

Circulation

JOURNAL OF THE AMERICAN HEART ASSOCIATION



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Circulation 2003;108;1044-1048

DOI: 10.1161/01.CIR.0000085656.57918.B1

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75214

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Resynchronization Therapy for the Treatment of Heart Failure

Leslie A. Saxon, MD; Kenneth A. Ellenbogen, MD

Heart failure remains a major cardiovascular health problem, afflicting 22 million individuals worldwide and approximately 5 million persons in the United States alone. Management of patients with this problem represents the largest single expense to Medicare. A common feature predictive of adverse clinical outcomes in patients with congestive heart failure is prolongation of the QRS duration. Several different types of studies suggested QRS delay was an independent risk factor for adverse outcome, particularly in patients with left ventricular dysfunction.^{1,2} These data were derived from both longitudinal population studies and retrospective studies performed in heart failure patients with pacemakers and “acquired” left bundle branch block (LBBB).^{1,2} The significance of QRS delay in heart failure patients is that this common finding may be observed in up to 30% of patients with moderate to severe heart failure.

Acute studies performed with hemodynamic measurements and nuclear imaging phase analysis demonstrate that QRS delay, particularly LBBB, creates electrical and mechanical dyssynchrony in patients with depressed

left ventricular function. Delayed and inhomogeneous left ventricular activation reduces stroke volume, left ventricular ejection fraction, and time for aortic ejection. Reductions in left ventricular dP/dT, increased left ventricular end-systolic and diastolic volumes, and abnormal patterns of wall stretch are also seen.³⁻⁵ Additionally, ventricular dyssynchrony promotes functional mitral regurgitation. Acutely pacing the right and left ventricle simultaneously or pacing the left ventricle alone results in marked improvements and restoration of a more homogeneous contraction pattern (Figure 1 and Figure 2).

The Patient Population

The characteristics of the patient population enrolled in chronic resynchronization trials are shown in Table 1. In the early trials, QRS duration alone was used to define eligibility criteria. In recent years, attempts to characterize mechanical dyssynchrony by echocardiographic measures have led to their inclusion as eligibility criteria and to determine if resynchronization therapy is improving these measures. Two initial clinical trials of chronic resynchronization therapy with a defibrillator (CRT-D)

included patients with New York Heart Association functional class (NYHA FC) II–IV heart failure symptoms. Because of lack of demonstrable benefit in functional status in class II patients, current Food and Drug Administration labeling and enrollment in clinical trials is currently restricted to patients with NYHA FC III–IV symptoms. Sixty percent of patients with heart failure caused by systolic dysfunction are NYHA FC II and III. The annual mortality rate for this group of patients is approximately 10%. The primary cause of death in this patient population is progressive heart failure and sudden death. Patients with more advanced heart failure are more likely to die from progressive pump failure, and patients with less advanced heart failure are more likely to experience sudden death.

Coronary Sinus Branch Vein Pacing to Achieve Left Ventricular Stimulation

The first clinical trials of CRT, achieved with simultaneous biventricular stimulation, were performed in the United States and Europe from 1995 to 1998. Left ventricular stimulation was initially achieved using an active fixation epicardial pacing lead usually placed via a

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(*Circulation*. 2003;108:1044-1048.)

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Circulation is available at <http://www.circulationaha.org>

