

Review Article

Cardiac Resynchronization Therapy in Asymptomatic and Mildly Symptomatic Chronic Systolic Heart Failure: A New Era of Systolic Heart Failure Management?

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The incidence and prevalence of heart failure syndrome continue to increase, and it therefore remains a significant health problem in developed western countries. It is accompanied by high morbidity and mortality, and significantly affects the burden on health care system as well as the patients' quality of life.

Cardiac resynchronization therapy (CRT) with biventricular stimulation has recently emerged as an adjunctive treatment modality in patients with chronic systolic heart failure and documented electrical and mechanical dyssynchrony. Electrical dyssynchrony may be expressed as atrioventricular, interventricular or intraventricular asynchrony. The latter is associated with the presence of a wide QRS complex (mainly left bundle branch block pattern) and implies that different segments of the left ventricle (LV) do not contract simultaneously, resulting in LV mechanical dyssynchrony. Electromechanical intraventricular asynchrony is associated with diminished stroke volume, susceptibility to mitral regurgitation, impaired LV filling, increased LV wall stress, delayed relaxation time and adverse neurohormonal activation.¹⁻³ Biventricular pacing resynchronizes the timing of global LV depolarization and theoretically improves mechanical contractility, with concomitant enhancement of reverse LV re-

modeling.⁴⁻⁷ Many heart failure experts maintain that LV reverse remodeling is achieved due to a therapeutic intervention when ejection fraction (EF) increases by more than 15% and/or the difference between LV end-systolic and end-diastolic volumes increases by more than 10%.⁸

The clinical benefit of CRT, especially in terms of mortality and morbidity, has been established in patients with advanced heart failure, who are in functional NYHA class III or IV despite optimal drug treatment. In the majority of recipients, an improvement in heart failure symptoms has been demonstrated by multiple controlled and uncontrolled randomized trials.⁴⁻⁶ According to the new guidelines, candidates for CRT include patients with dilated type cardiomyopathy, either ischemic or non-ischemic, EF <35%, QRS width >120 ms, in NYHA class III or IV despite optimal medical therapy (including loop diuretics, b-blockers, angiotensin-converting enzyme inhibitors or angiotensin receptor blockers).⁹ Despite the undoubted significance of mechanical dyssynchrony, no echocardiographic or magnetic resonance imaging criteria have yet been established in clinical practice.

Although CRT is an established treatment modality for patients with advanced systolic heart failure, uncertainty exists

about the safety and efficacy of this strategy in asymptomatic and mildly symptomatic heart failure patients (NYHA classes I-II). However, it has been documented that interventions enhancing reverse remodeling are associated with a long-term beneficial effect in terms of symptom relief, improvement in quality of life, and prolongation of survival.⁸ For this reason many investigators believe that biventricular pacing in the earlier stages of heart failure syndrome could prevent disease progression mediated by LV remodeling.

In the CONTAK-CD trial,¹⁰ heart failure patients with an intraventricular conduction delay and an indication for an implantable cardioverter-defibrillator (ICD) were randomized into two groups (parallel two arms study): CRT-on and CRT-off (control group). The devices used were capable of both ICD and CRT therapies. This study found a significant improvement in functional status, as expressed by peak VO_2 and 6-minute walk test distance, with a concomitant beneficial impact on LV function (improvement in LVEF) and reverse remodeling (reduction of LV systolic and diastolic dimensions), in the CRT-on group of mildly symptomatic patients.

A favorable effect of CRT therapy on heart failure progression in mildly symptomatic patients with an indication for ICD implantation was also documented by the MIRACLE-ICD II study.¹¹ According to the results of this study, a significant improvement in cardiac structure and function (in terms of LV volumes and EF) was reported, in combination with an improvement in the composite clinical response over a six-month follow-up period.

In the recently published InSync ICD Italian Registry, a total of 952 chronic heart failure patients in functional NYHA classes II-IV were enrolled (188 NYHA II class patients) in order to compare the effect of CRT in terms of clinical outcome and long-term mortality. The investigators concluded that although the improvement in reverse remodeling (as expressed by EF and LV dimensions) was similar all patients regardless of NYHA class, the functional improvement was better in NYHA class III/IV patients than in those in NYHA class II. However, the enhancement of LV reverse remodeling in these oligosymptomatic patients after CRT was associated with a beneficial effect on disease advancement.¹²

The investigators in the CARE-HF study retrospectively analyzed the patients who had been enrolled, using self-assessment symptom severity questionnaires in order to re-estimate their functional status. Of a total of 813 participants in this study, all of whom were char-

acterized as NYHA III/IV by their physicians, 175 patients (21.5%) produced self-assessments indicating that they were in NYHA classes I/II. According to the results of this late analysis, CRT therapy's beneficial effect on morbidity and mortality rates did not differ at all among the aforementioned groups. This led the authors to question the validity of symptom severity (as expressed by NYHA class) as a predictor in recognizing CRT candidates.¹³ Other well-organized studies (albeit single center and/or non-randomized) as well as meta-analyses of older large trials have also reported similar results with respect to the positive effect of CRT in oligosymptomatic ischemic and non-ischemic patients with chronic LV dysfunction.¹⁴⁻¹⁶

Although all the aforementioned studies indicate an improvement in cardiac function in terms of LV reverse remodeling, no specific benefit in terms of morbidity and mortality has been documented. This is in part due to the limitations of these studies: the short follow up period, the limited number of NYHA class I-II patients enrolled, and the lack of a randomization process. Two ongoing randomized trials may possibly give a more convincing answer to this question. The first is the REVERSE¹⁷ (REsynchronization reVERses Remodeling in Systolic left vEntricular dysfunction) study, which includes almost 500 patients with asymptomatic left ventricular dysfunction (NYHA I) or mild systolic heart failure (NYHA II), with $\text{EF} \leq 40\%$, left ventricular end-diastolic diameter ≥ 55 mm, under an optimal medical regimen. The follow-up period will be 12 months in the USA and Canada and 24 months in Europe. CRT therapy (with or without ICD modality, according to the patients' needs) plus pharmacological treatment will be compared with pharmacological treatment alone in terms of heart failure progression. The second ongoing study is the MADIT CRT trial,¹⁸ in which possible inhibition or amelioration of systolic heart failure will be assessed after prophylactic CRT implantation. Almost 1800 patients will be enrolled, with ischemic cardiac disease in classes NYHA I-II or non-ischemic cardiomyopathy in NYHA class II, $\text{EF} < 30\%$ and sinus rhythm with QRS complex duration > 130 ms. The follow-up period will be up to 24 months.

Important issues remain regarding the effectiveness of CRT devices in selected groups of NYHA class III-IV heart failure patients and these may, in the future, be extrapolated to NYHA class I-II patients. Great concern exists about the therapeutic role of CRT pacing in the subgroups of heart failure patients with right bundle branch block, with atrial fibrillation (His abla-

tion is of great significance), as well as in patients with established mechanical dyssynchrony but without overt electrical derangement.

Well-documented results from many prospective, randomized studies have come to light during the last few years and have established the effectiveness of device-mediated manipulation of heart failure, at least in severely symptomatic high-risk patients, in combination with optimal pharmaceutical treatment. However, despite the promising results of all these trials in terms of LV function and reverse remodeling, the existing data did not permit the investigators to make a precise evaluation of the beneficial impact of this therapeutic approach on mortality and morbidity, which is why this strategy is not yet universally recommended.

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