Cardiac resynchronization therapy in congestive heart failure: Ready for prime time?

Antonis S. Manolis, MD

From the A’ Department of Cardiology, Evangelismos General Hospital of Athens, Athens, Greece.

OBJECTIVES/BACKGROUND The aim of this article is to critically review the data accumulated to date on the application of cardiac resynchronization therapy (CRT) via biventricular pacing techniques to manage patients with advanced heart failure. The data from studies evaluating the effects of long-term right ventricular (RV) pacing are also briefly reviewed.

METHODS MEDLINE and selective journal searches of English-language reports and a search of references of relevant papers were conducted.

RESULTS Cardiac dyssynchrony as reflected by a prolonged QRS complex, often in the form of left bundle branch block, is encountered in about 30% of patients with moderate-to-advanced heart failure. Among these patients, 10% to 15% are candidates for CRT via biventricular pacing. Accumulated evidence from randomized controlled studies over the last few years has indicated a significant hemodynamic and clinical improvement conferred by CRT to class III or IV heart failure patients with idiopathic or ischemic dilated cardiomyopathy having a low left ventricular ejection fraction (≤35%) and a wide QRS complex (≥120–150 ms). Newer data suggest a significant reduction in overall mortality and heart failure hospitalization, particularly when CRT is combined with automatic defibrillator backup. Technical advances with percutaneous methods accessing the tributaries of the cardiac veins have raised the success rate of implantation of left ventricular leads to ≥90%. Further confirmation from ongoing trials is awaited, and more data from cost-effectiveness studies are needed before CRT is considered for prime time therapy in the heart failure population. If the data confirm a survival benefit from CRT, use of this electrical therapy at earlier stages of heart failure might be contemplated. New evidence from recent studies suggests a deleterious effect of the long-standing practice of producing an iatrogenic left bundle branch block by conventional RV apical pacing in patients receiving permanent pacemakers. Thus, having already become poignantly aware of the harmful effects of spontaneous left bundle branch block, this emerging new evidence about RV apical pacing would dictate a change of attitude and direct our attention to alternate sites of pacing, such as the left ventricle and/or the RV outflow tract, if not for all patients then at least for those with left ventricular dysfunction.

CONCLUSIONS CRT offers hemodynamic and clinical improvement to patients with moderate-to-advanced heart failure, and it might significantly prolong survival in selected patients, particularly if devices with defibrillation backup are used. Further confirmatory data from randomized mortality trials are needed, and issues of cost efficacy must be resolved before this vital therapeutic alternative is ready for prime time therapy of heart failure patients.

KEYWORDS Cardiac resynchronization; Biventricular pacing; Heart failure; Left ventricular pacing; Left bundle branch block; Cardiac dyssynchrony; Cardiomyopathy; Implantable cardioverter defibrillator

© 2004 Heart Rhythm Society. All rights reserved.

The prevalence of congestive heart failure has increased significantly over the last few decades. According to epidemiologic studies, an estimated 4 to 5 million people in the United States have heart failure (50% men), and the number rises to 22.5 million worldwide. An additional 2 million patients are reported each year. The prevalence of the disease is age dependent. In the years 1988 to 1991, the prevalence was estimated to be about 10% in the age group >70 years. Mortality of heart failure is dependent on its clinical severity; for advanced cases, mortality reaches 30% to 50% by 5 years. Cost estimates bring the health care cost for heart failure hospitalization, medications, and follow-up to $20 to $40 billion annually.1,2
Over the last decade, considerable progress has been made in the management of heart failure with the use of angiotensin-converting enzyme inhibitors (or angiotensin antagonists), aldosterone antagonists, and, more recently, new beta-blocking agents with vasodilating properties. Newer pacing techniques have emerged as a vital therapeutic alternative for patients who remain refractory to optimal medical therapy and prior to utilization of inotropes, mechanical support, or heart transplantation with its inherent problems and limited number of donors.

Beyond conventional pacing therapies that treat bradycardia, manage chronotropic incompetence, and provide atioventricular (AV) synchronization, the coordination of ventricular contraction (ventricular resynchronization) has emerged as an important and most promising pacing technique.

