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Review Article

Cardiac Resynchronization Therapy in Heart Failure: Rationale, Results, Indications, Limits and Perspectives

Abstract

Heart Failure is the result of heterogeneous structural heart diseases, especially ischemic disease, and is becoming increasingly common in all Western countries.

Many patients continue to be symptomatic in spite of progress in pharmacological therapy, and the risk of mortality remains high in the most advanced functional classes. Cardiac resynchronization therapy can be used as a therapeutic strategy for alleviating symptoms and reducing mortality in selected patients with heart failure.

Cardiac resynchronization therapy provides both immediate and medium/long-term results. The immediate results are the reduced QRS duration, the synchrony restoration between the ventricles and between the lateral and septal walls of the left ventricle, the reduced mitral regurgitation and the increased stroke volume. In the medium/long term, left ventricular reverse remodeling occurs and left ventricular ejection fraction is increased.

Several trials have documented both increased functional capacity and improvements in quality of life and New York Heart Association class. Moreover, cardiac resynchronization therapy has been seen to reduce HF hospitalizations and mortality and the total number of days of hospitalization.

In order to reduce the percentage of non-responders to cardiac resynchronization therapy, it is necessary to optimize the prognostic stratification of candidates for implantation through multi-parameter evaluations and to ensure correct device programming with periodic updates which are widely recommended but not so often performed.

Whether indications should be extended will need to be evaluated in view of the known complications mainly associated with lead implantation.

Introduction

Heart Failure (HF) is the result of heterogeneous structural heart diseases, especially ischemic disease, and is becoming increasingly common in all Western countries. Indeed, over than 7 million individuals in Europe [1] and over than 4 million in the United States [2] are currently affected. Moreover, this prevalence is expected to double over the next 20 years [3], thus making HF the new cardiovascular epidemic [4].

Since 1986, numerous clinical trials focused on HF therapy have been conducted, ranging from the simple control of risk factors to the implementation of advanced treatment modalities for patients with HF refractory to conventional therapy [5].

However, many patients continue to be symptomatic in spite of progress in pharmacological therapy, and the risk of mortality remains high in the most advanced functional classes [6]. Cardiac resynchronization therapy (CRT) can be used as a therapeutic strategy for alleviating symptoms and reducing mortality in a considerable percentage of HF patients.

Rationale

It is well known that QRS duration is inversely correlated with survival in HF patients in functional classes II-IV, and patients with QRS ≥200 ms have a 5-fold higher risk of death than those with a narrow QRS [7]. In particular, left bundle branch block (LBBB) usually delays activation of the posterior/lateral wall of the left ventricle, leading to asynchronous contraction between the septum and posterior-lateral wall and reducing the left ventricular ejection fraction (LVEF).

CRT can correct this asynchronous contraction through the pre-excitation of the posterior-lateral wall of the left ventricle, thereby improving systolic function [8,9]. Indeed, the dyssynchrony due to prolonged QRS duration involves the heterogeneous propagation of electrical activity in the ventricle, which determines various degrees of impaired coordination in filling and contraction [10]. Consequently the contractile efficiency of the heart is compromised and the myocardial oxygen consumption increases, worsening the clinical course of HF.

It is therefore important to consider that 1/3 of HF patients have a QRS duration >120 ms [11], and that the incidence of LBBB is 10.9% in the first year of follow-up [12]. In these patients, CRT enables synchronous stimulation of both ventricles, which reduces QRS duration and improves left ventricular systolic performance, although modestly increasing the myocardial oxygen consumption [13]. The beneficial effects of CRT on left ventricular systolic function and on neurohormonal activation lead to clinical improvements in symptoms, exercise capability and quality of life, and reduce HF hospitalizations and mortality [14].

Results

CRT provides both immediate and medium/long-term results in the so-called "positive responder patients". The immediate results are the reduced QRS duration, the synchrony restoration between the ventricles and between the lateral and septal walls of the left ventricle, the reduced mitral regurgitation and the increased stroke volume. In the medium/long term, left ventricular reverse remodeling occurs, left ventricular end-systolic volume (LVEsV) is variably reduced and EF is increased. Standard criteria adopted for defining positive response to the therapy are a reduction of at least 15% in LVEsV and an increase of 5% in EF.

