Use of Cardiac Resynchronisation Therapy – Change of Clinical Settings

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Abstract

Current guidelines recommend cardiac resynchronisation therapy (CRT) for patients with severe left ventricular dysfunction (left ventricular ejection fraction [LVEF] $\leq 35\%$), QRS duration of ≥ 120 –150 ms (Class IA and IB indications) on surface electrocardiogram (ECG) and New York Heart Association (NYHA) class III or IV heart failure (HF) symptoms. Ongoing studies aim to expand the use of CRT in patients with asymptomatic or minimal symptoms left ventricular dysfunction. There have been studies that have shown benefit of CRT extended to this group of patients. There have also been different implications of the role of CRT in patients with atrial fibrillation (AF), patients with narrow QRS duration or with right bundle branch block (RBBB) on surface ECG, as well as patients with end-stage renal failure on dialysis therapy. This article aims to review the current body of evidence of expanding use of CRT in these populations.

Keywords

Cardiac resynchronisation therapy, left ventricular ejection fraction, New York Heart Association (NYHA) class, heart failure

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Heart failure (HF) is a growing and major health burden in western countries. The prevalence of HF is estimated at 1–2 % in the western world, and the incidence approaches 5–10 per 1,000 persons per year.¹ Cardiac resynchronisation therapy (CRT) has been shown in multiple studies to improve HF symptoms, quality of life and improve survivals.^{2–6} The two landmark studies, Comparison of Medical Therapy, Pacing and Defibrillation in Heart Failure (COMPANION) and Cardiac Resynchronization-Heart Failure (CARE-HF), established the clinical indications for CRT, which form the basis for consensus international guidelines.^{5–7} These two trials randomised 2,333 patients in sinus rhythm (SR) with QRS prolongation on surface electrocardiogram (ECG) (≥ 120 ms), New York Heart Association (NYHA) functional class III and ambulatory class IV HF and a persistently reduced left ventricular ejection fraction (LVEF), despite optimal medical treatment. The trials showed that CRT reduced the risk of death from any cause and hospital admission for worsening HF.^{5,6} The effect of left ventricular reverse remodelling from CRT was sustained over time.⁸ This has significant clinical implications and has led to the development of the hypothesis that implanting CRT in patients at an earlier stage of HF and different characteristics of patients with HF may prevent disease progression and lead to improved clinical outcomes. This article reviews the use of CRT in the changing and new clinical setting and the implications for daily clinical practice.

Cardiac Resynchronisation Therapy in Patients with Mild Heart Failure – The Evidence

The earliest evidence of CRT in NYHA class I–II patients came from CONTAK CD and Multicenter InSync ICD Randomized Clinical Evaluation II (MIRACLE ICD) trials.^{4,9}

In CONTAK CD, 490 patients with implantable cardioverter defibrillators (ICDs) were randomised to either CRT-on or no CRT.⁴ All patients

were in NYHA class II–IV at the time of entry into the study. However, many patients demonstrated significant symptomatic improvement with medical treatment during this period. Thus, 227 patients were in NYHA class III/IV and 263 were in NYHA class I/II when the randomised therapy was initiated. At six months, CRT was linked to a significant reduction in left ventricular dimensions ($p < 0.001$) and improvement in LVEF (5.1 versus 2.8 %, $p = 0.020$).⁴ However, the reduction in HF progression and changes in NYHA class as well as quality of life were not statistically significant. Many patients responded positively once medical treatment was optimised before randomisation. This improvement in clinical status made it more difficult to show the benefit in healthier patients. Importantly, this trial showed that CRT improves left ventricular reverse remodelling.

Likewise, in the MIRACLE ICD trial all of the 186 patients with secondary indication for ICD were randomised either to CRT-on or CRT-off.⁹ CRT resulted in significant improvement in cardiac structure and function, and clinical HF composite endpoint over six months, but did not alter exercise capacity. It appeared that CRT offered important benefits to optimally medically managed, mildly symptomatic NYHA class II HF patients with ventricular dyssynchrony and an indication for an ICD. The study showed the potential of CRT to limit disease progression even in patients with mild HF symptoms.

