

Cardiac resynchronization therapy in heart failure: which type and for whom?

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Cardiac resynchronization therapy (CRT) offers a new therapeutic approach for patients with ventricular dyssynchrony and moderate-to-severe heart failure who have dilated cardiomyopathy, regardless of etiology, with depressed systolic function and a QRS ≥ 120 ms.

Clinical trials have shown that it is safe and effective, achieving significant improvement in clinical symptoms, multiple measures of functional status, and exercise capacity. Furthermore, CRT has reduced morbidity and mortality in patients with heart failure. Conclusive cost-effectiveness data are not yet available. Whether or not heart failure patients should be implanted with a CRT plus defibrillator (CRT-D) device versus CRT alone remains debatable, although growing evidence is pointing to extensive use of implantable cardioverter defibrillators (ICDs) in this population.

Keywords: heart failure; ventricular conduction disturbance; left bundle branch block; cardiac resynchronization therapy; implantable cardioverter-defibrillator

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Over the past decade, treatment of heart failure (HF) has markedly improved; mortality due to pump failure and sudden death has declined significantly.^{1,2} Hospitalizations for severe symptoms of HF have also decreased after use of angiotensin-converting enzyme (ACE) inhibitors, β -blockers, diuretics, digoxin, and most recently, spironolactone. However, despite better medical treatment, a significant number of patients remain symptomatic. Until recently, the mainstay of treatment for advanced HF was pharmacological, with very small number of patients considered for heart transplantation or left ventricular (LV) assist devices. While cardiac transplantation can be an extremely effective therapy, its availability is severely limited by lack of donor organs—and there is still the unresolved issue of tissue rejection after transplantation. Mechanical devices to augment cardiac output are currently only suitable for short-term use and the financial cost of

these devices is likely to limit their widespread application. Against this background, cardiac resynchronization therapy (CRT) has emerged as a promising treatment option for some patients with HF.

MECHANICAL AND STRUCTURAL CONSEQUENCES OF VENTRICULAR CONDUCTION DISTURBANCES

A complex blend of structural, functional, and biological abnormalities is found in patients with HF and dilated cardiomyopathy of various etiologies. Significant QRS prolongation is present in approximately 30% of patients with HF. Electrical delays generate abnormal atrioventricular timing and dyssynchronous contraction of left, right, or both ventricles. Furthermore, prolongation of atrioventricular timing delays atrial contraction relative to the onset of ventricular systole and reduces the efficiency of atrial systole for ventricular filling.

SELECTED ABBREVIATIONS AND ACRONYMS

COMPANION	COmparison of Medical therapy, Pacing And defibrillatioN In chrONic heart failure
CRT	cardiac resynchronization therapy
HF	heart failure
ICD	implantable cardioverter defibrillator
SCD-HeFT	Sudden Cardiac Death–Heart Failure Trial
TDI	tissue Doppler imaging

Left bundle branch block is the most common ventricular cause of delay reported in patients with impaired pump function. This conduction disturbance affects cardiac mechanics by altering right-left ventricular systolic and diastolic timing, causing abnormal ventricular contraction and relaxation, worsening

have to contract against a preexisting stiffened portion of the ventricular wall (the septum). This phenomenon has been termed mechanical dyssynchrony (Figure 1). Mechanical dyssynchrony generates increased wall stress with increased cardiac work, which may contribute to myocyte damage and to the develop-

cardiac performance by reducing inter- and intraventricular mechanical dyssynchrony, thereby reducing myocardial oxygen consumption. In order to achieve this, the regions of the LV that are activated latest during sinus rhythm are stimulated early by delivery of a pacing stimulus, usually simultaneously with the