Patients with intraventricular conduction delay, most evident in the presence of left bundle branch block, have significant intraventricular discoordination from delayed lateral wall contraction, which is excessively preloaded due to redistribution of regional wall stress and leads to dire hemodynamic consequences such as reduced stroke volume and cardiac output. If this also is associated with AV asynchrony limiting ventricular filling, then the hemodynamic problem is accentuated. Major hemodynamic benefit is derived from restoring AV and ventricular synchrony in such patients using AV biventricular pacing techniques (Figures 1 and 2). The prevalence of ventricular dyssynchrony, defined as an abnormality in electromechanical coupling occurring in conjunction with interventricular conduction block or prolonged QRS duration with measured QRS width >120 ms, ranges from 27% to 53%. Thus, a significant number of patients may be candidates for cardiac resynchronization therapy (CRT) (Table 1), even if only those patients refractory to optimal medical therapy, estimated to be around 10% to 15% of heart failure patients, are considered. In a recent study of 5,517 patients with congestive heart failure, the subgroup (25%) with left bundle branch block (n = 1,391) had a hazard ratio of 1.7 for total mortality and 1.6 for sudden death compared to patients without left bundle branch block.

**Clinical improvement trials**

Studies such as PATH-CHF (n = 42), CONTAK CD (n = 490), InSync (n = 103), InSync ICD (n = 554), MUSTIC (n = 131; 67 patients in sinus rhythm and 64 patients with atrial fibrillation), and, more recently, MIRACLE (n = 433) and MIRACLE ICD (n = 369) all have convincingly shown that CRT provides significant hemodynamic benefits and symptomatic improvement over 3 to 6 months in patients with moderate-to-severe heart failure (Table 2). The characteristics of these patients were as follows: New York Heart Association (NYHA) class III to IV, mean age 63 to 67 years, dilated (31%–63%) or ischemic (37%–69%) cardiomyopathy, mostly left bundle branch block (54%–87%), QRS duration ≥120 ms, PR interval >150 ms, and mean left ventricular ejection fraction 21%–24%. Electrical (CRT) therapy led to improved functional capacity (increase in 6-minute walk distance and peak VO₂), improved quality of life, symptom relief (improvement by at least one functional NYHA class), reduction in hospitalization rates, reduced mitral regurgitation, and positive trends toward improvement of left ventricular ejection fraction.

The long-term results of these studies were reported recently and indicate that the short-term improvement noted at 3 to 6 months is maintained over 1-year follow-up. In the MUSTIC study, the following findings at 12 months compared with baseline were noted in all patients in sinus rhythm and in 88% of patients with atrial fibrillation who...
were programmed to biventricular pacing: 6-minute walked distance increased by 20% \((P < .0001)\) and 17% \((P < .0004)\), respectively; peak VO2 increased by 11% and 9%, respectively; quality of life improved by 36% \((P < .0001)\) and 27% \((P < .0001)\), respectively. Left ventricular ejection fraction improved by 5% and 4%, whereas mitral regurgitation decreased by 45% and 50%, respectively. In other studies using Doppler echocardiography or the newly developed tissue Doppler imaging techniques, CRT has been shown to significantly improve left ventricular function and reverse left ventricular remodeling during long-term follow-up.19–21 Patients likely to benefit from CRT may be identified by tissue Doppler imaging before implantation of a biventricular pacemaker.

Based on the results of these studies, the revised ACC/AHA/NASPE 2002 guideline update for implantation of cardiac pacemakers and antiarrhythmia devices included CRT as a class IIa indication for medically refractory heart failure (class III–IV), prolonged QRS \((\geq 130\, \text{ms})\), left ventricular end-diastolic diameter \(\geq 55\, \text{mm}\), and left ventricular ejection fraction \(\leq 35\%\) (Table 1).22 This is a new development given that the earlier guidelines for heart failure therapy, published at the end of 2001, did not even mention this therapeutic modality.23 In addition, the generic pacemaker mode code recently was modified to include multisite pacing modes.24