DOI: 10.1161/01.CIR.0000085656.57918.B1

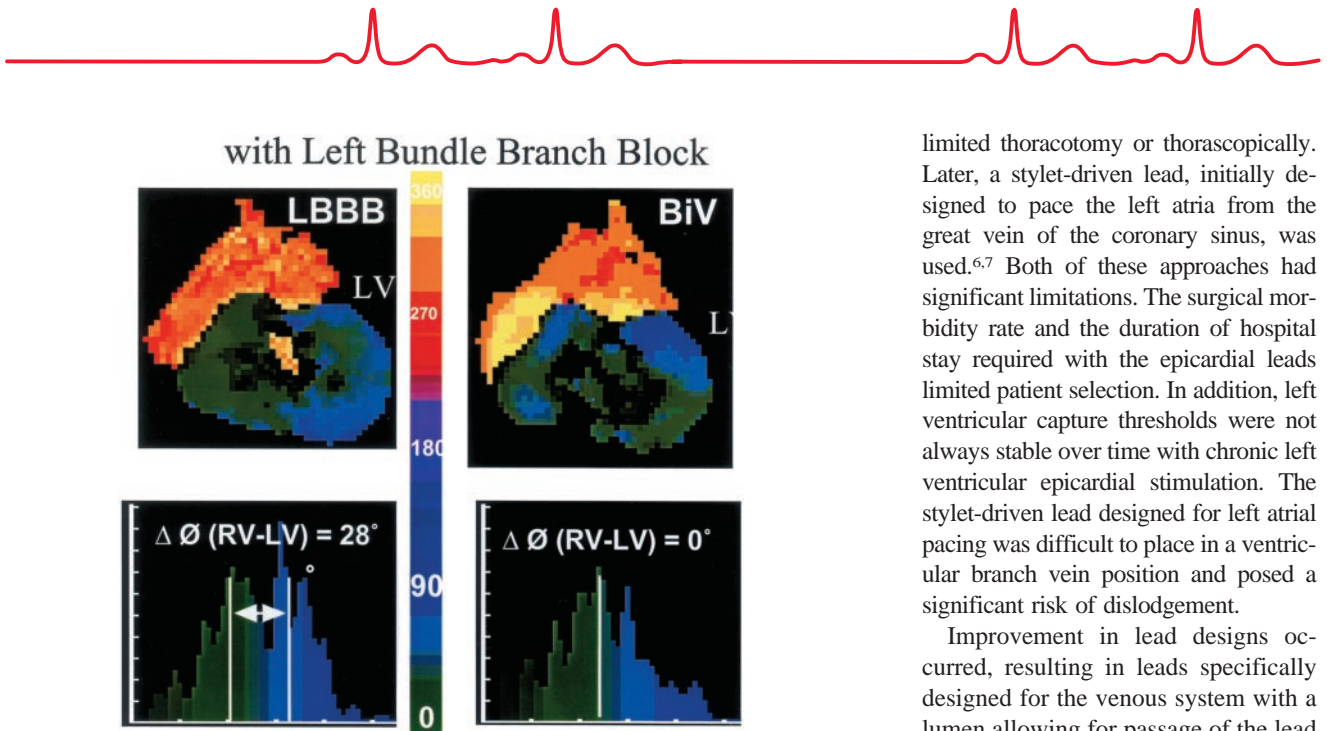


Figure 1. The upper panels represent phase images obtained during normal sinus rhythm with LBBB and during atrial sensed CRT. The contraction sequence is indicated by the color bar from early (green) to late (yellow). The histograms below each image illustrate the dispersion of the phase angle ϕ , computed for the RV and LV blood pools. In the first panel, the right ventricle (RV) contracts early relative to the body of the left ventricle (LV). The atria contract after the LV. The difference is calculated by the phase angle in the histogram. In the second panel, during CRT, the LV apex and septum are activated simultaneously with most of the RV and interventricular septum, and a marked decrease in phase angle is shown in the histogram below. BiV indicates biventricular. Reprinted with permission from reference 4 (Kerwin WF, Botvinick EH, O’Connell JW, et al. Ventricular contraction abnormalities in dilated cardiomyopathy: effect of biventricular pacing to correct interventricular dyssynchrony. *J Am Coll Cardiol.* 2000;35: 1221–1227). Copyright 2000, American College of Cardiology Foundation.

limited thoracotomy or thoroscopically. Later, a stylet-driven lead, initially designed to pace the left atria from the great vein of the coronary sinus, was used.^{6,7} Both of these approaches had significant limitations. The surgical morbidity rate and the duration of hospital stay required with the epicardial leads limited patient selection. In addition, left ventricular capture thresholds were not always stable over time with chronic left ventricular epicardial stimulation. The stylet-driven lead designed for left atrial pacing was difficult to place in a ventricular branch vein position and posed a significant risk of dislodgement.

