Cardiac Resynchronization Therapy: Current State of the Art

Cost Versus Benefit

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An overwhelming amount of evidence from prospective randomized controlled trials supports the clinical efficacy and safety of cardiac resynchronization therapy (CRT) in patients with moderate or severe heart failure and ventricular dyssynchrony. As noted below, CRT makes heart failure patients feel better, improves cardiac structure and function, and reduces all-cause as well as heart failure morbidity and mortality. Thus, there may be a clinical mandate for use of CRT in many patients with chronic heart failure. This notion raises important questions about the clinical application of this therapy. For example, will the availability of CRT change our current clinical approach to heart failure patients? Will it lead to new research advances? Will CRT patients also require an implantable cardioverter defibrillator (ICD) to optimize outcomes? Will the clinical benefits of these therapies justify the costs?

Ventricular Dyssynchrony: A Pathophysiological Cause or Contributor to Heart Failure

Patients with left ventricular (LV) systolic dysfunction and dilation, with or without clinical signs or symptoms of heart failure, frequently have ventricular conduction delays. In such patients, this is usually manifested as a left bundle-branch block (LBBB). This type of conduction abnormality is generally associated with delayed depolarization and contraction of the lateral LV free wall (Figure 1), whereas the interventricular septum exhibits a normal (early) contraction resulting in paradoxical septal motion.

The abnormal activation sequence induced by spontaneous LBBB or by right ventricular (RV) pacing generates changes in regional ventricular loading conditions (Figure 2), possibly redistributes myocardial blood flow, and creates a regional nonuniform myocardial metabolism. These effects of ventricular dyssynchrony might contribute to disease progression in LV systolic dysfunction patients. For example, studies in experimental heart failure induced by rapid ventricular pacing showed regional differences in the extent of ventricular hypertrophy with an apicobasal- and septolateral-oriented gradient. Moreover, experimentally induced LBBB has demonstrated a large effect on the expression of regional stress kinases and calcium-handling proteins. Preliminary evidence suggests that the expression of p38-MAPK (a stress kinase) is significantly elevated in the endocardium of the late-activated region, whereas phospholamban is significantly decreased. In addition, sarco(endo)plasmatic reticulum Ca2+ -ATPase is decreased in the region of early activation.

The meaning of such complex interactions between changes in regional loading conditions, blood flow distribution, regional myocardial metabolism, and gene and protein expression induced by an abnormal activation sequence is not fully understood. However, it is likely that these conse-
quences of ventricular dyssynchrony lead to rearrangement of both contractile and noncontractile cellular elements and perhaps the extracellular matrix in the heart, thus stimulating the process of ventricular remodeling. Thus, it is conceivable that dyssynchrony represents a newly appreciated pathophysiological process that directly depresses ventricular function and ultimately leads to ventricular dilatation and heart failure. Evidence from recent clinical trials comparing RV pacing versus either no pacing or atrial pacing in patients with LV systolic dysfunction supports this notion. In the Dual Chamber and VVI Implantable Defibrillator (DAVID) trial, RV pacing was associated with heart failure disease progression, including an increased incidence of worsening heart failure.

Mechanisms of Action of CRT
At the present time, we recognize 4 levels of electromechanical abnormalities that may be treated by CRT (Figure 3), as follows: (1) atrioventricular delay, (2) interventricular delay, (3) intraventricular delay, and (4) the most recently described intramural delay. Although the effect of CRT on the intramural delay has not been full investigated, the effect on interventricular delay probably plays a secondary role after the correction of both atrioventricular and intraventricular delay.

Pre-excitation of the LV lateral wall with atrial-synchronous left or biventricular pacing in heart failure patients with ventricular conduction delay can resynchronize the ventricular activation pattern by acting as an electrical bypass, thus restoring a more coordinated ventricular contraction. This novel pacing approach to treat heart failure is called CRT. Shortening or optimizing the atrioventricular interval necessary to resynchronize lateral-septal wall contraction also improves atrioventricular mechanical synchrony by abolishing the late diastolic ventriculoatrial gradient and so-called “presystolic” mitral regurgitation, which is seen in association with ventricular dyssynchrony, and prolongs ventricular filling time. Pacing from the left lateral wall, especially from the proximity of the posterior papillary muscle, produces early activation of the papillary muscle region and can decrease systolic mitral regurgitation. Optimization of ventricular loading conditions as provided by CRT improves myocardial efficiency and increases systolic function and LV contractility with a neutral or modestly positive effect on diastolic function. When combined, these various mechanical effects of CRT improve the function of the heart as a pump.