These studies provided a preview of the much larger trials such as the Resynchronization Reverses Remodeling in Systolic Left Ventricular Dysfunction (REVERSE), the Multicenter Automatic Defibrillator Implantation with Cardiac Resynchronization Therapy (MADIT-CRT) and the Resynchronization/Defibrillator for Ambulatory Heart Failure Trial (RAFT) studies in this group of patients with asymptomatic or mildly symptomatic HF.

The REVERSE trial was the first large randomised controlled trial that included 610 patients with NYHA class I and II symptoms, QRS ≥ 120 ms and LVEF ≤ 40 %.¹⁰ At 12 months of follow-up, only 16 % of patients with a CRT device turned on worsened compared with 21 % of those with CRT-off ($p=0.10$).¹⁰ However, CRT was associated with a significant improvement in left ventricular dimensions ($p<0.0001$). The reduction of left ventricular dimensions was particularly prominent in those patients with non-ischaemic cardiomyopathy, those with larger left ventricular end-systolic volumes and those with a broader QRS on surface ECG (≥ 152 ms). The time to the first HF hospitalisation was also significantly delayed in those with CRT-on (hazard ratio [HR] 0.47, $p=0.03$).¹⁰ Although CRT appeared to slow the HF disease progression in this study, the impact of clinical outcome was only modest. It is worth noting that the patients in the REVERSE trial were on optimal medical treatment. This might be a potential explanation for these 'negative' results. Also, this trial has a short follow-up of one year. The treatment effect of CRT might require a prolonged period, and therefore, it might not be surprising that a one-year trial of CRT including asymptomatic patients with HF was too short to demonstrate the efficacy of CRT.

The sub-analysis of the European data of the REVERSE trial provided further insights into the role of CRT in 262 mildly symptomatic HF patients. Over the 24 month period, 19 % of those patients with CRT-on versus 34 % of those with CRT-off worsened ($p=0.01$).¹¹ Furthermore, CRT was associated with a significant reduction in the left ventricular end-systolic volume index ($p<0.0001$). The time to first HF hospitalisation was significantly delayed in those with CRT-on ($p=0.03$).¹¹ These results provided additional data to support the use of CRT in delaying HF progression.

The MADIT-CRT study demonstrated a 34 % reduction in the risk of death or non-fatal HF among the mild HF patients with CRT defibrillators (CRT-D) as compared with those in the ICD only group ($p=0.001$).¹² This benefit was mainly driven by the 41 % reduction in the risk of HF events, and there was no difference between the patients with ischaemic or non-ischaemic cardiomyopathy. Furthermore, there were clear improvements in the left ventricular mechanical indexes, with reduction in the left ventricular volumes ($p<0.001$) and increase in LVEF ($p<0.001$), reiterating the reverse remodelling effect of CRT that was observed in the REVERSE study.

Another large study that compared ICD with CRT-D in patients with mildly symptomatic HF was the RAFT study. Among the 1,798 patients with LVEF ≤ 30 %, QRS durations ≥ 120 ms and NYHA class II or III HF, the primary outcome of death or hospitalisation for HF occurred in 33.2 % of those with CRT-D, compared with 40.3 % in those with ICD only ($p<0.001$).¹³ The time to the occurrence of the primary outcome was significantly delayed in the CRT-D group (HR 0.75, $p<0.001$). The time to death was also significantly prolonged in the CRT-D group (HR 0.75, $p=0.003$).¹³

A recent meta-analysis of the above five randomised trials was performed. At pooled analysis there was a significant decrease in mortality with CRT (odds ratio [OR] 0.78, $p=0.024$) and this benefit was largely driven by the RAFT study. CRT was shown to reduce HF events (OR 0.63, $p<0.001$) and induced significant left ventricular reverse remodelling ($p<0.001$).¹⁴ The analysis also showed that CRT was associated with a delay progression of HF symptoms (OR 0.54, $p=0.026$) and a significant improvement in exercise tolerance ($p<0.001$).¹⁴

With the additional findings from the above trials, the relative magnitude of the benefits of CRT in patients with NYHA class II symptoms is similar to those observed in patients with NYHA class III symptoms. Therefore, the European Society of Cardiology (ESC) Task Force agreed to give a new recommendation for patients with NYHA class II HF. In the 2013 ESC Guidelines on cardiac pacing and cardiac resynchronisation therapy, CRT (preferably a CRT-D) is a class IA indication for NYHA class II HF patients with LVEF ≤ 35 % and QRS duration ≥ 150 ms.⁷ However, the evidence for recommending CRT in patients with NYHA class I remains inconclusive due to the low number of patients enrolled in randomised trials.

