Interventional Electrophysiology and Cardiac Resynchronization Therapy
Delivering Electrical Therapies for Heart Failure

J. David Burkhardt, MD; Bruce L. Wilkoff, MD

Abstract—Implantable devices have become a readily available option for patients with heart failure. Not only do these patients develop bradycardia and ventricular tachycardia, but their ventricular dysfunction can often improve with cardiac resynchronization therapy. However, this is a complex and rapidly developing clinical science for which the physician chooses techniques and selects patients on the basis of the results of clinical trials, clinical experience, and rapidly evolving tools. The results depend on the interplay of these complex variables. Placement of the left ventricular lead has forced the device physician to develop new skills and/or interdisciplinary relationships with physicians with vascular intervention, imaging, and surgical skills. Familiarity with the cardiac venous anatomy, occlusive venography, venoplasty, guide wire tools, guiding catheters, stenting, and new intracardiac visualization and magnetic intracardiac lead positioning tools are examples of just a few of the novel skills that are useful in the delivery of cardiac resynchronization therapy. Beyond implantation, these patients and devices require specialized follow-up with continued medical therapy and echo-guided adjustments of device programming. Finally, there are ongoing controversies and many as yet unanswered questions that are the subject of ongoing and planned clinical trials. (Circulation. 2007;115:2208-2220.)

Key Words: electrical stimulation ▪ heart failure ▪ pacemakers ▪ defibrillators, implantable

Patients with advanced congestive heart failure (CHF) on maximal medical therapy have had very limited options until recently. The advent of cardiac resynchronization therapy (CRT) has revolutionized the treatment of these patients. Many patients with advanced CHF demonstrate dyssynchrony by evidence of a widened QRS complex on the EKG. Most frequently this takes the form of a left bundle-branch block morphology, but right bundle-branch block morphology and intraventricular conduction delay are also less frequently present.1,2 Electrical dyssynchrony usually implies that different portions of the ventricle contract at different times, unlike that of a normal heart in which contraction of all segments is nearly simultaneous. The presence of a widened QRS itself in the presence of CHF symptoms is associated with increased mortality.3,4 Dyssynchrony on EKG, particularly of the left bundle-branch type, is associated with delayed activation of the left lateral wall, mitral regurgitation, impaired left ventricular filling, and reduced measures of cardiac contractility.5–8 CRT operates on the premise that attempts to normalize the timing of activation of the left and right ventricle or lateral wall and septum may improve the consequences of this impaired activation.9

Multiple trials have shown that CRT improves heart failure symptoms in the majority of recipients.10–14 These trials include the Multicenter InSync Randomized Clinical Evaluation (MIRACLE) trial, which studied 453 patients. All patients had a CRT device implanted and were randomized to therapy on or off. As compared with the control group, patients assigned to CRT experienced improvements in 6-minute hall walk distance, quality of life scores, and New York Heart Association (NYHA) functional class. The Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure (COMPANION) trial studied 1520 patients. Patients were randomly assigned to optimal medical therapy, optimal medical therapy + CRT with a pacemaker, or optimal medical therapy + CRT with a pacemaker-defibrillator. The primary end point was a composite of death or hospitalization from any cause. CRT with a pacemaker reduced the risk of the primary end point by 34%, and CRT with a pacemaker-defibrillator reduced the risk of the primary end point by 40%. The Cardiac Resynchronization in Heart Failure (CARE-HF) trial included 813 patients randomly assigned to medical therapy alone or with CRT. The primary end point was time to death from any cause or an unplanned...
hospitalization for a major cardiovascular event. This trial did not combine defibrillator therapy with CRT. The primary end point was significantly reduced in the group that received CRT. The secondary end point of death from any cause was also significantly reduced in the group that received CRT.15

