Cardiac resynchronisation therapy in heart failure: Current status

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Abstract Cardiac resynchronization in heart failure already has a history of 12 years. However, the major advances have been the result of large multi center trials dating from 2001. In all these trials patients with a LVEF ≤ 35% were included, and a QRS above 120 msec. Follow up was from 3–36 months. The majority of these trials showed a positive effect in reduction of composite and points of death or hospitalization for major cardiovascular events. Many of these trials also showed a diminution of left ventricular and systolic diameter or volume. Even in NYHA class II patients an improvement was seen. Some unanswered questions still remain as regards the agreement on electrical or electromechanical dyssynchrony criteria. There is a number of patients with “wide” QRS who do not improve and conversely a number of patients with a narrow QRS who witness improvement. The benefit in patients with atrial fibrillation also remains unanswered. Finally the value of this modality in patients with mild heart failure or asymptomatic left ventricular systolic dysfunction, NYHA class I–II remains to be determined in large on going trials. Another question is whether biventricular or left ventricular patient is preferable. Finally whether biventricular patient should be complemented by a defibrillator insertion is being currently studied. Cardiac resynchronization therapy along or in combination with an ICD improves symptoms, reduces major morbidity and mortality in patients with a left ventricular EF<35%, ventricular dilatation and a QRS ≥ 120 msec in NYHA class III–IV. Further indications are currently being examined.

Keywords Cardiac resynchronization · Biventricular pacing · Intracardiac defibrillators · QRS duration · Ventricular dyssynchrony

The first descriptions of the short-term hemodynamic effects of left, or of simultaneous right and left ventricular (LV) stimulation were published over 35 years ago [1–4]. However, the clinical applications of the stimulation technique known as cardiac resynchronisation therapy (CRT) began in 1994, when Cazeau et al., in France [5], and Bakker et al., in the Netherlands [6], described the first cases of atrio-biventricular pacemakers implanted in patients with severe congestive heart failure (CHF) and no conventional indication for cardiac pacing. This concept was mainly based on the frequent observation of intraventricular conduction delays in patients with chronic CHF due to ventricular systolic dysfunction. In such patients a QRS duration >120 ms is prevalent in 25–50%, and left bundle branch block is found in 15–27%. In addition, atrioventricular (AV) dyssynchrony as indicated by a prolonged PR interval on the surface ECG is present in up to 35% of severe CHF patients.

1. Rationale of cardiac resynchronisation

AV and intraventricular conduction delays both further aggravate LV dysfunction in patients with underlying cardiomyopathies. Notably, left bundle branch block alters the sequence of LV contraction, causing wall segments to contract early or late, with redistribution of myocardial blood flow, non-uniform regional myocardial metabolism and changes in regional molecular processes, such as calcium handling and stress kinases proteins [7–11]. In addition to intraventricular conduction, delays in AV timing also influence mechanical function of the 4 cardiac chambers, in
which optimal timing of atrial systole is linked to an increase in cardiac output, and duration of diastolic filling to degree of pre-systolic mitral regurgitation. Thus, dysynchrony seems to represent a patho-physiological process that directly depresses ventricular function and, causes LV remodelling and CHF, and as a consequence therefore independently predicts a higher risk of death.

2. Evidence-based clinical effects of cardiac resynchronisation therapy

State-of-the-art management of CHF, besides alleviating symptoms, preventing major morbidity, and lowering mortality, increasingly strives to prevent disease progression, in particular the transition between asymptomatic LV dysfunction and overt CHF. The clinical effects of long-term CRT were firstly evaluated in non-controlled studies, in which a sustained benefit conferred by biventricular pacing was measured [12–16]. Randomised multicenter trials with cross-over or parallel treatment assignments were subsequently conducted to ascertain the clinical value of CRT in patients with advanced CHF and in sinus rhythm, with or without indications for an implantable cardioverter-defibrillator (ICD) [17–25]. Two meta-analyses were also published [26, 27]. The usual study enrolment criteria were:

1. New York Heart Association (NYHA) CHF functional class III or IV despite standard drug treatment (see exceptions below),
2. LV ejection fraction (EF) <35%, LV dilatation, and a QRS duration >120 or 150 ms (see Table 1).

2.1. Impact of cardiac resynchronisation therapy on symptoms and exercise tolerance

All the randomised trials have confirmed a significant alleviation of symptoms and increase in exercise capacity conferred by CRT. Mean NYHA functional class decreased by 0.5–0.8 points, the distance covered during a 6-minute walk increased by a mean of 20%, and peak oxygen consumption during symptom-limited cardiopulmonary exercise increased by 10 to 15%. Quality of life, usually measured with the “Minnesota Living with Heart Failure” questionnaire, was significantly improved in all trials. The magnitude of clinical improvement was similar or greater than observed in trials of pharmaceuticals. Furthermore, cumulative improvements were noted when CRT was added to standard medical management of CHF. An important limitation in these studies was their short follow-up (3 to 6 months). However, the clinical benefits observed after the 3-month crossover phases of MUSTIC remained stable at 1 and 2 years of follow-up over time in surviving patients [28]. This durable efficacy was recently confirmed in CARE-HF, where the clinical benefits conferred by CRT were sustained during a mean follow-up of 29 months [27].

2.2. Impact of cardiac resynchronisation therapy on HF-related major morbidity

The early randomised trials were designed with symptoms and functional capacity as primary endpoints. Though they were not powered to detect significant effects on morbidity and mortality, these trials showed a clear trend toward lower rates of hospitalisation for management of CHF in patients assigned to active therapy. In the MUSTIC trial, the monthly rate of hospitalisation for CHF during delivery of CRT was 7-fold lower than in absence of CRT [28], while in the MIRACLE trial, the number of hospitalised days was lowered by 77% in the group of patients assigned to CRT [18]. In a meta-analysis of all studies completed by 2003, Bradley et al. found a 30% reduction in the total number of hospitalisations for management of CHF, attributable to CRT [26]. In the COMPANION trial, CRT with or without cardioverter-defibrillator lowered the combined endpoint of total mortality and rehospitalisation for CHF by 35–40%, a proportion mainly driven by the 76% lower rate of rehospitalisations [24]. In CARE-HF, CRT lowered the proportion of unplanned hospitalisations for worsening CHF by 52%, and the number of unplanned hospitalisations for major cardiovascular events by 39% [25].

2.3. Impact of cardiac resynchronisation therapy on mortality

CARE-HF and COMPANION were trials designed to examine the effects of CRT on combined primary endpoints of morbidity and mortality [24, 25]. COMPANION included 1520 patients randomly assigned in a 1:2:2 ratio into 3 treatment groups: optimal medical treatment alone (OPT), OPT + CRT (CRT-P) and OPT + CRT + ICD (CRT-D). CRT-P and CRT-D were both associated with a 20% reduction in the primary combined end-point of all cause mortality and hospitalisation for any cause (P < 0.01). However, only CRT-D was associated with a significant decrease in total mortality (relative risk ratio = 36%; absolute decrease = 7%; P = 0.003), while the 24% relative reduction (absolute = 4%) in mortality associated with CRT-P was nearly statistically significant (P = 0.059). COMPANION, however, had 2 important methodological limitations. Firstly, the median follow-up was limited to 14 months. Secondly, there was no pre-specified analysis to compare CRT-D and CRT-P, precluding the demonstration of the superiority of one CRT strategy over the other [24].

The CARE-HF trial enrolled 813 patients. CRT-P plus standard pharmacological treatment for heart failure was compared to standard pharmacological treatment alone. At