Special Considerations and New/Future Indications of Cardiac Resynchronisation Therapy

Cardiac Resynchronisation Therapy and Patients with Atrial Fibrillation

Atrial fibrillation (AF) is a common arrhythmia, and its prevalence increases in the presence of HF. The development of AF in HF patients may significantly affect the outcomes. Population data from the Framingham Study suggest that new-onset AF after a diagnosis of HF conferred a hazard ratio (HR) for death of 1.6 in men and 2.7 in women.¹⁵ The role of CRT in patients with AF is less well established. The evidence of CRT in patients with AF predominantly came from observational case studies.^{16–18} The first prospective, randomised trial that evaluated the role of CRT in patients with permanent AF and severe HF is the Multisite Stimulation In Cardiomyopathies (MUSTIC) AF trial, which included 131 patients, at least half of whom were in permanent AF and in need of ventricular pacing. However, only patients with a biventricular pacing rate >85 % showed a slight but significant improvement in functional status at one-year follow-up.¹⁹ In the RAFT study, 229 patients (12.7 %) had permanent AF at baseline. There was no clear reduction in clinical events and patients with permanent AF appeared to gain minimal benefit from CRT-D compared with a standard ICD.²⁰ Despite apparently good rate control of AF before randomisation, the delivery of CRT remained suboptimal because of a low percentage of biventricular pacing. A recent meta-analysis including 23 observational studies followed a total of 7,495 CRT patients, 25.5 % with AF, for a mean of 33 months and found that AF was associated with an increased risk of non-response to CRT (34.5 versus 26.7 %; pooled relative risk [RR] 1.32; $p=0.001$) and all-cause mortality (10.8 versus 7.1 % per year, pooled RR 1.50; $p=0.015$).²¹

The benefits of CRT appear to be attenuated in patients with AF. Indeed, the presence of AF affects the effective delivery of biventricular pacing. In patients with AF, phases of effective biventricular capture alternate with phases of competing AF rhythm, which causes spontaneous, fusion or pseudofusion beats.²² This suggests that the global effective that CRT delivery has may be markedly reduced compared with atrial synchronous rhythm with a short atrioventricular (AV) interval as is achieved during SR. Moreover, in AF patients during exertion, spontaneous ventricular rate tends to override biventricular pacing rates, resulting in further reduction of paced beats precisely when patients are most in need of having biventricular capture, thus greatly limiting exercise tolerance. For this aspect, the indication of CRT for patients in AF with NYHA class III or IV, QRS duration ≥ 130 ms and LVEF ≤ 35 % remains Class IIA in the recent 2013 ESC Guidelines.⁷

In most patients with AF with intact intrinsic conduction, adequate biventricular pacing could only be achieved with AV nodal ablation. The use of AV nodal ablation was highly variable in majority of CRT trials.

In RAFT, AV nodal ablation was only used in one patient.²⁰ A recent meta-analysis of six studies that enrolled 768 CRT-AF patients, including 339 patients who underwent AV nodal ablation, showed that AV nodal ablation conferred a RR of 0.42 and 0.44 for overall mortality and for cardiovascular mortality, respectively.²³ AV nodal ablation was also shown to improve NYHA functional class in patients with AF. The current 2013 ESC Guidelines recommend a Class IIA indication for CRT in patients with AF, QRS duration ≥ 120 ms and LVEF ≤ 35 %, provided that AV nodal ablation is added to these patients with incomplete (<99 %) biventricular capture and those who are candidates for AV nodal ablation for rate control. A randomised controlled trial, Cardiac Resynchronisation Therapy and AV Nodal Ablation Trial in Atrial Fibrillation Patients (CAAN-AF) (www.clinicaltrials.gov/ct2/show/NCT01522898) is currently enrolling and its aim is to determine if AV nodal ablation combined with CRT in CRT-eligible AF patients will result in significant reductions in mortality and HF events compared with patients treated with CRT alone.

