Cardiac resynchronization therapy: the procedure and progress so far

Cardiac resynchronization therapy, also known as biventricular or multi-site pacing, has been shown to be an effective adjunct to conventional pharmacological therapy for advanced heart failure. This review considers the rationale and evidence for cardiac resynchronization and discusses the indications for its use in clinical practice.

More than 22 million people worldwide suffer from congestive heart failure (CHF). In the UK, it is estimated that the incidence of heart failure is 20–30 people per 1000 per year with an overall prevalence of 1% of the population. The prevalence of heart failure rises dramatically over the age of 65 years, with as many as 15% of individuals over the age of 75 years having evidence of systolic left ventricular impairment.

Despite advances in pharmacotherapy for heart failure, morbidity and mortality remains high. In the UK in 2001 there were 833 000 admissions to hospital for heart failure, a figure projected to rise to 1.5 million per year by 2015. The financial burden of heart failure on the NHS is also considerable, accounting for almost 2% of annual NHS expenditure; two thirds of which is spent on hospitalization (Stewart et al, 2002).

Pathophysiology of congestive cardiac failure

CHF is a complex, progressive syndrome with many causes; in the UK the most common causes are coronary artery disease, hypertension and dilated cardiomyopathy. In most patients, heart failure is caused by impairment of systolic left ventricular function, usually associated with left ventricular dilatation. Less appreciated is the importance and consequence of dyssynchronous myocardial contraction on cardiac performance and symptoms.

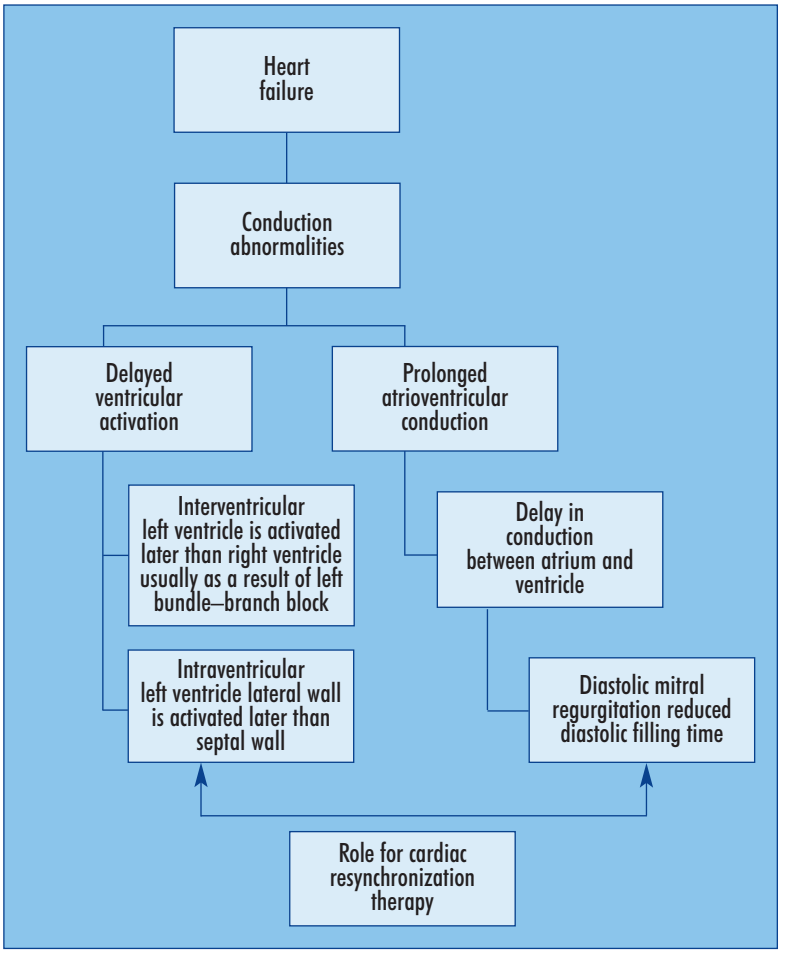
Dyssynchrony may be present at different levels in the failing heart; specifically between the atria and ventricles (atrioventricular; AV), within the ventricle (intraventricular) and between the ventricles (interventricular). One marker of ventricular dyssynchrony is left bundle–branch block (LBBB) on the surface electrocardiogram, which is present in approximately 30–50% of patients with advanced heart failure. LBBB causes premature depolarization of the interventricular septum and late activation of the lateral wall of the left ventricle (LV). This results in impaired systolic function, increased wall stress and functional mitral regurgitation (*Figure 1*), and is associated with reduced survival (Xiao et al, 1996; Shamim et al, 1999).