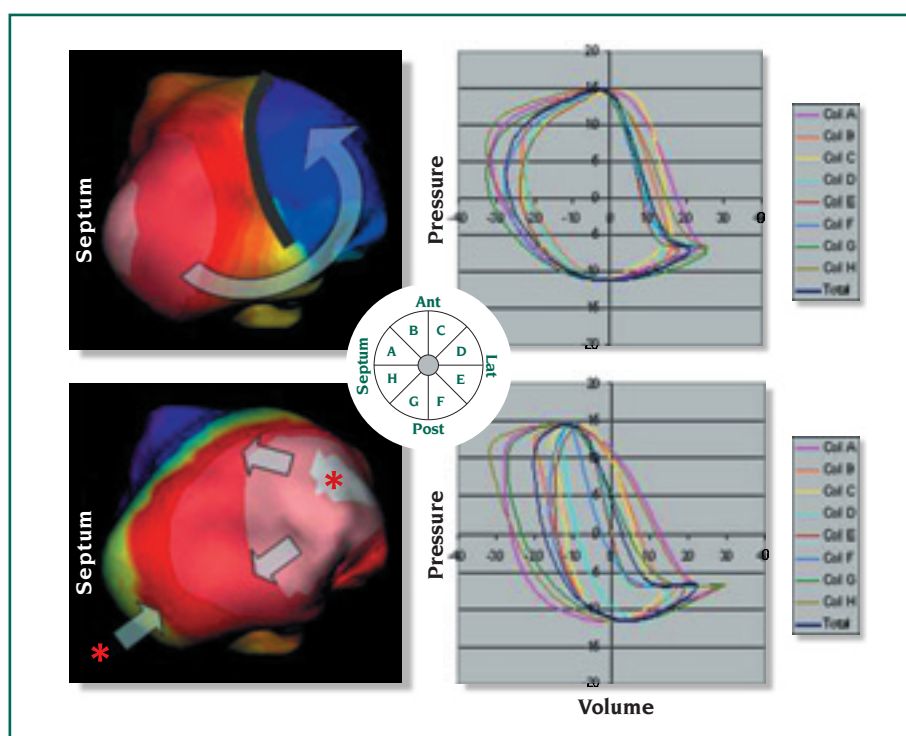


Figure 1. Recording of electrical activation (10-ms isochronous line) in a patient with dilated cardiomyopathy and left bundle branch block. The upper panels show electrical (left) and mechanical (pressure-volume, right) activation during left bundle branch block. A U-shaped activation sequence of the left ventricle (LV) is noted; the regional pressure-volume loops show large mechanical dyssynchrony. The lower panels present the effect of biventricular stimulation by pacing (asterisk) the apex of the right ventricle (not shown) and the free wall of the LV. The electrical activation sequence (left) shows two fronts, one coming from right and the other from left colliding over the septum. The pressure-volume loop (right) is now larger and shows a more homogeneous distribution of regional stroke work. The pie-shaped circle in the middle shows the 8 LV segments (lettered A to H) corresponding to the same-lettered regional pressure-volume recordings in the right panels.

the underlying systolic and diastolic performance and increasing cardiac energy requirements. Basically, at the beginning of the LV ventricular systole, the region of earliest ventricular activation (usually the interventricular septum) contracts against minimal workload because the remaining ventricular myocardium (usually the lateral and posterolateral LV region) is still in the relaxation or in a non-activated phase (Figure 1). The regions of early ventricular activation waste contraction energy as no effective intraventricular pressure can develop. On the other hand, the region of late ventricular activation and the lateral and posterolateral ventricular regions

ment of fibrous tissue, regional hypertrophy, and regional apoptosis.³ All these functional and structural changes caused by left bundle branch block may be associated with poor prognosis and increased morbidity.⁴

CARDIAC RESYNCHRONIZATION THERAPY

CRT is a novel nonpharmacological option for symptomatic patients with HF who have wide QRS complexes (>120 ms) on the 12-lead surface electrocardiogram (ECG) and who are refractory to medical therapy. The aim of CRT is to improve

right ventricle (RV) via a separate pacing lead, thus reducing the total activation time for the ventricles. In patients with sinus rhythm, the pacemaker system will sense the atrial electrical activation via a right atrial lead and stimulate the ventricles at a programmed atrioventricular time that is less than the intrinsic atrioventricular conduction time in order to ensure full ventricular capture.