Improvement in lead designs occurred, resulting in leads specifically designed for the venous system with a lumen allowing for passage of the lead over a guidewire placed distally in the vein. Acute data indicate that in most patients, optimal hemodynamic response is obtained if the LV lead is placed in a posterolateral, lateral, or anterolateral vein to provide resynchronization therapy, although this has not been well studied with chronic therapy.⁸ Subsequent controlled trials performed in the United States utilizing these leads designed to cannulate one of the branch veins of the coronary sinus showed a greater than 90% success rate with average procedure times of 2 to 4 hours.

The most common reasons for failure to implant a CRT device is inability to achieve a stable location in a

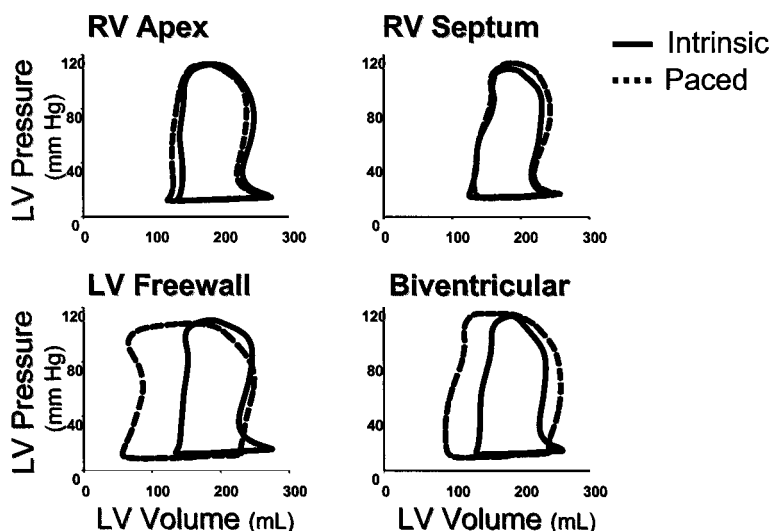


Figure 2. Pressure-volume analysis from a patient with heart failure and LBBB comparing RV septal, apical, LV free wall and simultaneous biventricular stimulation (dashed line) to intrinsic rhythm (solid line). No improvement in hemodynamic profile is observed with either RV pacing site. Both left free wall and biventricular stimulation reduced end-systolic volume and increased stroke volume (increased loop width) and stroke work (loop area). Reprinted with permission from reference 3.

TABLE 1. Inclusion Criteria for Chronic Resynchronization Studies Performed in the United States From 1996 to 2002

- Symptomatic heart failure due to systolic dysfunction (LVEF <35%, NYHA FC III–IV) and heart failure hospitalization in the past year*
- QRS Duration >120 or 130 msec and left bundle branch block and/or evidence of dyssynchrony on echocardiogram
- Normal sinus node function†
- Appropriate medical therapy for heart failure, including angiotension-converting enzyme inhibitors, diuretics, β receptor blocker therapy, and spironalactone if indicated

*Requirement for the COMPANION trial.

†All but 1 ongoing trial evaluating CRT in patients without permanent atrial fibrillation.

