Should all patients with heart failure and intraventricular conduction defect or dyssynchrony receive cardiac resynchronization therapy?

All Patients With Heart Failure and Intraventricular Conduction Defect or Dyssynchrony Should Not Receive Cardiac Resynchronization Therapy

Barry Greenberg, MD; Mandeep R. Mehra, MD

Case Presentation: J.S., a 72-year-old man, was diagnosed with heart failure 5 years ago. Before that, he had suffered a large anterior myocardial infarction and had undergone successful coronary artery bypass grafting surgery. An internal cardioverter-defibrillator (ICD) was implanted 3 years ago. He was hospitalized briefly for decompensated heart failure 9 months ago, and his medical regimen was intensified at that time. He subsequently resumed his usual activities, which included daily walks of up to several hundred yards around his company’s construction work site and 2 to 3 rounds of golf weekly. His only symptoms were fatigue after 36 holes of golf and shortness of breath while walking uphill rapidly. Medications included 0.125 mg digoxin, 40 mg furosemide, and target doses of an angiotensin-converting enzyme inhibitor, a β-blocker, and warfarin. An ECG demonstrated atrial fibrillation with a controlled ventricular response. The QRS duration was 130 ms with a left bundle-branch block pattern. On echocardiogram, the left ventricular (LV) ejection fraction (EF) was 23% with anterior wall akinesis; the LV internal diastolic dimension was 83 mm; and there was trace mitral regurgitation. Cardiac resynchronization therapy (CRT) was recommended. Placement of an LV pacing lead and “upgrading” his ICD to an ICD/biventricular pacemaker was performed uneventfully.

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Shortly after the procedure, he experienced recurrent ventricular tachyarrhythmias, and his ICD, which had not discharged since implantation, delivered 4 shocks over a 24-hour period to terminate episodes of ventricular fibrillation. There was no evidence of acute myocardial infarction, worsening heart failure, or a pericardial effusion. The ventricular arrhythmias were responsive to intravenous amiodarone. After 7 days, he was discharged on oral amiodarone in addition to his other medications. Over the next several weeks, he had only 1 episode of ventricular tachycardia terminated by pacing. During this period, however, he complained of fatigue, malaise, and gastrointestinal symptoms. Amiodarone was discontinued, and over the next several weeks, these symptoms resolved. There were no further ventricular arrhythmias, and J.S. resumed his activities at work and on the...
golf course. Repeat echocardiogram showed no interval change in LV size or function.

**Background**

In recognition of the fact that heart failure is an important and growing public health problem, a variety of new treatment approaches have been developed. Beginning in the 1980s, drugs that target maladaptive neurohormonal activation, such as angiotensin-converting enzyme inhibitors, β-blockers, angiotensin receptor blockers, and aldosterone antagonists, have been shown in large-scale clinical trials to produce impressive reductions in morbidity and mortality in heart failure patients. Additional agents such as the combination of hydralazine/isosorbide dinitrate also favorably affect the clinical course (at least in selected populations), and new drugs are in various stages of development. Although several of these drugs may yet prove to be effective in treating heart failure, there is concern that these newer agents (and particularly those that target neurohormonal activation) may not favorably alter the natural history nearly as well as the drugs that were incorporated into the therapeutic regimen over the past few years.

**Using CRT to Treat Heart Failure Patients**

In view of the increased prevalence of heart failure and the persistent unacceptably high morbidity and mortality associated with this condition despite current pharmacological treatments, novel therapeutic approaches have been sought. Recent attention has focused on cardiac dyssynergy as a viable therapeutic target. Many patients with heart failure have abnormalities in the temporal pattern of cardiac contraction that impair both systolic and diastolic functions of the heart and worsen mitral valvular incompetence. Mechanical dyssynergy often is seen in association with the electrical dyssynergy that is manifest by a widening of the QRS duration on the surface ECG. The prevalence of a wide QRS in heart failure populations is estimated to be in the range of 25% (or greater in more severely ill patients) and when present has been associated with increased mortality.

Recognition of the adverse impact of cardiac dyssynergy in heart failure patients has stimulated the development of novel pacing techniques to correct the problem. The most widely accepted and studied of these has been the use of a biventricular pacemaker in which pacing leads are positioned in the right atrium and right ventricle and a third lead is introduced through the coronary sinus into the venous system of the heart so that LV stimulation can be obtained. This approach allows optimization of timing between atrial and ventricular contractions and enhanced synchronization of interventricular and intraventricular contractions. The results of clinical trials using CRT have now provided incontrovertible evidence of the efficacy of this approach in highly selected patients. Not only have these studies demonstrated increased exercise capacity, relief of symptoms, and improvement in quality of life, but also there has been evidence that CRT can reduce morbidity and mortality even beyond what is offered by optimal medical therapy of heart failure. As a result, CRT has emerged over the past few years as an important adjunct to medical therapy and has brought unquestionable benefits to many patients. Whether it helps and should be offered to all patients with heart failure and intraventricular conduction defect or dyssynchrony, however, is another question entirely.

**Should CRT Be Used in All Heart Failure Patients?**

The decision to use CRT in heart failure patients must be based on evidence from clinical trials demonstrating that it is both effective and safe to use. The heart failure population is highly heterogeneous; patients exhibit considerable variability in many aspects of their condition. Differences between patients in age, gender, race, origin of heart failure, extent of cardiac dysfunction (both systolic and diastolic), degree of functional and symptomatic impairment, extent of cardiac dyssynchrony, presence of comorbidities, and background therapy all influence the clinical course and the response to additional treatment modalities. Ideally, clinical trials assessing new therapies should include large, well-defined populations that will help determine which patients are most likely to benefit. In this way, their results can be applied in a more rational way to patients seen in everyday clinical practice.

It is instructive to examine the characteristics of the patients who were included in clinical trials assessing the efficacy of CRT (Table 1). First, it is important to recognize that heart failure patients with preserved EF, a group now estimated to make up approximately half of the heart failure population, would not be considered for CRT, at least according to the results of available clinical studies that excluded patients with LV EFs >0.35. Second, for the most part, the clinical trial patients had evidence of marked prolongation of their QRS (usually with a left bundle-branch block pattern), were in sinus rhythm, and had advanced (but not end-stage) heart failure while being treated with good background medical therapy (Table 1).

