Effect of cardiac resynchronization therapy on quality of life: the best gets the least

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This editorial refers to ‘Effect of cardiac resynchronization therapy and implantable cardioverter defibrillator on quality of life in patients with heart failure: a meta-analysis’ by S. Chen et al., on page 1602

Heart failure (HF) is a syndrome that poses a substantial clinical and economic burden.1 Frequently, life-threatening ventricular arrhythmias may also accompany this condition.1 In the past, two large randomized clinical trials (RCTs), MADIT II (Multicenter Automatic Defibrillator Implantation Trial), and SCD-HeFT (Sudden Cardiac Death in Heart Failure Trial),2,3 have demonstrated that implantable cardioverter-defibrillator (ICD) therapy produces a significant reduction in total mortality when used for primary prevention in patients at risk for sudden cardiac death. Although ICDs reduce the risk of life-threatening ventricular arrhythmias, they have no effect on ventricular structure and function, and underling cardiomyopathy hence remains unchanged.

Biventricular pacing, introduced into clinical practice in the early 1990s, has become an accepted therapeutic modality for patients with HF in addition to optimum medical therapy (OMT). This novel pacing strategy, more generally defined cardiac resynchronization therapy (CRT), restores synchronized ventricular contraction, which consequently results in an improved pumping efficiency, enhanced left ventricular filling, and a reduction in the severity of mitral regurgitation. Cardiac resynchronization therapy has substantially modified the natural history of HF, exerting its physiological impact through favourable ventricular remodelling, with a reduction in left ventricular volumes and improvement in left ventricular ejection fraction (LVEF). This in turn translates into long-term clinical benefits such as improved symptoms, and functional capacity, with a concomitant reduction in hospitalization for HF and overall mortality.4 However, whether the combination of CRT and ICD (CRT-D) would bring any additional benefit over CRT or ICD alone has been a matter of debate for a long while.

In a systematic review of 4420 patients in 14 trials, McAlister et al.5 demonstrated a 22% relative risk reduction in all-cause mortality and a 37% relative risk reduction in HF hospitalization when CRT was added to OMT or to OMT plus ICD. However, the incremental benefit of combined CRT-D devices vs. ICD alone devices was uncertain since CRT had no effect on morbidity and mortality in trials which compared the devices. It has to be noted that this analysis was based on the aggregate data from several small trials (CONTAK-CD and MIRACLE-ICD for HF hospitalization; CONTAC-CD, MIRACLE-ICD, MIRACLE-ICD II, and RHYTHM-ICD for overall mortality), which limits the conclusion that can be drawn.5

Despite these observations, the international guidelines recommend CRT-D devices for HF patients who are eligible for CRT (LVEF ≤ 35%, New York Heart Association (NYHA) functional class III or IV despite OMT, QRS duration >120 ms, and sinus rhythm) and who would be otherwise candidates for ICD.1 However, at the time of the aforementioned systematic review, important questions remained regarding HF and CRT because nearly all participants (91%) in RCTs had NYHA class III or IV symptoms; thus the effect of CRT in patients with less severe symptoms was undefined. In the last few years, nearly 5000 patients have been included in three RCTs (REVERSE,6 MADIT-CRT,7 and RAFT8) assessing the impact of CRT on reverse remodelling, morbidity, and mortality in patients with mildly symptomatic NYHA class I–II HF.

The first two studies have shown reverse remodelling and a reduction in HF hospitalizations,6,7 but only data from RAFT (Resynchronization/defibrillation for Ambulatory heart Failure Trial) has convincingly demonstrated that CRT can also reduce mortality in patients with mildly symptomatic HF.8 Furthermore, although the results from REVERSE (RESynchronization reVErse Remodeling in Systolic left vEntricular dysfunction) and MADIT-CRT (Multicenter Automatic Defibrillator Implantation Trial with Cardiac Resynchronization Therapy) support the use of CRT in NYHA class II patients, evidence for CRT is less convincing in asymptomatic (NYHA class I) patients. The number of such patients enrolled in these trials was really small, thus the data remain inconclusive. However, the European Society of Cardiology extended its recommendation for CRT to include...
patients with mildly symptomatic HF who have QRS duration \( \geq 150 \text{ ms} \).

**Role of quality-of-life measurements in heart failure**

When evaluating the effects of CRT, functional capacity measured by changes in NYHA class, 6 min walk exercise capacity, and peak VO\(_2\), is the most frequently used indicator.\(^1\) However, HF is a chronic disease that often affects quality of life (QoL); therefore, when evaluating the effect of device therapy in HF, an improvement in QoL scores, measured by dedicated questionnaires, should also be an important clinical endpoint, probably as important as the traditional endpoints such as mortality and hospitalization, particularly when the effect of added CRT to ICD therapy is to be evaluated.

Quantitative studies on whether these implantable devices (CRT, ICD, or both) significantly affect QoL are scarce.