Implantation technique

The implantation technique is similar to a standard dual chamber sequential pacemaker or implantable cardioverter defibrillator (ICD). The most challenging aspect for achiev-

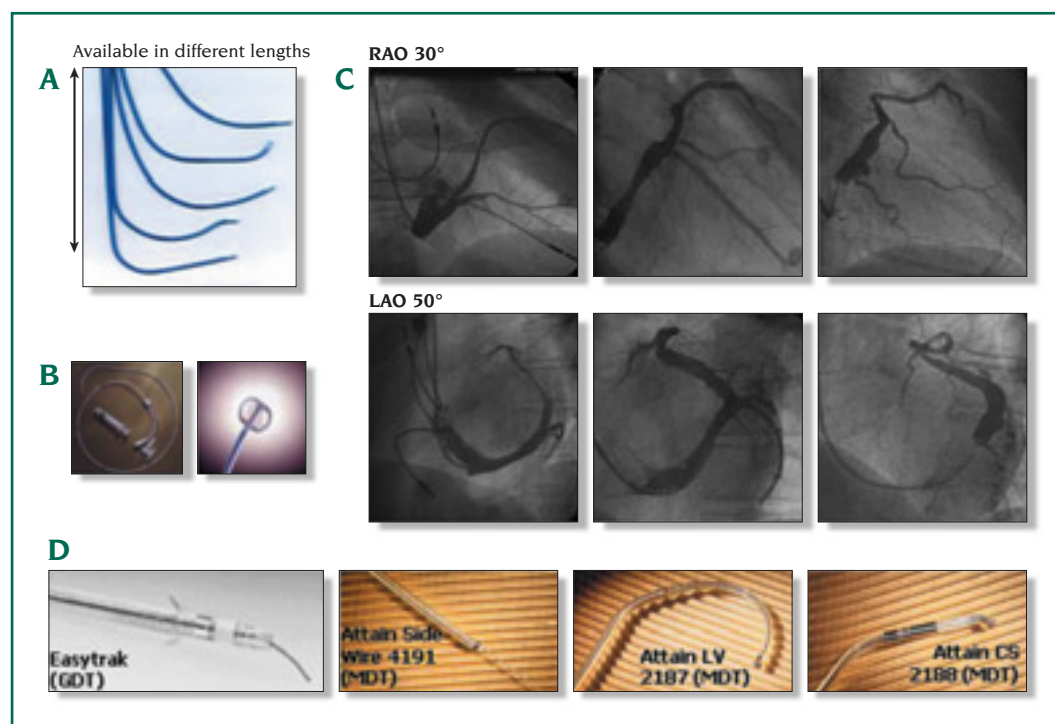


Figure 2. A family of catheters for selective cannulation of the coronary sinus is presented in **panel A**. After cannulation of the coronary sinus, a balloon occlusion using a standard Swan-Ganz catheter (**panel B**) is performed, followed by contrast dye injection. **Panel C** shows the large variability of the coronary veins. According to the differences in coronary venous anatomy, different pacing electrodes may be implanted (**panel D**).

ing resynchronization therapy is placing a permanent LV lead. The transvenous or thoracotomic approach can be used. The transvenous approach requires retrograde cannulation of the coronary sinus, selective angiography of the coronary sinus to delineate the venous anatomy (*Figure 2*), and final introduction into a coronary vein, which lies over the epicardial surface of

the LV, of a specifically designed pacing lead. *Figure 3* shows the typical configuration of pacing leads in a biventricular system implanted either transvenously or via limited lateral thoracotomy.

The transvenous approach may be a difficult and time-consuming technique. The major limitation is that options for lead placement are gov-

erned largely by the patient's venous anatomy, which shows considerable interindividual variability. In about 10% to 15% of cases, it is not possible to achieve a satisfactory LV pacing position, or left phrenic nerve stimulation may occur, thus causing an unpleasant sensation due to diaphragmatic contraction.

Clinical efficacy

The beneficial effects of CRT include improvement in exercise tolerance and quality of life. Furthermore, CRT reduces ventricular volumes and mitral regurgitation, and improves left ventricular ejection fraction (*Figure 4*, page 228).⁵⁻⁷ CRT has recently been shown to improve mortality and hospitalization in a large randomized trial.⁸

Most clinical trials have included patients with moderate or severe (New York Heart Association [NYHA] functional class III or IV) chronic HF due to ischemic or nonischemic cardiomyopathy and widened QRS

