# Expanding Cardiac Resynchronization for Systolic Heart Failure to Patients With Mechanical Dyssynchrony and Atrial Fibrillation

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*Despite progress in the management of heart failure (HF) using pharmacotherapy, the mortality and morbidity associated with this condition remain unacceptably high. Cardiac resynchronization therapy (CRT), a left-sided pacing therapy for drug-refractory and highly symptomatic HF patients with ventricular conduction delay, has been shown to improve left ventricular (LV) systolic function, myocardial oxygen consumption, and New York Heart Association functional class and to inhibit or reverse LV chamber dilation and remodeling. Atrial fibrillation is common in patients with HF and is associated with significant worsening of HF and myocardial function. Only recently have trials been designed to specifically study CRT in patients with HF and chronic atrial fibrillation. These studies have shown that CRT with biventricular or univentricular LV pacing in patients with atrial fibrillation corrects mechanical dyssynchrony and results in significant and sustained improvement in functional capacity, LV ejection fraction, quality of life, and QRS duration.*
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**Key words:** Atrial fibrillation • Biventricular pacing • Cardiac resynchronization • Heart failure • Mechanical dyssynchrony • Univentricular pacing

Heart failure (HF) affects more than 10 million patients in the United States and western Europe.[1,2] Its prevalence is age dependent and is estimated to be as high as 10% in patients older than 70 years. Annual HF mortality is associated with its clinical severity and could reach up to 50%.[3,4] Over the past few years, there has been considerable progress in the medical

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management of HF with the use of angiotensin-converting enzyme inhibitors, mineralocorticoid receptor antagonists, and more recently, nonselective β-blockers with vasodilating properties.[5] Despite these medical interventions, the mortality and morbidity associated with HF remain unacceptably high.[3,4]

Patients with dilated cardiomyopathy and uncoordinated left ventricular wall motion due to intraventricular conduction delay (ventricular dyssynchrony) are at increased risk for decompensated HF, arrhythmias, and mortality.[6] Infranodal conduction delay, most commonly in a left bundle branch block (LBBB) pattern, displays early activation of the septal wall. This is followed by delayed lateral contraction at higher stress and simultaneous stretch of the early-activated septum. The net result of reciprocal sloshing of blood from early- to late- to early-activated regions is a decline in systolic function, left ventricular ejection fraction (LVEF), and cardiac output.[7,8]

## Clinical Trials of Cardiac Resynchronization Therapy

Studies have shown that cardiac resynchronization therapy (CRT) with biventricular or left univentricular pacing in patients with severely depressed left ventricular (LV) function and LBBB or intraventricular conduction delay can resynchronize LV contraction. The major effect of pacing is to shift the phase of lateral contraction earlier.[6] The consequence of resynchronization is noted immediately. There is more simultaneous shortening of the septum and lateral wall of the LV, improvement of hemodynamic parameters such as the maximal rate of pressure rise ($dP/dt_{max}$), arterial pulse pressure, and net LVEF.[7] After 1 month or more of pacing, both end-systolic and end-diastolic chamber volumes decline.[8] This effect is sustained even after transient suspension of pacing within 3 months of CRT, supporting a true remodeling effect.[8] Long-term results from the Multisite Stimulation in Cardiomyopathies (MUSTIC) trial indicate that improvements in New York Heart Association (NYHA) class, quality-of-life measures, and LVEF at 3 to 6 months are maintained over a 1-year follow up.[9]

*After 1 month or more of pacing, both end-systolic and end-diastolic chamber volumes decline. This effect is sustained even after transient suspension of pacing within 3 months of CRT, supporting a true remodeling effect.*

In the Multicenter InSync Randomized Clinical Evaluation (MIRACLE) study, patients with moderate to severe symptoms of HF, QRS duration ≥ 130 milliseconds and LVEF ≤ 35% underwent biventricular pacemaker implantation and subsequently were randomly assigned to CRT or to a control group with no pacing for 6 months. Compared with the control group, patients assigned to CRT experienced an improvement in 6-minute walk distance, functional class, quality of life, and LVEF (Figure 1).[10]

Overall, it has been shown that CRT leads to improved LV systolic function with a decline in myocardial oxygen consumption[11] and NYHA functional class and an inhibition or reversal of LV chamber dilation and remodeling (Table 1).[12-16] In the recent Comparison of Medical Therapy, Pacing and Defibrillation in Heart Failure (COMPANION) trial,[17] it was shown that in patients with advanced HF and a prolonged QRS interval ≥ 120 milliseconds, CRT significantly decreased the combined risk of death from or hospitalization

**Figure 1.** *Multicenter InSync Randomized Clinical Evaluation (MIRACLE) trial results of the 6-minute walk test and quality-of-life score (Minnesota Living with Heart Failure; lower scores are better). Shown are median changes (with 95% confidence intervals) 1, 3, and 6 months after randomization in the control group (circles) and the CRT group (diamonds). Reproduced with permission from Abraham WT et al.*[10] www.medreviews.com

