# Cardiac resynchronisation therapy for heart failure

As a result of the ageing population and improved medical care causing people to survive previously fatal conditions (eg, myocardial infarction), heart failure occurs more and more often in the elderly population.[1,2] Despite intensive medical therapy, people with heart failure often have a reduced quality of life and poor prognosis — a large proportion of people die within one year of diagnosis.[3] Cardiac resynchronisation therapy (CRT) by means of biventricular pacing is a fairly new procedure that improves patient quality of life (based on the Minnesota Living with Heart Failure Quality of Life Questionnaire), increases distance walked in six minutes, improves oxygen uptake, lowers New York Heart Association classification, decreases QRS duration, increases left ventricular ejection fraction, and increases peak oxygen consumption.[4,5]

**Dr Satnam Singh** Research Registrar, University of Aberdeen, Level 3, Polwarth building, Aberdeen, AB25 2ZD
**email** s.singh@abdn.ac.uk

Heart failure (HF), a common health problem, is a complex syndrome that can result from any structural or functional cardiac disorder that impairs the heart's ability to function efficiently as a pump, in the presence of adequate preload, to support physiological circulation.

About 900,000 people in England and Wales have the condition, of whom at least half have left ventricular systolic dysfunction (LVSD).[6,7] The incidence of HF increases with age: 1 in 35 aged 65–74 have the condition, increasing to 1 in 15 in people aged 75–84, and 1 in 7 in people aged 85 or older.[8]

In spite of intensive medical management with angiotensin converting enzyme inhibitors, angiotensin receptor blockers, β–blockers, aldosterone receptor blockers and digoxin, the prognosis of congestive heart failure has not improved significantly over the last two decades and the five-year survival for patients with New York Heart Association (NYHA) symptom class III/IV is still very poor.[2,9]

In parallel with advances in medications, recently there has been a growth of interest in alternative approaches to managing heart failure by targeting cardiac remodelling, a crucial factor in heart failure.

## What is CRT?

The concept behind cardiac resynchronisation therapy (CRT) is quite simple. CRT is for patients with moderate-to-severe heart failure who face the twin risks of terminal heart failure decompensation and death due to unanticipated ventricular tachyarrhythmias.[10,11]

Resynchronisation restores the normal coordinated pumping action of the ventricles by overcoming the delay in electrical conduction caused by bundle branch block. This is accomplished by means of a special pacemaker with three electrodes. One is placed in the right atrium, one in the right ventricle, and one in a vein on the surface of the left ventricle. This allows the CRT device to simultaneously stimulate the left and right ventricles and restore a coordinated, or "synchronous," squeezing pattern. This is sometimes referred to as "biventricular pacing" because both ventricles are electrically stimulated (paced) at the same time.

This reduces the electrical delay and results in a more coordinated and effective heart beat. Some potential CRT candidates also have a high risk of sudden cardiac death. For these patients, CRT incorporates a standard implantable cardioverter defibrillator (ICD) with a CRT pacemaker creating a "CRT-D" device (the "D" refers to defibrillation). However, about 30% of heart failure patients who receive CRT do not respond to treatment.[12]

**Table 1:** Studies in CRT (adapated from reference 14)

| *Trial* | *Follow-up period* | *No* | *Inclusion criteria* | *Results* |
|---|---|---|---|---|
| PATH-CHF, Stellbrink et al, 2000 | Six months | 41 | • NYHA class (III/IV)<br>• RS≥120 ms<br>• EF ≤35% | Improvements in 6 MWT, QoL, and NYHA class; less hospitalisations |
| MUSTIC Cecilia et al, 2002 | 12 months | 58 | • NYHA class (III/IV)<br>• QRS ≥120 ms<br>• EF ≤35%<br>• LVEDD ≥60 mm | Improvements in 6 MWT, QoL, NYHA class, Peak $VO_2$, and LV volume, MR; less hospitalisations |
| MIRACLE Abraham et al, 2002 | Six months | 453 | • NYHA class (III/IV)<br>• QRS ≥130 ms<br>• EF ≤35% | Improvements in 6 MWT, QoL, NYHA class, LVEF, LVEDD, and MR |
| CONTAK-CD Higgins et al, 2003 | Six months | 490 | • NYHA class (III/IV)<br>• QRS ≥120 ms<br>• EF ≤35% | Improvements in 6 MWT, QoL, NYHA class, LVEF, and LV volume |
| MIRACLE-ICD Young et al, 2003 | Six months | 555 | • NYHA class (III/IV)<br>• QRS ≥130 ms,<br>• EF ≤35% | Improvement in QoL and NYHA class |
| PATH-CHF II Stellbrink et al, 2000 | Six months | 86 | • EF ≤30%<br>• $VO_2$ ≤18<br>• NYHA ≥II | Improvements in 6 MWT, QoL, and NYHA class |
| COMPANION Bristow et al, 2004 | 12 months | 1,520 | • NYHA class (III/IV)<br>• QRS ≥120 ms<br>• EF ≤35% | Reduced all-cause mortality and hospital admissions |
| CARE-HF Cleland et al, 2005 | 29·4 months | 814 | • NYHA class (III/IV)<br>• QRS ≥120 ms<br>• EF ≤35% | Reduced mortality and morbidity, improved QoL, NYHA class, LVEF, and LVESV |