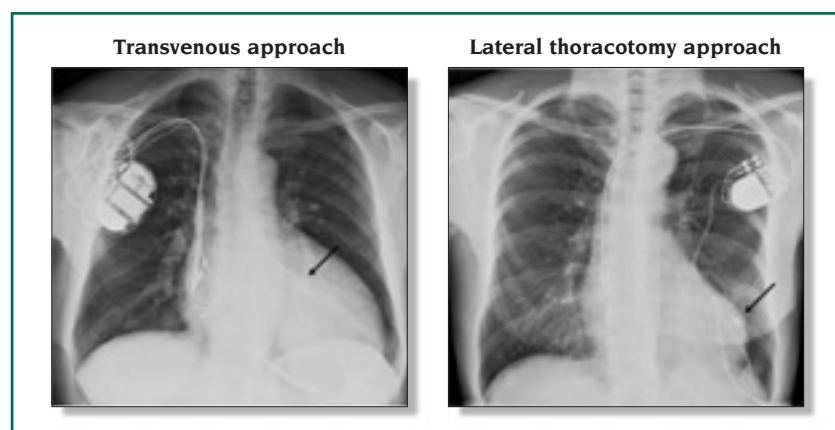


Figure 3. Two examples of implantation of cardiac resynchronization devices. In both cases, the atrial pacing lead and the right ventricular pacing lead are placed as in a conventional DDD pacemaker of an implantable defibrillator. The lead for the left ventricle (arrow) may be inserted transvenously as indicated in *Figure 2* or via a minimal lateral thoracotomy.