On the clinical side, several trials have documented both increased functional capacity, as evaluated by means of the 6-minute walking test and the VO2 peak, and improvements in quality of life and New York Heart Association (NYHA) class [15-23]. Moreover, CRT has been seen to reduce HF hospitalizations and mortality by 36% [22], and the total number of days of hospitalization by 77% [17]. The COMPANION study [22] evaluated the efficacy of CRT, with or without an Implantable Cardioverter Defibrillator (ICD), versus medical therapy alone, in reducing the risk of death and hospitalizations in HF patients. In 1520 patients with advanced HF (LVEF ≤35%, left ventricular end-diastolic diameter (LVEdD) ≥60 mm, NYHA class III-IV) and intraventricular conduction delay (QRS ≥120 ms), both CRT with and without ICD reduced the primary end-point of mortality/hospitalization for HF by 20% in one year compared with optimal medical therapy. It was clearly demonstrated that CRT in addition to optimal medical therapy with beta-blockers [24,25], ACE-inhibitors [26,27] and mineralocorticoid antagonists [28], further reduced mortality in HF patients, and that this reduction reached a value of 36% in the long term [22].

The CARE-HF study [23] evaluated the effect of CRT on morbidity and mortality in 813 patients with advanced HF and a clinical and instrumental profile similar to that of the COMPANION study population. The primary end-point was the combination of all-cause death and hospitalization for major cardiovascular events over a mean follow-up of 29.4 months. In this study, CRT reduced the primary end-point by 37% compared with medical therapy (HR 0.63, 95% CI 0.51-0.77, P <0.0001) in subgroups that showed no statistically significant differences.

These exciting results led to further studies in which the benefits of CRT have been assessed in patients in lower functional classes. Specifically, in the REVERSE study [29] the long-term benefits of CRT were evaluated in 610 European patients in NYHA class II (83%) or I (previously symptomatic), with QRS ≥120 ms, LVEF ≤40%, LVEdD ≥55 mm, with or without indication for an ICD, and undergoing optimized medical therapy. Patients were randomized 2:1 to CRT-ON or CRT-OFF and followed up prospectively for 24 months. The end-points of the study were the combined clinical score of all-cause mortality, hospitalizations for HF, cross-over due to worsening HF and NYHA class, and LVEsV reduction. Echocardiography revealed a significant improvement in LVEsV, left ventricular end-diastolic volume (LVEdV) and LVEF (69.7 vs. 94.5 ml/m^2, 103 vs. 132 ml/m^2, 34.8% vs. 29.9%, CRT-ON vs. CRT-OFF, respectively). Clinically, a significant 62% reduction was reported in mortality and hospitalizations for HF at 24 months (11.7% vs. 24%, HR 0.38, 95% CI 0.20-0.73, P =0.003, CRT-ON vs. CRT-OFF).

Similarly, the MADIT-CRT study [30] enrolled 1820 patients in NYHA class I or II (85%) and with QRS ≥130 ms and LVEF ≤30%. Patients were randomized 3:2 to CRT with ICD or ICD alone and followed up for a mean of 2.4 years. The end-point of the study was the reduction in all-cause mortality and/or hospitalizations for HF. CRT with ICD showed a significant advantage over ICD alone with regard to the primary end-point (17.2% vs. 25.3%, HR 0.66, 95% CI 0.52-0.84, P =0.001), the reduction in left ventricular volume (LVEsV -57 ml vs. -18 ml, LVEdV -52 ml vs. -15 ml, P <0.01, CRT with ICD vs. ICD alone, respectively) and the increase in LVEF (+11% vs. + 3%, P <0.001, CRT with ICD vs. ICD alone). The MADIT-CRT results were largely confirmed by the RAFT study [31], which enrolled 1798 HF patients in NYHA class II (80%) and III, with QRS ≥130 ms, LVEF ≤ 30%, randomized to CRT with ICD or ICD alone and followed up for 40 months. The reduction in the primary end-point of all-cause mortality/hospitalizations for HF was 25% greater in the CRT with ICD group than in the ICD alone group (HR 0.75, 95% CI 0.64-0.87, P <0.001), with 29% reduction of the risk of mortality in the sub-group of patients in NYHA class II. The results of these three studies (REVERSE, MADIT-CRT and RAFT) encouraged CRT indications to be extended to all NYHA class II patients. Moreover, a recent meta-analysis of 5 randomized studies has shown that CRT provides greater benefits in patients with QRS >150 ms [32].

