Cardiac resynchronization therapy in heart failure

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Cardiac resynchronization therapy (CRT) is a new therapeutic approach for a selected group of patients with symptomatic heart failure (NYHA functional class III-IV) despite optimal medical therapy, due to dilated cardiomyopathy of any etiology (left ventricular ejection fraction ≤ 35% and left ventricular end-diastolic diameter ≥ 55 mm), who present with electromechanical dyssynchrony (QRS ≥ 130 ms). Safety and effectiveness of CRT have been demonstrated by several clinical trials, with patients achieving significant improvement in both clinical symptoms as well as functional status and exercise capacity. Furthermore, CRT has reduced morbidity of heart failure patients, while its impact in improving survival still remains to be clarified. Whether or not heart failure patients candidate to CRT should receive a defibrillator back-up remains debatable, although growing evidence is pointing to extensive use of a defibrillator in such a population.

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Introduction

Despite striking advances in medical therapy of heart failure (HF)[1,2], morbidity and mortality of HF patients remain high[3]. Heart transplantation and ventricular assist devices offer an effective, but limited alternative therapy due to shortage of organ availability. Cardiac resynchronization therapy (CRT) has emerged as an effective option in selected HF patients with electromechanical dyssynchrony. Its safety and clinical efficacy have been proven in several prospective, randomized, controlled trials[4-7]. The impact of CRT in improving survival is not fully defined yet. However, meta-analysis data[8,9] and results of a first large trial[7] are pointing toward a survival benefit in HF patients with ventricular conduction delay, especially when treated by a combination device, CRT plus implantable cardioverter-defibrillator.

Mechanical consequences of electrical delays

HF patients often present with conduction delays located at various levels of the conduction system, which may depress cardiac performance. Spontaneous or pharmacologically-induced sinus node incompetence may contribute to further reduce the already impaired functional capacity of HF patients[10].

About 50% of HF patients show different degree of atrioventricular block, being the most frequent one a prolonged atrioventricular conduction time. Prolongation of atrioventricular time delays ventricular contraction (and consequently ventricular relaxation), so that early passive filling overlaps the active one, with reduced atrial booster contribution to ventricular filling. Finally, loss of atrioventricular synchrony may determine a ventricle-atrial end-diastolic gradient with early reopening of the mitral valve leading to significant so-called "pre-systolic or diastolic" mitral regurgitation[11]. All together these phenomena lead to impaired ventricular preload.

Significant prolongation of the QRS complex of > 120 ms may be found in approximately 30% of HF patients. The negative prognostic value related to QRS widening, independently of QRS morphology, has been shown in several studies[12,13]. At our best understanding, prolongation of QRS duration is the result of electrical asynchrony at the interventricular, intraventricular and intramural level[14]. Prolongation of QRS duration may result in mechanical ventricular dyssynchrony which, at the present time, has only been identified at the interventricular and intraventricular level.

Left bundle branch block is the most common ventricular conduction disturbance occurring in patients with depressed ventricular function. Recent electrophysiological findings have demonstrated that left

bundle branch block is a rather complex and heterogeneous electrical disease[15-17]. There is increasing evidence that disarray of myocardial layers may partly account for this heterogeneity[16]. In patients with left bundle branch block, the region of earliest ventricular activation (usually the interventricular septum) contracts while the remaining ventricular myocardium is still in a non-activated phase. Thus, a consistent part of contraction energy is wasted as no effective intraventricular pressure can develop. At the same time, the latest activated regions of the left ventricle (usually the lateral and postero-lateral walls) are passively stretched with increasing wall tension at this site and further wasting of energy. By the time that the latest depolarized ventricular regions contract, the septum starts to relax and is no more able to withstand the increasing pressure development, and is pushed toward the right ventricle (paradoxical septal motion). In this way, pressure is generated asynchronically by different regions of the left ventricle without effective ejection.

The delayed depolarization of the lateral wall causes a delayed and slow contraction of the postero-lateral papillary muscle. This event, in the presence of a dilated chamber and abnormal ventricular geometry, contributes to significant worsening of mitral regurgitation. Finally, the heterogeneous electrical and mechanical ventricular activation may further impair systolic ventricular function by delaying relaxation phase and reducing ventricular filling time.