### Mortality trials

Despite all of this progress, for a new therapeutic modality to survive and establish itself as a viable alternative, randomized studies that have total mortality, rather than symptomatic and functional improvement, as a primary endpoint are needed (Table 2). Such studies are in progress (PACMAN, CARE-HF, RAFT),14,25 and the preliminary results of the COMPANION trial have just been published.26 According to these data, CRT resulted in a 24% reduction in all-cause mortality over 12 months \((P = .06)\), whereas CRT plus defibrillation [implantable cardioverter defibrillator (ICD)] led to a 36% reduction in total mortality \((P = .003)\) compared to optimal medical therapy. This study recruited 1,520 high-risk patients with moderate-to-severe heart failure (NYHA class III–IV), left ventricular ejection fraction \(\leq 35\%\), LV end-diastolic diameter \(\geq 6\, \text{cm}\), QRS complexes \(> 120\, \text{ms}\), and PR intervals \(> 150\, \text{ms}\), who were randomized to 1 of 3 arms in a 1:2:2 scheme. Although all patients received maximal medical therapy, one group also received CRT and another group received CRT plus defibrillation with an ICD device. The study was prematurely halted by the safety committee because it met the prespecified stopping rule on November 21, 2002. According to the

### Table 1

**ACC/AHA/NASPE guidelines for cardiac resynchronization therapy in patients with congestive heart failure (class IIa/level of evidence: A)*

<table>
<thead>
<tr>
<th>Category</th>
<th>Description</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medical Refractory Advanced Heart Failure (NYHA class III/IV)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Idiopathic Dilated or Ischemic Cardiomyopathy with LV Ejection Fraction (\leq 35%), LVEDD (\geq 5.5, \text{cm})</td>
<td></td>
</tr>
<tr>
<td></td>
<td>LVEF (\leq 35%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>QRS Complex Duration (\geq 130, \text{ms})</td>
<td></td>
</tr>
</tbody>
</table>

*Patients who also have malignant ventricular arrhythmias or belong to defined high-risk patients (e.g., MADIT I or II patients) and therefore have an indication for an implantable cardioverter defibrillator (ICD) would be candidates for combined cardiac resynchronization therapy and ICD therapy.

LVEDD = left ventricular end-diastolic dimension; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association (classification).

### Table 2

**Clinical randomized trials of cardiac resynchronization therapy**

<table>
<thead>
<tr>
<th>Trial</th>
<th>No. of patients</th>
<th>Mean age (yr)</th>
<th>Mean LVEF</th>
<th>NYHA class</th>
<th>CAD</th>
<th>Mean QRS (ms)</th>
<th>LBBB</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical Improvement Trials</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CONTAK CD</td>
<td>490</td>
<td>66</td>
<td>21%</td>
<td>II–IV</td>
<td>69%</td>
<td>158</td>
<td>54%</td>
</tr>
<tr>
<td>InSync ICD</td>
<td>554</td>
<td>66</td>
<td>21%</td>
<td>II–IV</td>
<td>65%</td>
<td>165</td>
<td>69%</td>
</tr>
<tr>
<td>MUSTIC</td>
<td>58*</td>
<td>63</td>
<td>23%</td>
<td>III</td>
<td>37%</td>
<td>176</td>
<td>87%</td>
</tr>
<tr>
<td>MIRACLE</td>
<td>453</td>
<td>64</td>
<td>22%</td>
<td>III–IV</td>
<td>54%</td>
<td>166</td>
<td>80%</td>
</tr>
<tr>
<td>MIRACLE ICD</td>
<td>369</td>
<td>67</td>
<td>24%</td>
<td>III–IV</td>
<td>69%</td>
<td>164</td>
<td>87%</td>
</tr>
<tr>
<td>Mortality Trials</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Meta-analysis</td>
<td>1,634</td>
<td>63–66</td>
<td>21%–23%</td>
<td>37%–69%</td>
<td>158–176</td>
<td>54%–87%</td>
<td>23%</td>
</tr>
<tr>
<td>COMPANION</td>
<td>1,520</td>
<td>65</td>
<td>22%</td>
<td>56%</td>
<td>158</td>
<td>71%</td>
<td>24%†</td>
</tr>
</tbody>
</table>

*Patients in sinus rhythm (58/67 randomized). There was another group of 64 patients with atrial fibrillation who also benefited from CRT but to a lesser degree.

†CRT alone \((P = .06)\). MR ↓ was 36% when CRT was combined with ICD therapy \((P = .003)\).