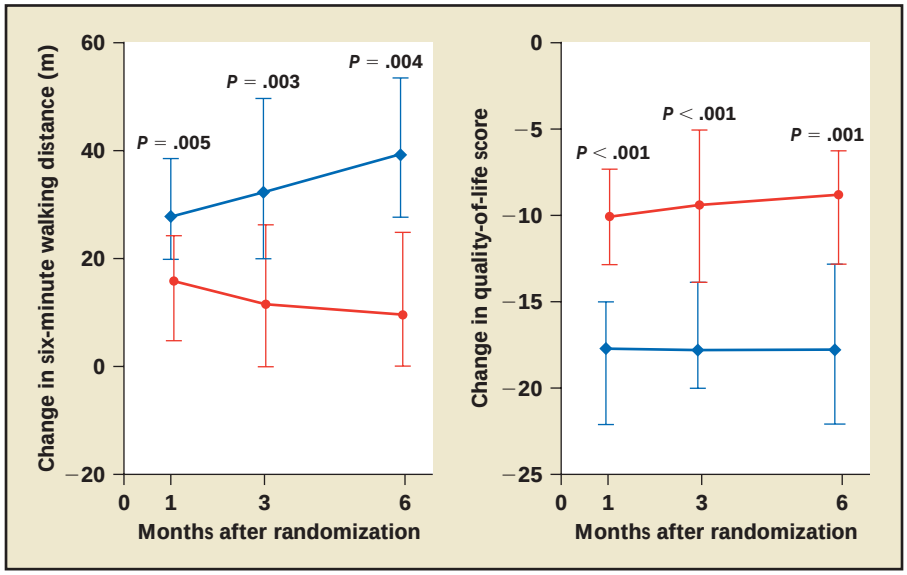


Table 1
Trials of CRT for Congestive Heart Failure

| Study | N | Design | Inclusion Criteria | QRS (milliseconds) | Rhythm | End Points | Results |
|---|---|---|---|---|---|---|---|
| PATH-CHF[14,21,22] | 42 | Prospective randomized single-blind crossover study | Dilated cardiomyopathy of any etiology<br>NYHA class III-IV<br>Sinus rhythm ≥ 55 beats/min | ≥ 120 | Sinus | 6-min walk test<br>Peak $VO_2$ at anaerobic threshold<br>NYHA class<br>QOL | Improvement in all primary and secondary end points at 3 and 12 mo |
| MUSTIC SR[23] | 67 | Prospective randomized single-blind crossover study<br>Controlled study | NYHA class III<br>6-min walk test < 450 m<br>LVEDD > 60 mm<br>LVEF < 35% | > 150 | Sinus | 6-min walk test<br>QOL<br>Peak $VO_2$<br>Hospitalizations<br>Patient's preference | Improved 6-min walk test, QOL, and peak $VO_2$<br>Reduced hospitalizations<br>85% of patients preferred biventricular pacing |
| MUSTIC AF[24] | 59 | Prospective randomized single-blind crossover study<br>Controlled study | NYHA class III<br>Chronic atrial fibrillation with slow ventricular response<br>6-min walk test < 450 m<br>LVEDD > 60 mm<br>LVEF < 35% | > 200 | AF | 6-min walk test<br>QOL<br>Peak $VO_2$, hospitalizations, patient's preference | Improved 6-min walk test, QOL, and peak $VO_2$<br>Reduced hospitalizations<br>Patients preferred biventricular pacing |
| MIRACLE[10,25] | 453 | Prospective randomized double-blind controlled study | NYHA class III-IV<br>Idiopathic or ischemic dilated cardiomyopathy<br>6-min walk test ≤ 450 m<br>LVEDD ≥ 55<br>LVEF ≤ 35% | ≥ 130 | Sinus | NYHA class<br>6-min walk test<br>QOL<br>Peak $VO_2$<br>Hospitalizations<br>Cardiac structure and function using echo indices | Improved NYHA class, 6-min walk test, EF, QOL, and peak $VO_2$<br>Reduced hospitalizations<br>Improved cardiac structure and function by echo |
| VENTAK CHF/CONTAK CD[26,27] | 581 | Prospective randomized crossover study<br>Parallel controlled<br>Double-blind | NYHA class II-IV<br>LVEF ≤ 35%<br>Indication for ICD implantation | > 120 | Sinus | Peak $VO_2$<br>QOL<br>NYHA class<br>6-min walk test<br>Biventricular antitachycardia pacing efficiency<br>Defibrillation therapy safety<br>Hemodynamic echo assessment | Safety of ICD + CRT confirmed<br>Improvements in peak $VO_2$; NYHA class, particularly in III-IV; 6-min walk test; QOL |

(*continued*)

Table 1 (*continued*)

| Study | N | Design | Inclusion Criteria | QRS (milliseconds) | Rhythm | End Points | Results |
|---|---|---|---|---|---|---|---|
| COMPANION[17] | 1520 | Prospective randomized controlled study | NYHA class III-IV<br>Ischemic or nonischemic cardiomyopathy<br>LVEF ≤ 35%<br>No clinical indication for pacemaker or ICD<br>Hospitalization for heart failure in last 12 mo | ≥ 120 | Sinus | Mortality from and hospitalization for any cause<br>All-cause mortality | CRT reduced death from and hospitalization for any cause<br>CRT + ICD reduced mortality from any cause |
| PAVE (not formally published) | 252 | Prospective randomized study | NYHA class I-III<br>Chronic atrial fibrillation for at least one month<br>Post AV nodal ablation<br>6-min walk test < 450 m<br>Enrollment regardless of LV systolic function | N/A | AF | 6-min walk test<br>QOL<br>Peak $VO_2$<br>LVEF | Biventricular pacing improved 6-min walk test, peak $VO_2$, and exercise duration compared with RV pacing<br>LVEF with biventricular pacing was maintained whereas LVEF was reduced with RV pacing at 6 mo |
| CARE-HF[19] | 813 | Prospective randomized controlled study | NYHA class III-IV<br>LVEF ≤ 35%<br>QRS ≥ 150 msec or QRS ≥ 120 msec with echo dyssynchrony criteria<br>LVEDD ≥ 30 mm (indexed to height) | ≥ 120 | Sinus | Mortality from any cause<br>Hospitalization for a major CV event<br>NYHA class<br>QOL<br>LVEF | Significant reduction of mortality from any cause and hospitalizations for a major CV event<br>Improvement in NYHA class, QOL, and LVEF |
| PACMAN | 300 | Prospective randomized single-blind study | NYHA class III with indication for ICD or<br>NYHA class III without indication for ICD<br>LVEF < 35% | > 150 | Sinus | 6-min walk test<br>NYHA class<br>QOL<br>Mortality<br>Hospitalizations<br>Ventricular arrhythmia | Not released |