In a recent meta-analysis of 14 RCTs, CRT was associated with a reduction in scores (the greater the score, the worse the QoL) of the Minnesota Living with Heart Failure Questionnaire (MLHFQ) compared with control, OMT, or OMT plus ICD therapy \(4283\) patients; weighted mean difference (WMD): 6.56 points; confidence interval (CI) 4.08–9.04 points]).\(^10\) However, a substantial statistical heterogeneity was found \(I^2 = 72\%\) that was largely attributable to the symptomatic status at baseline. Patients with NYHA class I or II had better MLHFQ scores at baseline and did not show any appreciable improvement with CRT (WMD: 1.82; CI −0.77 to 4.41). In contrast, in patients with NYHA class III or IV, MLHFQ scores were poorer at baseline and significantly improved with CRT (WMD: 7.39; CI 4.87–9.91). Thus, symptomatic status at baseline strongly influences the effect of CRT on QoL in HF patients.

The clinical value of this approach assessed in several RCTs has been summarized in a systematic review by Chen et al.\(^11\) published in this issue of the journal.

The authors included RCTs that more specifically compared the efficacy of CRT-D therapy with ICD alone therapy in patients with HF. The primary outcome was the improvement of QoL. Consequently, four RCTs in 1655 patients were included. Overall, the results are in agreement with those of the previous meta-analysis\(^10\): the QoL score (using MLHFQ) significantly improved (WMD: \(-6.02; \text{CI} -10.56 \text{ to } -1.48\)) in patients in the CRT-D group compared with the ICD only group. However, the QoL benefit in the CRT-D group was not maintained when subset analysis was performed for patients with NYHA I–II (WMD: 0.19; CI −3.89 to 4.72). By contrast, patients with NYHA III–IV in the CRT-D group exhibited a significant improvement in QoL compared with the ICD alone group (WMD: \(-8.49; \text{CI} -13.39 \text{ to } -3.59\))

When all four studies were combined, a significant heterogeneity was detected, as a result of differences across studies. The relative magnitude of the heterogeneity was the inclusion of patients with different NYHA class. The overall benefit in QoL from CRT-D over ICD alone has been completely driven by improvement in patients with moderate or severe HF symptoms, who obtained the maximum benefit. The improvement in QoL was small in patients with mild HF symptoms or in asymptomatic patients, due to better QoL scores at baseline.

The results of this meta-analysis are an important complement to previous meta-analysis, testing the effect of CRT in patients with different levels of HF symptoms.\(^10\)–\(^12\)

Compared with controls (OMT or OMT plus ICD), CRT reduces all-cause mortality and HF hospitalizations in HF patients at different stages of the disease. The relative magnitude of the benefit on survival and hospitalization is greater in patients with left ventricular systolic dysfunction, prolonged QRS duration, and NYHA class III or IV symptoms; however, this benefit is still present, even if to a lesser extent, in patients with milder symptoms or with no symptoms of HF.\(^10\)

There is now conclusive evidence that the addition of CRT to OMT and ICD therapy reduces mortality and morbidity in patients with mild HF symptoms. The overall beneficial incremental effect of CRT is supported by the findings obtained from large studies such as REVERSE, MADIT-CRT,\(^6\)\(^,\)\(^7\) and mainly RAFT.\(^3\) The sequential monitoring boundary has been crossed with the publication of the RAFT study results, indicating the definite cumulative evidence, since the restrictive nature of the boundary design leaves no more doubt about the benefit.\(^13\) Before the publication of RAFT, the cumulative evidence available from the previous 11 studies were not sufficient for the boundary to be crossed.

However, the issue of QoL is more difficult to analyse. Randomized clinical trials are essential for testing the effect of therapy on clinical outcomes, and device trials are particularly challenging. Unfortunately, only a few trials with relatively small number of HF patients with the devices assessed the QoL. MADIT-CRT and RAFT have not yet produced reports on QoL.

Furthermore, the lack of benefit of CRT in terms of QoL in patients with NYHA class I or II symptoms may be explained by the fact that improvement in QoL scores is difficult to measure in these patients, and longer follow-up is probably required to show any benefit than in those with more symptomatic HF.

All these limitations may result in the underestimation of the true effect of CRT in patients with HF.

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**References**


Cramping of temporary pacemaker lead via femoral vein during laparoscopic nephrectomy: a rare condition

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A 73-year-old male patient was referred with right renal carcinoma and admitted for laparoscopic nephrectomy. Routine electrocardiography showed sinus rhythm, right bundle branch block, and left anterior fascicular block. The patient had history of dizziness. A temporary pacemaker was implanted via right femoral vein before surgery to prevent the occurrence of bradycardia (panel A). After surgery, the lead of a temporary pacemaker was fixed. An echocardiogram was performed to ensure position of the lead and to rule out entanglement of the lead in the chordae tendineae. Abdominal CT scan showed absence of right kidney and a high density imaging in the right renal vein (panel B1). This indicated that the titanium clip (panel B2, black arrow) of laparoscopic nephrectomy cramped the lead of the temporary pacemaker (panel B2, white arrow). During repeat laparoscopy, the titanium clip was found to cramp the renal vein, leading to cramping of the lead of the temporary pacemaker. The titanium clip was released and the lead was removed successfully. It is a rare complication in which a titanium clip cramps the lead of a temporary pacemaker. We conclude by suggesting that the subclavian vein pathway should be used to prevent such rare complications.

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