CARE-HF = Cardiac Re ynchronization Heart Failure; CONTAK-CD; CONTAK = Cardiac Defibrillator

COMPANION = Comparison of Medical Therapy, Pacing and Defibrillation in Heart Failure

LV = Left ventricular; LVEDD = Left ventricular end-diastolic dimension; LVEF = Left ventricular ejection fraction; LVESV = Left ventricular end-systolic volume

MIRACLE = Multicenter InSync Randomized Clinical Evaluation; MIRACLE-ICD = Multicenter InSync Implantable Cardioverter Defibrillator trial

MR = Mitral regurgitation; MUSTIC = Multisite Simulation in Cardiomyopathies

PATH-CHF = Pacing Therapies in Congestive Heart Failure trial

6 MWT = Six minute walk test.

### Patient selection

NICE published its guidance for CRT in heart failure in 2007.[13] Its recommendations for CRT with a pacemaker state that patients must:

- Have experienced or recently experienced NYHA class III–IV symptoms
- Be in sinus rhythm with either QRS ≥150 ms estimated by standard ECG or QRS 120–149 ms estimated by ECG and mechanical dyssynchrony that is confirmed by ECHO
- Have LVEF ≤35%
- Be receiving optimal pharmacological therapy.

The benefits of CRT in patients with atrial fibrillation have not yet been established. Thus, it is only recommended for patients who are in sinus rhythm.

## Evidence base

Multiple randomised clinical trials have demonstrated the safety and efficacy of CRT (Table 1).[14] They have been consistent in demonstrating improvement in quality of life, EF by reversing LV remodelling, severity of MR, the six minute walk test, and NYHA class.

The first landmark trial, PATH-CHF, that compared medical therapy with CRT showed significant reduction in morbidity and mortality with improvement in quality of life.[3] Since then, various trials have consistently shown the benefits of CRT in addition to optimised medical therapy. In fact in the RD-CHF trial, the patients who were previously paced for other indications and met the criteria for CRT, upgrading from right ventricular to biventricular pacing, saw a significant improvement in exercise tolerance.[15] Two of the largest trials (CARE-HF and COMPANION) consistently showed reduction in all-cause mortality and significant reduction in unplanned hospital admissions.[16]

However, approximately one-quarter to one-third of patients receiving CRT devices have been defined as non responders, meaning they have had no significant clinical or functional improvement after device implantation.[14]

It is important to evaluate the clinical response of CRT and ensure the optimal function of the device. This is usually done by assessing the clinical state of the patient and the ECG morphology based on the QRS duration and axis as well as the R-wave changes. The device is interrogated to ensure maximal use of biventricular pacing. Similarly, ECHO can be used for optimisation of atrioventricular and interventricular pacing timing.

## Complications

Pacemaker implantation is an invasive procedure, prone to a variety of possible types of failures and side effects, such as intraoperative pneumothorax, haematomas in the region of generator pocket, lead dislodgement, and functional problems (eg, pacemaker syndrome, pacemaker mediated tachycardia and crosstalk phenomenon).

**Box 1:** Key points

- CRT improves NYHA functional class, quality of life, improves LVEF, and reduces LV diameter and MR severity
- CRT reduces heart failure related hospitalisations and mortality
- 30% of patients selected to have CRT do not respond to this treatment
- The longer the conduction delays, as indicated by a QRS duration, the greater the benefit.

