossovers demonstrated clinical efficacy of CRT for improving symptoms and reducing rehospitalization rates.¹⁴⁻¹⁷ The COMPANION study reported in mid-2004¹⁶ was the largest trial that further provided data on mortality, but

TABLE 1
Reverse Remodeling from CRT: Summary of Recent Moderate-Sized Chronic Trials

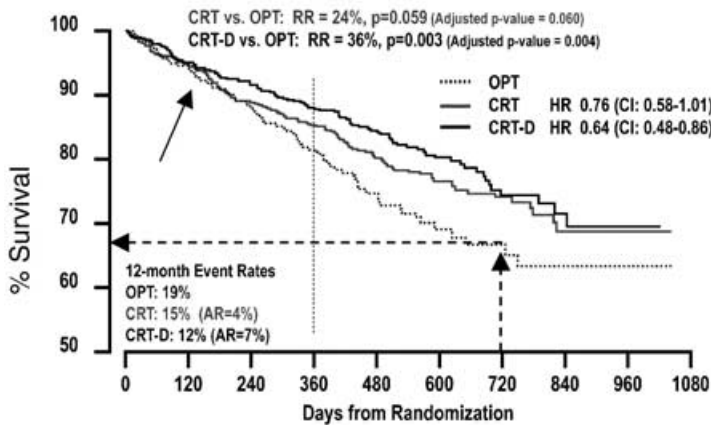
Study		Stellbrink et al. ¹⁰	Saxon et al. ¹¹	Yu et al. ¹²	St John Sutton et al. ¹³
No. of patients		25	35	25	323
Trial		SB/XO	SB	NB	DB/PT
QRS		163 ± 27	177 ± 34	162 ± 30	165 ± 11
LBBB (%)		84	63	—	—
β-blocker		56	27	68	60
FU		6mos	3mos	3mos	6mos
EDV	Baseline	253 ± 83	128.7 ± 37	205 ± 68	295 ± 102
	Post-CRT	227 ± 112	120.6 ± 45	168 ± 67	268.4
	%	-10.3	-6.3	-18.0	-9.0
		0.017	0.08	<0.01	<0.05**
ESV	Baseline	202 ± 79	100.3 ± 36	162 ± 54	227.7 ± 93
	Post-CRT	174 ± 101	92.1 ± 40	122 ± 42	201.9
	%	-13.9	-8.2	-24.7	-11.3
		0.009	0.02	<0.01	<0.05**

SB = single blind; NB = non-blind; DB = double blind; XO = sequential treatment; PT = parallel treatment.

also contrasted treatment with CRT devices alone versus CRT devices combined with an internal automatic defibrillator. For the principal endpoint—reduction in all cause mortality combined with rehospitalization for worsened heart failure, both

CRT and CRT+D (CRT-D) provided significant and nearly identical improvements, with a risk reduction of 24%. Data for event-free survival (i.e., all cause mortality) are shown in Figure 4A. Here there was a significant decline in the CRT-D

A



B

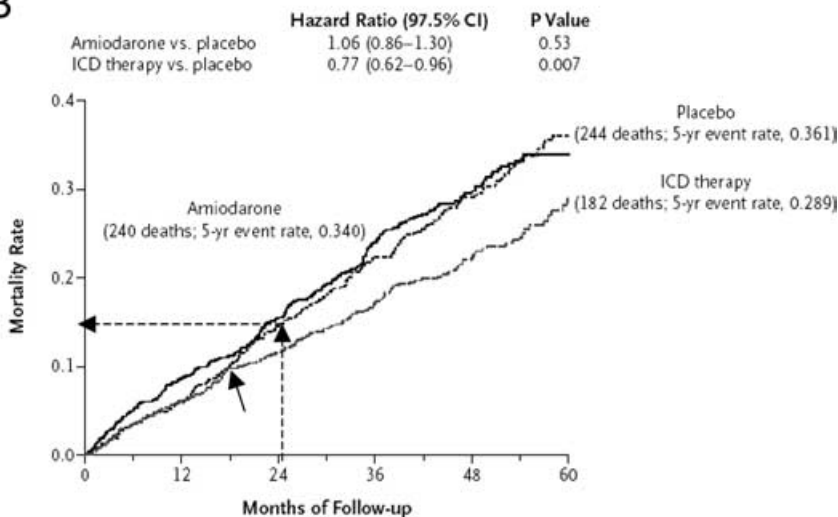


Figure 4. (A) All cause mortality data from the COMPANION trial.¹⁶ Mortality was significantly reduced with the CRT+defibrillator treatment (CRT-D), and borderline improved by CRT alone. Reproduced with permission. Copyright © 2004 Massachusetts Medical Society. (B) Mortality data from SCDHEFT trial.¹⁹ See text for details. Reproduced with permission. Copyright © 2005 Massachusetts Medical Society.