CAD = coronary artery disease (ischemic cardiomyopathy); CRT = cardiac resynchronization therapy; LBBB = left bundle branch block; LVEF = left ventricular ejection fraction; MR ↓ = (all-cause) mortality rate reduction; NYHA = New York Heart Association.
cause of heart failure, CRT with an ICD was associated with a 27% reduction in total mortality in patients with ischemic cardiomyopathy and a 50% mortality reduction in patients with nonischemic cardiomyopathy.26

More data regarding total mortality have been provided by a recent meta-analysis of 11 reports of four randomized trials evaluating CRT in 1,634 patients.12 According to the results of this meta-analysis, CRT reduced heart failure hospitalization by 29% and reduced death from progressive heart failure by 51% relative to controls (1.7% vs 3.5%). CRT showed a trend toward reducing all-cause mortality, being responsible for an overall 23% fewer deaths in heart failure patients. More data from ongoing randomized studies (PACMAN, CARE-HF, RAFT) evaluating the effect of CRT on total mortality will soon be available.14

Iatrogenic dyssynchrony caused by right ventricular apical pacing and alternate sites of pacing

Another important point to consider is the accumulating evidence that not only is spontaneous left bundle branch block harmful to our patients, but the iatrogenic left bundle branch block produced by right ventricular apical pacing is equally deleterious. In a study involving 24 young patients (mean age 19.5 years) in need of permanent pacing compared with 33 age- and basal surface area-matched healthy control individuals over a mean follow-up of 9.5 years, right ventricular apical pacing led to irreversible left ventricular dysfunction.27 Another recent study, the DAVID trial, examined the possible harmful effect of unnecessary right ventricular pacing in ICD patients.28 Patients (n = 256) with their ICD device programmed to standby VVI mode at 40 beats/min fared much better compared with those (n = 250) who had the device programmed to DDDR pacing at 70 beats/min.28 Over 1 year, the hazard ratios for the DDDR pacing group compared with the VVI group were 1.61 for heart failure hospitalization or death, 1.54 for heart failure hospitalization, and 1.61 for death. A MADIT II substudy reported during the NASPE meeting in May 2003 raised similar concerns about right ventricular apical pacing. Patients with high cumulative right ventricular pacing (>50%) had a higher incidence of heart failure (hazard ratio 2.1) and heart failure or death (hazard ratio 1.9) compared to patients with infrequent right ventricular pacing.29

More data on the adverse effect of right ventricular apical pacing have become available via a recent study assessing the prevalence of heart failure or left ventricular dysfunction among 307 chronically paced patients (about half of whom had dual-chamber devices).30 Low left ventricular ejection fraction (<40%) was detected in 94 (31%) patients, of whom 83 had symptoms of heart failure. Although the etiology of heart failure in this population may be multifactorial, a good percentage probably is pacing induced.30 A subanalysis of the MOST trial refutes the assumption that dual-chamber pacing mitigates the adverse effects of right ventricular pacing.31 Of 1,339 patients with sinus node dysfunction and baseline QRS <120 ms, 707 (53%) were randomly assigned to DDDR and 632 (47%) to VVIR pacing. The overall rates of heart failure hospitalization were similar (10% DDDR, 9% VVIR). Despite maintenance of AV synchrony, ventricular pacing in the DDDR mode >40% of the time conferred a 2.6-fold increased risk of heart failure hospitalization compared with less pacing among similar patients with normal baseline QRS duration.31 In another recently published randomized trial, 177 patients (age 74 ± 9 years) with sinus node dysfunction were randomized to 1 or 3 modes of pacing: AAIR (n = 54), DDDR with short AV delay (n = 60), or DDDR with long AV delay (n = 63). Over 2.9 ± 1.1 years, the patients in the two DDDR groups with conventional right ventricular apical pacing had increased left atrial diameter and more common atrial fibrillation, and those with a high proportion of right ventricular pacing (DDDR pacing with short AV delay) had significantly decreased left ventricular fractional shortening compared to patients with AAIR pacing.32