The concept of cardiac resynchronization therapy (CRT) is based on the hypothesis that patients with LV dyssynchrony and delayed ventricular activation might benefit from pacing from sites that accelerate left ventricular activation and thereby improve synchrony.

Procedure for cardiac resynchronization

Early studies of biventricular pacing used electrodes placed on the surface of the heart (epicardial). The modern technique is based on electrodes that have been specifically designed for percutaneous implantation. The procedure is performed under local anaesthetic from the subclavicular approach, via the subclavian or brachiocephalic veins.

Figure 1. Dyssynchrony and conduction abnormalities in congestive heart failure.



Dr Sanjay K Kohli *is Research Fellow in the Inherited Cardiovascular Disease Unit and* **Dr Perry Elliott** *is Senior Clinical Lecturer at The Heart Hospital, University College London, London W1G 8PH*

Correspondence to: Dr P Elliott

Electrodes are positioned in the right atrium and right ventricle (RV); a third is passed via the coronary sinus into a lateral vein on the surface of the LV (*Figure 2*).

In experienced hands, successful CRT implantation can be achieved in approximately 90% of patients. Lead-related complications (e.g. fracture, displacement or venous thrombosis) in the first year are <10%, and 30-day mortality associated with CRT implantation is <1%. Bleeding, sepsis, haematoma or damage to the nearby neurovascular bundle are rare.

Proposed mechanisms of action for CRT

Intraventricular

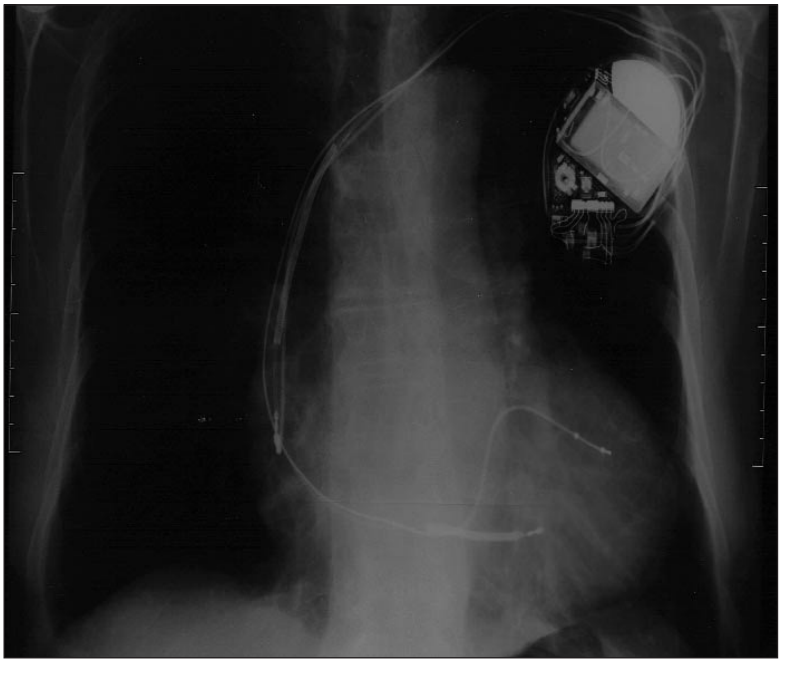
In patients with LBBB, dyssynchronous left ventricular contraction and relaxation cause a delay in activation of the left lateral wall compared to the septal wall, an increase in LV wall tension and an increase in LV pressure. Together, these phenomena result in impairment of left ventricular function and elevated filling pressures.

By synchronizing intraventricular activation and coordinating septal and free wall contraction, there is improvement in left ventricular systolic performance and a reduction left ventricular filling pressures (Yu et al, 2002). This effect on systolic performance occurs without increasing myocardial oxygen demand (unlike positive inotropic therapy) (Nelson et al, 2000a; Molhoek et al, 2004).