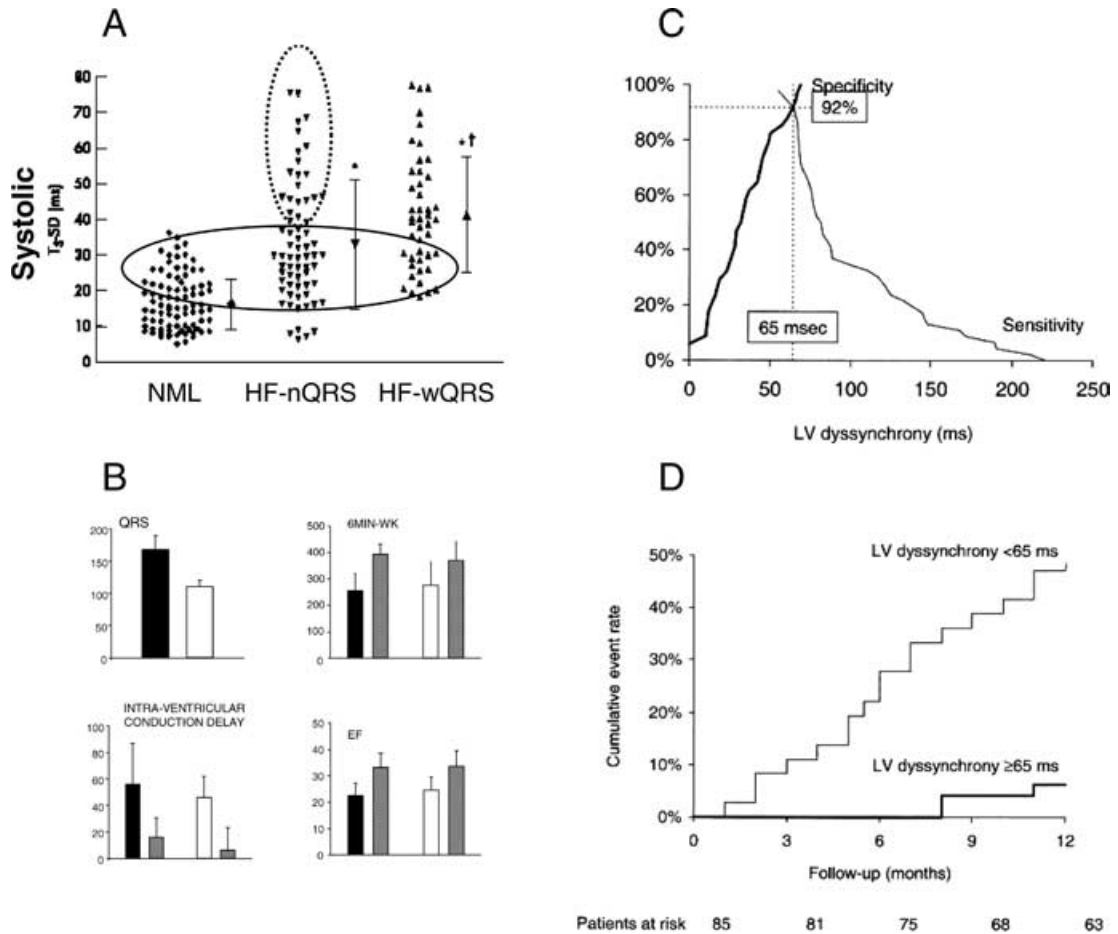


Figure 5. Predicting CRT responders. (A) Presence of mechanical dyssynchrony defined by tissue Doppler imaging in normal patients (NML), and heart failure subjects with a narrow QRS (HF-nQRS) and wide QRS (HF-wQRS) complex. There are patients in all three groups without dyssynchrony, and patients with substantial dyssynchrony in the HF group despite having a narrow QRS complex. Adapted from Yu et al.²⁰ (B) Evidence that CRT treatment in narrow-complex HF patients with mechanical dyssynchrony improves outcome. Two patient groups are shown, both with similar mechanical dyssynchrony but one with a narrow QRS complex. Chronic CRT improved exercise capacity and ejection fraction (EF) in both. Adapted from Achilli et al.²² (C,D) Evidence that a tissue Doppler derived dyssynchrony index can provide high sensitivity and specificity to predict chronic clinical response to CRT. See text for details. Reproduced from Bax et al.²³ Reprinted with permission from the American College of Cardiology Foundation.

group of 36% (P = 0.004). CRT provided about two thirds of this effect, but its impact on total mortality alone was borderline significant (P = 0.06). Most recently, data have been reported for the CARE-HF trial, a study of more than 800 class III and IV heart failure patients who underwent CRT.¹⁸ Here, there was no defibrillator arm. Importantly, CRT was found to reduce all cause mortality, by more than 30% (P < 0.002), although this effect did not appear until ~12 months after implantation, and became increasing prominent over time.