In a search for alternate sites of ventricular stimulation, a recent pooled analysis of nine studies evaluating the hemodynamic effects of right ventricular outflow tract pacing in 217 patients indicated a significant hemodynamic benefit compared with right ventricular apical pacing (odds ratio 0.34).33 In the same direction, a recently completed, randomized multicenter study examined the feasibility of a new steerable system using novel technology that allows implantation of a very thin, active-fixation lead at alternate sites in the right atrium and right ventricular outflow tract. The success rate of implantation was 93% in 30 patients at our center, with excellent measurements obtained intraoperatively and during short-term 3-month follow-up.44 However, a recently reported, randomized cross-over trial (ROVA), which compared right ventricular outflow tract with right ventricular apical pacing in 103 pacemaker patients with congestive heart failure and chronic atrial fibrillation, did not show any consistent improvement in quality of life after 3 months of right ventricular outflow tract pacing compared to right ventricular apex pacing.35 Finally, experimental animal data confirm the harmful effect of right ventricular apex pacing on left ventricular function and indicate that the optimal ventricular pacing site is in the left ventricle.36

Eligible patients and other issues for CRT application

A key issue for CRT is the identification of eligible patients who are most likely to respond and receive the most benefit. QRS duration has been deemed a primary variable as a principal electrical marker of spatially dispersed mechanical activation; thus, patients with wider QRS complexes seem to have a greater mechanical response to CRT. In addition,
the worse the ventricular dysfunction, which probably reflects the degree of dyssynchrony, the greater the response to CRT.

The percentage of nonresponders varies between 18% and 32%. Responders are more likely to have idiopathic dilated cardiomyopathy and no history of myocardial infarction. In contrast, prior myocardial infarction, no significant degree of mitral regurgitation, and ischemic cardiomyopathy have been suggested as independent predictive factors for identifying nonresponders prior to pacemaker implantation.

In patients with dilated cardiomyopathy, significant interventricular dyssynchrony as measured by radionuclide angioscintigraphy could predict a good response to CRT. Direct evaluation of ventricular dyssynchrony also may be possible with newer techniques, such as tissue Doppler (or velocity) imaging, which show promise in identifying responders to CRT. Several studies have suggested the presence of systolic dyssynchrony at baseline as measured by tissue Doppler imaging to be an independent predictor of reverse remodeling and capable of identifying responders to CRT.

In 25 patients with end-stage heart failure scheduled for biventricular pacemaker implantation, the only variable that differed between responders and nonresponders was a septal-to-lateral delay in peak systolic velocity at baseline \( \geq 60 \) ms. Two thirds of patients in this study had an immediate improvement in left ventricular ejection fraction, which was followed by an improvement in NYHA class, exercise capacity, and quality of life score at 6 months. In another study of 25 patients with severe heart failure and bundle branch block who underwent biventricular pacemaker implantation, the extent of left ventricular basal asynchrony as detected by tissue Doppler techniques before pacemaker implantation predicted long-term efficacy of CRT. QRS duration failed to predict CRT efficacy in this patient group. Echocardiography with tissue Doppler imaging was performed at baseline and 3 months after biventricular pacing in 30 patients, of whom 17 were responders to reverse remodeling and had significant clinical improvement by CRT. Of all factors analyzed, systolic dyssynchrony was the only independent predictor of reverse remodeling. A preimplant dyssynchrony index of 32.6 ms was able to totally identify responders from nonresponders to CRT.

The degree of QRS shortening with biventricular pacing (Figure 2), used to indicate CRT efficacy, has remained a controversial issue. The optimal positions of the right and left ventricular leads (usually in the lateral or posterolateral left ventricular aspect in noninfarcted segments for the left ventricular lead) should be those that induce the greatest shortening of QRS duration, at least \( >25\% \) pacing-induced QRS narrowing. Of the three modes of resynchronization—total (reflected by QRS duration), interventricular, and intraventricular resynchronization—experimental data give more credence to intraventricular resynchroniza-

tion for optimal left ventricular function in the presence of left bundle branch block and suggest a modulating role of optimizing AV delay based on systolic left ventricular function. Thus, effective left ventricular or biventricular pacing with adequate preexcitation is a prerequisite to ensure left ventricular resynchronization. This requires appropriate programming of a suitable AV delay, if feasible, or AV nodal ablation, particularly in patients without prolonged PR interval or in patients with atrial fibrillation and normally conducting AV node. On a different note, preliminary data have indicated that there are no significant differences between single-site left ventricular pacing and biventricular pacing for CRT. This suggests that right ventricular pacing may be redundant and left ventricular pacing alone might suffice.