Cardiac Resynchronisation Therapy and Patients with Chronic Kidney Disease

Renal impairment is common in patients with HF. In a systematic review of a HF population, a total of 63 % of the patients had any renal impairment, and 29 % had moderate to severe impairment.²⁴ Adjusted all-cause mortality was increased for patients with any renal impairment (HR 1.56; $p < 0.001$) and moderate to severe impairment (HR 2.31; $p < 0.001$).²⁴

The effect of CRT on renal function has not been studied in large randomised trials. A retrospective study showed the survival rate among those with standard ICD alone (88 patients) and CRT-D patients (787 patients) within glomerular filtration rate (GFR) < 30 mL/min/1.73 m² and GFR ≥ 60 mL/min/1.73 m² groups was similar, whereas CRT-D patients with GFR 30–59 mL/min/1.73 m² (moderate renal impairment) had significantly better survival compared with those with ICD alone (HR 2.23, $p = 0.002$).²⁵ This survival benefit was associated with improved renal and cardiac function. However, among patients with a baseline GFR < 30 mL/min/1.73 m², a group largely ignored in most CRT trials, survival was limited.²⁵ It might imply that the CRT implantation procedure itself had no lasting impact on renal function.

Many patients with chronic kidney disease (CKD) have concomitant cardiac disease with indications for device therapy, but the majority of trials have excluded this group of patients. Recently, a study of 482 CKD patients treated by CRT reported higher survival in those with normal or mild renal impairment than in those with CKD (defined as a GFR of ≤ 60 mL/min/1.73 m²) (72 versus 57 % at three years, $p < 0.01$).²⁶ This study excluded patients on dialysis.

There is also a paucity of data on the role of CRT in patients with CKD on dialysis therapy. Based on current limited data, the benefits and risks should be taken into consideration when considering the implantation of a CRT device in a dialysis patient. More research in this field is warranted to guide appropriate clinical decisions in this group of patients.

Cardiac Resynchronisation Therapy and Patients with Heart Failure but with Narrow QRS Complex

Previous studies have shown that approximately 30 % of HF patients have narrow QRS duration < 120 ms and thus these patients will not qualify for CRT according to current guidelines.²⁷ Yet these patients have

depressed left ventricular systolic function and exhibit left ventricular mechanical dyssynchrony as assessed by echocardiography.^{28,29}

Several small studies have reported that HF patients with narrow QRS have demonstrated a substantial echocardiographic and clinical improvement following CRT.^{30–32} Based on these encouraging outcomes of the smaller observational studies, the Cardiac Resynchronisation Therapy with Heart Failure and Narrow QRS (RethinQ) study was conducted to evaluate the efficacy of CRT in patients with standard indication for ICD, NYHA class III HF, a QRS duration < 130 ms and evidence of mechanical dyssynchrony on echocardiography.³³ At the end of follow-up, there was no difference between those with narrow and wide QRS patients. However, this study was of too short a duration to observe any effects on morbidity and mortality.

Recently, the Evaluation of Resynchronization Therapy for Heart Failure (LESSER-EARTH) trial that assessed whether CRT improves exercise capacity and left ventricular reverse remodelling outcomes in patients with LVEF ≤ 35 %, symptoms of HF and a QRS duration < 120 ms was interrupted prematurely after 85 patients were randomised. The trial showed that CRT did not improve clinical outcomes or left ventricular reverse remodelling in those with a narrow QRS duration < 120 ms.³⁴ In fact, there was an associated with a non-significant trend toward an increase in HF-related hospitalisation.

Similarly, the Echocardiography Guided Cardiac Resynchronization Therapy (EchoCRT) study was recently terminated early due to the futility of CRT in this population. The mean QRS duration was 105 ms for the CRT group. The primary outcome, death from any cause or hospitalisation for worsening HF, occurred in 28.7 % in the CRT group, compared with 25.2 % in the control group (HR with CRT, 1.20; $p = 0.15$).³⁵ There was an excess of deaths due to cardiovascular causes in patients randomly assigned to CRT (37 deaths versus 17 in the control group; $p = 0.004$). There was also a non-significant trend towards an increase in mortality related to HF.³⁵

Despite the hypothesis that CRT might be beneficial to those with HF but narrow QRS duration, the current published studies have consistently failed to demonstrate a benefit in this group of patients. The current guidelines do not recommend CRT in patients with chronic HF with QRS duration < 120 ms (Class IIIB evidence).

