Cardiac resynchronization therapy in chronic heart failure

Cardiac resynchronization devices are used with increasing frequency in the treatment of chronic heart failure. This review focuses on the pathophysiological basis of cardiac dyssynchrony, and the rationale for resynchronization therapy.

Chronic heart failure is an increasingly common cause of morbidity and mortality with escalating cost implications to health economies around the world. A central feature of disease progression is the process of left ventricular remodelling. Remodelling manifests as an increase in left ventricular volume and sphericity, resulting in functional mitral regurgitation, worsening myocardial function and an unfavourable clinical course. Neurohormonal activation of both the renin–angiotensin system and the sympathetic nervous system plays a central role in promoting the remodelling process. Consequently drug therapy with angiotensin-converting enzyme (ACE) inhibitors, beta-blockers, angiotensin receptor blockers and aldosterone receptor antagonists have improved survival from heart failure (CONSENSUS Trial Study Group, 1987; CIBIS-II Study Group, 1999; Pitt et al, 1999; Granger et al, 2003). Although clinical trials of these treatment modalities have demonstrated highly significant reductions in mortality, the absolute mortality reduction with ACE inhibitor therapy averages only 3–4%, and with adjuvant beta-blocker therapy, an additional 4–5%. Moreover, drug therapy presents inherent challenges including patient compliance, drug interactions and side effects. Heart failure patients are prescribed an average of six medications, but only 10% of individuals are fully compliant with drug therapy and approximately one third do not refill their prescriptions (English and Mastream, 1995).

An important pathophysiological consequence of impaired left ventricular systolic function, not directly addressed by drug therapy, is the development of ventricular conduction abnormalities, which can lead to a reduction in cardiac output by promoting poorly coordinated ventricular contraction (ventricular dyssynchrony). Cardiac resynchronization therapy with biventricular pacing devices has been developed to improve systolic function by resynchronizing intraventricular and interventricular contraction. Over the last decade, a number of clinical studies have been conducted to evaluate the safety and efficacy of cardiac resynchronization therapy in patients with moderate to severe chronic heart failure on optimal drug therapy. The main aims of this article are:

- To describe the pathophysiological consequences of conduction abnormalities in patients with chronic heart failure
- To outline the rationale for cardiac resynchronization therapy in these patients
- To summarize the evidence base for the treatment effects of cardiac resynchronization therapy
- To highlight the key limitations of previous cardiac resynchronization therapy studies and directions for future research.

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Conduction abnormalities in heart failure

Replacement of normal myocardium with fibrotic tissue is one of the morphological changes contributing to worsening systolic and diastolic function in the failing heart (Weber and Brilla, 1991). Electrical conduction through fibrotic tissue is much slower than through healthy myocytes, and fibrosis may therefore result in conduction system abnormalities. The normal conduction system modulates the rate of contraction, as well as the mechanical efficacy of atrial systole and contractile coordination of the ventricles. Disease of any one of these components can lead to suboptimal cardiac performance. Two conduction abnormalities commonly affecting patients with systolic heart failure are delayed ventricular activation and prolonged atrioventricular conduction.

Ventricular conduction delay

Ventricular conduction delay, represented by a prolonged QRS duration, is a progressive phenomenon and frequent finding in patients with moderate to severe heart failure (Wilensky et al, 1988). Notably, prolonged QRS duration, usually manifest as left bundle–branch block, has been shown to be an independent marker of prognosis in chronic heart failure patients (*Figure 1*). Under normal circumstances, ventricular activation proceeds rapidly from the interventricular septum down both bundle branches, the base of the right side of the heart

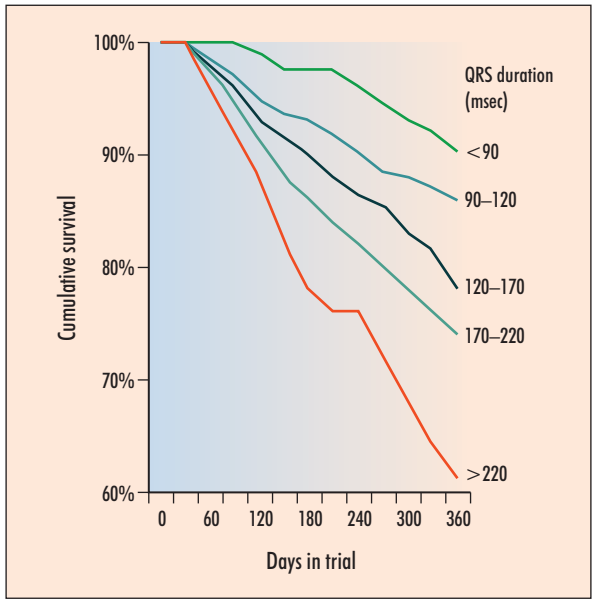


Figure 1. QRS complex and mortality. Adapted from Gottipaty et al (1999). Taken from the VEST study analysis of patients with New York Heart Association class II–IV, in whom 3654 electrocardiograms were performed. QRS duration was found to be an independent predictor of mortality.