Are the patients who were included in the clinical trials demonstrating efficacy of CRT representative of the heart failure patients who are seen on a daily basis in clinical practice? This question can be answered by examining the clinical characteristics of the US heart failure population. A reasonable scenario is that 50% will have evidence of systolic dysfunction with an EF ≤0.35, 30% will have New York Heart Association (NYHA) class III or “ambulatory” class IV symptoms, and 30% will have a QRS duration ≥120 ms. In this case, only ~4.5% of heart failure patients would be considered candidates for CRT.

Even this analysis, however, greatly overestimates the number of patients for whom there are convincing data supporting the use of CRT. Most of the patients in the clinical trials were in sinus rhythm and had a left bundle-branch block pattern on the surface ECG. Because synchrony between
atrial and ventricular contractions and, in particular, improved synchronization of LV contraction both appear to contribute to the benefits of CRT, the efficacy of CRT in patients with atrial fibrillation and those with conduction abnormalities other than a left bundle-branch block is uncertain. Many potential candidates also are likely to be very elderly (i.e., >80 years of age). Because the number of such patients in the clinical trials in this age range was limited, there is less certainty about the response to CRT than there is in a younger population, particularly in regard to improving exercise capacity and quality of life. Furthermore, important comorbidities and other issues (both medical and nonmedical) in these patients would diminish enthusiasm for proceeding with CRT and would raise questions about the ultimate cost-efficacy of this approach.

In addition to the above caveats, a substantial number of the remaining potential patients will have a QRS duration between 120 and 150 ms. Although such patients were entered in the clinical trials assessing the efficacy of CRT, it is clear that the average QRS duration was considerably longer in the patients studied and on average was in the range of 160 to 170 ms (Table 1). Whether patients with moderate prolongation of the QRS interval will benefit to the same extent as those with more marked prolongation is debatable. In the Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure (COMPANION) trial, who mandated that patients with a QRS duration between 120 and 150 ms have evidence of ventricular dyssynergy by echocardiographic examination to be included in the trial, the number of patients excluded because of an absence of demonstrable dyssynergy was not reported. That the favorable effects of CRT in COMPANION seem to show less dependence on QRS duration than they do in the COMPANION study (which did not require evidence of mechanical dysynchrony) is likely a manifestation of a lower prevalence of dyssynergy in the COMPANION patients with shorter QRS duration.

Finally, it is important to recognize that the database supporting the use of CRT included patients who were receiving optimal medical management. To the great credit of the investigators who participated in these studies, the percentage of patients receiving angiotensin-converting enzyme inhibitors (and/or angiotensin receptor blockers) and β-blockers was very high. This is relevant to this discussion because the use of these drugs in general practice appears to be considerably less than in the CRT studies. Besides being an indication of poor medical practice, the failure to optimize medical therapy in potential CRT candidates could have 2 potential consequences. The first is that the impact of CRT on the clinical course might be different (and either more or less effective) when initiated against a background of suboptimal medical treatment. The second is that many patients being treated with a suboptimal treatment regimen will experience significant improvement in either EF or NYHA functional class when the treatment regimen is optimized. In this case, CRT might not offer the same degree of benefit as it did to patients in the clinical trials.

**TABLE 1. Characteristics of Patients Included in Trials of CRT**

<table>
<thead>
<tr>
<th>Trial</th>
<th>n</th>
<th>Sinus Rhythm, %</th>
<th>NYHA Functional Class II/III/IV, %</th>
<th>QRS, ms</th>
<th>LV EF Entry Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>MUSTIC</td>
<td>67</td>
<td>100</td>
<td>0/100/0</td>
<td>176±19</td>
<td>≤0.35</td>
</tr>
<tr>
<td>PATH-GHF</td>
<td>36</td>
<td>100</td>
<td>0/86/14</td>
<td>175±32</td>
<td>NA</td>
</tr>
<tr>
<td>MIRACLE</td>
<td>4153</td>
<td>100</td>
<td>0/91/9</td>
<td>166±20</td>
<td>≤0.35</td>
</tr>
<tr>
<td>MIRACLE-ICD (severe)</td>
<td>369</td>
<td>100</td>
<td>0/89/11</td>
<td>164±22</td>
<td>≤0.35</td>
</tr>
<tr>
<td>CONTAK</td>
<td>490</td>
<td>100</td>
<td>33/59/8</td>
<td>158±26</td>
<td>≤0.35</td>
</tr>
<tr>
<td>COMPANION</td>
<td>1520</td>
<td>100</td>
<td>0/85/15</td>
<td>160</td>
<td>≤0.35</td>
</tr>
<tr>
<td>CARE-HF</td>
<td>813</td>
<td>100</td>
<td>0/94/6</td>
<td>160</td>
<td>≤0.35</td>
</tr>
<tr>
<td>MIRACLE-ICDII (mild)</td>
<td>186</td>
<td>100</td>
<td>100/0/0</td>
<td>165</td>
<td>≤0.35</td>
</tr>
</tbody>
</table>

Values for QRS are mean±SD.

MUSTIC indicates Multi-site Stimulation In Cardiomyopathy; PATH-GHF, Pacing Therapies in Congestive Heart Failure; and MIRACLE-ICD, Multicenter InSync Randomized Clinical Evaluation-Internal Cardioverter Defibrillator.
TABLE 2. Determining the Appropriate Timing for CRT for Heart Failure Patients

1. Have all correctable underlying cardiac causes of heart failure (eg, myocardial ischemia, significant valve, or other structural abnormalities of the heart or rhythm disturbances) been defined and treated?
2. Have all correctable noncardiac factors that either produce or worsen heart failure (eg, anemia, thyroid disorders, renal abnormalities) been defined and treated?
3. Have drugs that worsen heart failure and/or cardiac function (eg, class I and III antiarrhythmic agents, NSAIDs) been excluded from the treatment regimen?
4. Is the patient on an appropriate diet (eg, salt restriction and avoidance of excessive alcohol use)?
5. Has optimal medical management (including agents that block the effects of the renin-angiotensin-aldosterone and sympathetic nervous systems) been prescribed, and are they being used at target dose based on previous clinical trial results?
6. Have approaches for the treatment of heart failure beyond drugs and diet (eg, weight reduction, exercise training, positive airway pressure during sleep) been considered?
7. Is the patient compliant with diet and drugs? If not, what measures (eg, education, referral to a formal heart failure management program) have been taken to try to improve compliance?
8. Has enough time been allowed to elapse for medical management to exhibit beneficial effects (eg, minimum of 3 mo on optimal medical therapy)?