Interventricular delay

As well as intraventricular dyssynchrony, LBBB results in a delay in left ventricular activation in relation to the RV. Several studies have shown that much of the benefit of CRT results from correction of this delay. The mechanism by which this occurs is still speculative, but it may result from the alleviation of a phenomenon called diastolic ventricular interaction.

Figure 2. The chest X-ray shows a cardiac resynchronization device in the left pectoral region with electrodes in the right atrium, right ventricle and left ventricle.



Diastolic ventricular interaction refers to the situation in which volume and pressure changes in one ventricle have a direct effect on the volume and pressure of the other ventricle. It occurs because the pericardium resists or 'constrains' an increase in total cardiac volume. Therefore, for example, in severe right ventricular volume or pressure overload, the intrapericardial pressure rises and increases the external constraint on the LV resulting in increased filling pressures and a reduction in stroke volume.

A number of studies have shown that patients with CHF and high capillary wedge pressures have external constraint and that CRT can improve left ventricular contraction and filling by allowing the LV to activate before the RV (Bleasdale et al, 2004).

Atrioventricular dyssynchrony

Some patients with CHF have co-existent mitral regurgitation caused by dilatation of the mitral annulus. In some patients, mitral regurgitation begins in diastole thereby shortening the time available for left ventricular filling. It occurs when there is a delay between atrial systole and ventricular contraction (e.g. when there is a prolonged PR interval or when left ventricular contraction is delayed). In this situation, the atrial pressure starts to fall below the left ventricular pressure before ventricular systole, resulting in diastolic mitral regurgitation. CRT with an optimal AV delay can eliminate or reduce diastolic mitral regurgitation (Aurrichio et al, 1999;Kass et al, 1999).

Neurohumoral activation

Natriuretic peptide (atrial natriuretic peptide (ANP), brain natriuretic peptide (BNP)) levels are elevated in patients with CHF, and have been shown to be useful prognostic markers in heart failure (Molhoek et al, 2004). CRT results in a substantial decrease in plasma concentrations of BNP and ANP in parallel with the improvement in the clinical status of patients. Left ventricular and biventricular pacing also decrease sympathetic nerve activity compared with RV pacing in patients with left ventricular dysfunction regardless of QRS duration (Hamdan et al, 2000).

The evidence for cardiac resynchronization therapy

The safety and efficacy of CRT was established in a number of small observational studies (*Table 1*). These demonstrated the immediate benefits of CRT on haemodynamics, including improvements in cardiac output, increased systolic arterial pressure, reduced capillary wedge pressure and reduced myocardial energy consumption. The positive outcomes from these studies led to a number of single and double blind randomized control studies (*Table 2*).

In total, approximately 5000 patients have been studied. In the InSync Trial (Gras et al, 2002), New York

Heart Association (NYHA) class improved by one full functional class at 12 months. In the MUSTIC trial (Multisite Stimulation in Cardiomyopathies trial) the effects of biventricular pacing were evaluated in patients with sinus rhythm (MUSTIC SR) (Cazeau et al, 2001; Duncan et al, 2003) and with chronic atrial fibrillation (MUSTIC AF) (Leclercq et al, 2002). Following pacemaker implantation patients were randomly selected and paced for 12 weeks, followed by a period free of pacing for 12 weeks and then a further period of 12 weeks in patients' preferred mode.

During CRT in the sinus rhythm cohort there were statistically significant improvements in the timed walk distance (23%, $P<0.001$), quality of life score (32%, $P<0.001$) and NYHA class as well as fewer hospitalizations. Similar results were seen with the atrial fibrillation group but the statistical significance was less. The MIRACLE trial (Multicentre InSync Randomized Clinical Evaluation) (Young et al, 2003) was the first prospective randomized, parallel double blind study for CRT. Patients were randomized to CRT therapy or to conventional drug therapy without pacing for 6 months. At 6 months patients in the control group were given the opportunity to cross over to the CRT group. This study confirmed the results of the MUSTIC trial and demonstrated the persistence of the clinical benefit at 12 months.

The MIRACLE ICD trial (Young et al, 2003) was similar in design to the MIRACLE trial but with a biventricular implantable cardiac defibrillator (ICD). The results showed that heart failure patients with an indication for an ICD benefit as much from CRT as those heart failure patients without an indication for an ICD. The CONTAK CD trial was similar to the MIRACLE ICD study and provided additional data showing that CRT reduced left ventricular end-systolic and end-diastolic dimensions.