being activated last. Left ventricular activation and contraction occurs synchronous with, or slightly earlier than, right ventricular contraction.

In the presence of left bundle–branch block, the normal sequence of activation is altered and delayed (Gerber et al, 2001); the interventricular septum is typically activated via the right bundle, activation then proceeding intramyocardially (and therefore more slowly) to depolarize the left ventricle (*Figure 2*). The lateral and posterior walls of the left ventricle tend to be activated last. However, left bundle–branch block is heterogeneous, and the surface electrocardiogram (ECG) correlates poorly with the pattern of ventricular activation as determined by endocardial mapping (Fung et al, 2004). Patients with left bundle–branch block on a surface ECG may in fact have intact left bundle conduction, with slow conduction at other sites. Conduction block may occur at various sites within the left ventricle, and may be functional, changing when the ventricle is paced (and therefore activated) from a different site (Aurricchio et al, 2004). These heterogeneous patterns of ventricular activation may be related to underlying ischaemic heart disease, areas of slow conduction reflecting segments of myocardium that are electrically and mechanically non-functional.

The effect of any delay in left ventricular activation is to prolong left ventricular systole, and to contribute to the loss of synchronous contraction of the right and left ventricles. The delayed activation of the posterolateral wall of the left ventricle may give rise to a 'slish-slosh' movement of blood in the ventricle, reducing efficiency of ventricular ejection, as the interventricular septum moves blood towards the lateral wall during the initial period of systole, the lateral wall pushing the blood back towards the septum in the latter part.

The prolongation of systole also delays isovolumic relaxation, and reduces the relative duration of diastole, thus leading to impaired left ventricular filling, further impairing cardiac output.

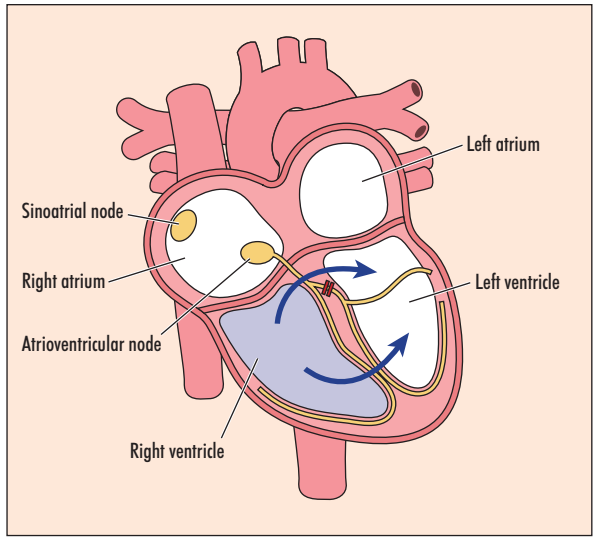
Atrioventricular conduction delay

When atrioventricular conduction is normal, atrial systole precedes, and is coordinated with ventricular systole, contributing to as much as 25–30% of cardiac output. Prolongation of the atrioventricular interval can lead to superimposition of atrial contraction on passive early ventricular inflow, ultimately leading to a reduction in ventricular filling and pre-load. An optimal atrioventricular delay is also important in maintaining mitral valve competence. Prolonged atrioventricular conduction effectively shortens the diastolic filling period, leading to relatively early atrial contraction followed by a pause before ventricular systole. During this delay before ventricular contraction, left atrial pressure falls as the atrium relaxes, resulting in pre-systolic mitral regurgitation. This may occur in addition to systolic mitral regurgitation already present in patients with heart failure, as a result of adverse left ventricular geometrical changes which cause mitral annular dilatation and tethering of the valve leaflets. Overall these abnormalities decrease preload and reduce the contribution of atrial systole, limiting net ventricular filling and ultimately resulting in a reduction in cardiac output.