It may well be that the indications for CRT will expand over the coming years and that the population that benefits will be larger than our estimate. For instance, CRT has been shown to reduce LV volumes and to increase EF in patients with NYHA functional class II symptoms of heart failure. This presumed reversal of cardiac remodeling argues well for the use of CRT in this population because reverse remodeling usually is associated with an improvement in the clinical course, including a reduction in mortality. However, reverse remodeling remains a surrogate for clinical outcomes, and it is noteworthy that these less severely impaired patients failed to achieve a significant improvement in exercise capacity (which was the primary end point of the study) or in quality of life. Thus, more definitive evidence of efficacy of CRT in this less symptomatic population is needed. Similarly, smaller clinical trials in patients with atrial fibrillation or QRS prolongation with other than left bundle-branch block pattern or with evidence of dyssynchrony in the absence of QRS prolongation on the surface ECG have shown trends which suggest that CRT may be helpful in these groups. If these results are confirmed by larger and more rigorous studies, the paradigm for the use of CRT will have to be broadened to include these patients. Similarly, studies using larger numbers of very old patients will help to determine the efficacy of CRT in this important subgroup.

Issues Related to CRT Use in Practice

What then are the major problems encountered with the implementation of CRT in clinical practice? From our observations, they are largely related to physicians being “too quick to pull the trigger” for recommending CRT and extrapolation of the current database so that the indications for CRT are expanded well beyond those that can justified by currently available clinical trial results. Although such practices may serve to expand the population in which CRT is used, there is little justification for this approach.

The timing of the implementation of CRT should be based on an algorithm that incorporates evidence from the clinical trials with existing knowledge of the natural progression of the disease and its response to available treatments. Typically, clinical trials of CRT enrolled patients when they were clinically stable but still demonstrated substantial symptomatic limitation despite optimal medical treatment. Thus, patients in clinical practice presenting with recent-onset heart failure and those in whom there has been a recent decompensation or recent significant cardiac event should not be considered candidates for CRT until the treatment regimen has been optimized as outlined in Table 2. Many patients who at first appear to be candidates for CRT based on presence of low EF and limitation of activities as a result of symptoms may well show improvement in one or both of these parameters with appropriate treatment. Substantial improvement in EF (and even normalization in some cases) with treatment of ischemia, with improvement in loading conditions, or after administration of neurohormonal blocking agents may not be immediate and often becomes apparent only over time. Similarly, there is evidence that QRS changes may occur in response to treatment of heart failure. Although this may pose a dilemma in some cases, it argues for delaying CRT for a period (usually for 3 to 6 months in our practices) after initiation and optimization of treatment to determine whether the patient continues to manifest evidence of cardiac dysfunction and heart failure symptoms that would classify them as candidates for this therapy according to entry criteria in the relevant clinical trials. Thus, it is important for potential candidates to wait for a period of 3 months, during which time therapy is optimized and the response is assessed before CRT therapy is initiated.

The patient subgroups in which the efficacy of CRT remains uncertain are listed in Table 3. Although use of CRT in these subgroups might well prove to be beneficial, discrim-
inaring responders from nonresponders is difficult and currently uncertain. The benefits of CRT in patients at both ends of the spectrum of heart failure (ie, with either more or less severe symptoms) remain problematic. The uncertainties of extending indications into less severely ill populations (eg, “class creep”) are exemplified by a recent study of NYHA functional class II in which the primary end point of increased exercise capacity with CRT was not met, nor was there evidence of improved quality of life in these patients. Even more troublesome is the use of CRT as “bailout” therapy in patients with end-stage heart failure. Such patients were excluded from the clinical trials of CRT, and there is virtually no convincing evidence that they will improve at this late stage with resynchronization. Proceeding with CRT could expose these patients to an unnecessary procedure that often is taxing, compromises safety, and raises false hopes and expectations for both the patients and their families. Similarly, the concept of “drive-by” CRT during a planned ICD implant for sudden death prophylaxis remains unsupported. It is more prudent to place a programmable ICD set to a backup rate that discourages frequent pacing. Whether CRT is additive in benefit during an ICD implantation in those with demonstrable mechanical dyssynchrony or simply with a QRS lengthening remains unproved at this time.

Even when patients are selected for CRT on the basis of entry criteria used in the relevant clinical trials, it is clear that not all patients will respond to this form of therapy. In the pivotal Multicenter InSync Randomized Clinical Evaluation (MIRACLE) study, for instance, increases in distance covered during the 6-minute walk test averaged 39 m in the CRT group compared with 10 m in the control patients (P = 0.005), a net increase of 29 m on average. Similarly, 68% of patients in the CRT arm of the MIRACLE study improved their NYHA functional class by at least 1 step compared with 38% of patients in the control group (P < 0.001). Importantly, this study randomized patients only after a successful implantation; up to 10% of patients were not able to achieve placement of the CRT device. Although these differences are important, they point out that the changes in exercise capacity and symptomatic status that occur over the entire study population are of relatively small magnitude (particularly when changes in the control population are taken into account). When corrected for changes in the control population, for instance, only 30% of the CRT population experienced improvement in their NYHA functional class. These findings suggest that improved criteria for selection are needed to help define patients who are most likely to derive benefit. A variety of echocardiographic approaches, including determination of interventricular dyssynchrony by assessing the differences in timing between the onset of the QRS to peak aortic versus peak pulmonic flow, determination of intraventricular dyssynchrony by assessing sepal to posterior wall motion delay, and the use of tissue Doppler measurements, have been used to measure the amount of dyssynchrony in patients. The effects of timing of the performance of these studies (eg, during active treatment for decompensation) and their reproducibility, however, have not been adequately defined. Consequently, despite the fact that they would appear to help define the patients who are most likely to benefit from CRT (particularly when the QRS duration is <150 ms), they are not routinely used in clinical practice.