AF, atrial fibrillation; AV, atrioventricular; echo, echocardiography; CRT, cardiac resynchronization therapy; EF, ejection fraction; ICD, implantable cardioverter-defibrillator; LV, left ventricular; LVEDD, LV end-diastolic diameter; LVEF, LV ejection fraction; NYHA, New York Heart Association (functional class); peak $VO_2$, peak oxygen consumption (cardiopulmonary exercise test); QOL, quality of life; RV, right ventricular.

for any cause as compared with pharmacologic therapy alone (hazard ratio 0.81, $P = .014$; Figure 2A). In combination with an implantable defibrillator, CRT significantly reduced the risk of death from any cause by 36% ($P = .003$; Figure 2B).

A recent meta-analysis of 11 reports of 4 randomized trials in 1634 patients demonstrated that CRT reduced death from progressive HF by 51% (odds ratio [OR] = 49; 95% CI, 0.25-0.93) and HF hospitalizations by 29% (OR = 0.71; 95% CI, 0.53-0.96) compared with controls

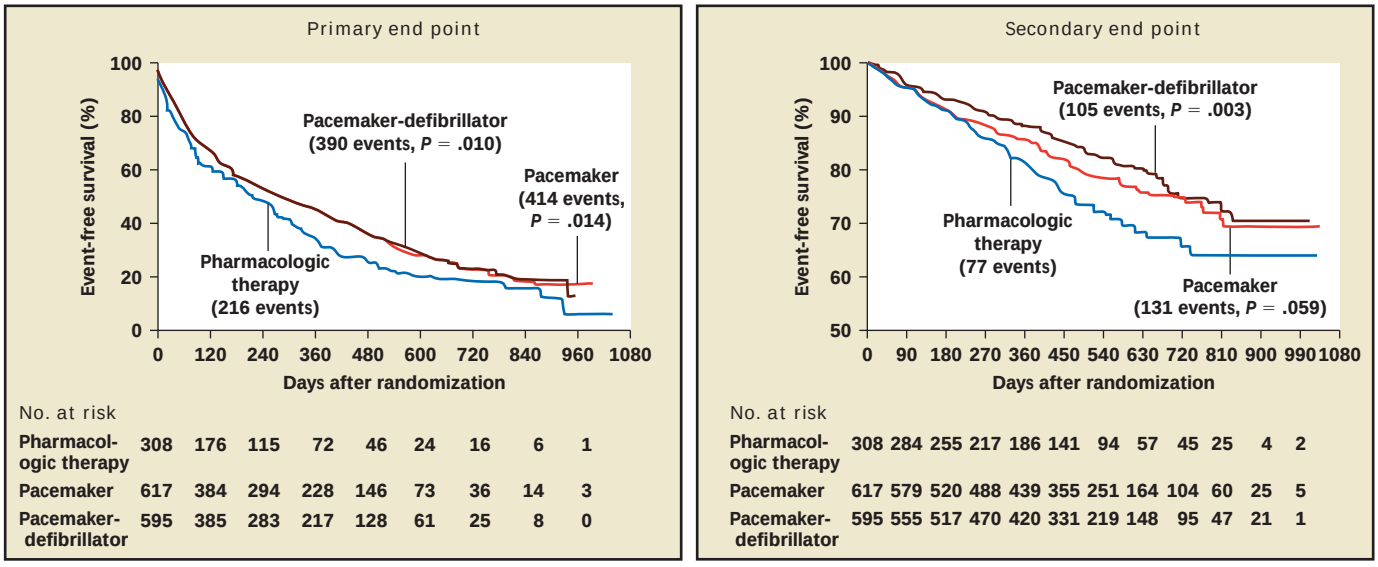



**Figure 2.** *Comparison of Medical Therapy, Pacing and Defibrillation in Heart Failure (COMPANION) trial. Kaplan-Meier estimates of* ***(A)*** *the time to the primary end point of death from or hospitalization for any cause and* ***(B)*** *the time to the secondary end point of all-cause mortality. Reproduced with permission from Bristow MR et al.*[17]

(Figure 3).[18] There are 2 additional randomized trials, the on-going Pacing for Cardiomyopathy: a European Study (PACMAN) and the recently published Cardiac Resynchronization in Heart Failure (CARE-HF) trial,[19] evaluating clinical outcomes of patients receiving CRT.