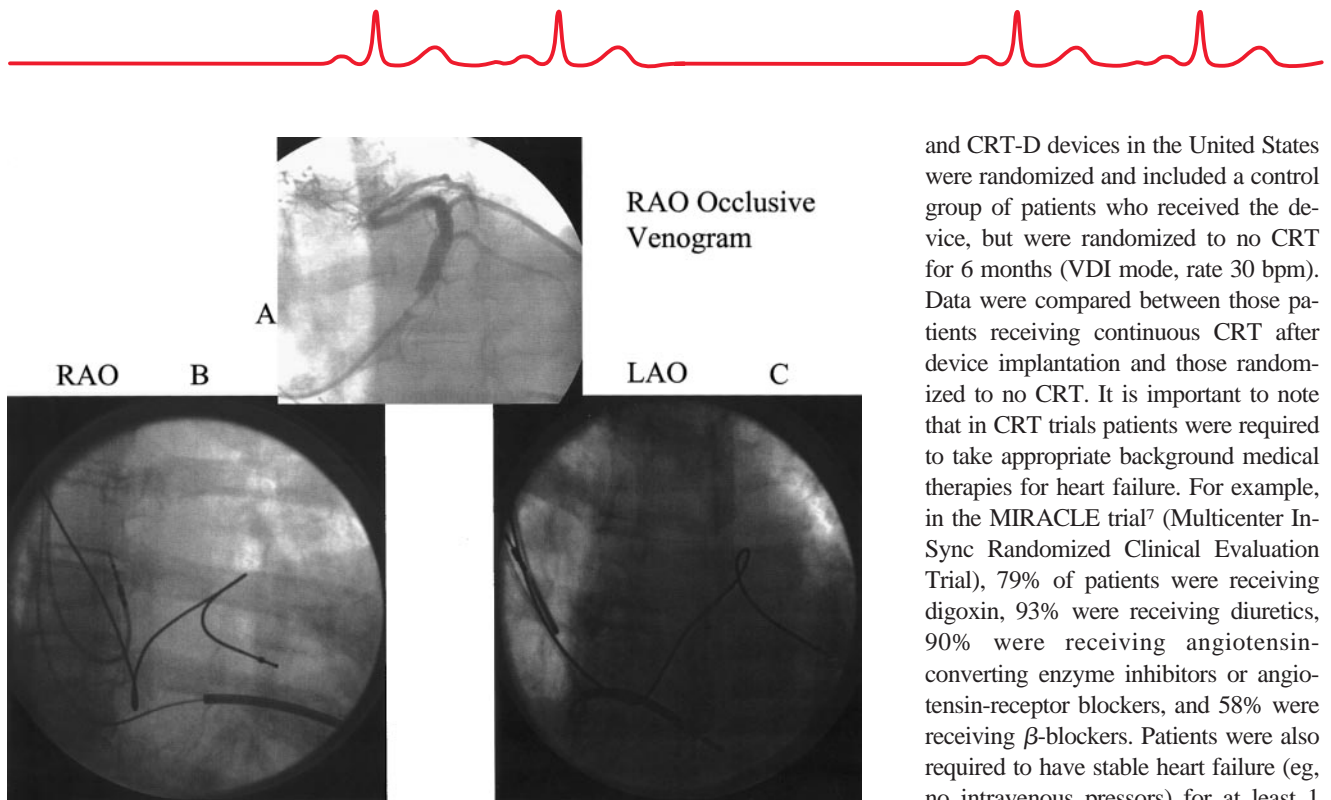


Figure 3. A, RAO occlusive venogram of the great cardiac vein and branch veins of the coronary sinus. Visualized branch veins include (top to bottom) anterior, anterolateral, and lateral vein. B and C, RAO and LAO views of the left ventricular lead placed in the lateral branch vein, midway between the base and apex of the left ventricle.

coronary vein, inability to obtain a distal location in a coronary vein, inability to cannulate the coronary sinus, unacceptable pacing thresholds, and phrenic nerve stimulation. Fluoroscopic time, procedure time, and percent of patients undergoing successful implantation of a biventricular device increase with experience. Chronic capture thresholds remain very stable over 6 months to 2 years of follow-up.

Figure 3A demonstrates an occlusive venogram of the coronary sinus, showing great cardiac vein and branch vein anatomy. Figure 3B and 3C illustrate right and left anterior oblique (RAO and LAO) projections of a cor-

onary sinus lead placed in a lateral branch vein. Endocardial right atrial and right ventricular leads placed in the right atrial appendage and right ventricular apex are also seen. There can be marked variability in the location of the coronary sinus ostium and in branch vein anatomy. The upper panel of Figure 4 demonstrates the ECG of a patient before and after biventricular stimulation.

Trial Design and Study Endpoints

The clinical trial designs of the 3 studies^{7,9,10} that resulted in approval for CRT

and CRT-D devices in the United States were randomized and included a control group of patients who received the device, but were randomized to no CRT for 6 months (VDI mode, rate 30 bpm). Data were compared between those patients receiving continuous CRT after device implantation and those randomized to no CRT. It is important to note that in CRT trials patients were required to take appropriate background medical therapies for heart failure. For example, in the MIRACLE trial⁷ (Multicenter InSync Randomized Clinical Evaluation Trial), 79% of patients were receiving digoxin, 93% were receiving diuretics, 90% were receiving angiotensin-converting enzyme inhibitors or angiotensin-receptor blockers, and 58% were receiving β -blockers. Patients were also required to have stable heart failure (eg, no intravenous pressors) for at least 1 month before enrollment.