Guidelines

On the basis of the evidences collected, the main American and European scientific societies have modified CRT indications in the aim to include patients not only in NYHA classes III and IV, but also in NYHA class II with LBBB, in particular if with QRS >150 ms [33,34]. The benefit of CRT in patients in sinus rhythm with wide QRS but without LBBB is uncertain. In these patients, the indication for CRT is therefore less prescriptive.

Furthermore, in HF patients in permanent atrial fibrillation with wide QRS and left ventricular dysfunction, CRT is indicated only in an advanced NYHA class and on condition that 100% biventricular stimulation can be achieved, even through AV junction ablation if needed. Finally, there is indication to up-grade a conventional PMK or ICD to CRT or CRT with ICD in HF patients in an advanced NYHA class with left ventricular dysfunction and a high percentage of ventricular pacing.

As yet, in patients with mild-moderate left ventricular dysfunction in whom conventional pacing is indicated, the indication for "de novo" CRT implantation, in order to reduce the risk of HF worsening due to the high percentage of right apical pacing, is less established.

Limits

Because of its widespread involvement of clinical, instrumental, metabolic and endocrine factors, the response to CRT is not easy to precisely establish. Nevertheless, there is general agreement that patients in whom the LVEdV reduction in the medium/long term is less than 15% should be classed as non-responders. This is not a low percentage, mostly considering that these patients account for at least 30% of all undergoing implantations [35]. The response to CRT may be sub-optimal for many reasons, ranging from the etiopathogenic and clinical heterogeneity of HF patients to the widespread and variable presence of co-morbidities or to the lack of optimization of medical therapy [36].

In the aim to increase the probability of response to CRT, it is important to ensure that left ventricular stimulation is concordant with the most delayed activation site, as identified by Tissue Doppler Imaging [37] or speckle-tracking [38] echocardiography. Moreover, the presence of large areas of fibrous scarring in the left ventricle can impair the CRT response [39], particularly if these are located in the posterior-lateral wall [40]. By contrast, the presence of vital myocardium, as identified by means of echo-dobutamine [41] or nuclear medicine techniques [42,43], has a favorable prognostic significance in CRT candidates. Briefly, in order to reduce the percentage of non-responders to CRT, it is necessary to optimize the prognostic stratification of candidates for implantation through multi-parameter evaluations [44] and to ensure correct device programming, with periodic updates of the A-V and V-V intervals which are widely recommended but not so often performed [45].

At last, the recent diffusion of remote control systems for implanted devices has improved the assistance available to CRT patients through strict monitoring of numerous vital parameters during follow-up [46]. Indeed, a strong association between remote monitoring and survival has been observed in CRT-ICD patients [47].

Perspectives

Lead positioning

Alternative forms of CRT, including biventricular endocardial and multisite epicardial pacing, have been recently proposed. Left ventricular leads cannot be implanted in up to 10% of patients undergoing CRT implantation [48]. These implant failures are not due to patient selection but rather challenges posed by anatomy leading to lead stability problems, phrenic nerve stimulation, and poor electrical measurements [49]. The quadripolar leads recently made available in the market, allowing multiple pacing configurations, provide an opportunity to optimize the electrical performance and minimize phrenic nerve stimulation. Moreover, preliminary data suggest that simultaneous stimulation of multiple left ventricular sites using two or more pacing sites in a quadripolar lead could enhance the acute effectiveness of CRT [50]. However, the results appear conflicting [51,52] and prospective follow-up studies are required to demonstrate clinical benefit.

During CRT device implantation, the pacing lead is usually positioned in the coronary sinus to stimulate the left ventricular epicardium. Transvenous left ventricular endocardial pacing via transeptal puncture has been proposed as an alternative method. Several experimental studies have demonstrated that endocardial pacing should elicit beneficial effects, allowing more homogeneous and rapid electric depolarization and repolarization [53,54]. In particular, pacing at an optimal individual endocardial site seems to yield enhanced left ventricular performance in comparison with conventional coronary sinus site stimulation [55]. Thus, endocardial left ventricular pacing might provide an alternative approach to CRT, when coronary sinus pacing is not viable. However, the possibility of adverse effects of endocardial CRT (eg, the risk of thromboembolic complications and the induction of mitral valve dysfunction) should be considered and carefully addressed during the evaluation of risks and benefits of the procedure.