Structural changes related to electromechanical dyssynchrony

In different heart models[18-20], it has been demonstrated that the abnormal loading and work distribution caused by electromechanical dyssynchrony may induce regional alterations of myocardial metabolism, gene expression, and protein synthesis[19]. It may be postulated that these changes could lead to rearrangement of both contractile and non-contractile cells, fibrosis and apoptosis. Experimentally-induced left bundle branch block causes eccentric hypertrophy[21] with an apical-basal- and septal-lateral-oriented gradient and determines unequal synthesis of stress kinases and calcium-handling proteins[19]. Furthermore, it has been demonstrated that mechanical dyssynchrony causes a redistribution of regional flows[22] with consequent chronic hypoperfusion of unloaded regions. All together it appears that electromechanical dyssynchrony favors maladaptive structural remodeling process. Such structural changes further depress ventricular function.

Cardiac resynchronization therapy

CRT improves cardiac performance at reduced myocardial metabolism cost through different mechanisms[23]. Preexcitation of the left ventricular lateral wall with atrial synchronous left or biventricular pacing restores a normal atrioventricular timing, resynchronizes right and left ventricular activation as well as septal and lateral wall contraction. In addition to an improved coordination of the septal and lateral wall contraction[4], a reduction of mitral regurgitation and an improvement of ventricular filling[24,25], recent data possibly suggest that CRT may improve cardiac efficiency by slowing the heart rate. This may have a beneficial effect on diastolic times and on myocardial oxygen demand.

Clinical and structural effects of cardiac resynchronization therapy

Several prospective, randomized, controlled trials[4-6,26], conducted in patients with NYHA functional class III-IV, due to dilated cardiomyopathy of any etiology, presenting with electromechanical dyssynchrony, have proven the safety and clinical effectiveness of CRT. All these studies demonstrated a significant improvement of quality of life, NYHA functional class, exercise tolerance, and a significant reduction in hospitalizations for HF. Furthermore, there was a consistent report of significant improvement of left ventricular ejection fraction and partial reversal of maladaptive remodeling process[6,24]. CRT also showed a favorable effect on sympathetic-parasympathetic activity with a reduction of plasma norepinephrine levels and an increase of heart rate variability[27].

Based on these evidences, CRT is indicated (class IIa ACC/AHA/NASPE guidelines) (Table I) for patients with symptomatic HF (NYHA functional class III-IV) despite optimal medical therapy, due to dilated cardiomyopathy of any etiology (left ventricular ejection fraction ≤ 35% and left ventricular end-diastolic diameter ≥ 55 mm), who present with ventricular electrical dyssynchrony (QRS ≥ 130 ms) for the improvement of symptoms, functional status and exercise capacity[28].

It has been reported that a small proportion of patients treated with CRT remain symptomatic. These individuals are usually considered as non-responder patients to CRT. All randomized clinical CRT trials have used statistical techniques to define the response of groups of patients to CRT. No standardized criteria are

Table I. Current guidelines for cardiac resynchronization therapy (ACC/AHA/NASPE guidelines, class IIa indication).

Medically refractory heart failure
NYHA functional class III or IV
Idiopathic dilated or ischemic cardiomyopathy
QRS duration ≥ 130 ms
Left ventricular ejection fraction ≤ 35%
Left ventricular end-diastolic diameter ≥ 55 mm

available to predict reliably the clinical response of a given individual. The large clinical improvement that is observed in some individuals after CRT has created the perception that patients who do not exhibit such an improvement are not responding positively to CRT. However many patients who do not show overt improvement may nevertheless benefit from a slowing of disease progression by living longer and not undergoing hospitalizations. Although major efforts have been made for identifying such patients, there are still several unresolved issues in the definition of non-responders and in how to best identify and then treat these patients.

Effects on morbidity and mortality

The recently concluded Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure (COMPANION) trial[7] has shown a marked reduction in combined measures of morbidity and mortality with both CRT alone and with CRT plus defibrillator back-up (CRT-D) with a similar 1-year event-free survival rate. Nevertheless, 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%) and significant relative risk reduction in all-cause-mortality compared to optimal drug therapy ($p = 0.003$). These results are consistent with data of a recent meta-analysis showing that CRT alone may be able to reduce all-cause mortality by about 21%[8]. Based on these data, the number of patients who needed to be treated to save 1 life is about 25 for CRT alone and 14 for CRT-D. These numbers are comparable with many pharmacological trials which enrolled similarly sick HF patients.

Finally, data of the COMPANION study and those from another important meta-analysis[9] were consistent in showing a similar risk reduction for the combined endpoint – hospitalization and death – in patients treated with CRT. This finding may suggest a substantial reduction of medical resources.