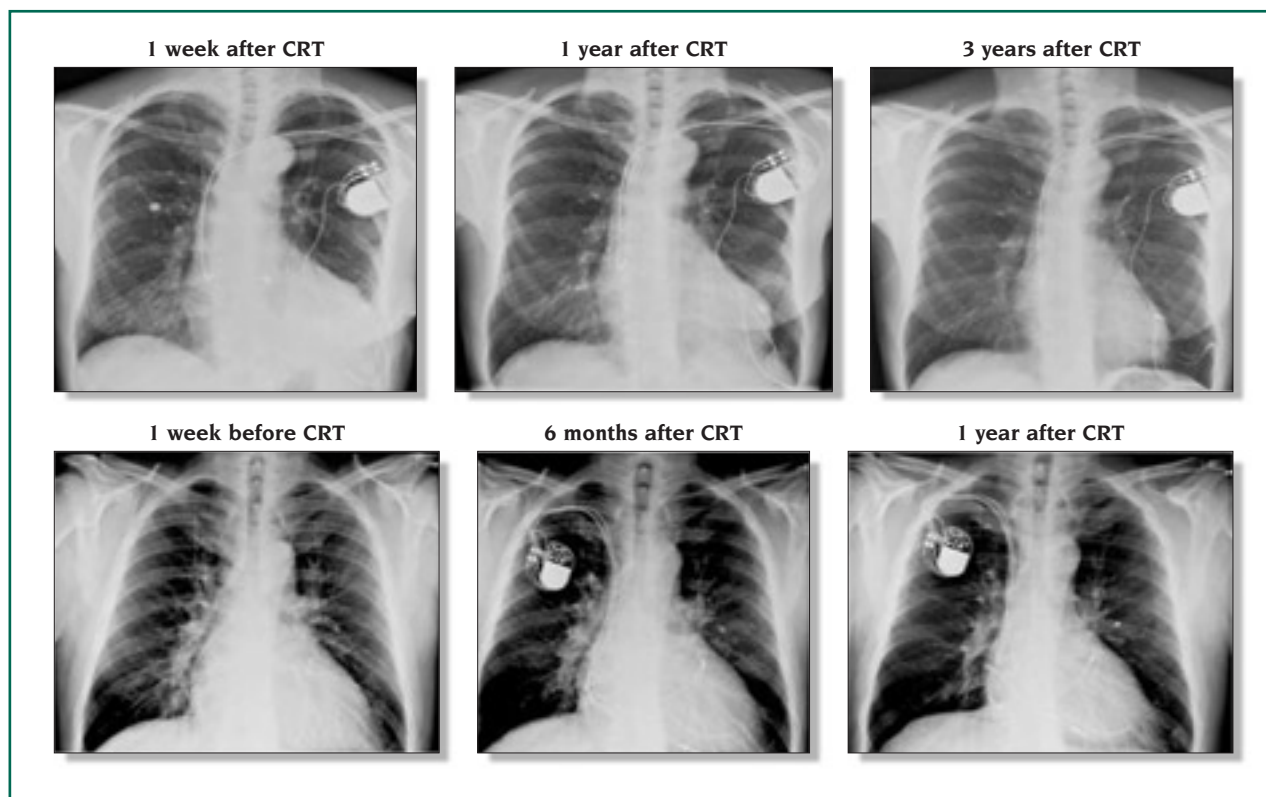


Figure 4. Reverse remodeling in two patients implanted with a cardiac resynchronization device.

duration on the surface electrocardiogram. A QRS duration of 120 ms or more has been the typical selection threshold.⁹ *Table I* summarizes clinical criteria for patients selected for CRT and current clinical evidence supports the value of CRT for these patients.

Few data have been collected on CRT in patients with NYHA class II, and currently this patient group is not routinely recommended for CRT. Insufficient data are available for patients with atrial fibrillation; although preliminary data support the efficacy of CRT in this setting, definitive data are lacking. Similarly, the question of whether heart failure patients with a standard pacemaker indication for bradycardia benefit from CRT is still unanswered. In contrast, there is increasing evidence that the implantation of CRT instead of a standard single-chamber or dual-chamber pacemaker

may be appropriate for patients with paroxysmal or permanent rapidly conducting atrial fibrillation who undergo His bundle ablation.

AHA/ACC/NASPE Guidelines	
Pacing recommendations (Class IIa Indication)	
•	Medically refractory heart failure
•	Functional New York Heart Association Class III or IV
•	Idiopathic dilated or ischemic cardiomyopathy
•	QRS duration ≥ 130 ms
•	Left ventricular ejection fraction $\leq 35\%$
•	Left ventricular end-diastolic diameter ≥ 55 mm

Table I. Inclusion criteria listed in the recently published AHA/ACC/NASPE guidelines for cardiac resynchronization therapy.

Abbreviations: ACC, American College of Cardiology; AHA, American Heart Association; NASPE, North American Society for Pacing and Electrophysiology.

IDENTIFYING INDIVIDUAL RESPONDERS

All randomized clinical CRT trials have used statistical techniques to define the response of groups of patients to CRT. No technique is available to predict reliably the clinical response of a given individual. The large clinical improvement observed in some individuals after CRT (the so called “Lazarus” effect) has created the perception that patients who do not exhibit such improvement are not responding positively to CRT. However, many patients who do not show overt improvement may nevertheless benefit from a less observable slowing of disease progression by living longer and remaining out of the hospital. Since these benefits can only be determined for populations, it may be inappropriate to withhold CRT from patients who meet mortality and morbidity trial indications, but



who do not have indicators predicting individual functional improvement. With this caveat, various factors that may influence the clinical impact of CRT in individual patients are described below.

QRS duration

Duration of the QRS complex is one of the simplest ways to measure timing abnormalities that may have a mechanical correlate. Indeed, all randomized studies to date have used this variable to select patients. Basal QRS duration has been shown to be associated with the degree of mechanical dyssynchrony and with the short-term clinical improvement obtained from CRT (*Figure 1*). Clinical trials have consistently shown that in patients with QRS complex >150 ms, functional capacity, quality of life, and exercise tolerance are significantly improved after a few months of CRT. In contrast, patients with a shorter QRS complex (120-150 ms) show less or no significant changes in functional capacity, quality of life, and exercise tolerance.¹⁰ However, preliminary evidence indicates that patients with shorter QRS also may improve after CRT longer than 6 months, suggesting a time-dependency effect of CRT based on the baseline QRS width. The effect of CRT on disease progression in these two subgroups of patients, as evaluated by reverse remodeling, morbidity, or mortality is still unknown. However, CRT has been shown to decrease hospitalization and all-cause mortality in NYHA class III/IV patients with QRS >120 ms.