The CARE-HF trial evaluated clinical outcomes of CRT in patients with NYHA class III or IV heart failure and severe LV systolic dysfunction, with an EF of 35% or less. Patients enrolled in this trial also had QRS duration of either 150 msec or more, or of 120 msec to 149 msec with evidence of mechanical dyssynchrony on echocardiogram including at least 2 of the following 3 criteria: aortic preejection delay of more than 140 msec, interventricular mechanical delay of more than 40 msec, or delayed activation of the posterolateral left ventricular wall.

A total of 813 patients were enrolled in this study and were followed for a mean of 29.4 months. The primary endpoint, death from any cause or an unplanned hospitalization for a major cardiovascular event, was reached significantly less often in the CRT group when compared to the optimal medical therapy group of patients (39 percent vs 55 percent, respectively; HR, 0.63; 95% CI, 0.51-0.77; $P < .001$). In addition, a significant reduction of death from any cause was noted in the CRT group of patients (20% vs 30% in the medical therapy group; HR 0.64; 95% CI, 0.48-0.85; $P < .002$). Furthermore, CRT reduced interventricular mechanical delay, end-systolic volume index, and improved LVEF, symptoms, and quality of life ($P < .01$ for all comparisons). All of these effects were judged in addition to standard pharmacological therapy, indicating that CRT should routinely be considered in such patients.

## Current Indications for CRT and CRT plus Defibrillator

The American College of Cardiology and National Society of Pacemaker and Electrophysiology 2002 guidelines consider CRT a class IIa indication for patients with medically refractory HF (NYHA class III-IV), prolonged QRS duration ($\geq$ 130 milliseconds), LV end-diastolic diameter $\geq$ 55 mm, and LVEF $\leq$ 35%.[20]

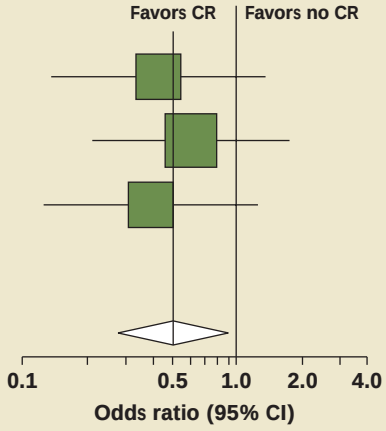
## Is a Wide QRS Enough of a Screening Tool? The Case for Mechanical Dyssynchrony

Interestingly, many recent studies with short- and long-term follow-up have shown that prolonged QRS duration is a poor predictor of clinical response to CRT.[28] In fact, 20% to 30% of patients with QRS duration > 120 milliseconds do not benefit from CRT.[10,29,30] On the other hand, direct detection of mechanical dyssynchrony by M-mode and pulsed-wave (PW) Doppler echocardiography (Figure 4)[31] or by tissue Doppler imaging (TDI; Figure 5)[32] has been shown to be a better predictor of clinical response to CRT than QRS complex prolongation, which is thought to be a rather "coarse" and indirect index of mechanical dyssynchrony.[33] Additionally, mechanical dyssynchrony assessed by magnetic resonance imaging (MRI) also showed better correlation with hemodynamic benefit from CRT compared

A

Progressive heart failure mortality

| Study | Cardiac resynchronization: No. of patients | Cardiac resynchronization: No. (%) of heart failure deaths | No cardiac resynchronization: No. of patients | No cardiac resynchronization: No. (%) of heart failure deaths | Weight (%) | Odds ratio (95% CI) |
|---|---|---|---|---|---|---|
| CONTAK CO | 245 | 4 (1.6) | 245 | 9 (3.7) | 29.6 | 0.44 (0.13–1.43) |
| InSync ICD | 272 | 6 (2.2) | 282 | 10 (3.5) | 39.9 | 0.61 (0.22–1.71) |
| MIRACLE | 263 | 4 (1.5) | 269 | 10 (3.7) | 30.6 | 0.40 (0.12–1.29) |
| MUSTIC | 29 | 0 | 29 | 0 | 0 | |
| Overall | 809 | 14 (1.7) | 825 | 29 (3.5) | | 0.49 (0.25–0.93) |




B

| Study | Cardiac resynchronization: No. of patients | Cardiac resynchronization: No. (%) of patients hospitalized | No cardiac resynchronization: No. of patients | No cardiac resynchronization: No. (%) of patients hospitalized | Weight (%) | Odds ratio (95% CI) |
|---|---|---|---|---|---|---|
| CONTAK CO | 245 | 32 (13.1) | 245 | 39 (15.9) | 32.4 | 0.79 (0.48–1.32) |
| InSync ICD | 272 | 47 (17.3) | 282 | 58 (20.6) | 44.5 | 0.81 (0.53–1.24) |
| MIRACLE | 228 | 18 (7.9) | 225 | 34 (15.1) | 23.1 | 0.48 (0.26–0.88) |
| Overall | 745 | 97 (13.0) | 752 | 131 (17.4) | | 0.71 (0.53–0.96) |