**Patient Selection and Therapeutic Results**

Based on the results of many trials, candidates for CRT include those with dilated cardiomyopathy (either ischemic or nonischemic) with an ejection fraction of ≤35%, a QRS duration of ≥120 milliseconds on EKG, NYHA class 3 to 4 CHF symptoms despite optimal medical therapy such as β blockers, angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, and loop diuretics.16 Most patients that meet criteria for CRT are also candidates for defibrillator therapy.17 Before implantation, patients need to be evaluated according to history and physical data that concentrate on classification of heart failure class, medical optimization, and potential reversible causes. Preoperative testing should include EKG for QRS duration and classification of dyssynchronous pattern as well as echocardiography for evaluation of ejection fraction, mitral regurgitation, and left ventricular dimensions. Special attention should be given to the EKG. Computer-derived values of QRS duration frequently underestimate the true duration of the QRS complex. Terminal forces may not be included in the estimate, and hand-calibered durations may reveal a QRS of longer duration. The echocardiogram may also be used to evaluate dyssynchrony if the indication for CRT is borderline or to assist in decision making.18 Echo-based ventricular dyssynchrony may be classified as interventricular or intraventricular. Interventricular dyssynchrony refers to delayed ejection of one of the ventricles, and intraventricular dyssynchrony describes delay in contraction of segments within the left ventricle.19 Patients with QRS durations <130 milliseconds may have significant echo-defined dyssynchrony and have been found to benefit from CRT.20 If the patient has newly diagnosed CHF or the heart failure and left ventricular dysfunction is felt to be reversible, such as a case with rate-related cardiomyopathies, then medical therapy should be instituted and a reevaluation performed after at least 3 months before CRT therapy is initiated. In patients who meet indications for device-based therapy, such as a pacemaker or defibrillator, but who would not usually qualify for CRT therapy because of recent surgery, revascularization, or myocardial infarction, then the operator may choose to proceed with CRT therapy to avoid the additional risk of a system change in the near future. Patients with reduced left ventricular function who require pacing for complete heart block have been shown to have improved left ventricular ejection fraction and quality of life with biventricular pacing compared with right ventricular pacing in the Homburg Biventricular Pacing Evaluation (HOBIPACE) trial.21 Patients with reduced left ventricular function and atrial fibrillation who underwent atrioventricular (AV) junction ablation also appeared to benefit from biventricular pacing compared with right ventricular pacing in the Post AV Node Ablation Evaluation (PAVE) study.22 Patients who will have pacing-induced dyssynchrony should also receive CRT.

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| **Based on the results of many trials, candidates for CRT include those with dilated cardiomyopathy (either ischemic or nonischemic) with an ejection fraction of ≤35%, a QRS duration of ≥120 milliseconds on EKG, NYHA class 3 to 4 CHF symptoms despite optimal medical therapy such as β blockers, angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, and loop diuretics.**16 Most patients that meet criteria for CRT are also candidates for defibrillator therapy.17 Before implantation, patients need to be evaluated according to history and physical data that concentrate on classification of heart failure class, medical optimization, and potential reversible causes. Preoperative testing should include EKG for QRS duration and classification of dyssynchronous pattern as well as echocardiography for evaluation of ejection fraction, mitral regurgitation, and left ventricular dimensions. Special attention should be given to the EKG. Computer-derived values of QRS duration frequently underestimate the true duration of the QRS complex. Terminal forces may not be included in the estimate, and hand-calibered durations may reveal a QRS of longer duration. The echocardiogram may also be used to evaluate dyssynchrony if the indication for CRT is borderline or to assist in decision making.18 Echo-based ventricular dyssynchrony may be classified as interventricular or intraventricular. Interventricular dyssynchrony refers to delayed ejection of one of the ventricles, and intraventricular dyssynchrony describes delay in contraction of segments within the left ventricle.19 Patients with QRS durations <130 milliseconds may have significant echo-defined dyssynchrony and have been found to benefit from CRT.20 If the patient has newly diagnosed CHF or the heart failure and left ventricular dysfunction is felt to be reversible, such as a case with rate-related cardiomyopathies, then medical therapy should be instituted and a reevaluation performed after at least 3 months before CRT therapy is initiated. In patients who meet indications for device-based therapy, such as a pacemaker or defibrillator, but who would not usually qualify for CRT therapy because of recent surgery, revascularization, or myocardial infarction, then the operator may choose to proceed with CRT therapy to avoid the additional risk of a system change in the near future. Patients with reduced left ventricular function who require pacing for complete heart block have been shown to have improved left ventricular ejection fraction and quality of life with biventricular pacing compared with right ventricular pacing in the Homburg Biventricular Pacing Evaluation (HOBIPACE) trial.21 Patients with reduced left ventricular function and atrial fibrillation who underwent atrioventricular (AV) junction ablation also appeared to benefit from biventricular pacing compared with right ventricular pacing in the Post AV Node Ablation Evaluation (PAVE) study.22 Patients who will have pacing-induced dyssynchrony should also receive CRT. **TABLE 1. Statistically Significant Improvements Demonstrated With CRT in Major Clinical Trials**