Echocardiographic assessment

In patients with HF and ventricular conduction delay, four different levels of ventricular asynchrony have been recognized: atrioventricular delay, interventricular and intraven-

tricular delay, and intramural delay. Some patients with HF with depressed LV ejection fraction despite normal duration of the QRS complex may present with echocardiographically assessed mechanical dyssynchrony of similar magnitude as patients with considerably prolonged QRS duration. The reasons for this "electromechanical dissociation" are not clear, but possible explanations include the relatively poor representation on the surface ECG of electrical impulses from diseased areas of the LV and "uncoupling" of mechanical contraction from electrical stimulation due to abnormalities of calcium homeostasis in cardiac myocytes. Although preliminary data suggest that patients with mechanical dyssynchrony despite normal QRS may benefit, CRT should not be extended to this group without prospective randomized studies.

With the exception of intramural delay, conventional or Doppler echocardiography allows a direct quantification of the degree of mechanical asynchrony. Some of the echocardiography-guided indices are based on timing abnormalities of specific LV regions, others explore the mechanics of the entire LV, and others evaluate a difference in timing between the right and left ventricles. Although pilot studies are promising, the validity of these mechanical indices of dyssynchrony to predict outcome after CRT has not been prospectively established. These indices also may not help identifying the patients who would benefit from the potential preventative effect of CRT in stopping progression of dyssynchrony and its associated negative effects on cardiac function, hypertrophy, and remodeling. However, measures of mechanical resynchronization may help optimize therapy by determining best lead position and proper atrioventricular delay programming.

Mechanical abnormalities detected by conventional echocardiography

Interventricular delay time is usually defined as the time difference between the onset of pulmonary artery flow and the onset of aortic flow with respect to the beginning of the QRS complex. A delay >40 ms is considered indicative of significant dyssynchrony. Because the time to ejection of the RV and LV could be influenced by several factors, the predictive utility of such interventricular delay has been questioned. Intraventricular delay is considered the most important one for identifying patients who will experience the largest short-term clinical responses by CRT, and is defined as the mechanical dispersion of motion of the LV. M-mode echo-imaging has been used to determine the delay exclusively between the initial septal inward motion, and posterior wall motion. This delay time has been correlated with chronic improvement in LV diameters after CRT. The major limitation of this index is that it does not account for delays possibly located elsewhere in the LV. Heterogeneous regional wall motion synchrony with left bundle branch block QRS morphology has also been demonstrated by 2-D echocardiography.

Mechanical abnormalities detected by tissue Doppler imaging

Regional systolic and diastolic synchrony can be evaluated by tissue Doppler imaging (TDI) by comparing the time to peak systolic contraction and early diastolic relaxation of multiple segments. TDI appears to offer a comprehensive assessment of cardiac mechanical synchrony. Although improvement of interventricular dyssynchrony after CRT has been demonstrated by TDI, TDI pa-

rameters of interventricular delay have not been shown to predict the improvement of cardiac function.

A number of parameters based on TDI have been proposed to evaluate intraventricular dyssynchrony. These parameters examine either the time to peak myocardial systolic contraction (Ts) between two or more segments or the dispersion (standard deviation) of Ts (Ts-SD) over multiple segments in the LV, typically 12.

A Ts-SD >33 ms has been shown to strongly predict short-term reverse remodeling. Other proposed indices of systolic dyssynchrony include counting the number of segments with postsystolic shortening and possibly strain rate parameters. The former parameter has been observed to correlate with a beneficial change in systolic function. However, a recent comprehensive analysis suggested that assessment of Ts-SD is the best predictor of reverse remodeling. This may be the best current candidate to replace QRS with an index of mechanical dyssynchrony for the selection of new patients in expanded CRT trials.

PROTECTION FROM SUDDEN CARDIAC DEATH BY IMPLANTABLE CARDIOVERTER DEFIBRILLATOR

Sudden cardiac death is a catastrophic event, the annual incidence of which increases from 2% to 6% per year in patients with NYHA class II symptoms up to 24% per year for patients with class III to IV symptoms.¹¹ Ventricular tachycardia or fibrillation is the predominant mode of death. It has been shown that the implantable cardioverter defibrillator (ICD) is the most powerful—and therefore first-line—therapeutic approach for secondary as well as primary prevention for

sudden death. The recently concluded Sudden Cardiac Death–Heart Failure Trial (SCD-HeFT), has provided further evidence that ICD implantation in addition to the best pharmacological therapy (including ACE inhibitors, angiotensin II type 1 (AT₁) receptor blockers, β -blockers, diuretics, and spironolactone) is the most effective long-term (at 5 years) therapy compared with conventional optimal therapy alone or with amiodarone given on top of the best medical therapy for prolonging life in patients with HF.