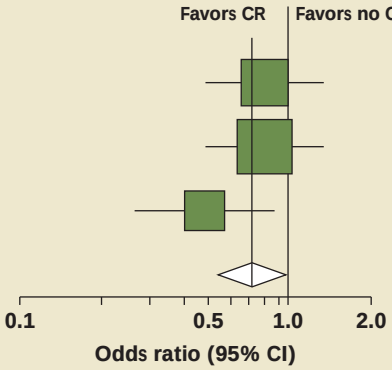



**Figure 3.** *Results of a meta-analysis of clinical trials of cardiac resynchronization therapy. Odds ratio (OR) < 1.0 favors cardiac resynchronization (CR). Weight refers to weight given to each trial in a statistical model. Boxed area is proportional to weight.* ***(A)*** *OR refers to OR of death from progressive heart failure among patients randomized to CR versus no CR. Heterogeneity* $\chi^2_2 = 0.34$ *(P = .85).* ***(B)*** *OR refers to the OR of heart failure hospitalization among patients randomized to CR versus no CR. Heterogeneity* $\chi^2_2 = 0.43$ *(P = .93). MIRACLE, Multicenter InSync Randomized Clinical Evaluation. Reproduced with permission from Bradley DJ et al.*[18]

with electrical dyssynchrony.[34] Until recently, it was assumed that QRS prolongation was synonymous with mechanical dyssynchrony. However, about 30% to 40% of HF patients with QRS duration > 120 milliseconds do not exhibit LV mechanical dyssynchrony as assessed by TDI.[35]

As a possible explanation for this finding, it has been shown by LV endocardial activation mapping that there is heterogeneous LV activation among HF patients with LBBB morphology, with the inability of surface electrocardiographic recordings to predict the location and extent of ventricular conduction delays.[36,37] This is in accordance with experimental data showing heterogeneity between electrical and mechanical dyssynchrony in patients with dilated cardiomyopathy and LBBB.[38] It appears that electrical and mechanical dyssynchrony are not unconditionally coupled, which may explain the significant amount of CRT nonresponders in patients selected for CRT purely on the basis of QRS prolongation > 120 milliseconds and not by direct measures of mechanical dyssynchrony.

There is currently an abundance of different modalities to directly assess mechanical dyssynchrony, including PW Doppler (Figure 4),[31] TDI (Figure 5),[32] M-mode echocar-

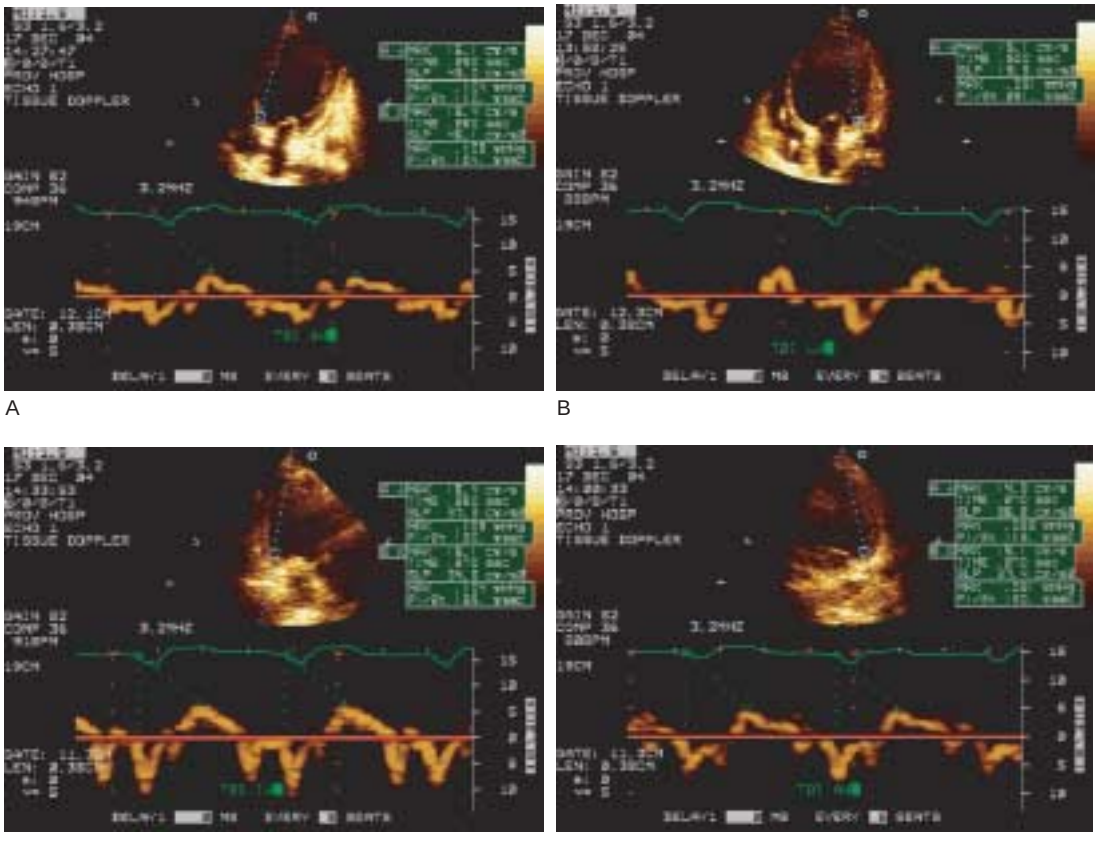


**Figure 4.** *Conventional pulsed-wave tissue Doppler imaging (TDI) obtained from the myocardium one centimeter above the* ***(A)*** *septal (TDI SW),* ***(B)*** *lateral (TDI LW),* ***(C)*** *inferior (TDI IW), and* ***(D)*** *anterior (TDI AW) mitral annulus in a patient with intraventricular electromechanical dyssynchrony. Velocity recordings represent systolic velocity profile (upward Doppler signal) and diastolic velocity profiles (downward Doppler signals). Tissue Doppler electromechanical delay time (TDEMD) of different myocardial wall segments are measured from QRS onset to maximal systolic tissue Doppler velocity. The difference between longest and shortest TDEMD equals intraventricular electromechanical delay. Courtesy of Providence Hospital Echocardiography Laboratory, Southfield, MI.*