Rationale for cardiac resynchronization therapy

It has previously been hypothesized that pacing with a short atrioventricular delay could be of benefit in heart

Figure 2. In the presence of left bundle–branch block, myocardial depolarization occurs via the right bundle branch and then intramyocardially, reaching the posterolateral left ventricular wall more slowly than in the presence of normal conduction.



failure, based on the principle that optimization of left ventricular filling, and therefore preload, may improve cardiac output. However, if atrioventricular delay is too short, the atrium will contract against a closed or closing mitral valve, resulting in cannon waves and loss of atrial contribution to cardiac output. Clearly, therefore, there is an optimal atrioventricular delay such that ventricular systole begins concurrently with the termination of atrial contraction.

The effect of short atrioventricular delay pacing was initially investigated using traditional dual chamber pacemakers, with leads positioned in the right atrium and right ventricular apex. In a subgroup of patients with chronic heart failure, dual chamber pacing has been shown to improve acute haemodynamics and longer-term outcome, primarily as a result of optimization of atrioventricular synchrony with an associated reduction in presystolic mitral regurgitation. However, right ventricular pacing leads to incoordinate ventricular contraction because of the non-physiological pattern of myocardial activation. Ventricular activation during right ventricular apical pacing is very similar to that seen in left bundle–branch block (Tse et al, 2002); stimulation of the apical portion of the right ventricle occurs first, followed by slow transeptal activation of the left ventricle resulting in intraventricular dyssynchrony. Interestingly, right ventricular pacing has been associated with a higher incidence of myocardial perfusion defects, regional wall motion abnormalities, altered regional myocardial blood flow and metabolism and an increase in the diastolic pulmonary artery pressure (Tse et al, 2002).

These effects tend to worsen cardiac haemodynamics, negating or outweighing the benefits of improved atrioventricular synchrony. It has been well demonstrated in large clinical trials that these deleterious effects of right ventricular pacing on regional and global left ventricular ejection fraction may result in the development of new or worsening heart failure (Sweeney et al, 2003). To overcome these difficulties, the ability to pace both the right and left ventricles has been developed, with the aim of not only restoring atrioventricular synchrony, but also interventricular and intraventricular synchrony.

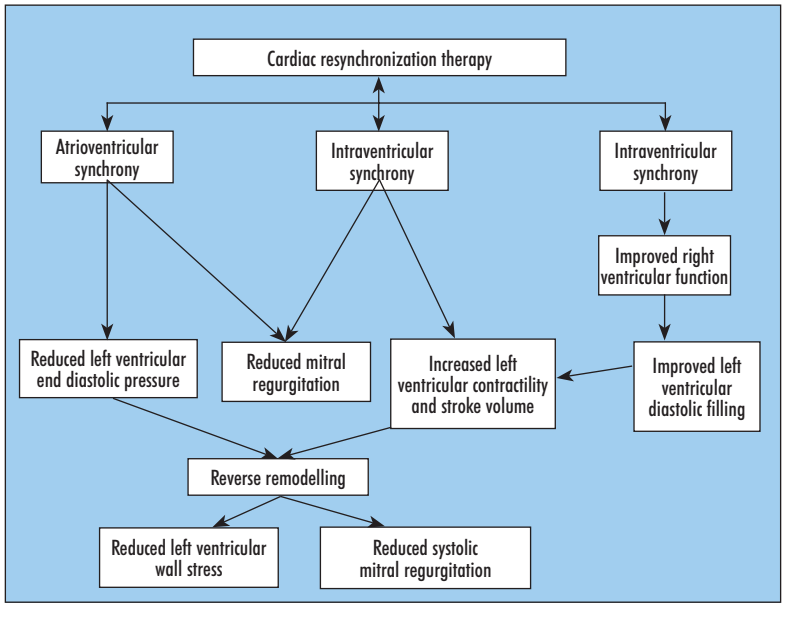
The technique of biventricular pacing entails the placement of pacing leads in the right atrium, right ventricle and left ventricle (via the coronary venous system), using a fully transvenous approach. The principle of biventricular pacing is to electrically address the mechanical ventricular dyssynchrony resulting from conduction delay, such that the right and left ventricles can be depolarized in a more physiological fashion, improving coordination of left ventricular contraction.