<table>
<thead>
<tr>
<th>Subjective improvements with CRT</th>
<th>Objective improvements with CRT</th>
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<tr>
<td>NYHA class</td>
<td>Mortality</td>
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<tr>
<td>Hospitalization from any cause</td>
<td>6-Minute hall walk distance (m)</td>
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<tr>
<td>Hospitalization for IV diuretics</td>
<td>Increased systolic blood pressure (mm Hg)</td>
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<tr>
<td>Hospitalization for congestive heart failure</td>
<td>Increased diastolic blood pressure (mm Hg)</td>
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<tr>
<td>Hospitalization requiring IV medications</td>
<td>Decreased blood N-terminal pro-brain natriuretic peptide levels (pg/ml)</td>
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<td>Quality of life scores</td>
<td>Peak oxygen consumption (ml/kg per min)</td>
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<tr>
<td>Patient’s view of progress (scale)</td>
<td>Exercise time (sec)</td>
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<td>LV end-diastolic dimension (mm)</td>
<td>Echocardiographic parameters</td>
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<tr>
<td>Mitral regurgitation area (cm²)</td>
<td>Ejection fraction (%)</td>
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<td>LV end-systolic volume index (ml/m²)</td>
<td>LV indicates left ventricle.</td>
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Patients who are not candidates for CRT include those who are not ill enough or those who might be too ill. In patients with reduced left ventricular function but no CHF symptoms at all, the risk of the procedure likely outweighs the potential benefits. Patients who are nonambulatory or require continuous intravenous inotropes are likely too ill to receive enough benefit to justify the risk. Patients with a diagnosis that would result in death within 6 months are generally not considered to be candidates.

In CHF patients who meet standard criteria, CRT has been shown to improve objective and subjective signs of CHF. Improvements have been noted in heart failure questionnaires, NYHA class, ejection fraction, mitral regurgitation, quality of life scores, left ventricular pressure, cardiac index, and pulmonary capillary wedge pressure.23–25 Patients have also been found to undergo ventricular remodeling by diminishing left ventricular dimensions.26–27 These improvements appear to last over time, although mortality remains higher than in the population without CHF.28–30 Table 1 lists the reported statistically significant improvements in parameters recorded in major CRT trials. In a large trial, CRT alone has been associated with decreased mortality, but CRT and defibrillation therapy have been repeatedly shown to reduce mortality.13,15 The effect of CRT on arrhythmic burden appears to be modest at best. There appears to be no significant reduction in atrial fibrillation burden in those with CRT.31 Cases have been reported of CRT inducing ventricular arrhythmias, but several trials report a reduction in these events.32–36 A review of the 2 largest CRT trials did not show significant increases or decreases in ventricular arrhythmia.37
Pacing for Resynchronization

In CRT, pacing leads are placed in the right ventricle, right atrium, and a branch of the coronary sinus, although originally the left ventricular leads were placed on the epicardium in the operating room.38 The coronary sinus typically has several branches: middle cardiac vein, posterior vein, posterolateral vein, lateral vein, anterolateral vein, and anterior vein (Figure 1).39 The preferred site of the coronary sinus lead is in the posterolateral and lateral location. This can be achieved from the venous branches of the same name, but the venous system is variable, and the distal segments of many of the branches may lead to the posterolateral position. Evidence suggests that these locations are associated with the greatest response rates.40 In the original trials, the pacemaker was programmed to the DDD mode at a rate of 40 beats per minute at an AV delay shorter than the patient’s intrinsic conduction. Most patients did not have sinus node dysfunction.10,13,15 This resulted in tracking of sinus rhythm with biventricular pacing. Patients with atrial fibrillation were excluded from these trials. In earlier trials, the right ventricular lead and coronary sinus lead were electrically connected together to conform to the ventricular pacing port of a dual-chamber system. As a result, simultaneous activation of both ventricles was also required. The coronary sinus lead was a unipolar lead, and pacing outputs were determined by the highest threshold of either lead. Advances have resulted in devices with separate left ventricular and right ventricular outputs, bipolar leads of various shapes and sizes, and the ability to alter the timing between both ventricular leads. CRT has also been combined with defibrillation therapy on the basis of the results of trials that showed reduced mortality with defibrillator therapy in patients with reduced left ventricular function, such as the Multicenter Automatic Defibrillator Implantation Trial II (MADIT II) and Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT).14,17,41