**Disadvantages of CRT**

Although CRT is clearly not going to be helpful for all heart failure patients, it is important to review some of the reasons why caution is needed in expanding use of this therapy beyond the clinical populations in which it was studied. The most obvious considerations are cost, resources consumed, and the risks of the procedure. The costs include not only those associated with hospitalization and the device itself but also those that accrue during the follow-up of the patient. Implantation involves hospitalization in a monitored setting, followed by frequent clinic visits to assess the adequacy of wound healing and the appropriate functioning of the device. Although adverse events are relatively uncommon with CRT, serious complications can occur. These include bleeding (≈1%), infection (≈1%), hemotoma (≈1%), pneumothorax (≈1%), pericardial effusion with/without cardiac tamponade (≈1%), myocardial infarction and/or stroke (≈0.2%), dissection or perforation of the coronary sinus (≈1%), lead dislodgement (≈5%), extracardiac stimulation (≈5%), and risks associated with the use of intravenous contrast. As seen in the patient whose history is described above, provocation of arrhythmias is another potential complication of CRT. There also are risks associated with the exposure to radiation during the procedure, particularly to the operator who often participates in multiple implantation procedures over an extended period of time.

**Discussion of the Clinical Case**

The clinical history described above illustrates several aspects of the argument. The patient certainly met EF and QRS criteria for CRT. All issues outlined in Table 2 had been addressed, and he was receiving optimal medical management, including target doses of neurohormonal blocking agents. He had a very healthy lifestyle and diet and was compliant with the treatment regimen. Moreover, he demonstrated substantial LV enlargement as a result of adverse remodeling of the chamber, a factor known to be associated with increased risk for future morbidity and mortality. He was, however, only minimally symptomatic. In addition, he had atrial fibrillation, and the QRS duration was 130 ms. The database from clinical trials for the use of CRT in such patients is limited, and the likelihood of success is much less assured than in patients who are in sinus rhythm but have more advanced symptoms of heart failure. Similarly, given the QRS duration, evidence of dyssynchrony would have provided a firmer basis for recommending CRT. So, in this case, the likelihood of gain was uncertain (and almost certainly of lesser magnitude than for more standard indications), but both the costs and risks were the same as in patients more likely to benefit. Initiation of both atrial and
ventricular arrhythmias has been associated with CRT, and this patient experienced an increase in life-threatening ventricular arrhythmias immediately after CRT placement. Although the occurrence of ventricular rhythm disturbances cannot be attributed to the placement of the LV pacing wire with absolute certainty, the temporal association is striking and highly suggestive that either alterations in electrical activity caused by initiation of LV pacing or mechanical irritation resulting from the pacing lead was responsible. In the end, the patient had a protracted medical course related to the procedure without evidence of tangible benefit from CRT.

Conclusions
It is clear that CRT is an important new modality of therapy that can benefit the clinical course of selected heart failure patients. Available clinical trial results indicate that patients with systolic dysfunction (ie, EF ≤0.35), NYHA functional class III symptoms, or ambulatory class IV symptoms despite optimal medical management and a prolonged QRS are the most likely to benefit. However, a prolonged QRS does not necessarily connote the presence of dyssnergy, and particularly for patients with a QRS between 120 and 150 ms, evidence of mechanical dyssnergy should be sought before CRT is recommended. Similarly, patients with either less or more severe heart failure symptoms would not in most cases be considered candidates for CRT on the basis of the database that is presently available. A point that cannot be overstated is that CRT should be considered only when a patient continues to fulfill EF, symptom, and QRS criteria for candidacy even after optimal medical management has been used. By carefully selecting patients, we can avoid the costs and risks of implantation in patients with a low likelihood of a favorable response. As more information from clinical trials, particularly those using various echo Doppler techniques to quantify dyssynchrony, becomes available, we anticipate that the use of CRT may well be shown to benefit a higher percentage of patients than we have reckoned. This would indeed be a welcome addition to our therapeutic arsenal, provided that physicians who are implanting in the community continue to adhere to the general guidelines for patient selection that have been outlined.

Disclosures
Dr Greenberg has received a research grant from Aventis; has been on the speakers’ bureau for GlaxoSmithKline, Merck, Pfizer, and Medtronic; has received honoraria from GlaxoSmithKline, Merck, Pfizer, and NitroMed; and has served on the advisory boards for GlaxoSmithKline and NitroMed. Dr Mehra has received research grants from Scios, Medtronic, Guidant, GlaxoSmithKline, and Roche, and ORQIS; has served on the speakers’ bureau for and received honoraria from Scios, Medtronic, Guidant, GlaxoSmithKline, and AstraZeneca; and has served on the advisory boards for XDX and Scios.