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diography, strain Doppler imaging,[39] MRI, and others. However, there remains a major need to simplify and standardize the process of assessment of mechanical dyssynchrony to achieve a widely available parameter to best select patients for CRT.[33]

Cardiac resynchronization therapy is currently not recommended in patients with refractory HF and normal QRS duration $< 120$ milliseconds. However, a high prevalence of mechanical dyssynchrony has been found in patients with LV dysfunc-

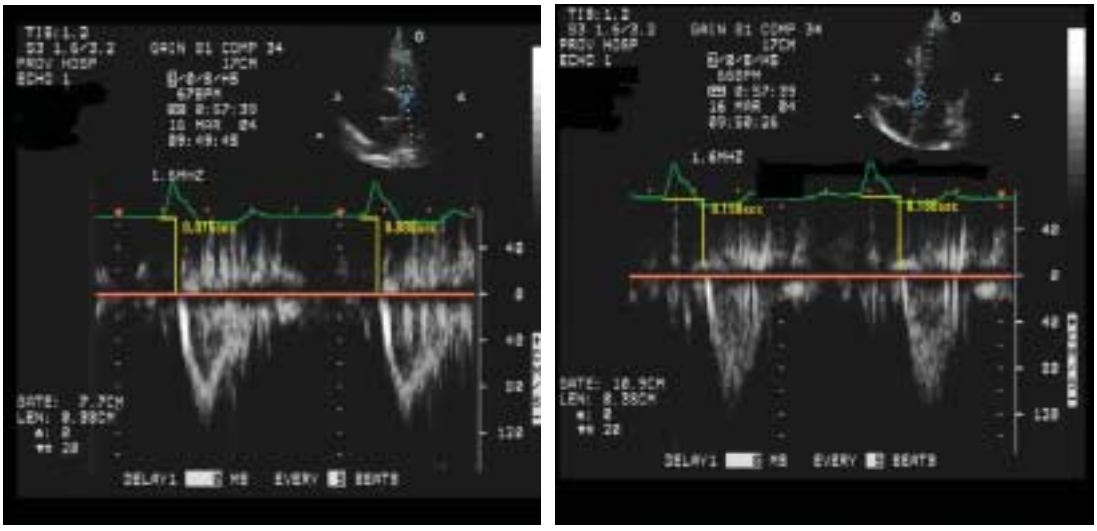

**Figure 5.** *Measurement of the interventricular mechanical delay (IVEMD) by Doppler echocardiography in a patient with interventricular dyssynchrony. The* ***(A)*** *right ventricular (RV) and* ***(B)*** *left ventricular (LV) preejection intervals (PEIs) are measured from the onset of the QRS on the electrocardiogram to the onset of pulmonary (RV-PEI) and aortic outflow (LV-PEI). IVEMD is calculated by subtracting the RV-PEI from the LV-PEI. In the above example, 190 milliseconds (ms) − 77.5 ms = 117.5 ms, which suggests interventricular dyssynchrony. Reproduced with permission from Hassunizadeh et al.*[40]

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tion and normal QRS duration, ranging from 27% to 56% in different studies.[35,40,41] In fact, in a small study by Achilli and colleagues,[42] 14 patients with evidence of mechanical dyssynchrony detected by PW Doppler and M-mode echocardiography and normal QRS duration $<$ 120 milliseconds underwent CRT. During a mean follow-up of 546 $\pm$ 277 days, significant improvements in NYHA functional class, LVEF, ventricular volumes, and induction of reversed remodeling were found. In another study by Turner and associates,[43] 9 patients with severe HF, narrow QRS complex $<$ 120 milliseconds, and mechanical dyssynchrony detected by TDI were treated with LV and biventricular pacing. Significant improvements in NYHA functional class and LVEF were found after CRT. Additionally, significantly improved interventricular (time delay between right ventricular [RV] and LV contraction) and intraventricular (time delay between contraction of different segments of LV) systolic synchrony as assessed by the applied TDI parameters was detected. However, currently there are no large randomized trials of CRT in patients with LV dysfunction and a narrow QRS complex. Likewise, there are no published trials of CRT in patients selected by indices of mechanical dyssynchrony in place of QRS duration.