Table 1. Short-term studies with temporary left ventricle or biventricle pacing

Reference	No. of patients	Pacing modes compared	Endpoint
Cazeau et al (1996)	8	No pacing/RV/BiV	Haemodynamics
Blanc et al (1997)	23	No pacing/BiV/LV	Haemodynamics
Leclercq et al (1998)	18	AAI/RV/BiV	Haemodynamics
Saxon et al (1998)	11	No pacing/RV/LV/BiV	Echocardiography
Kass et al (1999)	18	No pacing/RV/LV/BiV	Haemodynamics
Auricchio et al (1999)	27	No pacing/RV/LV/BiV	Haemodynamics
Nelson et al (2000b)	22	No pacing/LV	Haemodynamics MRI
Nelson et al (2000a)	10	No pacing/LV	Haemodynamics ENERGETICS
Kerwin et al (2000)	13	No pacing/BiV	Radionuclide
Hamdan et al (2000)	13	RV/LV/BiV	SNA neurography

From Leclercq and Kass (2001). BiV = biventricle; LV = left ventricle; MRI = magnetic resonance imaging; RV = right ventricle; SNA = sympathetic nerve activity

Impact of CRT survival

The InSync, MUSTIC, MIRACLE and CONTAK CD trials were not designed or powered to determine the effect of CRT on all-cause or cause-specific mortality (St John Sutton et al, 2003). However, a meta-analysis of all these trials demonstrated a 51% reduction in the risk of death and a 29% reduction in hospitalization from worsening heart failure (Bradley et al, 2003).

Two large randomized control trials have reported significant benefits of CRT on prognosis. In the Comparison of Medical Therapy, Pacing and Defibrillation in Chronic Heart Failure Trial (COMPANION) (Bristow et al, 2000, 2004) there was reduc-

Table 2. Basic demographic criteria and results for the cardiac resynchronization therapy trials

Study	Reference	No. of patients	QRS (ms)	NYHA	LVEF <35%	ICD	Rhythm	Quality of life score	NYHA class	6-minute walk test	Exercise capacity VO2
MIRACLE	Abraham (2000); St John Sutton et al (2003); Young et al (2003)	524	>130	3/4	Yes	No	Sinus	+	+	+	+
MUSTIC SR	Cazeau et al (2001)	58	>150	3	Yes	No	Sinus	+	+	+	+
MUSTIC AF	Leclercq et al (2002)	43	>200	3	Yes	No	AF	+	+	+	+
PATH CHF	Breithardt et al (2002)	42	>120	3/4	Yes	No	Sinus	+	+	+	+
CONTAK CD	Thackray et al (2001)	581	>581	3/4	Yes	Yes	Sinus	+	+	+	+
MIRACLE ICD	Abraham (2000); St John Sutton et al (2003); Young et al (2003)	362	>130	3/4	Yes	Yes	Sinus	+	+	+	x
COMPANION	Bristow et al (2004)	1520	>120	3/4	Yes	No	Sinus	+	+	+	-
MIRACLE ICD II	Abraham (2000); St John Sutton et al (2003); Young et al (2003)	186	>130	2	Yes	Yes	Sinus	+	+	+	x
CARE HF	Cleland et al (2005)	800	>140	3/4	Yes	No	Sinus	+	+	x	x

Adapted from Abraham (2003). + = improvement, -- = no change, x = not assessed. AF = atrial fibrillation; ICD = implantable cardiac defibrillator; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association

tion in the primary composite end point (the time to death or hospitalization for any cause) for the biventricular ICD cohort and biventricular pacing cohort of 40% and 34% respectively, compared to optimal medical therapy alone. This reduction was only statistically significant in the ICD arm of the study.

In the Cardiac Resynchronisation Therapy Trial in Heart Failure (CARE-HF) (Cleland et al, 2005), patients were selected on the basis of severe left ventricular systolic dysfunction and pre-determined measures of cardiac dyssynchrony (*Table 3*) derived from conventional echocardiography. They were then randomized to medical therapy alone or for CRT without an ICD. CRT resulted in a 39% reduction in the primary end point (time to death from any cause or unplanned hospitalization for a major cardiovascular event) compared to the medically treated cohort.