CRT Lead Delivery

The major limitation to delivery of CRT therapy is anatomic. Because the left ventricular lead is delivered via the coronary sinus, and the preferred position of the lead is lateral, a prospective patient must have an accessible coronary sinus and a branch located in the posterior and lateral position large enough to accept a pacing lead. It can be difficult to access the coronary sinus in some patients. The ostium of the coronary sinus is located inferior and posterior to the tricuspid valve. It is protected inferiorly by the thebesian valve and laterally by the crista terminalis (Figure 2). The coronary sinus ostium may be tortuous, angulated, or vertically pos-
Cannulation of the coronary sinus has become easier with improved technology. Sheaths have been developed to take advantage of the existing anatomy. Outer sheaths with a large primary curve and a smaller secondary curve allow support from the lateral atrial wall and superior vena cava (Figure 3). The preferred technique of coronary sinus intubation is to advance the sheath into the right ventricle and withdraw it with counterclockwise rotation. This maneuver avoids the lateral crista terminalis and inferior thebesian valve because the approach is medial and superior. Cannulation of the coronary sinus tends to be easier with a left-sided implant. The angulation of the subclavian venous system relative to the superior vena cava from the left side allows support from the superior vena cava and right atrium. In a right-sided implant, the angulation tends to force the sheath medially and the supportive effect is lost. A standard 0.035-mm diameter wire, inner catheter, electrophysiologic recording catheter, and contrast dye may be used to assist in this process. Contrast dye improves the visualization of the anatomy in difficult cases. It may reveal unusually high ostia, an overriding thebesian valve, an early bifurcation, or separate ostium of the middle cardiac vein. Most frequently, it reveals that the sheath is in the sulcus of right atrium and tricuspid valve, which suggests that a sheath with a longer reach is required. The deflectable electrophysiologic recording catheter adds reach and maneuverability to the system. The signals obtained from the distal poles of the catheter also assist in the definition of the ostium location. The coronary sinus has a very typical electrical appearance with a large atrial electrogram and a smaller ventricular electrogram. Fluoroscopy alone may be helpful. The “fat stripe” serves as a marker for the location of the coronary sinus. Like peripheral veins, the coronary sinus may contain valves. A valve is typically present in the mid-coronary sinus. This may prevent advancement of the catheter or wire. Careful manipulation of the instruments can usually overcome this obstacle.

Once the coronary sinus has been cannulated, balloon occlusive venography is performed to identify the existing anatomy and possible target vessels. The venogram should be performed in at least 2 oblique projections to fully understand the anatomy. The vessels are analyzed for location, size, and angulation and tortuosity of the initial segments. The target vessel is identified, and a plan for placement of the lead, which includes the decision of what vessel to use, is formulated based on the anatomy. As stated, the posterior and lateral position results in the best response rates. One study reports that if the left ventricular electrogram is located in the latter half of the QRS complex, then response rates are

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Figure 3. A, Guide catheter with a large proximal curve. B, Display of the relationship of the catheter with the coronary sinus ostium after insertion. The large curve allows the guide to extend over the Eustachian ridge. The superiorly directed tip allows the guide to engage the ostium above the thebesian valve. Reproduced from Ellenbogen KA et al. Clinical Cardiac Pacing, Defibrillation and Resynchronization Therapy, 3rd ed. Philadelphia, Pa: Elsevier, Inc; 2006:685, with permission from Elsevier, Inc. Copyright 2006.

higher. Our current technique involves the attempted placement of the lead in the most posterior and lateral position as possible on the basis of several fluoroscopic projections. If multiple vessels are available for this location, then we may attempt to find the latest occurring electrogram. Conventional electroanatomic mapping software has been used to locate the latest occurring signals and reconstruct the anatomy.

Several technologies are being evaluated to help refine optimal lead positioning. Echocardiographic and computed tomographic evaluation of delayed mechanical activation are also being tested to identify individual lead placement that maximizes resynchronization. The benefit of computed tomography is that coronary sinus anatomic information is obtained in addition to the mechanical activation. Use of transthoracic echocardiography in the electrophysiology laboratory can be tedious and difficult. Image quality may be suboptimal as a result of the flat position of the patient, ambient lighting, and limitation of the sterile field. Intracardiac echocardiography shows promise as an adjunctive tool. Vector velocity imaging has been tested in conjunction with intracardiac echo to refine lead position. The lead can be placed into several positions and a visual or graphic evaluation can be performed with pacing at that location. The best parameters may result in a better lead position.

If the vessel chosen is at least of moderate size and does not appear to have a difficult anatomy, the operator may elect to proceed with the lead and an inner 0.015-mm diameter guide wire. The wire is advanced into the vessel, and the lead is advanced over this wire. If the initial segment of the target vessel appears challenging, then an appropriately shaped inner sheath may be used to deliver the wire or the wire and lead. Very difficult branches may require inner catheters that are capable of lead delivery. These catheters are shaped so that they are supported from the opposite wall of the coronary sinus body, which allows appropriate forward pressure to be applied to the lead. These catheters are available in various shapes that conform to differing anatomies. These sheaths may also straighten out tortuous segments for delivery. Occasionally, techniques such as venoplasty are required for significant stenosis of the target branch. After the lead is advanced, the site is tested for capture thresholds and presence or absence of phrenic nerve stimulation. The choice of lead depends on the anatomy of the branch. In general, if the branch is large, a larger diameter lead is chosen. If the branch is very large and possible dislodgement is a concern, a lead with a curled or sigmoid shape may be chosen. Bipolar leads are used most frequently because of the ability to program different configurations to overcome phrenic nerve stimulation or elevated pacing thresholds. Unipolar leads are used for sizing purposes. Leads with the smallest and largest diameters are unipolar and may be used for vessels that require these sizes. If the site is acceptable, then the sheath is removed, usually by mechanical splitting. Sheaths may have an inner wire braiding. This type of construction requires that a razor-bladed splitting device be used to cut the braids. This process may dislodge the lead. Splitting of the sheath should be performed under fluoroscopic guidance to ensure that the lead is not rotated or retracted during the process.