CRT Induces Reverse Ventricular Remodeling
The benefits of reverse ventricular remodeling have been demonstrated by pharmacological agents, such as β-blockers and angiotensin-converting enzyme (ACE) inhibitors, which improve ventricular geometry and function and reduce morbidity and mortality in heart failure patients. Acting through several mechanisms, including redistribution of regional ventricular loading, reduction or abolition of mitral regurgitation, reduction of sympathetic activity, increase of parasympathetic activity, and others, CRT also induces reverse remodeling of the failing left ventricle. Hence, the left ventricle gets smaller and contractility is improved after a period of CRT. Moreover, as mentioned above, functional mitral regurgitation is reduced acutely and chronically during CRT. The effects of CRT on reverse ventricular remodeling have been consistently demonstrated in all randomized prospective controlled studies and in smaller mechanistic studies. Although Yu et al have demonstrated both an onset as well as an offset of the favorable remodeling effects of
CRT, it is not known whether reverse remodeling will sustain over the long term. Of note, CRT has mostly been implemented in addition to optimal medical therapy for heart failure (ACE inhibitors, β-blockers, diuretics, and in many cases spironolactone); however, recent data from the Multicenter InSync Randomized Clinical Evaluation (MIRACLE) study have shown that reverse remodeling during CRT can also take place in patients not receiving β-blocking agents. Another important issue—whether patients with different degrees of electrical or mechanical

Figure 2. Effect of pacing and pacing site on ventricular dyssynchrony. Using the same 3D mapping system as in Figure 1, changes in ventricular volumes during the entire cardiac cycle can be continuously monitored along with LV pressure. The EnSite balloon catheter has the possibility to evaluate in vivo regional radial volume changes. Thus, global and regional pressure-volume (P-V) loops can be obtained and a detailed analysis of stroke work can be performed. In a patient with dilated cardiomyopathy, symptomatic heart failure, and large QRS complex (156 ms), regional stroke work has been measured, normalized, and plotted at each region of the left ventricle. Measurements were performed at during sinus rhythm (SR) as well as during different pacing sites and atrioventricular delays. Septal regions showed the lowest stroke work, whereas the lateral regions had the largest stroke work. Pacing from RV apex did not substantially change the distribution of the stroke work, but pacing the left ventricle (LV) at different atrioventricular delay did. The most optimal atrioventricular delay was between 50 ms and 100 ms.

Figure 3. Schematic representation of the 4 levels of electromechanical delays correctable by CRT. The first level is represented by the atrioventricular (AV) mechanical latency (AVL) (from Auricchio et al14; used with permission from the American College of Cardiology); slightly prolonged electrical atrioventricular delay in presence of LBBB causes a significant delay of the ventricular contraction (LS) with respect to atrial contraction, thus significantly reducing preload. The second level is represented by interventricular delay; a 10-ms isochronal color-coded activation map (red indicating the earliest and purple the latest activation) was generated and superimposed on the reconstructed 3D geometry of both right and left ventricles showing considerable electrical delay between the right (RV) and the left ventricle (LV). The left ventricle is activated 60 ms after RV. The mechanical consequences of such electrical delay between the 2 ventricles are also detectable using 2D color Doppler motion imaging (DMI), which showed a considerable delay of peaking of systolic contraction between the right ventricle (yellow), the septum (blue), and the left ventricle (red). The third level is represented by intraventricular delay as demonstrated by Yu et al26 (reprinted with permission) with tissue Doppler imaging performed at different ventricular regions. Finally, the comparison of activation maps obtained with two different mapping techniques showed that the endocardial layer has a different activation timing and sequence from the transmural activation sequence. That may suggest the presence of intramural activation delay between the endocardial and myocardial layer. P-V indicates pressure-volume.
abnormality will show similar degrees of reverse remodeling—is still unclear.

**Benefit at a Cost**

In contrast to standard pacemakers, a CRT device has more sophisticated software and hardware that requires more extensive follow-up visits and higher cost. Current technology allows automatic storage of intracardiac electrograms and monitoring of patient’s physical activity, as well as heart rate and heart rate variability. In the near future, monitoring of hemodynamic parameters, respiratory characteristics, body temperature, and body water content could be possible while specific information is continuously downloaded via the Internet (Figure 4). Therefore, advanced and extensive monitoring would allow home-based management of the heart failure patient at an undetermined cost at the present time.