References
Response to Greenberg and Mehra

William T. Abraham, MD

Drs Greenberg and Mehra and I agree that not all heart failure patients with ventricular dyssynchrony should receive cardiac resynchronization therapy (CRT). On the other hand, current evidence and contemporary heart failure guidelines support the use of CRT in all eligible patients defined by the inclusion and exclusion criteria of the major clinical trials. Those criteria have been emphasized in both articles. Where we disagree is the application of CRT within this indicated population. To date, no reliable predictors of response to CRT have emerged (including QRS morphology or duration in the range >120 ms). Likewise, no such predictors are known to forecast the treatment effect of heart failure drug therapies, yet we offer evidence-based, guideline-recommended drug therapies to all eligible patients unless contraindicated. In fact, physician adherence to the use of these drug therapies is used as a national metric for physician performance and quality of care in heart failure. In this regard, heart failure device therapies such as CRT should not be viewed as different from drug therapies, particularly when the evidence base is equally strong. Until data prove otherwise, it is unethical to exclude patients from CRT because of right bundle-branch block morphology or a QRS duration between 120 and 150 ms on the basis of underpowered post hoc subgroup analyses of clinical trials. Likewise, the belief that mechanical rather than ECG measures of dyssynchrony provide better patient selection criteria for CRT must be proved in an adequately powered prospective trial before the definition of ventricular dyssynchrony is changed. At present, there exists a moral obligation to offer this life-sustaining therapy to all eligible patients with a reasonable expectation for survival and likelihood of responsiveness to CRT.
Cardiac Resynchronization Therapy Is Important for All Patients With Congestive Heart Failure and Ventricular Dyssynchrony

William T. Abraham, MD

More than 4000 patients have been evaluated in randomized controlled trials of cardiac resynchronization therapy (CRT). These studies have demonstrated that CRT with or without an implantable cardioverter-defibrillator (ICD) consistently improves quality of life, functional status, exercise capacity, and cardiac structure and function and reduces morbidity and mortality in heart failure patients with ventricular dyssynchrony. The magnitude of benefit seen with CRT is comparable to or exceeds that seen with evidence-based drug therapies for heart failure but occurs in patients who are already receiving such medications. Thus, CRT has been added to the list of evidence-based therapies that make heart failure patients feel better and live longer (the Table). Consequently, a strong ethical mandate exists for the use of CRT in heart failure. This mandate is reflected in our current practice guidelines for the management of chronic heart failure, which state that all eligible patients should receive CRT unless contraindicated.1,2 End of debate! CRT should be a routine part of any evidence-based treatment regimen for heart failure.

Of course, things are never quite so simple, so let us take a look at the evidence supporting this clinical mandate for CRT and address patient selection, some of the limitations of CRT, and some of the unanswered questions about the use of CRT in heart failure. None of this discussion will lessen the role of CRT in the treatment of heart failure; rather, it will guide the selection of appropriate patients and speculate on the future application of CRT to an even broader group of heart failure patients.

The Rationale for CRT

Approximately one third of patients with systolic heart failure exhibit ventricular dyssynchrony, defined as a QRS duration >120 ms on the surface ECG.3,4 Ventricular dyssynchrony produces suboptimal ventricular filling, a reduction in left ventricular contractility, prolonged duration of mitral regurgitation, and paradoxical septal wall motion, which conspire to further reduce the ability of the failing heart to eject blood.5–8 The adverse consequences of ventricular dyssynchrony have been reviewed in detail previously.9,10 Importantly, ventricular dyssynchrony has been associated with increased morbidity and mortality in heart failure pa-
patients. Thus, in the mid 1990s, applying pacing therapies to overcome ventricular dyssynchrony began to be explored. CRT, or atrial-synchronized biventricular pacing, emerged as the most promising approach for the treatment of ventricular dyssynchrony.

The first application of CRT was performed by Cazeau et al., who used 4-chamber pacing in a middle-aged man with New York Heart Association (NYHA) class IV heart failure and a prolonged QRS duration. Standard transvenous pacing leads were placed in the right atrium and right ventricle. The left atrium was paced by a lead placed in the coronary sinus; the left ventricle was paced by an epicardial lead located on the left ventricular free wall. After 6 weeks of pacing, the patient’s clinical status improved markedly, with a weight loss of 17 kg and the disappearance of peripheral edema. His functional class improved to NYHA class II.

Such favorable case experiences led to small studies evaluating the short-term effects of CRT on systemic hemodynamics and echocardiographic measures of cardiac performance. These studies demonstrated that CRT could reverse the deleterious hemodynamic and echocardiographic effects of ventricular dyssynchrony. These short-term hemodynamic investigations of CRT led to long-term observational (uncontrolled) trials of CRT that showed consistent, sustained improvements in exercise tolerance, quality of life, NYHA functional class, and cardiac performance. Of course, the definitive proof supporting a role for CRT in heart failure management awaited the completion of subsequent large-scale, randomized, single- and double-blind, controlled clinical trials.

Randomized Controlled Trials of CRT
As noted, a series of randomized controlled trials have evaluated the safety and efficacy of CRT in heart failure patients. Collectively, these trials have studied virtually all the clinically meaningful end points that are routinely evaluated in clinical trials of heart failure, including end points that measure quality of life, functional status, exercise capacity, morbidity, and mortality. The beneficial effects of CRT on such end points have been striking. Moreover, these trials have provided convincing evidence that CRT produces reverse remodeling of the failing heart. That is, CRT makes the failing heart smaller and stronger, an effect that is generally associated with improved survival in heart failure clinical trials. Thus, it is not surprising that CRT prolongs life just like angiotensin-converting enzyme inhibitors and β-blockers do.

Although more than a dozen randomized controlled trials have contributed to our knowledge of CRT in heart failure, 6 studies have been most influential in establishing CRT as a routine therapy for heart failure. These 6 trials are the Multisite Stimulation in Cardiomyopathy (MUSTIC) studies, the Multicenter InSync Randomized Clinical Evaluation (MIRACLE), the Comparison of Medical Therapy, Pacing and Defibrillation in Heart Failure (COMPANION) trial, and the Comparison of Medical Therapy, Pacing and Defibrillation in Heart Failure (COMPANION) trial.

MUSTIC was designed to evaluate the safety and efficacy of CRT in patients with advanced heart failure, ventricular dyssynchrony, and either normal sinus rhythm or atrial fibrillation. The unique contribution of MUSTIC to the evolution of CRT is that it represents the first randomized (single-) blinded trial of CRT for heart failure. The normal sinus rhythm arm involved 58 randomized patients with NYHA class III heart failure, normal sinus rhythm, and a QRS duration of ≥150 ms. All patients were implanted with a CRT device, and after a run-in period, patients were randomized in a single-blind fashion to either active pacing or no pacing. After 12 weeks, patients were crossed over and remained in the alternate study assignment for 12 weeks. After this second 12-week period, the device was programmed to the patient’s preferred mode of therapy. The atrial fibrillation arm involved fewer patients (37 completers) with atrial fibrillation and a slow ventricular rate, either spontaneously or from radiofrequency ablation. A VVIR biventricular pacemaker and leads for each ventricle were implanted, and the randomization procedure described above was applied, but biventricular VVIR pacing was compared with single-site right ventricular VVIR pacing rather than no pacing in this group of patients with atrial fibrillation.