When a coronary sinus lead is added to an existing system, additional challenges may be present. The presence of pre-existing leads increases the possibility of occlusion of the subclavian system. If this occurs, the access for the coronary sinus lead can be performed proximal to the site of occlusion; however, this medial approach may increase the risk of lead failure and pneumothorax. Extraction of one of the exiting leads may be performed to allow for access for new leads. Alternatively, the system may be implanted from the opposite side, but this presents a new set of possible complications. The existing leads may be used in the generator if testing reveals appropriate function.

The complication rates associated with implantation of CRT have been remarkably low. The most common complication is inability to deliver coronary sinus pacing for one of the reasons mentioned above, but the overall delivery rate exceeds 90%. The need for reoperation to replace or reposition the coronary sinus lead occurs in 6% of cases. Dissection or perforation of the coronary sinus occurs in up to 4% of patients, but tamponade results in <1% of implants. Other infrequent complications include pneumothorax, complete heart block, infection, and hematoma. The rate of death associated with implantation is <0.5%. Table 2 reports the range of complications from 3 major CRT trials.

Most coronary venous dissections do not result in tamponade and do not require abandonment of the procedure. If a dissection occurs, then the outer sheath should be withdrawn and a wire used to find the true lumen of the coronary sinus. Once this is located, then the sheath may be advanced over the wire. If the tear impedes the advancement of the system, a large-diameter angioplasty balloon can be inflated and withdrawn to seal the tear. In the rare event that tamponade occurs, this usually responds to pericardiocentesis. If the patient does not respond or the blood continues to accumulate in the pericardial sac, then a surgeon should be called for evaluation.

### Technological Advances

New technologies exist and are being tested to improve the placement of the coronary sinus lead. Endoscopic catheters that allow direct visualization are being evaluated (online-only Data Supplement). These provide remarkable pictures of the anatomy in real time and in motion. The ability to directly visualize the obstacles may improve the ability to overcome them as well as limit the time spent struggling with implantation based on fluoroscopy and general knowledge of loca-

<table>
<thead>
<tr>
<th>Complications</th>
<th>Rates, %</th>
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<tr>
<td>Procedure-related death</td>
<td>0.2 to 0.6</td>
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<tr>
<td>Coronary venous dissection</td>
<td>0.3 to 4.0</td>
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<tr>
<td>Dislodgement</td>
<td>5.7 to 6.0</td>
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<tr>
<td>Coronary venous perforation</td>
<td>0.8 to 2</td>
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<tr>
<td>Tamponade</td>
<td>0.3 to 0.5</td>
</tr>
<tr>
<td>Infection/pocket erosion</td>
<td>1.3 to 2.7</td>
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</table>
tion of the coronary sinus. Another catheter that allows visualization by an attempt to filter out red blood cells has been used clinically and can reveal side branches without the need of contrast (Figure 4). This catheter can deliver some remarkable images, but it is unreliable. It also has a limited depth of field. Further refinement of these concepts may change the method of coronary sinus canalization. This technology could also be used to refine the positioning of the other leads, such as placement of the atrial lead near Bachman’s bundle.

Remote magnetic navigation uses maneuverable rare earth magnets to allow the control of a magnetic field. A magnet-tipped wire can be manipulated in this field to bend in any prespecified direction. The wire can be directed on the basis of the operator’s desire or of anatomy from venography. With the use of 2 orthogonal projections, the vectors that correspond to a specific site in the venous anatomy can be calculated, which results in a virtual roadmap of vectors (Figure 5). Other data such as preprocedural computed tomography can be imported and used as a guide to determine the vectors. This technology is useful in traversing a wire across very tortuous segments. The main limitation, that although a wire can be inserted into a branch, the lead may not follow, remains. This procedure is also limited to the technology of the current sheaths, leads, and wires. Magnet-tipped sheaths and delivery systems are being developed for future use.