The results of these two studies raised the question of whether patients with CRT indications should receive a biventricular pacemaker alone or a biventricular ICD. The fact that the hazard ratio for death in patients receiving CRT alone in the CARE-HF trial (0.64, 95% confidence interval (CI), $P<0.002$) was similar to that in the biventricular ICD arm of the COMPANION trial (0.64, 95% CI, $P<0.003$) suggests not.

However, the patient selection criteria differed in that only CARE-HF required echocardiographic demonstration of dyssynchrony, suggesting that this cohort derived greatest benefit from CRT alone. The interpretation of these data has been made all the more difficult given the findings in the SCDHeFT trial (Sudden Cardiac Death in Heart Failure Trial) (Bardy et al, 2005). This has shown that patients with severe heart failure and mild to moderate symptoms live longer when given an ICD alone (Bardy et al, 2005).

Current guidelines for CRT

In the UK, the National Institute for Clinical Excellence released guidelines on the use of CRT in heart failure in July 2003. These state that CRT should be considered in patients with drug refractory symptomatic heart failure (NYHA III/IV), a QRS duration of >120 ms, a left ventricular ejection fraction of <35% and a left ventricular end diastolic size of >6 cm.

Table 3. Patient selection criteria for the COMPANION and CARE-HF trials

Criteria	COMPANION	CARE-HF
New York Heart Association class	III or IV	III or IV
Left ventricular ejection fraction	≤ 35%	≤ 35%
QRS	≥ 120ms	≥ 120ms
PR	≥ 150ms	–
Left ventricular end diastolic dimension	–	≥ 30mm
Cardiac dyssynchrony	Not assessed	Assessed*

* For cardiac dyssynchrony two out of the following three must be present with a QRS between 120–149 ms: an aortic pre-ejection delay of more than 140 ms; an interventricular mechanical delay of more than 40 ms; delayed activation of the posterolateral left ventricular wall. CARE-HF = Cardiac Resynchronisation Therapy Trial in Heart Failure (Cleland et al, 2005); COMPANION = Comparison of Medical Therapy, Pacing and Defibrillation in Chronic Heart Failure Trial (Bristow et al, 2000, 2004)

Future issues in biventricular pacing

Left ventricular *vs* biventricular pacing

Several studies have shown that ventricular haemodynamics improve with left ventricular pacing alone rather than biventricular pacing, in spite of the fact that it often prolongs rather than shortens the QRS duration (Kass et al, 1999). These and other data showing that correction of the QRS does not correlate with either mechanical or haemodynamic improvement imply that the effect of CRT is dependent on improved coordination of the timing of regional contraction in the LV rather than electrical resynchronization itself.

Patients with heart failure and a narrow QRS

The phenomenon of ventricular dyssynchrony is not confined to patients with broad QRS complexes on the surface electrocardiogram (Turner et al, 2004a, b). Recent data suggest that at least some patients with a narrow QRS and ventricular dyssynchrony can benefit from CRT; randomized studies are currently in progress to assess this.

Patient selection and dyssynchrony criteria

CRT is unsuccessful in approximately 30% of patients. A number of non-invasive methods for assessing ventricular dyssynchrony (Nelson et al, 2000b; Breithardt et al, 2002; Pitzalis et al, 2002; Sogaard et al, 2002; Cazeau et al, 2003) (radionuclide ventriculography, two-dimensional and M-mode echocardiography, conventional and tissue Doppler) have been suggested as markers of likely success following CRT. However, the use of various definitions of a positive response to CRT means there is still no consensus on the optimal measures. Until such a consensus is reached, current published guidelines on patient selection should be used.

Conclusions

There is now substantial evidence for the use of CRT in advanced CHF. Ongoing research in the next few years should solve the outstanding issues related to patient selection, and will perhaps extend this promising therapy to new groups of patients, including asymptomatic patients and individuals with other myocardial diseases. **BJHM**

Conflict of interest: none.

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KEY POINTS

- The mortality and morbidity associated with congestive heart failure is high despite advances in pharmacological therapy.
- Left bundle–branch block (LBBB), a marker of left ventricle dyssynchrony, is present in 30% of patients with advanced heart failure.
- Cardiac resynchronization therapy in patients with LBBB improves symptoms and exercise tolerance, and reduces mortality.