Correction of delayed left ventricular activation is achieved ideally by pacing at the site of latest activation in the left ventricle, usually the left lateral wall, thus creating a more symmetrical conduction and contraction pattern. The lateral wall is often chosen as the site for left ventricular pacing, both because coronary venous anatomy usually allows positioning of a lead over the lateral wall, and because comparison of pacing at anterior and lateral sites demonstrated a superior response with lateral site pacing (Butter et al, 2001). Studies performed in animal models, wherein ventricular dyssynchrony was induced either by right ventricular pacing, or by ablation of the left bundle branch, have shown that the area of the lateral wall from which pacing may stimulate appropriate resynchronization is in fact relatively large (Helm et al, 2007). In terms of measured cardiac output 70% or more of maximal response is seen within an area subtending an angle of 100° overlying the lateral, and to a degree the anterior and posterior, walls of the left ventricle.

These results may not be applicable to patients with ischaemic heart disease given the variability of conduction speed in areas of ischaemic myocardium. Electrical mapping studies have demonstrated that pacing in areas of slow conduction may preclude any haemodynamic benefit, whereas pacing in areas of normal conduction velocity was associated with a greater improvement in cardiac output (Lambiase et al, 2004). If a lead is implanted in an area of slow conduction, alteration of the timing of the pacing stimulus to achieve simultaneous activation of the largest possible bulk of myocardium can provide some haemodynamic improvement.

As with traditional dual-chamber pacing, cardiac resynchronization therapy also allows optimization of the atrioventricular interval for patients in sinus rhythm, but avoids the deleterious effects of right ventricular apical pacing. Theoretically, by means of optimized left ventricular filling and improved coordination of left ventricular contraction, biventricular pacing should result in an enhanced stroke volume and increased cardiac output (*Figure 3*).

Figure 3. The mechanism of beneficial effects seen following cardiac resynchronization.



Haemodynamic and mechanical effects of cardiac resynchronization therapy

Over the last decade, a number of studies have evaluated the safety and efficacy of cardiac resynchronization therapy in patients with moderate or severe heart failure, and QRS duration >120 msec as a marker of ventricular dyssynchrony. The initial studies were observational or mechanistic in design and enrolled small numbers of patients (Gras et al, 2002). These investigations provided support for the concept of cardiac resynchronization therapy by demonstrating improvements in symptomatic status, exercise capacity and cardiovascular haemodynamics; cardiac resynchronization therapy was shown to improve cardiac output, systolic pressure, maximal rate of pressure rise, myocardial contractility and left atrial pressure.

Echocardiographic studies have also shown that cardiac resynchronization therapy may induce a reversal of the remodelling process with reduction in left ventricular volume, an increase in ejection fraction and attenuation of mitral regurgitation (St John Sutton et al, 2003). Although chronic therapy is required to observe the improvements in left ventricular geometry, the global haemodynamic effect of cardiac resynchronization therapy is immediate in that haemodynamic parameters such as the maximal rate of pressure rise (dP/dtmax) or arterial pulse pressure are improved within a few beats of pacing, indicating a prompt increase in cardiac output (Kass et al, 1999). Importantly, unlike inotropic drug therapy, cardiac resynchronization therapy can improve cardiac contractility without increasing myocardial oxygen demand (Nelson et al, 2000). Heart rate variability may also improve, suggesting that cardiac resynchronization therapy may counteract the deleterious effects of the increased sympathetic drive associated with chronic heart failure (Adamson et al, 2003) and thereby interrupt the downward spiral of disease.

Randomized clinical trials of cardiac resynchronization therapy

At least ten randomized controlled trials have evaluated the role of biventricular pacing with or without implantable defibrillators in the treatment of patients with chronic heart failure (Lozano et al, 2000; Cazeau et al, 2001; Abraham et al, 2002; Aurricchio et al, 2002, 2003; Leclercq et al, 2002; Young et al, 2003; Bristow et al, 2004; Cleland et al, 2005; Doshi et al, 2005) (*Table 1*). The number of patients included in these trials have ranged from 41 to 1520 patients. Most trials used similar inclusion criteria of New York Heart Association (NYHA) class II–IV heart failure, left ventricular ejection fraction <35%, prolonged QRS duration (>120 ms), and most excluded patients with a bradycardia indication for a permanent pacemaker (with the exception of the Post-AV nodal ablation Evaluation (PAVE) study (Doshi et al, 2005) in which atrioventricular nodal ablation was performed). All patients were required to have been on stable medical therapy for heart failure before enrolment.