The primary end points for MUSTIC were exercise tolerance assessed by measurement of peak VO2 or the 6-minute hall walk test and quality of life determined with the Minnesota Living With Heart Failure questionnaire. In the normal sinus rhythm arm of MUSTIC, the mean distance walked in 6 minutes was 23% greater with CRT than during the inactive pacing phase (P<0.001). Significant improvement also was seen in quality of life and NYHA functional class ranking. There were fewer hospitalizations during active resynchronization therapy, an effect that was surprisingly significant given the small number of patients enrolled. The

<table>
<thead>
<tr>
<th>Major Benefits of Evidence-Based Heart Failure Therapies</th>
<th>ACE-I/ARB</th>
<th>β-Blockers</th>
<th>Aldosterone Antagonists</th>
<th>CRT</th>
<th>ICD</th>
</tr>
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<tbody>
<tr>
<td>Improves functional status</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
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<tr>
<td>Promotes reverse remodeling</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
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<td>Prolongs life</td>
<td>Yes</td>
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</table>

ACE-I indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker.
atrial fibrillation group demonstrated similar improvements, although the magnitude of benefit was slightly less.

MIRACLE was the first prospective, randomized, double-blind, parallel-controlled clinical trial designed to evaluate the risks and benefits of CRT.26,27 Four hundred fifty-three patients with moderate to severe symptoms of heart failure associated with a left ventricular ejection fraction ≤35% and a QRS duration of ≥130 ms were randomized (double blind) to CRT (n=228) or to a control group (n=225) for 6 months while conventional therapy for heart failure was maintained.28 Primary end points were NYHA class, quality-of-life score (using the Minnesota Living with Heart Failure questionnaire), and 6-minute hall walk distance.

Compared with the control group, patients randomized to CRT demonstrated a significant improvement in all 3 primary end points: the quality-of-life score (−18.0 versus −9.0 points; P=0.001), 6-minute walk distance (39 versus 10 m; P=0.005), and NYHA functional class ranking (−1.0 versus 0.0 class; P<0.001).29 Moreover, treadmill exercise time (81 versus 19 seconds; P=0.001), peak VO$_2$ (1.1 versus 0.1 mL·kg$^{-1}$·min$^{-1}$; P<0.01), and left ventricular ejection fraction (4.6% versus −0.2%; P<0.001), as well as other measures of ventricular structure and function, were significantly improved. Patients randomized to CRT demonstrated a highly significant improvement in a composite clinical heart failure response end point compared with control subjects, suggesting an overall improvement in heart failure clinical status. In addition, ∼50% fewer patients in the CRT group required hospitalization or intravenous medications for worsening heart failure (both P<0.05). The major limitation of the therapy was the unsuccessful implantation of the device in 8% of patients. In August 2001, the results of this trial led the US Food and Drug Administration to approve the InSync CRT device for use in the treatment of heart failure in May 2002.

The MIRACLE ICD study was designed to be almost identical to the MIRACLE trial. MIRACLE ICD was a prospective, multicenter, randomized, double-blind, parallel-controlled clinical trial designed to assess the safety and efficacy of a combined CRT-ICD system in patients with NYHA class III or IV heart failure, ventricular dyssynchrony, and an indication for an ICD. Three hundred sixty-nine patients were randomized, 182 to the control arm (ICD activate, CRT inactive) and 187 to the active CRT group (ICD activate, CRT active).30 Primary end points were the same as those evaluated in the MIRACLE trial; measures of ICD function also were assessed.

Like MIRACLE, the MIRACLE-ICD trial demonstrated the efficacy of CRT although in a slightly different group of heart failure patients (ie, those with secondary prevention indications for an ICD). At 6 months, patients assigned to active CRT had a greater improvement in median quality-of-life score (−17.5 versus −11.0; P=0.02) and functional class (−1 versus 0; P=0.007) than control subjects; however, there was no change in the distance walked in 6 minutes (55 versus 53 m; P=0.36) between groups.30 This latter observation may simply be a fluke; virtually all other controlled trials of CRT have demonstrated improvements in the 6-minute hall walk distance, and MIRACLE ICD demonstrated a significant improvement in peak oxygen consumption (1.1 versus 0.1 mL·kg$^{-1}$·min$^{-1}$; P=0.04) and an increase in treadmill exercise time (56 versus 11 seconds; P=0.006), confirming the benefit of CRT on exercise capacity. The CRT-ICD device used in this study was approved by the US Food and Drug Administration for use in NYHA class III and IV systolic heart failure patients with ventricular dyssynchrony and an ICD indication in June 2002, further establishing a place for CRT in the routine management of heart failure.

The COMPANION study enrolled 581 symptomatic heart failure patients with ventricular dyssynchrony and malignant ventricular tachyarrhythmias who were also candidates for an ICD.31 After unsuccessful implantation attempts and withdrawals, 490 patients were available for analysis. Although the study did not meet its primary end point of a reduction in disease progression, defined by a composite end point of heart failure hospitalization, all-cause mortality, and ventricular arrhythmia requiring defibrillator therapies, the trends were in a direction favoring improved outcomes with CRT. However, the CONTAK CD trial confirmed the benefits of CRT seen in other randomized controlled trials and led the US Food and Drug Administration to approve yet another CRT device for use in the treatment of heart failure in May 2002.

Thus, these trials demonstrated that CRT improved multiple functional measures of heart failure clinical status and established CRT as an approved therapy for heart failure. However, debate ensued on the advisability of implanting expensive devices associated with modest but real implant- and device-related adverse events only to improve so-called soft end points such as quality of life and NYHA class ranking. The unequivocal mandate for the use of CRT would subsequently come from the large-scale morbidity and mortality studies, namely COMPANION and CARE HF.