The MIRACLE trial⁷ reported significant improvements in the primary functional endpoints of symptom status and exercise capacity. Heart failure hospitalizations were also decreased over the 6-month follow-up interval. The InSYNC ICD and CONTAK CD^{9,10} studies utilized a CRT-D device and enrolled patients who were candidates for resynchronization therapy in addition to having an implantable cardioverter-defibrillator (ICD) indication. Significant improvements were noted in symptom status and exercise capacity in enrolled patients with NYHA FC III or IV symptoms. Patients enrolled in the CRT-D studies had a higher incidence of ischemic versus non-ischemic etiology of heart failure when compared with those enrolled in the MIRACLE trial.^{9,10} Table 2 summarizes the changes in symptom status and exercise capacity observed across the 3 trials. Only 1 trial, the Multicenter Stimulation in Cardiomyopathy-Atrial Fibrillation (MUSTIC-AF) trial,^{10a} examined patients with atrial fibrillation. In the small number of patients studied, the exercise and quality of life benefits appeared to be of similar magnitude to those in patients in sinus rhythm in the same study. On average, 70% of patients receiving CRT therapy

TABLE 2. Clinical Differences Comparing CRT With No CRT at 6-Month Follow-Up

Parameter	MIRACLE	InSync ICD	CONTAK CD
Total No.	345	258	227
MN QOL score, points	-9 ($P=0.003$)	-9 ($P=0.01$)	-10 ($P=0.02$)
NYHA FC, % improved ≥ 1 class	30% ($P<0.001$)	16% ($P=0.03$)	18% ($P=0.01$)
6-minute walk distance, m	30 ($P=0.003$)	3 ($P=ns$)	39 ($P=0.03$)
Peak $\dot{V}O_2$, mL \cdot kg ⁻¹ \cdot min ⁻¹	0.8 ($P=0.04$)	0.6 ($P=0.05$)	1.8 ($P=0.003$)

MN QOL score indicates Minnesota Living With Heart Failure Quality of Life score; Peak $\dot{V}O_2$, peak oxygen consumption.