## Atrial Fibrillation and Heart Failure

Atrial arrhythmias are common in patients with HF, regardless of the underlying etiology.[44] The prevalence of atrial fibrillation in patients with HF is between 10% and 40%, depending in part on the severity of HF.[45-47] Atrial fibrillation has deleterious effects on myocardial function via three pathways: 1) loss of atrial contribution; 2) irregular rhythm and variable filling of the LV; and 3) rapid ventricular rate, leading to rate-related ventricular cardiomyopathy.[48-50] Observational studies have demonstrated that development of chronic atrial fibrillation in HF patients is associated with significant worsening of HF and myocardial function.[51] Thus, it is important to control atrial fibrillation in patients with HF. There are two main issues that must be addressed in the treatment of atrial fibrillation: the choice between rhythm control and rate control, and prevention of systemic embolization.[52,53] A third issue of relative significance, which is underaddressed in the literature, is *rate regularization*. Rate control and rhythm control lead to improved LV function.[54] Recent data from the Atrial Fibrillation Follow-Up Investigation of Rhythm Management (AFFIRM) and Rate Control Versus Electrical Cardioversion (RACE) trials have demonstrated that both rate and rhythm control are acceptable options for long-term treatment of atrial fibrillation.[55,56] These results may not be applicable to patients with systolic HF. The Atrial Fibrillation in Congestive Heart Failure (AF-CHF) trial is ongoing and is evaluating rhythm control versus rate control strategies in patients with atrial fibrillation and systolic HF. There is an array of pharmacologic and nonpharmacologic therapies available for rate control. The US Carvedilol Heart Failure Trials Program demonstrated that rate control with carvedilol in patients with atrial fibrillation and HF could significantly increase LVEF, with a trend toward reduction in the combined end point of death or HF hospitalization.[57] Restoration and maintenance of sinus rhythm by pulmonary vein catheter ablation in patients with HF and atrial fibrillation has also been shown to significantly improve LVEF, LV diastolic and systolic dimensions, exercise capacity, symptoms, and quality of life.[58] A hybrid therapy combining septal pacing with a ventricular rate regularization feature also demonstrated improvement in acute hemodynamics in a selected group of atrial fibrillation patients.[59]

Nonpharmacologic therapies have been reserved for patients with chronic atrial fibrillation with rapid ventricular conduction that is refractory to pharmacologic treatment.[60] The most commonly utilized nonpharmacologic method for rate control is atrioventricular nodal ablation (AVNA) using radiofrequency and permanent pacemaker placement. The Ablate and Pace Trial showed overall safety and efficacy of this therapy.[61] In this study, treatment with AVNA and permanent pacemaker implantation was associated with improved NYHA functional class and quality of life in a highly symptomatic population of patients with refractory atrial fibrillation. The patients with reduced ventricular function at baseline had the greatest improvement in LV systolic function after 12 months of pacing.

In a published meta-analysis, it was noted that AVNA and RV pacing improve ventricular function, symptoms, and quality of life in patients with atrial fibrillation refractory to drug therapy.[62] However, some patients may have persistent or progressive HF symptoms after AVNA and RV pacing.[63] One explanation may be that cardiac pacing from the RV apex leads to an abnormal LV activation sequence with an LV conduction pattern similar to LBBB. Pacing from the RV apex creates a nonphysiologic dyssynchronous contraction and leads to paradoxic septal motion with reduction in ejection fraction and a detrimental effect on systolic pressure and cardiac output.[64] In one study performed in

patients with HF, RV pacing was associated with a significant deterioration of cardiac function of about 10% to 20%.[24]

### CRT in Patients With Atrial Fibrillation

Cardiac resynchronization therapy, a left-sided pacing therapy for drug-refractory and highly symptomatic HF patients with ventricular conduction delay, is currently indicated in patients with preserved normal sinus rhythm. It can be delivered in different fashions, either by simultaneous pacing of the RV and LV (referred to as biventricular pacing) or by pacing the LV alone. As summarized above, CRT improves systolic function, quality of life, and exercise tolerance in patients with severe HF despite optimal medical therapy (Table 1).[21] Most clinical trials of CRT have excluded patients with atrial fibrillation or chronic RV pacing. Only recently have trials been designed to specifically look at CRT in patients with HF and chronic atrial fibrillation with and without AVNA.[65] In a study by Leclerq and coworkers,[24] patients with NYHA functional class III with LV systolic dysfunction (ejection fraction $< 35\%$) and chronic atrial fibrillation with slow ventricular response underwent biventricular pacemaker implantation. These patients had a wide RV-paced QRS complex of $> 200$ milliseconds. Patients were treated for 3 months with conventional right univentricular pacing and subsequently with biventricular pacing for 3 months. In patients who completed the crossover phases, it was noted that effective biventricular pacing improved exercise tolerance as well as peak oxygen uptake compared with conventional VVIR pacing. Leon and colleagues[66] studied patients with ejection fraction $< 35\%$, prior AVNA and RV pacing, and chronic atrial fibrillation. They demonstrated that switching from RV pacing to biventricular pacing is associated with significant improvements in NYHA functional class, hospitalization frequency, quality of life, and LVEF, and leads to reversed remodeling. These benefits are similar to those seen in patients in sinus rhythm in previous CRT trials, suggesting that benefits of biventricular pacing may result from resynchronization rather than optimization of atrioventricular nodal delay. In the Optimal Pacing Site (OPSITE) trial,[67] patients with permanent atrial fibrillation and a drug-refractory, severely symptomatic, uncontrolled, rapid ventricular rate were treated with AVNA and underwent biventricular pacemaker implantation. These patients also had drug-refractory HF and depressed LV function and/or LBBB. Univentricular RV pacing was compared with univentricular LV pacing in a prospective randomized crossover study design. Right ventricular and LV pacing studies were performed during the same session in each patient. Compared with RV pacing, LV pacing resulted in a significant increase in ejection fraction, a decrease in mitral regurgitation, and a reduction in QRS duration. Similarly beneficial results were seen in patients with normal or depressed cardiac function and also in patients with or without LBBB in this study. Left ventricular pacing resulted in a statistically significant clinical advantage over RV pacing. The authors did not compare the effects of biventricular pacing, which may be more effective than LV pacing alone. This may be especially true in patients with previous AVNA as preexcitation of only the left ventricle may create a delayed activation of the septum and RV, which may worsen overall LV systolic function, analogous to the negative effects generated by RV pacing only.[68] The Post AV Node Ablation Evaluation (PAVE) trial was presented at the American College of Cardiology Annual Scientific Session in 2004. It was the first prospective randomized comparison of RV and biventricular pacing and studied 184 patients with chronic atrial fibrillation who underwent AVNA and pacemaker implantation. Inclusion criteria were chronic atrial fibrillation of $\geq 1$ month's duration, NYHA functional class I to III, and 6-minute walking distance of $< 450$ m. Enrollment of patients was regardless of LV function and QRS duration. Improvement in 6-minute walking distance was significantly more in the biventricular pacing group compared with the RV-paced group of patients after 6 months of therapy ($+ 82.5$ m vs $+ 56.8$ m, $P = .03$). Exercise duration during cardiopulmonary testing, peak oxygen consumption, and quality of life significantly improved with biventricular pacing compared with RV pacing alone. At 6 months, LVEF remained stable compared with baseline in the biventricular pacing group (45.6% vs 46.0 %, $P =$ not significant) whereas a deterioration was seen in the RV-paced group (44.9% vs 40.7%, $P = .03$). There was no difference in survival between the two groups.