COMPANION was a multicenter, prospective, randomized, controlled clinical trial designed to compare drug therapy alone with drug therapy combined with CRT in patients with NYHA class III or IV heart failure, ventricular dyssynchrony, and no indication for a standard pacemaker or ICD device.34,35 The trial was begun in 2000 and terminated early at the unanimous recommendation of an independent data and safety monitoring committee on November 21, 2002, because of marked efficacy. That is, independent assessment of the risks and benefits of CRT so overwhelmingly supported the use of the therapy that it was deemed unethical to continue patients in the control arm of the study. The study was terminated, and control patients were offered treatment with a CRT device.

In COMPANION, 1520 patients were randomized into 1 of 3 treatment groups in a 1:2:2 allocation.35 Group 1 (308 patients) received optimal medical care only; group 2 (617
patients) received optimal medical care and the Guidant CONTAK TR (biventricular pacemaker); group 3 (595 patients) received optimal medical care and the CONTAK CD (combined CRT-ICD device). The primary end point of the COMPANION trial was a composite of all-cause mortality and all-cause hospitalization, measured as time to first event, beginning from time of randomization. Other measures of morbidity and mortality were assessed as secondary end points. Compared with optimal medical therapy alone, the combined end point of mortality or heart failure hospitalization was reduced by 35% for patients receiving CRT and 40% for patients receiving CRT-ICD (both \(P < 0.001\)). For the mortality end point alone, CRT patients had a 24% risk reduction (\(P = 0.060\)) and CRT-ICD patients experienced a risk reduction of 36% (\(P < 0.003\)) compared with optimal medical therapy. Thus, COMPANION showed for the first time the impact of CRT with or without an ICD in reducing morbidity and mortality in heart failure patients. Although CRT combined with an ICD had a greater impact on mortality alone compared with CRT without an ICD, the 2 forms of CRT devices reduced combined measures of morbidity and mortality to a similar extent. However, COMPANION was not prospectively designed nor adequately powered to compare CRT without an ICD with medical therapy alone. Thus, the CARE HF trial that followed COMPANION uniquely evaluated the effect of CRT without a defibrillator on morbidity and mortality in an adequately powered comparison to optimal medical therapy.

The CARE HF trial was designed to evaluate the effects of CRT without an ICD on morbidity and mortality in patients with NYHA class III or IV heart failure and ventricular dyssynchrony.\(^2\) Eight hundred nineteen patients with systolic heart failure and ventricular dyssynchrony, defined as a QRS duration ≥120 ms or a QRS duration between 120 and 150 ms with echocardiographic evidence of dyssynchrony, were enrolled in this randomized, unblinded, controlled trial and followed up for an average of 29.4 months.\(^3\) Four hundred four patients were assigned to receive optimal medical therapy alone; 409 patients were randomized to optimal medical therapy plus CRT. The risk of death from any cause or unplanned hospitalization for a major cardiac event, the primary end point analyzed as time to first event, was significantly reduced by 37% in the treatment group compared with control subjects (hazard ratio, 0.63; 95% CI, 0.51 to 0.77; \(P < 0.001\)). In the CRT group, 82 patients (20%) died during follow-up compared with 120 patients (30%) in the medical group, yielding a significant 36% reduction in all-cause mortality with CRT (hazard ratio, 0.64; 95% CI, 0.48 to 0.85; \(P < 0.002\); the Figure). CRT also significantly reduced the risk of unplanned hospitalization for a major cardiac event by 39%, all-cause mortality plus heart failure hospitalization by 46%, and heart failure hospitalization by 52%.

Who Should Receive CRT?
The 2005 American College of Cardiology/American Heart Association heart failure guidelines propose a class I indication for CRT.\(^1\) The 2006 heart failure guidelines from the Heart Failure Society of America likewise promote a strong indication for CRT.\(^2\) On the basis of the inclusion criteria of the many randomized controlled trials, patients with left ventricular ejection fractions ≤35%, normal sinus rhythm, and NYHA functional class III or ambulatory class IV symptoms despite recommended optimal medical therapy who have ventricular dyssynchrony should receive CRT unless contraindicated. Currently, the guidelines define ventricular dyssynchrony as a QRS duration of ≥120 ms. This may change in the future because echocardiography has emerged as a promising way to define ventricular dyssynchrony that may be better than the ECG.

Limitations of CRT
The success rate for placement of a transvenous cardiac resynchronization system has ranged from 88% to 92%
clinical trials. Thus, some patients undergoing an implantation procedure will not receive a functioning system with this approach. In this instance, the option of surgical placement, via full thoracotomy, or a minimally invasive approach, via a left ventricular epicardial lead, may be pursued. However, as always, an appropriate preoperative assessment of risk versus benefit should be considered. Moreover, it should be noted that major clinical trials of CRT used a transvenous approach to left ventricular lead placement and excluded patients undergoing surgical epicardial lead placement. Thus, the equivalence of these 2 approaches to left ventricular lead placement is not proved but rather presumed in clinical practice.

Implant-related complications are similar to those seen with standard pacemakers and defibrillators, with the additional risk of dissection or perforation of the coronary sinus. This rare event may lead to substantial morbidity and even mortality in heart failure patients. One theoretical risk raised during the early study of CRT was proarrhythmia. This concern has been addressed by the observation that CRT without a defibrillator reduces total mortality and tends to reduce the incidence of sudden cardiac death in heart failure patients. Moreover, serial 24-hour ambulatory ECG monitoring was used during early CRT trials and demonstrated no proarrhythmic effect.

Although most patients respond favorably to biventricular pacing, some do not respond. The nonresponder rate for CRT appears to be \( \approx 25\% \), a rate similar to the nonresponder rate for heart failure drug therapies. Suboptimal left ventricular lead placement, suboptimal AV and VV timing, ventricular scar, heart failure disease progression, and a variety of other factors have been proposed as contributing to the nonresponder rate associated with CRT. To date, however, no prospective predictors of responsiveness to CRT have been identified from the major clinical trials, including pooled analysis of nearly 2000 patients from 3 large-scale CRT trials (unpublished observation). As mentioned below, 1 trial is underway in an attempt to identify echocardiographic predictors (including the degree of mitral regurgitation) of CRT response. Ongoing and future studies may facilitate a better understanding of the limitations of CRT and aid in better patient selection.