Cardiac Resynchronisation Therapy and Patients with Right Bundle Branch Block

Left bundle branch block (LBBB) has been shown to have a detrimental effect in patients with HF. Short-term mortality rates for the subgroups of patients with decompensated HF with QRS < 120 ms, right bundle branch block (RBBB) and LBBB were 46.1 %, 56.8 % and 57.7 %, respectively ($p < 0.0001$).³⁶ Another population-based study of HF patients showed that those with LBBB had features consistent with more severely decompensated HF. Furthermore, even after accounting for these baseline factors and validated predictors of mortality, a LBBB on the presentation ECG conferred a 10 % increased risk of death and a 32 % increase in HF rehospitalisation in long-term follow-up.³⁷

In patients with LBBB, the normal sequence of electrical activation is reversed leading to significant electromechanical coupling delay. On the other hand, patients with RBBB might have minimal electrical or electromechanical coupling delay unless left fascicular hemiblock

is present.³⁸ A study using a three-dimensional non-fluoroscopic electroanatomic contact mapping system (3D-Map) showed that patients with RBBB, compared with LBBB, have a greater right-sided conduction delay, while the degree of left ventricular delay is not significantly different between the two groups.³⁹ These findings seem to suggest that in HF patients with RBBB, CRT should benefit those in whom an underlying left-sided intraventricular conduction delay is masked by RBBB.

The number of patients with RBBB included in large randomised controlled trials of CRT was low. A single-centre registry of 636 CRT patients with only 59 patients with RBBB (9.3 %) found that the composite endpoint of death, heart transplantation or ventricular assist device implantation occurred in 147 patients (23.0 %) – most frequently in the RBBB group ($p=0.004$).⁴⁰ The highest symptomatic NYHA response rate was observed in those with LBBB, whereas few patients with RBBB responded ($p<0.001$). This differential response remained significant after controlling for baseline differences among groups ($p=0.02$).⁴⁰

Similarly, pooled data from the MIRACLE and CONTAK-CD trials showed that patients with RBBB had no evidence of improvement in symptoms, six-minute walk test or quality of life scores at six months.⁴¹ A meta-analysis of four publications from five studies reported that data on patients with RBBB showed no favourable outcomes of CRT in patients with RBBB.⁴² In a recent *post hoc* analysis of the MADIT-CRT trial, patients with RBBB and a non-left anterior fascicular block showed improvement in left ventricular volumes and function. However, there was no difference in the three-year probability of death or HF admissions among those with RBBB or ICD only ($p=0.962$ and $p=0.374$).⁴³

At present, for those with non-LBBB with QRS >150 ms the indication remains as Class IIB for CRT device.⁷ Physicians and patients should be aware of the likely reduced benefit from CRT in patients with RBBB, and this should be factored into decision making. However, until more data are available it is too early to change guidelines.

Cardiac Resynchronisation Therapy and Patients with Mechanical Dyssynchrony

The hypothesis of CRT in narrow QRS with ventricular dyssynchrony cannot be neglected, albeit the evidence remains weak so far. Similar questions remained for patients with mechanical dyssynchrony and wide QRS – how do we select the right patients for CRT? Predictors of Response to Cardiac Resynchronization Therapy (PROSPECT), a prospective, multicentre, non-randomised study was unable to find a single echocardiographic measure of dyssynchrony through which patient selection for CRT could be improved, even though up to 12 echocardiographic parameters had been used.⁴⁴ The recent study using apical rocking (ApRock) as a surrogate marker for left ventricular (LV) dyssynchrony in patients with wide QRS implies that patients with an increase in myocardial contractile reserve resulting in more dyssynchrony may derive a greater benefit from CRT. The Prospective Comparison of ARNI with ARB on Management of Heart Failure with Preserved Ejection Fraction (PARAMOUNT) trial suggested that dyssynchrony may play a pathophysiological role in HF patients with preserved LVEF.⁴⁵ However, strong evidence for the usefulness of echocardiography for patient selection in CRT is still lacking. Despite these well-presented and convincing data, the answer at this point in time is clearly that physicians will only implant CRT in those meeting

current guideline criteria, irrespective of echocardiographically measured dyssynchrony.