*In one study performed in patients with HF, RV pacing was associated with a significant deterioration of cardiac function of about 10% to 20%.*

Preliminary data from the Registry of Cardiac Resynchronization Therapy–United States (RESTORE-US) were presented at the Heart Failure Society of America's 2004 scientific meeting. This analysis found that

Table 2
Proportion of Cardiac Resynchronization Therapy Recipients Improving in New York Heart Association Functional Class over 6 Months*

| End point | AF (n = 83) | No AF (n = 162) |
|---|---|---|
| Improved by 1 functional class (%) | 49.4 | 41.4 |
| Improved by > 2 functional classes (%) | 28.9 | 36.4 |

*Change from baseline to 6 months, $P < .001$ for both groups. No significant difference between the two patient groups in changes at 6 months.
AF, atrial fibrillation.
Data presented at the Heart Failure Society of America 8th Annual Scientific Meeting (RESTORE-US); September 9-15, 2004; Toronto, Ontario.

Table 3
Mean Quality-of-Life Scores* over 6 Months in Patients Receiving Cardiac Resynchronization Therapy

| Interval | AF (n = 69) | No AF (n = 121) |
|---|---|---|
| Baseline | 58.7 | 54.3 |
| 6 mo | 31.1 | 29.5 |

*Minnesota Living with Heart Failure questionnaire (lower scores imply better quality of life). Change from baseline to 6 months, $P < .001$ for both groups. No significant difference between the two patient groups in degree of change at 6 months.
AF, atrial fibrillation.
Data presented at the Heart Failure Society of America 8th Annual Scientific Meeting (RESTORE-US); September 9-15, 2004; Toronto, Ontario.

atrial fibrillation had no negative impact on CRT-related improvements in NYHA class or quality-of-life measures. An improvement of 1 in NYHA functional class was found in 49.4% of patients in the atrial fibrillation group compared with 41.4% in the non–atrial fibrillation group ($P$ = not significant). An improvement of 2 in NYHA functional class was found in 28.9% of the atrial fibrillation group compared with 36.4% of the non–atrial fibrillation group ($P$ = not significant; Table 2). Mean quality-of-life scores in patients who received CRT were 31.1 in atrial fibrillation patients and 29.5 in patients without atrial fibrillation after 6 months ($P$ = not significant; Table 3).

## Conclusion

Cardiac resynchronization therapy with biventricular or univentricular in LV pacing in patients with HF and chronic atrial fibrillation is safe and effective. In the future, rather than using QRS duration, assessments of mechanical dyssynchrony by cardiac imaging may provide better criteria for selection of CRT candidates. Univentricular RV pacing may be associ-

## Main Points

- Despite considerable progress in the medical management of heart failure (HF) with the use of angiotensin-converting enzyme inhibitors, mineralocorticoid receptor antagonists, and nonselective β-blockers with vasodilating properties, the mortality and morbidity associated with HF remain unacceptably high.
- Several studies have shown that cardiac resynchronization therapy (CRT) with biventricular or left univentricular pacing in patients with severely depressed left ventricular (LV) function and left bundle branch block or intraventricular conduction delay can resynchronize LV contraction.
- Overall, it has been shown that CRT leads to improved LV systolic function with a decline in myocardial oxygen consumption, New York Heart Association functional class, and inhibition or reversal of LV chamber dilation and remodeling.
- Direct detection of mechanical dyssynchrony by M-mode and pulsed-wave (PW) Doppler echocardiography or by tissue Doppler imaging has been shown to be a better predictor of clinical response to CRT than QRS complex prolongation, which is thought to be a rather "coarse" and indirect index of mechanical dyssynchrony.
- Biventricular or univentricular LV pacing in patients with atrial fibrillation may provide more physiologic correction of mechanical dyssynchrony than that achieved with right ventricular pacing alone and results in significant and sustained improvements in functional capacity, LVEF, quality-of-life parameters, and QRS duration.

ated with poorer outcomes as a result of alteration of the natural sequence of electrical activation and dyscoordinate mechanical contraction. Biventricular or univentricular LV pacing in patients with atrial fibrillation may provide more physiologic correction of mechanical dyssynchrony and may result in significant and sustained improvements in functional capacity, LVEF, quality-of-life parameters, and QRS duration. ■

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