Based on several positive trials, CRT is indicated (Class II A ACC/AHA/NASPE Guidelines) for a selected group of symptomatic heart failure patients (functional New York Heart Association [NYHA] class ≥ III, QRS duration ≥ 130 ms, LV ejection fraction ≤ 35%, and LV end-diastolic diameter ≥ 55 mm) for the improvement of symptoms, functional status, and exercise capacity. The recently concluded COMPari-son of Medical therapy, PacinG, ANd defibrillation in chronic heart failure (COMPANION) trial has demonstrated marked reduction in combined measures of morbidity and mortality as well as for mortality alone with CRT and with CRT plus defibrillator therapies, thus potentially extending the indication for CRT. Heart failure patients who still remain moderately or severely symptomatic despite the effective medical therapy as those included in COMPANION trial may be considered a minority (about one third of the symptomatic heart failure patients), but they utilize the most health care
resources, being frequently hospitalized or seen in outpatient clinics.\textsuperscript{30}

A reduction in all-cause mortality and heart failure hospitalization by 40\% after CRT suggests a substantial reduction in the use of medical resources. These findings are supported by other trials of CRT, including the MIRACLE trial,\textsuperscript{1} and by a recent meta-analysis.\textsuperscript{31} For example, in MIRACLE, CRT produced a significant 50\% reduction in the risk of hospitalization for worsening heart failure and a significant 77\% decrease in the number of days hospitalized for heart failure during a 6-month period of controlled observation. In the CRT meta-analysis, there was demonstrated a significant 51\% reduction in mortality due to worsening heart failure and a significant 29\% decrease in the incidence of hospitalization for heart failure decompensation. Intriguing data recently presented from the COMPANION study suggest that death and hospitalization due to cardiovascular events were significantly reduced during CRT (CRT versus optimal medical therapy, 27\% \textit{P}<0.001 relative risk reduction, and CRT+Defibrillator versus optimal drug therapy, 30\% \textit{P}<0.001 relative risk reduction).

Altogether, the gain in life expectancy and, in particular, the reduction in hospitalization after CRT is as large as that observed for both pharmacological and nonpharmacological approaches evaluated in the treatment of patients with advanced heart failure (Figure 5). Similarly, this benefit may correspond to a favorable cost-effectiveness ratio for CRT.

A preliminary economic analysis from Germany has concluded that CRT is a cost-effective intervention.\textsuperscript{32} The modestly higher upfront cost (+22\% compared with medical treatment) due to implantation of a CRT device was offset by a significant decrease in hospitalization within the first year of treatment. Longer-term data are not available, and a comparison with CRT+defibrillator (a more expensive form of implantable device therapy) has not been performed. In this regard, an important issue raised by the COMPANION study is whether all heart failure patients indicated for CRT should be treated with an additional ICD (CRT-D). The morbidity data from COMPANION indicated a near-equal 1-year benefit for both groups (with and without an ICD). However, in contrast to CRT alone, which demonstrated a relative risk reduction in all-cause mortality of \~24\% \textit{P}=0.060, CRT-D provided a 36\% relative risk reduction in mortality compared with optimal drug therapy \textit{P}=0.003). Therefore, despite the fact that the CRT-D device has a 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.

At the present time, it is debatable whether the results of COMPANION can be translated to other, somewhat less ill patients or to patients with different CRT indications. Data from ongoing or future prospective randomized trials may help in further defining patient cohorts that may benefit from CRT. Moreover, formal cost-effectiveness analyses (not yet performed) from existing CRT trials may provide additional information regarding the cost implications of these therapies.

### Contraindications

Currently, there is no known contraindication to CRT. Isolated anecdotal experience suggests that CRT may be contraindicated in patients in whom weaning from parenteral inotropic therapy has not been possible. These patients have frequently presented with severe pulmonary hypertension and intractable right heart failure. No data are available as to whether patients with moderate pulmonary hypertension are contraindicated for CRT. Whether comorbidities such as previous valve replacement, atrial fibrillation, chronic obstructive pulmonary disorder, peripheral artery disease, etc, present a contraindication is not known yet.
According to the most recent guidelines for pacing, CRT is indicated when drug therapy has failed (ie, for patients who have refractory symptoms despite optimal drug therapy for heart failure). Patients who do not tolerate β-blockers (ie, bradycardia, hypotension, etc) or those in whom optimal dosage of ACE inhibitors or β-blocking agents cannot be reached may benefit from CRT as well. Indeed, CRT may enable initiation or up-titration of ACE inhibitors and β-blockers in such patients. Hopefully, upcoming prospective trials will address these issues.

**Identifying Therapeutic Nonresponders**

A variable proportion of patients undergoing CRT appear to derive no benefit from this therapy. As this group of patients may substantially diminish the cost-benefit ratio of CRT, efforts should be directed toward reducing the proportion of nonresponders. However, several points should be considered with respect to “nonresponder” patients, as follows.