**Epicardial Lead Placement**

Most of the aforementioned technologies are being developed to overcome the limitations inherent in relying on coronary venous anatomy. The minimally invasive subxiphoid epicardial approach is being used by cardiac electrophysiologists for epicardial ablation. This approach uses a spinal needle placed under the xiphoid process and advanced toward the cardiac border. A small puff of contrast is used to confirm position. The pericardial sac is punctured with the needle and a wire is advanced into the space. After the needle is
Figure 5. A, The remote magnetic navigation workstation screen shows the venography and roadmap in the lower 2 panels. B, The same workstation reveals the final lead position.
withdrawn, a sheath may be placed over the wire for access into the space. This technique lends itself to the placement of an epicardial left ventricular lead, and possibly other leads without the constraint of venous anatomy. Placement of leads in this manner allows a great deal of freedom in lead positioning. This could be combined with methods of rapid lead position evaluation and timing that result in a completely optimized system. Another possible benefit of this approach is the avoidance of the intravascular system, which could reduce the risk of venous occlusion and possibly system extraction. One of the major limitations of this approach is the mechanism of lead fixation. The epicardial space allows for nearly free movement of objects. A lead system would need to be developed that allows for fixation to occur against the myocardium preferentially. Epicardial leads and delivery systems for this approach are being developed. Also, not every pericardial space is easily accessible. Patients with previous open-heart surgery may develop fibrosis in the pericardial space that does not allow access.

Surgical placement of epicardial leads is becoming more commonplace. These leads may be placed at the time of bypass or valve surgery for future use. Minimally invasive and robot-assisted surgeries are also performed to place leads after attempts through the venous system have been unsuccessful. This method does not require the full sternotomy and reduces the patient recovery time.

Follow-Up and Response to Therapy

After placement and testing of the CRT device, the patient is discharged to follow-up with an evaluation of response to therapy at a later visit. At the follow-up visit, the patient should be questioned about heart failure symptoms and specific activity limitations compared with before therapy. Electrocardiography should be performed. Appropriate biventricular pacing can be confirmed by EKG. In general, a system with a well-placed coronary sinus lead yields a paced complex in which the initial forces in lead V1 are positive and leads 1 and aVL are more negative (rightward axis shift). This EKG should be compared with the postimplant and baseline EKG. Although it would seem that the QRS duration should decrease with CRT, this is not always the case. Also, in a review of many studies, a decrease or increase of the QRS duration does not appear predictive of response.

The device should be completely evaluated for normal functioning parameters. At this follow-up visit, echocardiography is frequently performed to evaluate ejection fraction, left ventricular dimension, mitral regurgitation, and possibly dyssynchrony. At this point, optimization of timing should be performed. If any ventricular remodeling has occurred, then the previously optimized values are likely to have changed. The methodology of optimization is discussed later.

At this visit, the key question to be answered is whether the patient has responded to therapy. No standard definition exists for the definition of responders versus nonresponders. Certainly, the main component is the patient’s subjective assessment, but CRT therapy has a profound placebo effect, and distinguishing a true response from this effect can be difficult. Objective measures, such as an exercise evaluation, or echo-based parameters, such as improvement in ejection fraction or left ventricular dimensions, may yield additional useful information. Response to CRT may take several months. In general, most of the benefit appears to occur by 3 months and persists thereafter.

Response rates to CRT have been less than ideal. Most trials report response rates in the range of 60 to 70%. Several reasons may exist for the lack of response from some patients (Table 3). CRT must first be delivered to be effective. Originally, the coronary sinus lead was adapted to the right ventricular lead to fit into a dual-chamber device, which made threshold testing difficult. Now that separate outputs are available, this testing has become simplified. The presence of atrial fibrillation with rapid response also prevents CRT from being delivered. Lead position appears to be an important factor in response rates.