The rationale for the use of ICD in CRT devices is primarily based on the assumption that sudden death prevention in patients with HF will provide mortality benefits above those of CRT alone. The Comparison of Medical therapy, Pacing And defibrillation In chrONic heart failure (COMPANION) study has shown marked reduction in combined measures of morbidity and mortality as well as for mortality with CRT alone and with CRT plus defibrillator therapies (CRT-D). The morbidity data from COMPANION indicated a near-equal 1-year benefit for both groups (with and without an ICD); in contrast to CRT alone, which demonstrated a relative risk reduction in all-cause mortality of about 24% ($P=0.060$), CRT-D provided a larger (36%) relative risk reduction in mortality compared with optimal drug therapy ($P=0.003$). A reduction in all-cause mortality and hospitalization for HF by 40% following CRT suggests a substantial reduction in the use of medical resources. These findings are supported by other CRT trials.¹²

The important issue raised by the COMPANION study is whether all patients with HF indicated for CRT should be treated with an additional ICD. Therefore, despite the fact that the CRT-D device has larger

initial cost, and may require more extensive follow-up than CRT alone, this strategy may be most cost-effective particularly when measured in terms of quality-adjusted life-years gained. However, longer-term data are not available and a direct comparison between CRT and CRT-D has not been performed yet.

MONITORING FEATURES OF CRT DEVICES

The monitoring features of conventional pacemakers or ICDs mainly focus on device-related parameters such as pacing threshold, impedance, R-wave amplitude, and storage of intracardiac electrograms. Careful hemodynamic control and electrical monitoring is now implemented into CRT devices. Hemodynamic parameters can be either directly or indirectly monitored via the implanted devices. Specific sensors of the maximum pressure derivative are already implemented.

Furthermore, heart rate and heart rate variability can also be continuously monitored with an implanted CRT device. Finally, recording of accelerometer signals, which usually reflect the patient's physical activity, is already used in pacemakers and implantable cardioverter-defibrillators. This is now used for monitoring the HF-treated patient activity, as well. Initial experience with recording of patient activity tracked by accelerometer has shown that activity monitored by accelerometers is highly sensitive and specific in detecting the patient's physical activity. However, the accuracy of monitoring chronic hemodynamics, lung water content, heart rate, and physical activity changes in patients with HF has yet to be determined. It is also unknown whether major cardiac events can be forecasted by monitoring one or more of these parameters.



SUMMARY

Cardiac resynchronization therapy is now proven to be a valuable adjunctive treatment to standard pharmacological therapy for patients with HF with dyssynchrony. This therapy has demonstrated large symptomatic improvements as well as a strong impact on disease progression. The likelihood is that the indication for device implantation will expand in the future, so that patient selection techniques need to improve to ensure that the overwhelming majority of patients receiving this therapy also benefit from it. QRS duration remains the most practical and validated means for selecting patients for CRT, because it is clinically simple to measure and widely available, and its value as a selection criterion has been proven in large, randomized outcome trials demonstrating a mortality and hospitalization benefit with CRT.

The predictive value of QRS duration may derive from a close correlation of long QRS and a corresponding mechanical dyssynchrony, which increasingly is believed to be the main substrate for CRT efficacy. Evidence that QRS duration is an imperfect indicator of mechanical dyssynchrony, added to the desire to identify individual patients likely to experience immediate large improvements in clinical condition with CRT, has led to a search for other noninvasive techniques, based mainly on imaging, that directly measure mechanical dyssynchrony.

However, particular indices of mechanical dyssynchrony that best predict clinical improvement have not been established, and it is unclear whether CRT is preventing disease progression in patients with prolonged QRS before severe mechanical dyssynchrony is apparent.

At the present time, evidence-based medicine supports the use of prolonged QRS (>120 ms) as an indicator of patients with severe HF who should be prescribed CRT. Noninvasive imaging techniques can be used to verify that resynchronization has been achieved.

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