One identifiable cause of poor response is loss of resynchronization. A specific programming sequence should be performed in the clinic to determine capture thresholds and to document that left ventricular capture is present. Lead dislodgement or a change in capture threshold may result in the loss of left ventricular and thus biventricular pacing. It also is possible that left ventricular lead placement and pacing thresholds are fine, but resynchronization is lost for other reasons. Anything that frequently or consistently inhibits left ventricular stimulation can effectively inhibit CRT. If the AV interval is too long and the patient’s intrinsic PR conduction inhibits biventricular pacing, deterioration may occur. The AV interval may have been programmed appropriately, but accelerated intrinsic AV conduction could result in loss of effective biventricular pacing. This is commonly seen when atrial fibrillation occurs, resulting in a rapid ventricular response competing with biventricular pacing. Frequent premature ventricular contractions also may inhibit ventricular pacing output. Although follow-up of the device itself and battery life are similar to that seen for contemporary dual-chamber pacemakers and defibrillators and generally managed by an implanting physician, heart failure specialists, general cardiologists, and primary care providers must possess the knowledge required to recognize the aforementioned limitations of CRT and to troubleshoot them.

### Unanswered Questions in CRT

Although CRT is considered a proven and routine therapy in those patients who have been evaluated in randomized controlled trials to date, many unanswered questions remain. For example, does CRT improve outcomes in patients with asymptomatic (NYHA class I) or minimally symptomatic (NYHA class II) heart failure? Is CRT better than standard right-sided pacing in heart failure patients without ventricular dyssynchrony who require cardiac pacing? Is echocardiography a better way to measure ventricular dyssynchrony and to select candidates for CRT than an ECG? Do patients with narrow QRS durations and echocardiographic evidence of dyssynchrony benefit from CRT? Recent pilot data and ongoing clinical investigations promise to answer such questions.

Results of 1 pilot study, the MIRACLE ICD II trial, support the potential efficacy of CRT in class II heart failure. In this study, CRT significantly improved ventricular remodeling indexes, specifically left ventricular diastolic and systolic volumes \( (P=0.04\) and \( P=0.01\), respectively) and left ventricular ejection fraction \( (P=0.02)\). CRT also significantly improved \( \text{Ve/VC}_{\text{O}}\) \( (P=0.01)\), NYHA class \( (P=0.05)\), and a heart failure clinical composite response \( (P=0.01)\), suggesting the potential for improved outcomes with CRT in this patient population. The safety and efficacy of CRT in NYHA class I and II patients are being evaluated further in the REnhanced synchronizatioNa in RESynchronization in Systolic left vEntricular dysfunction (REVERSE) study and the Multi-center Automatic Defibrillator Implantation Trial with CRT (MADIT-CRT), randomized controlled trials evaluating the effects of biventricular pacing on disease progression and outcomes, respectively.

The PRe dic tors Of reSPonse to CrT (PROSPECT) study is evaluating the utility of echocardiography as a measure of ventricular dyssynchrony in 450 patients receiving CRT devices. In this regard, echocardiography has identified evidence of dyssynchrony in some patients with QRS durations <120 ms. Whether these patients benefit from CRT is currently under investigation. Moreover, the optimal pacing strategy for heart failure patients with bradycardia or heart block but no evidence of ventricular dyssynchrony remains controversial. Right ventricular pacing produces “iatrogenic”
left ventricular dyssynchrony and may worsen heart failure, as demonstrated in the Dual Chamber and VVI Implantable Defibrillator (DAVID) trial. Ongoing studies are evaluating the effects of biventricular pacing versus right-sided pacing in narrow QRS heart failure patients with a pacemaker indication.

Finally, the comparative efficacy of left ventricular versus biventricular pacing needs to be evaluated further in large-scale clinical trials. Observations in animals, in humans studied in the short-term setting, and in smaller trials of long-term pacing in heart failure support the potential of effectiveness of left ventricular pacing without a right ventricular lead. Of course, this possibility needs to be confirmed in an adequately powered randomized controlled trial.

Conclusions
The benefits of CRT are substantial and unequivocal in the group of patients studied to date. CRT represents guideline-recommended, evidence-based therapy for the treatment of chronic heart failure. As such, it should be routinely offered to all heart failure patients who meet the criteria stated above.

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Response to Abraham

Barry Greenberg, MD; Mandeep R. Mehra, MD

As clinicians caring for heart failure patients, we welcome the addition of cardiac resynchronization therapy (CRT) as a treatment option. Where we differ with Dr Abraham, however, is in defining “appropriateness” for CRT therapy. Clinical experience and results of recent trials that demonstrate a high nonresponder rate emphasize the problems inherent in using CRT in patients with a low likelihood of benefit. Clinicians should carefully consider the risk-to-benefit ratio of CRT in the approximately one third of otherwise “eligible” patients with atrial fibrillation, isolated right bundle-branch block, or a posterolateral scar because efficacy in these subgroups is uncertain. We also urge caution in using CRT in patients with mild symptoms (ie, New York Heart Association functional class I and II) because clinical trials have not yet provided convincing evidence of efficacy. Although the use of methods to detect mechanical ventricular dyssynchrony to select appropriate patients for CRT appears logical, there are significant concerns about the accuracy, validity, and interobserver and intraobserver variability of available techniques. Thus, until these measurements are refined and validated, their use in deciding whether to recommend CRT in patients with heart failure and preserved ejection fraction and those with reduced ejection fraction with a QRS traventricular conduction defect or dyssynchrony should receive CRT.
All Patients With Heart Failure and Intraventricular Conduction Defect or Dyssynchrony Should Not Receive Cardiac Resynchronization Therapy
Barry Greenberg and Mandeep R. Mehra

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