There remains a distinct subgroup of patients with dilated cardiomyopathy, poor left ventricular function, and normal or not so wide QRS complex in whom preliminary data indicate that CRT may provide benefit. Tissue Doppler imaging studies indicate that mechanical dyssynchrony occurs even in patients with normal QRS duration. Among 52 patients with severe heart failure and echocardiographic evidence of interventricular and intraventricular asynchrony, 14 patients with QRS duration \( \leq 120 \) ms benefited from CRT equally as well as those with a wider QRS. Similarly, 30 heart failure patients with QRS \( <150 \) ms had an equal or better response to CRT compared to 128 patients with a wider QRS. Further studies are needed to shed more light on this critical issue.

With regard to patients with atrial fibrillation, some data have become available from a subpopulation with permanent atrial fibrillation in the MUSTIC trial. These patients did benefit from CRT, although to a lesser degree compared to patients with sinus rhythm. In a different subgroup of patients who undergo AV nodal ablation for chronic atrial fibrillation, the preliminary results of a randomized trial (PAVE) indicate that CRT \( (n = 82) \) provides an improvement in functional capacity \( (P = .03) \) over RV apical pacing \( (n = 102) \) (ACC meeting 2004).

Although there is an abundance of information on patients with idiopathic or ischemic dilated cardiomyopathy, the data are scanty regarding young patients with congenital or other forms of underlying heart disease.

Other important issues for CRT implementation are (1) the significant learning curve as proper physician training in the technique becomes an essential part of training in complex pacing and heart failure management, and (2) the increased cost of biventricular pacing systems, almost dou-
ble that of standard dual-chamber systems, which will be a significant obstacle to wider application of this novel therapy. Cost-efficacy data are scanty, and are eagerly awaited from future studies. The issue of whether these systems should routinely provide ICD backup renders the cost issue even more difficult. Nevertheless, the impact that CRT may have on mortality in heart failure patients most probably will, in the long run, be tied in with ICDs, as suggested by the results of the COMPANION trial. However, this remains a complex issue. Recent data from the CAT and AMIOVIRT trials, which included patients with idiopathic dilated cardiomyopathy with mild-to-moderate congestive heart failure, cast some doubt on the efficacy of ICDs in prolonging survival compared with standard treatment or amiodarone therapy. However, data from a larger study (DEFINITE), which included 458 patients with nonischemic dilated cardiomyopathy, indicate that ICDs (n = 229) significantly reduce arrhythmic mortality by 80% (P = .006) and tend to reduce total mortality by 35% (P = .08) compared to standard medical therapy (n = 229).

Implantation techniques and difficulties

The major problem with applying this mode of therapy has been access to, and maintenance of, effective left ventricular pacing. Epicardial leads had been used initially, but the practical approach of inserting the left ventricular lead via the coronary sinus tributaries has since been adopted. A new method to the epicardial approach via robotic-enhanced thoracoscopic implantation of the left ventricular lead has been proposed recently. A transseptal approach to endocardial left ventricular pacing also has been attempted but not seriously pursued due to technical difficulties and the need for permanent anticoagulation to prevent thromboembolism. Technologic advances have led to the use of specially preformed, mainly unipolar, leads and have culminated in more widespread use of special guiding catheters for cannulating the coronary sinus and implanting the pacing lead with over-the-wire or monorail steerable systems similar to angioplasty equipment (Figure 1). Such techniques have increased the procedural success rate to >90% to 95% and have reduced the complication and reintervention rate from ~20% (mainly due to a high dislodgment rate) to <10%. Coronary vein angiography, which is effected via these delivery systems, has played a major role in successfully reaching the most suitable coronary vein branch for attaining an optimal and effective left ventricular pacing site (Figure 1). In most patients with dysynchrony, lateral wall contraction is delayed in comparison to the septum. Studies have indicated that optimal resynchronization is achieved when the lateral or posterolateral left ventricular wall is paced rather than the anterior or apical region. Practically, this can be achieved only by visual guidance obtained through coronary vein angiography (Figure 1). Novel leads have been developed that can reach the target site more easily, maintain lead stability, and provide satisfactory pacing and sensing thresholds. The development of newer versatile devices with dedicated ports for each lead and independent channels and programmability for each paced chamber is a significant technologic advance.