TABLE 3. Potential Reasons for Nonresponse to CRT

<table>
<thead>
<tr>
<th>Reason</th>
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<tr>
<td>Failure of the LV lead to capture</td>
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<tr>
<td>Atrial fibrillation with rapid response</td>
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<tr>
<td>Suboptimal lead placement (anterior)</td>
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<tr>
<td>Absence of dyssynchrony</td>
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<tr>
<td>Suboptimal AV delays</td>
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<tr>
<td>Suboptimal V to V delays</td>
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<tr>
<td>Latency to LV stimulation</td>
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<tr>
<td>Lack of perfusion to the lateral wall</td>
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<tr>
<td>Lack of viable myocardium</td>
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<tr>
<td>Overwhelming intramyocardial delay</td>
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LV indicates left ventricular; V to V, timing between the right ventricular and left ventricular leads.
The posterior and lateral position, which is opposed to the right ventricular lead, has been shown to be associated with improved response rates. The presence of scar tissue in the posterolateral left ventricle and lack of viable myocardium has been found to be associated with reduced response rates. The evaluation of dyssynchrony by echo parameters has been developed to help define patients who are more likely to respond to therapy. Patients without dyssynchrony are less likely to benefit from CRT. Another method to improve response rates is optimization of CRT timing. All CRT devices allow adjustment of the AV delay. Too long an AV delay permits inefficient diastolic filling, which affects subsequent cycles. Diastolic mitral regurgitation may occur, and direct measures of contractility are reduced. Echo-based evaluation of transmitral Doppler flow is frequently used for optimization. The normal transmitral pattern reveals distinct E and A waves. The E wave represents passive ventricular filling, and the A wave represents atrial contraction (Figure 7). Prolonged AV conduction results in fusion of these 2 waves. The opposite end of the spectrum is an AV delay that is too short. On transmitral Doppler, this is seen by truncation of the A wave. Patients will frequently report increased pulmonary symptoms and pacemaker syndrome type symptoms. It is a misconception that CRT only treats CHF by treatment of systolic dysfunction. As is seen on the transmitral flow patterns, CRT improves diastolic ventricular filling, which continues to improve over time as the ventricle remodels. Another timing variable present in most devices is alterable pacing intervals between the left and right ventricular leads. Patients vary in the amount of delay between myocardial segments. The treatment of nonresponders should first focus on whether the patient is receiving CRT. The device function should be evaluated to ensure appropriate sensing and capture of all leads. Of course, medical therapy should continue to be optimized after implantation of the device. The patient should also be evaluated for the presence of atrial fibrillation. Atrial fibrillation with a rapid response will prevent the device from pacing if the heart rate in atrial fibrillation is above the programmed rate. This should prompt the need for improved rate control and, possibly, attempts to restore sinus rhythm. A chest x-ray for evaluation of lead position should be performed.

Table 4. Dyssynchrony Evaluation Techniques and Some Reported Definitions

<table>
<thead>
<tr>
<th>Technique</th>
<th>Definition</th>
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<tr>
<td>QRS Duration (&gt;120 ms)</td>
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<tr>
<td>LV electrogram onset (&gt;50% of QRS)</td>
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<tr>
<td>M-Mode septal to posterior wall motion delay (&gt;130 ms)</td>
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<tr>
<td>QRS onset to right and LV ejection difference (&gt;40 ms)</td>
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<td>Aortic prejection time (&gt;160 ms)</td>
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<td>Pulsed wave tissue Doppler</td>
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<td>Time to onset of ventricular motion</td>
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<td>Time to peak ventricular motion</td>
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<td>Color tissue Doppler</td>
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<tr>
<td>Time to peak sustained tissue velocity</td>
<td></td>
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<td>Time to maximal velocity</td>
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<td>Segmental analysis of tissue Doppler</td>
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<tr>
<td>&gt;65 ms between 4 segments</td>
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<td>LV dyssynchrony index &gt;32.6 ms</td>
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<tr>
<td>Strain/strain rate analysis</td>
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<td>Tissue synchronicity imaging</td>
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<td>Vector velocity imaging</td>
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<tr>
<td>Real-time 3-dimensional echocardiography</td>
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LV indicates left ventricular.
formed. If the lead is in a suboptimal position, then repositioning based on the limitations of anatomy could be considered. Surgical epicardial lead placement is another option, because there are no limitations based on venous anatomy. Optimization of atrial to ventricular and right ventricular to left ventricular timing should also be performed in the nonresponder, although technology advancements will allow this to be performed in all patients after implant.

**Controversies**

Current controversies in CRT are mostly focused on patients who are indicated or those who are felt to be less likely to respond. Patients with an increased QRS but without dyssynchrony on the basis of echocardiographic criteria have been found to be less likely to respond to CRT. Current indications only use an increased QRS duration as an indication for dyssynchrony. Some feel that some additional evaluation of dyssynchrony may reduce the rate of nonresponders.18,62,72 The QRS-based definition of dyssynchrony may also limit patients who may benefit from CRT. Some patients with shorter QRS durations have been found to exhibit dyssynchrony. These patients may also benefit from CRT.73 Another controversial issue is the presence of a right bundle-branch block pattern on EKG. The majority of patients with CHF and an increased QRS duration have a left bundle-branch block pattern and activate the left lateral wall later as compared with the right ventricle and septum. It is on the basis of this premise that CRT seems to be beneficial by activating the left lateral wall more synchronously with the septum.5 A right ventricular delay with intact left lateral wall timing would seem to be less likely to benefit from this type of pacing. In fact, some studies have shown that patients with right bundle-branch block are less likely to benefit from CRT; however, the original trials included those with right bundle-branch block patterns, and some maintain that CRT should still be offered to the populations included in these trials.74,75 Another consideration is that either a left bundle-branch block or right bundle-branch block pattern does not truly represent the conduction. These patients have conduction abnormalities in addition to simple bundle-branch blocks.76 Severing the right bundle-branch leads to a QRS duration of about 120 milliseconds in humans. Severing the left bundle-branch results in a QRS duration of about 150 milliseconds. CHF patients may have QRS durations >200 milliseconds. The remainder of the delay is intra- and interventricular, so classification of a patient as right bundle-branch or left bundle-branch block may not truly represent the type of dyssynchronous pattern. Overall, no other criteria for dyssynchrony other than QRS duration have been used in major trials, and no consensus exists on the optimal echo parameters to define dyssynchrony.