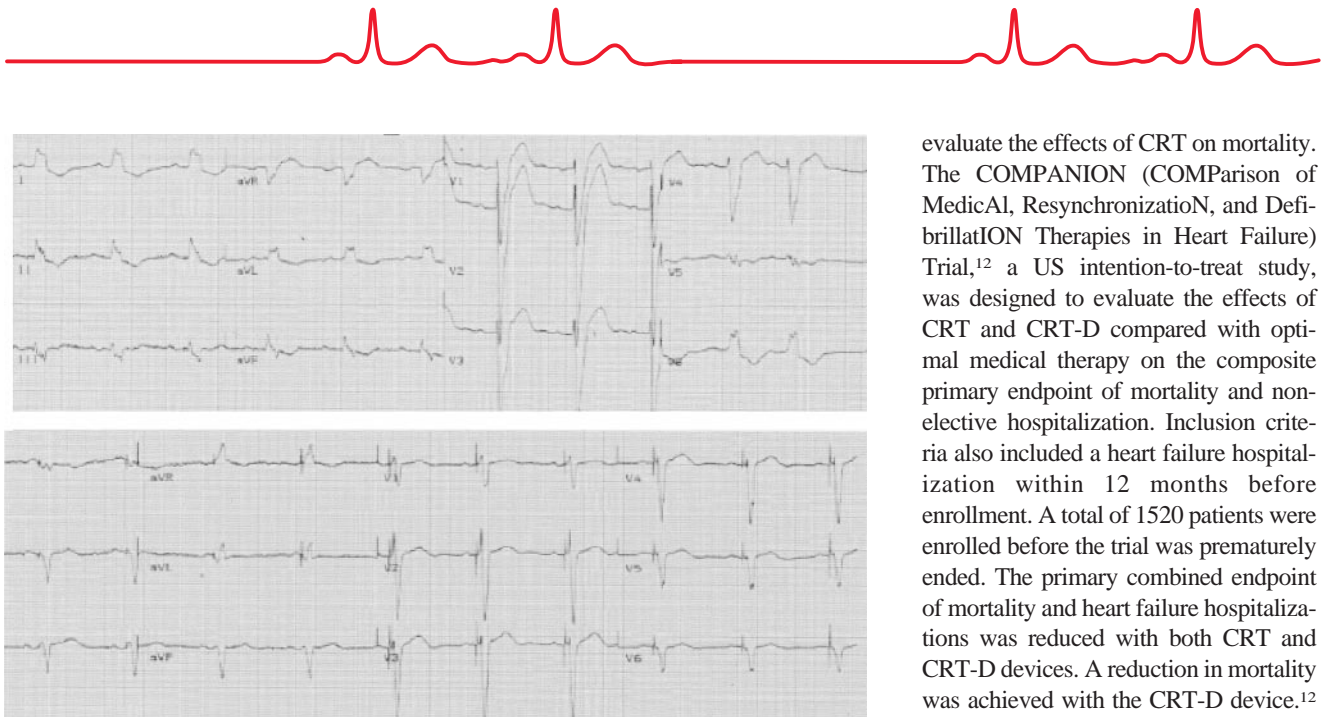


Figure 4. Top, Normal sinus rhythm with LBBB. Bottom, Atrial sensed biventricular stimulation. Paced QRS complex has narrowed and frontal axis has shifted leftward.

have an improvement in at least one functional class compared with the patients who do not have CRT. The magnitude of improvement in exercise capacity is about 1 to 2 mL · kg⁻¹ · min⁻¹, with an increase in exercise duration of 30 to 60 seconds and an increase in the 6-minute walk test of 20 to 40 meters.

Several other observations relating to the effect of chronic cardiac resynchronization therapy on heart failure disease progression are also available from the completed clinical trials. Echocardiographic substudies demonstrated significant reductions in left ventricular size and dimensions after 3 and 6 months of continuous CRT. Left ventricular ejection fraction also increased and the degree or area of mitral regurgitation decreased.^{9,10} Although the above changes are modest, they are consistent across all

3 studies and suggest that CRT slows measures of disease progression and results in anatomic remodeling. These changes appear to be a direct effect of CRT because they drift back toward baseline if the device is programmed off.¹¹ Table 3 summarizes the improvements in echocardiographic measures.

Assessment of neurohormonal activation was also performed, including serial measurement of norepinephrine, epinephrine, dopamine, endothelin, and brain natriuretic peptide. None of these measures increased or decreased significantly with chronic CRT. This neutral effect may reflect the fact that patients enrolled were required to have optimized heart failure medical therapies that include neurohormonal antagonists.^{9,10}

The next generation of clinical studies, initiated in 2000 were designed to

evaluate the effects of CRT on mortality. The COMPANION (COMPARison of MedicAI, ResynchronizatiON, and DefibrillatiON Therapies in Heart Failure) Trial,¹² a US intention-to-treat study, was designed to evaluate the effects of CRT and CRT-D compared with optimal medical therapy on the composite primary endpoint of mortality and non-elective hospitalization. Inclusion criteria also included a heart failure hospitalization within 12 months before enrollment. A total of 1520 patients were enrolled before the trial was prematurely ended. The primary combined endpoint of mortality and heart failure hospitalizations was reduced with both CRT and CRT-D devices. A reduction in mortality was achieved with the CRT-D device.¹² A recent meta-analysis pooling data from 4 studies showed that CRT therapy reduced death from progressive heart failure by 51% compared with control (odds ratio, 0.49; 95% confidence interval, 0.25 to 0.93), and reduced heart failure hospitalization by 29% (odds ratio 0.71; confidence interval, 0.53 to 0.96). CRT was not associated with a statistically significant effect on non-heart failure mortality or a reduction in number of patients experiencing ventricular tachycardia or ventricular fibrillation.¹³