In addition to difficulties in cannulating the coronary sinus and selecting and placing the pacing lead in the optimal venous branch, there are problems with pace/sense thresholds and phrenic nerve stimulation. Preformed leads that assume a spiral shape after removal of the stylet allow for more stable positions and better thresholds. Furthermore, problems arise when the biventricular pacing device is also a defibrillator, when double or triple counting may cause inappropriate shocks. Improved technology that provides programmable sensing from a single ventricle will remedy this drawback of contemporary devices.

ICD backup

From the data accumulated to date, a major question or dilemma that arises is the use of CRT alone or in combination with backup ICD protection. Barring cost, it appears that ICD protection is not only desirable but clearly more effective in prolonging life in patients with moderate-to-severe heart failure. Of course, the decision is made easier when patients with heart failure have already experienced malignant ventricular tachyarrhythmias and received devices with combined CRT and ICD therapy. A worrisome new element regarding a possible proarrhythmic effect of biventricular pacing inducing QT interval prolongation and leading to the development of torsades de pointes points to the need for combined CRT and ICD therapy. Until more data supporting such an approach in patients with congestive heart failure who have not yet manifested life-threatening ventricular arrhythmias become available, evidence to date (COMPANION trial) suggests that we seriously consider both CRT and ICD therapies for this particular patient population. From our own anecdotal experience, among the first 20 patients who received CRT, 14 who had devices with ICD backup were alive at mean follow-up of 8 months. In contrast, despite the impressive clinical improvement sustained by the 6 patients who had biventricular pacemaker alone, 3 died of ventricular tachyarrhythmias (one with an electrical storm at 2 weeks, one of sudden death at 4 months, and one with refractory ventricular tachycardia at 48 hours). Some caveats to this approach were discussed earlier and concern patients with dilated cardiomyopathy; the role of prophylactic ICDs is less clear (CAT, AMIOVIRT, DEFINITE studies). The upcoming results from newer studies (SCD-HeFT, CARE-HF, RAFT) may shed further light on this important issue. Preliminary results of SCD-HeFT indicate that a significant (23%; P = .007) reduction of 5-year mortality is conferred by the ICD (n = 829) compared to amiodarone (n = 845) or placebo (n = 847) among 2,521 patients with ischemic (52%) or nonischemic (48%)
Cardiomyopathy, NYHA class II or III heart failure, and left ventricular ejection fraction ≤35%, regardless of the QRS complex duration (ACC and HRS Meetings 2004).

Conclusion

Cardiac dyssynchrony as reflected by prolongation of the QRS complex plaques a significant percentage of patients (range 27%–53%) with advanced heart failure. When one sorts out those with refractory heart failure despite optimal pharmacologic treatment, 10% to 15% of such patients still are candidates for CRT. Accumulated evidence from randomized controlled studies over the last few years has indicated a significant hemodynamic and clinical improvement conferred by CRT. Newer data point to a significant reduction of overall mortality and heart failure hospitalizations, particular when CRT is combined with ICD backup. Now that technical advances have raised the success rate of implantation of the left ventricular lead to >90%56 and newer echo Doppler techniques could assist in identifying potential responders to cardiac resynchronization,64 more heart failure patients may benefit from a wider application of CRT. Nevertheless, further confirmation from ongoing trials is awaited, and more data from cost-effectiveness studies are needed before CRT is considered for prime therapy in the heart failure population. It seems, however, that such a time is near and approaching at a fast pace. An important issue to be resolved is the use of this electrical therapy at stages much earlier than NYHA class III and IV so that more patients with dyssynchrony who are eligible for CRT can benefit from this vital therapeutic alternative, given the higher mortality and problems with donor hearts for transplantation encountered at these advanced stages.

The evidence presented herein suggests that the deleterious effect of right ventricular apical pacing alone cannot be ignored and may dictate a change in attitude toward alternate sites of pacing, such as the left ventricle and/or right ventricular outflow tract. The recently emerging data from the DAVID trial and the MADIT II substudy are alarming and disconcerting with regard to our long-standing practice of producing an iatrogenic left bundle branch block in patients, especially in heart failure patients, at a time when we have already become poignantly aware of the harmful effects of spontaneous left bundle branch block.

References