Safety and Cost-effectiveness Issues

With the current progress in research, the clinical applications for CRT are expanding. However, the cost, invasiveness and morbidity (e.g. infection) of CRT needs to be considered carefully.

Cost-effectiveness

The cost-effectiveness study from the European cohort of REVERSE indicated that CRT in mildly symptomatic HF has a similar cost-effectiveness ratio as in moderate to severe HF. Compared with CRT-off, 0.94 life years or 0.80 quality-adjusted life years (QALYs) were gained in the CRT-on group at an additional cost of €11,455, yielding an incremental cost-effectiveness ratio of €14,278 per QALY gained.⁴⁶

The 2007 Health Technology Assessment found that CRT pacemakers (CRT-P) and CRT-D devices reduce mortality and hospitalisations due to HF, improve quality of life and reduce sudden cardiac death in those with NYHA classes III and IV, and evidence of dyssynchrony. Compared with optimal medical treatment, the devices are estimated to be cost-effective at a willingness-to-pay (WTP) threshold of £30,000 per QALY; CRT-P is cost-effective at a WTP threshold of £20,000 per QALY.⁴⁷ However, the estimated net benefit from CRT-D is less than with the other two strategies, until the WTP threshold exceeds £40,160 per QALY.⁴⁷ The cost of CRT-P devices is already substantial; the addition of ICD will be more expensive since the latter technology involved will be more sophisticated. The hypothesised incremental benefits in survival from CRT-D would need to be balanced by possible increases in morbidity owing to, for example, device-related complications and inappropriate shocks.

Safety

CRT implantation is an invasive procedure and the implant often takes considerably longer than other pacemaker and ICD procedures, and is undertaken in a patient group at increased risk of haemodynamic compromise because of the underlying HF and poor LVEF. Overall peri-operative complication rates range from 4 % in more recent trials to as high as 28 % in earlier CRT trials.^{10,48}

The success rate of LV lead implantation in the REVERSE trial was 97 %, which is higher than those reported in previous studies.¹⁰ The rate of LV lead dislodgement was 8 % at one year. However, all the centres that participated in the REVERSE trial had a long experience with CRT implantations, suggesting that these procedures should be limited to centres with high volumes and excellence.

In the MADIT-CRT trial, serious device-related adverse events occurred with a frequency of 4.5 per 100 device-months in the CRT-D group and 5.2 per 100 device-months in the ICD-only group.¹² Although the adverse events were infrequent in both groups, they could not be completely ignored.

The rate of adverse events within 30 days after device implantation was significantly higher among patients in the CRT-D group than among those in the ICD group, in the RAFT study. There were 118 device- or implantation-related complications among the 888 patients receiving CRT-D, as compared with 61 of 899 patients in the ICD group ($p<0.001$).¹³ The adverse events reported were consistent with

the rates in other studies.^{48,49} LV lead dislodgement and an increased rate of infection remain significant problems. Although many of these adverse events did not have substantial long-term consequences, they may prolong hospitalisation.

With the increasing number of CRT device implantations, infection becomes a major challenge that an implanting physician has to face. The first large prospective study analysing both incidence and prevalence of CRT device-related infection showed that the risk of CRT infection is twice that of a standard pacemaker implant risk. The prevalence was close to 4.3 % at 2.6 years, an incidence of 1.7 % per annum.⁵⁰ Four independent predictive factors were identified:

- procedure time (p=0.002);
- dialysis (p=0.0001);

- re-intervention (p=0.006); and
- procedure type (CRT-D versus other procedures; p=0.01).⁵⁰

These factors should be considered carefully in the evaluation of patients selected for CRT implantation.

Conclusion

CRT has demonstrated favourable survival and symptom benefits in prior trials, especially those with highly symptomatic HF, LVEF ≤ 35 % and QRS ≥ 120 ms. The issue of whether CRT might be extended to other patient populations has been raised. Ongoing clinical randomised trials will provide stronger evidence for any potentially new indications. Considering the cost and safety issues of CRT, one has to be cautious of translating all the trial findings into the wider and routine use of CRT. ■

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