1. A standardized definition of benefit and quantification of benefit after CRT still lacks uniformity. Changes in functional classification or walked distance are rather soft endpoints, which may be influenced by spontaneous changes as well as by placebo effect. Changes of oxygen uptake at anaerobic threshold during exercise or reduction of LV systolic and diastolic volumes should be targeted as harder endpoints for the definition of a nonresponder patient. If exercise tolerance increases while the ventricle is getting smaller, a large improvement in cardiac and systemic hemodynamics has occurred at a lower myocardial energetic cost. However, there are no data about the minimum change of ventricular chamber dimensions that may be predictive of change in prognosis and symptoms.

2. Recent data from the COMPANION study showed that patients assigned to optimal medical therapy had progressive reduction of systolic blood pressure, consistent with progression of the underlying disease, whereas patients assigned to CRT did not. Therefore, stabilization of patients even without subjective improvement (eg, remaining in NYHA class III rather than progressing to class IV) may be considered to a certain extent a benefit and not a failure of CRT.

3. Acute hemodynamic studies have demonstrated that pacing site is crucial for improving ventricular mechanics. Thus, it can be postulated that nonresponder patients are paced at a suboptimal site. Recent echocardiographic studies have shown that in a substantial proportion of patients, the anatomic selected pacing site does not always coincide with ventricular regions having large mechanical delay. Whether MRI, fast CT, or echocardiography will help in identifying the most optimal pacing site is still under investigation. All these techniques are aimed at quantifying intra- and interventricular asynchrony. Finally, 3-dimensional electroanatomic mapping, which is an invasive approach and at the present time both costly and time-consuming, may have the unique advantage of providing the full picture of electrical disarrangement along with assessment of regional and global ventricular function (Figure 2).

4. Recent prospective data collected have shown a time-dependent effect of CRT by baseline QRS duration, ie, patients with QRS duration >150 ms showed large and almost immediate benefits, whereas patients with QRS duration 120 to 150 ms showed a delayed improvement (after 6 months) in functional class and exercise capacity.

5. Some patients have reached a “point of no return,” and any intervention will not change the course of the end-stage disease process. At present, we have no variable for selecting these patients.

In summary, although several objective reasons why specific patients may not respond to CRT have been identified, better characterization of pacing site and patient selection is needed.

**New Techniques for Detecting Electromechanical Asynchrony**

As all patients with a ventricular conduction abnormality may not benefit from CRT and some patients with a normal QRS duration derive benefit from this therapy, it is logical to conclude that electrically measured ventricular dyssynchrony (by ECG) is a relatively crude reflection of mechanical ventricular dyssynchrony. It is logical to consider new techniques for quantifying the degree of mechanical asynchrony. What degree of mechanical asynchrony (no matter how quantified) should be treated and what abnormalities can be reversible have not been determined. Echocardiography-guided measurements of ventricular asynchrony are as yet not standardized, and none of the reported variables have been prospectively tested. A related question is whether or not patients with mechanical asynchrony represented by a wall motion abnormality is related to abnormalities of ventricular strain. It is conceivable that improvement in ventricular strain distribution by CRT should be targeted for achieving a larger degree of reverse remodeling.

**Should CRT Be Widely Applied to Patients With Heart Failure or Depressed Ventricular Function?**

Based on the data cited previously, the answer to this question is no. However, there are intriguing observations that may further widen the indications for CRT. Chronic RV pacing may induce changes of ventricular volume and geometry and abnormal ventricular regional loading, thus favoring adverse remodeling and heart failure. Patients indicated for conventional pacing who have impaired ventricular function have not been prospectively studied. Similarly, no large randomized controlled study has addressed whether or not patients who have atrial fibrillation with or without prior His-bundle ablation should be implanted with CRT instead of a conventional and less expensive dual-chamber or single-chamber device. Because CRT induces reverse remodeling, it is conceivable that the use of CRT in NYHA class II patients,
who also present with some degree of electromechanical abnormality, may halt the pathological remodeling process. Of course, extending the indication of CRT to patients with less severe symptomatic heart failure or to those with asymmetric LV dysfunction raises additional questions regarding costs and cost efficacy of the therapy. Another question to be explored is whether or not patients with isolated diastolic dysfunction and ventricular conduction abnormalities such as LBBB will benefit from CRT.

Summary

The Table summarizes many of the known effects induced by CRT. These responses have, for the most part, been documented in highly symptomatic heart failure patients who have dilated cardiomyopathy regardless of etiology with depressed systolic function and ventricular conduction abnormalities such as aortic valve disease, prior His-bundle ablation, prior previous valve surgery, etc) who have been treated “off-label” with CRT in whom no controlled data are yet available to justify treatment with this device.

References


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