Patient selection

As previously reported, duration of QRS interval ≥120 or 130 ms was the inclusion criterion used in major CRT trials. However, sub-group analyses based on QRS morphology [30,31,56] and a meta-analysis [57] suggested that patients with complete LBBB showed a greater benefit on the composite of morbidity/mortality from CRT, compared with patients with non-specific intraventricular conduction delay or right bundle branch block. Based on this evidence, current class I recommendations were restricted to patients with complete LBBB. However, recent studies showed that fragmented QRS complexes in the electrocardiograms of patients with nonischemic dilated cardiomyopathy and narrow QRS complexes are associated with significant intraventricular dyssynchrony [58,59], and other studies suggested that fragmented QRS complexes might be useful in predicting response to CRT [60,61]. Ongoing studies are investigating the possibility of maximizing CRT benefits by refining ECG selection criteria [62].

Single-center studies suggested that echocardiographic parameters of mechanical dyssynchrony may improve patient selection for CRT. Moreover, since mechanical dyssynchrony may also be present in patients with normal QRS duration, potential benefits could be expected in this population, too.

In 2008, the PROSPECT study tested the performance of echocardiographic parameters to predict CRT response [63], and revealed that these parameters do not appear to have a clinically relevant impact on improving response rates.

Moreover, one randomized study that enrolled patients with QRS duration <130ms (the RethinQ trial) did not show any improvement in peak oxygen consumption on CRT [64]. Similarly, in the LESSER-EARTH trial [65], which randomized patients with an LVEF ≤35%, symptoms of HF, and a QRS duration <120 milliseconds to active versus inactive CRT therapy, CRT did not result in an improvement in exercise capacity, symptoms, quality of life, or reverse LV remodeling. More recently, the EchoCRT study [66] showed that in patients with systolic heart failure and QRS duration of less than 130 msec, CRT does not reduce the rate of death or hospitalization for heart failure and may increase mortality.

Several studies have addressed the issue of the interventricular and left intraventricular dyssynchrony caused by right apical pacing. These studies have tested "de novo" CRT implantation in patients with a conventional pacing indication, both with preserved left ventricular systolic function [67-69] and with moderate-severe left ventricular dysfunction [70-72]. The results suggest that CRT plays a preventive role with regard to HF mortality/hospitalizations only in patients with left ventricular dysfunction (LVEF <40%). Indeed, left ventricular systolic dysfunction has recently been suggested as an independent predictor of the adverse clinical impact of pacing [73,74], even though the preventive impact of CRT on HF in these patients must be carefully evaluated considering the increase in complications due to the greater number of leads implanted (6.5% vs. 18%, conventional pacing vs. CRT in the BLOCK-HF study) [72].

An alternative strategy in these patients is to up-grade to CRT after first implanting a conventional PMK. This approach provides the same clinical benefit as "de novo" CRT implantation, but is however associated with a considerable percentage of complications [75].

Further evidence of the potential benefit of "de novo" CRT implantation in patients with conventional pacing indications in whom right apical stimulation cannot be avoided is expected from the BIOPACE trial (ClinicalTrials.gov Identifier: NCT00187278), while the on-going MIRACLE-EF study (ClinicalTrials.gov Identifier: NCT01735916) is testing the efficacy of CRT in patients with left ventricular dysfunction (LVEF 36%-50%) and LBBB but without indication for definitive pacing.

Finally, in patients with a prolonged PR interval, LBBB and left ventricular dysfunction, the REAL-CRT (Bivent Ricular pacing in prolongEd AV interval) study will evaluate the synergic effect of atrio-ventricular and inter-ventricular synchronization provided by CRT in patients with a minimum or intermittent indication for pacing (ClinicalTrials.gov Identifier: NCT02150538).

Conclusions

A large number of studies have already demonstrated that, compared with optimal medical therapy alone, CRT can reduce HF mortality and hospitalizations in selected HF patients in NYHA classes II-IV. Whether indications for CRT should be extended to patients with an indication for convention pacing, mild-moderate (or even no) left ventricular dysfunction and a high percentage of right apical pacing will need to be evaluated in view of the expected increase in complications due to the greater number of leads implanted.

Conflict of Interest

S.V. and U.R. are employees of Boston Scientific Italy; there are no other conflicts of interest.

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