Implantation issues

The implantation technique is similar to a standard dual-chamber sequential pacemaker or implantable cardioverter-defibrillator. The most challenging aspect for achieving resynchronization therapy is placing a permanent left ventricular lead. A transvenous or thoracotomic approach can be used. The transvenous approach requires the retrograde cannulation of the coronary sinus, a selective angiography of the coronary sinus which delineates the venous anatomy and the final placement of a specifically designed pacing lead into the coronary veins lying over the epicardial surface of the left ventricle. Several reports[29] have demonstrated the importance of targeting the most delayed wall which requires implantation of a pacing lead into a lateral or postero-lateral vein. The transvenous approach may be a difficult and time-consuming technique. The major limitation is that options for lead placement are governed 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 left ventricular pacing position or left phrenic nerve stimulation may occur, so that a thoracotomic approach becomes necessary.

Selection of patients

Duration of QRS complex has so far been used as the most practical and readily available criterion to select patients candidate to CRT. Indeed, QRS duration is one of the simplest ways to measure electrical abnormalities that may have a mechanical correlate. Baseline QRS duration has been shown to be associated with degrees of mechanical dyssynchrony and with short-term clinical improvement obtained from CRT. Nevertheless there are increasing data[30] suggesting that a considerable proportion of HF patients presenting with narrow QRS complex (< 120 ms) may present echocardiographically-assessed mechanical dyssynchrony of similar magnitude as patients with prolonged QRS duration (> 120 ms).

Recently introduced tissue Doppler imaging techniques permit precise evaluation of regional systolic and diastolic synchrony by comparing the time to peak systolic contraction and early diastolic relaxation of multiple segments. Tissue Doppler imaging appears to offer a comprehensive assessment of cardiac mechanical synchrony. A number of parameters based on tissue Doppler imaging have been proposed to evaluate intraventricular dyssynchrony but the validity of tissue Doppler imaging and other echocardiographic parameters in selecting patients with both narrow and wide QRS who can benefit from CRT needs to be confirmed in prospective, randomized long-term studies.

Open questions

CRT is not currently indicated in patients with NYHA functional class II, even though there are increasing data suggesting that application of CRT in mildly symptomatic HF patients could prevent or slow HF progression. Furthermore, the increasing indications to defibrillator implantation, based on the results of recent big trials (MADIT, MADIT II, SCD-HeFT) rise the problem of considering implementation of the implantable cardioverter-defibrillator devices with a CRT back-up in less symptomatic (NYHA functional class II) patients.

Not enough data are so far available about CRT in patients with atrial fibrillation, although preliminary results support its efficacy in this clinical setting[31]. Furthermore, there are increasing evidences that the implantation of a CRT device instead of a standard single- or dual-chamber pacemaker may be appropriate for patients who undergo His-bundle ablation.

The question of whether HF patients with a standard pacemaker indication for bradycardia benefit from CRT is still unanswered. Nevertheless, data of the Dual Chamber and VVI Implantable Defibrillator (DAVID) trial[32] encourage implantation of a CRT device in patients with impaired ventricular systolic function candidate to chronic pacing.

Recent data suggest that also patients with narrow QRS (< 120 ms), but with echocardiographic evidence of mechanical dyssynchrony may benefit from CRT. Nevertheless, CRT should not be extended to this group before results of prospective randomized trials will be available.

The important issue raised by the COMPANION study[7] is whether all HF patients candidate to CRT should be treated with an additional defibrillator back-up. The recently concluded trial, the Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT)[33], has provided further evidence that implantation of a defibrillator in addition to best pharmacological therapy is the most effective long-term (5-year) treatment compared to conventional optimal therapy alone or with the adding of amiodarone, to prolong life in HF patients. Therefore, despite the fact that CRT-D devices have larger initial costs, and may require more extensive follow-up than CRT alone, this strategy may be more cost-effective particularly when measured in terms of quality-adjusted life-years gain.

Summary

CRT is an effective, adjunctive treatment to pharmacological therapy for a selected group of HF patients who remain symptomatic despite optimal medical therapy, and who present with electromechanical dyssynchrony. Safety and effectiveness of CRT have been demonstrated by many clinical trials, with patients achieving significant improvement in symptoms, functional status and exercise capacity. Furthermore, CRT promotes reverse remodeling and reduces morbidity of HF patients, while its impact in improving survival is not yet definitely clear. Thus, CRT should not be considered as an alternative to medical therapy but as a synergistic therapy. Indeed, in those patients in whom optimal dosage of angiotensin-converting enzyme inhibitors or beta-blockers can not be achieved because of hemodynamic intolerance or severe bradycardia, CRT may be considered in order to support ventricular systolic function allowing to optimize beta-blocking and angiotensin-converting enzyme inhibitor treatment.

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