Resynchronization Therapy Viewed in the Current Context of Expanding ICD Indications

The patient population currently indicated for a CRT device may be greatly expanded based on the results of 2 recently published implantable defibrillator (ICD) trials.^{14,15} The MADIT II (Multicenter Automatic Defibrillator Implantation Trial) trial¹⁴ demonstrated that ICD therapy, compared with conventional medical therapy, decreased total mortality in postinfarction survivors with compromised left ventricular function, defined as a left ventricular ejection fraction <30%. A total of 1232 patients were randomized, and at 20 months of follow-up the relative risk reduction in mortality for the ICD-treated group was 31%. Interestingly, 50% of patients en-

TABLE 3. Changes in Echocardiographic Measures Comparing CRT With No CRT at 6-Month Follow-Up

Parameter	MIRACLE	InSync ICD	CONTRAK CD
Total No.	345	258	227
Left ventricular ejection fraction, %	+3.6 (P=0.016)	+3 (P=0.016)	+6 (P=0.03)
LVEDD/LVESD, cm	-4.9/-5 (P=0.001/0.002)
LVEDV/LVESV, mL	-25/-27 (P<0.001)	-24/-25 (P<0.001)	

LVEDD indicates left ventricular end-diastolic dimension; LVESD, left ventricular end-systolic dimension; LVEDV, left ventricular end-diastolic volume; and LVESV, left ventricular end-systolic volume.

rolled in this study had QRS delay and 30% had NYHA FC III-IV heart failure symptoms. These data indicate that a significant subset of patients indicated for an ICD under MADITT II criteria may actually benefit from a CRT-D device.

The DAVID (Dual Chamber and VVI Implantable Defibrillator) trial¹⁵ evaluated the impact of ICD bradycardia programming on the composite endpoint of heart failure hospitalization and mortality in patients with depressed ventricular function who had indications for an ICD. A total of 506 patients were randomized to ICD programming with no ventricular pacing or dual chamber pacing. In the dual chamber paced group, 59% received continuous right ventricular pacing. At 1 year, a relative increase in the risk of heart failure hospitalization or mortality of 39% was observed in the patients programmed to DDD pacing. This study provides the most direct evidence to date that right ventricular pacing itself, by promoting a dyssynchronous ventricular activation sequence, worsens outcome.

Future Directions in Research in

Resynchronization Therapy

One of the most basic and compelling mechanistic questions that remains unanswered is how to identify or refine currently used electrical and mechanical markers of dyssynchrony. Careful analysis of clinical trials show that up to 30% of patients receiving a CRT device may not benefit from this therapy. Although QRS duration has been utilized to identify electrical and mechanical dyssynchrony, it has not been shown that the extent of QRS delay at baseline predicts clinical response. Additionally, it has not been shown that the extent of QRS narrowing by biventricular pacing predicts the magnitude of the clinical or remodeling response. Several studies have shown that the degree of left ventricular dyssynchrony measured by a variety of techniques, including tagged MRI imaging, echocardiographic and

echo-contrast imaging, and color tissue Doppler imaging, have all shown that the degree of left ventricular dyssynchrony can successfully predict responders to resynchronization therapy.

Additional questions relating to optimization of CRT device function using atrial ventricular delay programming during chronic CRT also remain largely unanswered. The next generation of CRT devices will allow for enhanced programming options, including the ability to vary the timing of right and left ventricular stimulation to optimize an individual patient's response. It is as of yet unclear what measures should be used to assess the benefit of these programming changes.

Conclusions

Resynchronization therapy has proven to be an efficacious adjunctive device therapy to standard medical therapies for symptomatic heart failure in association with QRS delay. The therapy improves symptom status and exercise duration, slows measures of disease progression, and improves hospitalization rate and mortality. Recent data provide a rationale for studying the expanded use of CRT devices to a significant subset of patients indicated for standard ICD therapy. Important mechanistic questions remain to be answered, including how to identify new and refine current criteria used to assess dyssynchrony and how to measure extent of resynchronization with therapy.

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