One procedure that is frequently performed is the upgrade of an existing pacemaker or defibrillator to a CRT device. This was not addressed in the initial clinical trials; however, subsequent smaller studies have shown that these patients seem to benefit from CRT therapy.77,78 These patients may be excellent candidates, because right ventricular apical pacing is a dysynchronous activation pattern.6 Animal studies have shown that long-term right ventricular pacing induces myofibrillar disarray, asymmetric hypertrophy, and dilatation of the left ventricle.79–81 In humans, echo studies confirm the dysynchronous activation and reduced efficiency, and others have found elevated serum markers of CHF and stress.82–84 Major trials, such as the Mode Selection Trial (MOST) and the Dual Chamber and VVI Implantable Defibrillator (DAVID) Trial, have determined that this type of pacing is detrimental in terms of CHF symptoms, and the current practice is to avoid unnecessary ventricular pacing.85,86 Methods to reduce unnecessary right ventricular pacing include reprogramming the device to maximize the AV delay or changing the mode to VVI at a low rate. Some devices allow programming in the AAI mode with reversion to DDD if AV conduction is lost. Pacing the right ventricle from a site other than the apex, such as direct His bundle pacing, may reduce dyssynchrony and CHF.21 Otherwise, CHF patients with an indication for pacing, who may require a great deal of ventricular pacing, could benefit from a strategy that employs CRT, but this indication is not yet approved. The HOBIPACE study revealed that patients with AV block and left ventricular dysfunction had improved quality of life, left ventricular ejection fraction, and exercise duration with CRT compared with standard dual-chamber pacing.21

Another major controversy is the inclusion of patients with NYHA class 1 or 2 CHF. These patients with minor symptoms may benefit from CRT. Some trials have shown echo-cardiographic improvement in this population, but, as expected, clinical symptomatic improvement was not seen in such a minimally symptomatic population.87 Some believe that treatment in this population could prevent heart failure symptoms, worsening cardiac function, or adverse remodeling.88 Atrial fibrillation is another area of controversy. Smaller studies have demonstrated improvements in patients with atrial fibrillation, but they were excluded from the major trials.89–91 Patients with permanent atrial fibrillation do not receive the benefit of AV synchrony, but ventricular dyssynchrony may persist. Most trials looking at atrial fibrillation have included patients who underwent AV junction ablation. This ensures appropriate rate control and delivery of CRT therapy; however, AV junction ablation and pacing alone has been shown to improve symptoms and functional capacity in patients with atrial fibrillation and a rapid response.92,93 The PAVE study prospectively evaluated the approach of AV junction ablation and biventricular pacing versus right ventricular pacing in a population with CHF symptoms and showed improvement in functional status, exercise time, and quality of life in the overall population, but most of the benefit was seen in those with preexisting left ventricular dysfunction.22

**Clinical Research**

Clinical research seeks to find answers to some of the controversies. The Multicenter Automatic Defibrillator Implantation Trial–Cardiac Resynchronization Therapy (MADIT-CRT) and the Resynchronization Reverses Remodeling in Systolic Left Ventricular Dysfunction (REVERSE) trial are evaluating the role of defibrillators with and without CRT in large groups of NYHA class 1 or 2 patients. The
Resynchronization Therapy in Normal QRS (RETHINQ) trial is evaluating CRT in patients with CHF and echo-based dyssynchrony with a narrow QRS. Other areas of interest in clinical research include multisite left ventricular pacing. The theory is that resynchronization can be delivered more efficiently if pacing comes from several sites. Another thought is that because most patients have intact right bundle-branch conduction and right ventricular apical pacing has been found to be detrimental, CRT timing could be altered to allow right-sided conduction and pace the left ventricle at a time to allow the electrical forces to meet at the septum.

Conclusion

CRT has been an important tool in the armamentarium of CHF treatment. Advances in equipment and techniques have improved the delivery of this therapy. Interventional electrophysiologists have been able to overcome some of the limitations inherent in variable coronary venous anatomy with techniques such as venoplasty and inner catheter technology. Timing cycle optimization and guided lead placement may result in response rates >90%. The results of future clinical trials may expand this therapy to those with less severe heart failure or with narrower QRS.

Disclosures

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