It is useful to contrast the COMPANION mortality curves with those of the recent Sudden Cardiac Death in Congestive Heart Failure (ScdHeft) trial¹⁹ (Fig. 4B). Here, patients were treated with a defibrillator, amiodarone, or no antiarrhythmic therapy. ICD treatment significantly reduced mortality, but notice how the placebo and ICD curves do not diverge until about 18 months after implant. In the COMPANION trial, the CRT-D curves diverge from placebo after only 120 days (4 months), and continued to separate after that. Since both groups had defibrillators, one might speculate that the difference lies in some benefit of CRT on nonsudden death mortality and/or blunting the progression of heart failure.

Overall, 2-year mortality was about 15% in the ScdHeft trial versus nearly 35% in the COMPANION trial—emphasizing the worsened prognosis of patients with wide QRS and heart failure (dashed arrows).

Selecting Patients

One ongoing concern is how to best target CRT therapy to heart failure patients so that those most likely to benefit are appropriately treated. Studies have reported between 25% and 30% of patients receiving CRT do not appear to gain in benefit. The recently completed CAREHF trial, the largest with longest follow-up CRT-only trial to date, found about 40% of subjects receiving CRT still had worsening of heart failure.¹⁸ There are several potential reasons for this. First, these patients suffer severe heart failure and cardiac dyssynchrony is but one of the components contributing to their symptoms and dysfunction. As true for all effective heart failure therapies, a single therapy is not necessarily going to stop the process and the disease can and often does continue to progress. Second, the patients may themselves have not been adequately identified as candidates—based on the

current criteria. Lastly, the therapy may not have been adequately instituted. We will look at the last two issues in some more detail.

All of the clinical trials used QRS duration as the primary identifier for cardiac dyssynchrony, with a few also adding Doppler timing criteria to index discoordinate contraction. However, as noted earlier, QRS duration is useful but is not the sine qua non indicator of mechanical dyssynchrony, and there is growing evidence that the latter is a much better predictor of chronic CRT response. First of all, mechanical dyssynchrony may be in a normal range in heart failure patients despite having a wide QRS complex. This was shown by Yu et al.²⁰ in a study employing tissue Doppler to assess systolic dyssynchrony (Fig. 5A). The dark shaded ellipse shows patients in control, and heart failure with or without a widened QRS complex that all have similar levels of coordinate contraction. In addition, patients with a narrow QRS can also have as much mechanical dyssynchrony as those with a wider QRS (lighter shaded region). Estimates are that about 30% of patients with a narrow QRS and heart failure may have clinically significant mechanical dyssynchrony.²¹ Furthermore, in a recent clinical trial, Achilli et al.²² found that patients with a similar extent of mechanical dyssynchrony respond favorably to chronic CRT with respect to clinical symptoms and reverse remodeling regardless of whether their baseline QRS duration is normal or widened (Fig. 5B).

Several groups have tested the utility of using mechanical dyssynchrony to predict chronic CRT response. Most of these studies have defined a positive response on the basis of cardiac functional improvement (ejection fraction, reverse remodeling). Recently, Bax et al.²³ reported data using a clinical outcome variable as well. Cardiac dyssynchrony was assessed by tissue Doppler imaging, with samples taken in the LV anterior, inferior, septal, and lateral walls, and the maximal time delay from QRS onset to peak systolic velocity used as the dyssynchrony index. As shown in Figure 5C, a delay of 65 msec or more predicted improvement from CRT, where improvement was defined by lowering of New York Heart Association functional class of at least 1 unit, and $\geq 25\%$ increase in 6-minute walk distance. Similar findings were obtained if a marker of reverse remodeling ($\geq 15\%$ decline in end-systolic volume). Using this cutoff, the patients appear to define separate groups (Fig. 5D), where the cumulative event rate (cardiac death, hospitalization for decompensated heart failure) rose in those with less initial dyssynchrony (21 of 80 total patients), but remained low in those with more dyssynchrony ($n = 59$). Importantly, this plot was derived from the same data set used to establish the cut-off for dyssynchrony and does not represent a true prospective assessment of its utility to predict responders.

In summary, many studies have now firmly established that CRT provides substantial clinical symptomatic and likely mortality benefits in appropriate targeted populations. The latter is further impacted by the addition of an ICD, and as arrhythmia is particularly prominent in patients with failure and dyssynchrony, this combination appears justified in many. Dyssynchrony has been defined by QRS duration to date, and as we attempt to refine this definition, it is important to keep this fact in perspective since all our large trial data showing efficacy of CRT was obtained using this simple indicator. Recent data are consistently finding that more direct measures of mechanical dyssynchrony are likely better for predicting CRT response, although exactly how best to index

dyssynchrony remains uncertain. Recent evidence suggests that measures based on long-axis motion (typically used in tissue Doppler velocity analysis) do not provide as much sensitivity and specificity to synchrony/dyssynchrony as those based on circumferential motion.²⁴ Nonetheless, we currently have several reasonable approaches to test, and need larger trials now in which these measures using a predetermined cutoff are prospectively applied to determine their predictive value for CRT responsiveness.

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