## Conclusion

CRT is an efficacious and cost effective therapy for patients with NYHA class III or IV heart failure despite optimal medical management, an LVEF of 35% or less, sinus rhythm, and ventricular dyssynchrony (currently identified by prolonged QRS duration). It improves ventricular function and remodelling, symptoms, and exercise capacity, while also reducing frequency of heart failure hospitalisations by 37% and death by 22%.[17]

Although no randomised controlled trial has evaluated CRT specifically in elderly patients, many of the patients included in the CRT trials were aged 70 and older. Data suggest that CRT is a safe and efficacious treatment of HF in geriatric patients. However, implantation of a CRT pacemaker (in particular the LV lead) can be technically challenging, and device malfunctions or lead problems (most frequently with the LV lead) are not infrequent. Even when lead placement is thought to be successful, CRT does not always restore mechanical synchrony.[17]

**Conflict of interest: none**

## References


1. Kannel WB, Plehn JF, Cupples LA. Cardiac failure and sudden death in the Framingham Study. *Am Heart J* 1988; **115**: 869–75
2. Khand A, Gemmel I, Clark AL, Cleland JG. Is the prognosis of heart failure improving? *J Am Coll Cardiol* 2000; **36**: 2284–86
3. Auricchio A, Stellbrink C, Sack S, Pacing Therapies in Congestive Heart Failure (PATH-CHF) Study Group, et al: Long-term clinical effect of hemodynamically optimized cardiac resynchronization therapy in patients with heart failure and ventricular conduction delay. *J Am Coll Cardiol* 2002; **39**: 2026
4. Cleland JG, Daubert JC, Erdmann E, et al. The effect of cardiac resynchronization on morbidity and mortality in heart failure. *N Engl J Med* 2005; **352**:1539
5. Ellenbogen KA, Wood MA, Klein HU. Why should we care about CARE-HF? *J Am Coll Cardiol* 2005; 20; **46**: 2199–203
6. Fox M, Mealing S, Anderson R, et al. The clinical effectiveness and cost-effectiveness of cardiac resynchronisation (biventricular pacing) for heart failure: systematic review and economic model. *Health Technology Assessment* 2007; **11** (47)
7. British heart foundation. Incidence of heart failure, January 2006. http://bit.ly/mLN53i (accessed 6 June 2011)
8. NICE. CG108 Chronic heart failure. http://guidance.nice.org.uk/CG108/Guidance (accessed 26 May 2011)
9. Albouaini K, Egred M, Rao A, et al. Cardiac resynchronisation therapy: evidence based benefits and patient selection. *Eur J Intern Med* 2008; **19**: 165–72
10. Jessup M, Brozena S. Medical progress. Heart failure. *NEJM* 2003; **348**: 2007–18
11. Donal E, Leclercq C, Linde C, Daubert JC. Effects of cardiac resynchronization therapy on disease progression in chronic heart failure. *Eur Heart J* 2006; **27**: 1018–25
12. Reuter S, Garrigue S, Barold SS, et al. Comparison of characteristics in responders versus nonresponders with biventricular pacing for drug-resistant congestive heart failure. *Am J Cardiol* 2002; **89**: 346– 50
13. NICE. Cardiac resynchronisation therapy for the treatment of heart failure. http://guidance.nice.org.uk/TA120 (accessed 26 May 2011)
14. Bax JJ, Abraham T, Barold SS, et al. Cardiac resynchronization therapy: Issues before device implantation. *J Am Coll Cardiol* 2005; **46**: 2153–67
15. Leclercq C, Cazeau S, Lellouche D, et al: Upgrading from right-ventricular pacing to biventricular pacing in previously paced patients with advanced heart failure: a randomized controlled study [abstract]. *Eur Heart J* 2003; **24**(Suppl): 364
16. Bristow MR, Saxon LA, Boehmer J et al (Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure (COMPANION) Investigators). Cardiac-resynchronization therapy with or without an implantable defibrillator in advanced chronic heart failure. *N Engl J Med* 2004; **350**: 2140
17. McAlister FA, Ezekowitz J, Hooton N, et al. Cardiac Resynchronization Therapy for Patients With Left Ventricular Systolic Dysfunction: A Systematic review *JAMA* 2007; **297**: 2502–14