Although the majority of studies have exclusively assessed patients in sinus rhythm, the benefits of biventricular pacing have also been evaluated in patients with atrial fibrillation (Leclercq et al, 2002) and in those with right ventricular pacing following atrioventricular node ablation (Doshi et al, 2005). The earlier, smaller scale randomized studies showed significant improvements in the primary end points of NYHA functional class, exercise capacity, and quality of life in those treated with cardiac resynchronization therapy. An improvement in mean NYHA class of at least one class was consistently demonstrated, and in all studies in which the 6-minute walk test was the primary end point, a significant increase in mean walking distance, ranging from 20 to 40 metres, was noted in the cardiac resynchronization therapy group (*Table 1*). Moreover, peak oxygen uptake, which directly reflects maximal cardiac performance, was evaluated in six studies, all of which demonstrated an increase in peak oxygen uptake by 1–2 ml/kg/min with cardiac resynchronization therapy. Objective echocardiographic markers of left ventricular function and geometry were evaluated as secondary end points in five randomized studies; these reported varying degrees of improvement in left ventricular volumes, ejection fraction and mitral regurgitation.

Unfortunately, the small sample sizes in these earlier studies did not permit an assessment of the effects of cardiac resynchronization therapy on long-term clinical outcome. However, this was addressed by the publication of two larger scale, randomized trials designed specifically to evaluate the effect of cardiac resynchronization therapy on hospitalization and all-cause mortality. The Cardiac-Resynchronisation Therapy with or without an Implantable Defibrillator in Advanced Chronic Heart Failure (COMPANION) (Bristow et al, 2004) study was a controlled, multicentre, open label study on 1520 patients with NYHA class III–IV heart failure caused by ischaemic or non-ischaemic cardiomyopathy. Patients were randomly assigned to receive optimal drug therapy alone or in combination with a biventricular pacemaker or a biventricular pacemaker–defibrillator. The median duration of follow up was 16 months. When compared with drug therapy, cardiac resynchronization therapy with or without a defibrillator decreased the risk of the primary composite end point of all-cause death or hospitalization by at least 34% (P<0.002). A significant decrease in the secondary end point of all-cause death was seen only in the pacemaker–defibrillator group (36%, P=0.003).

The cardiac resynchronization – heart failure (CARE–HF) (Aurricchio et al, 2003) trial was a multicentre, randomized trial of 813 patients with NYHA class III–IV heart failure assigned to receive either optimal drug therapy alone or in combination with cardiac resynchronization therapy. Other inclusion criteria were QRS duration ≥ 120 msec, left ventricular ejection fraction <35% and left ventricular end diastolic dimension

≥30 mm (indexed to height). This study was unique in using echocardiographic markers of ventricular dyssynchrony in the selection process; patients with a QRS interval of 120–149 msecs were required to meet two of the three following criteria: an aortic preejection delay of >140 msec, an interventricular mechanical delay of >40 msec, or delayed activation of the posterolateral left ventricular wall. There was an equal proportion of patients with ischaemic and non-ischaemic cardiomyopathy. During a mean follow-up period of 29 months, the composite primary end point of all-cause death and hospitalization was significantly lower in the cardiac resynchronization therapy compared to the drug therapy group (39% *vs* 55% respectively, $P<0.001$). The secondary end point of all-cause death was also reached in fewer patients receiving cardiac resynchronization therapy (20% *vs* 30%, $P<0.002$). In addition, as compared with drug therapy, cardiac resynchronization therapy reduced interventricular dyssynchrony, end-systolic volume index, mitral regurgitation and N-terminal pro-brain natriuretic peptide level, as well as increasing ejection fraction.

Primarily as a result of these studies, the American Heart Association/American College of Cardiology and European Society of Cardiology guidelines (Hunt et al, 2005; Swedberg et al, 2005) for the management of chronic heart failure have been updated and now strongly recommend the use of cardiac resynchronization therapy in chronic heart failure patients with the following characteristics: sinus rhythm, QRS duration ≥120 msec, ejection fraction ≤35%, NYHA class III–IV symptoms, ischaemic or non-ischaemic aetiology, and optimal medical therapy.

Non-response to cardiac resynchronization therapy

Despite the demonstrated benefits of cardiac resynchronization therapy, it has been observed that about 20–30%

Table 1. Summary of randomized cardiac resynchronization therapy trials

Study	Inclusion criteria	Number	Results
Pacing therapies in congestive heart failure (PATH-CHF) (Auricchio et al, 2002)	NYHA class III–IV; QRS>120 ms Sinus rate ≥55 beats/min PR ≥150 ms	41 Follow up: 12 months	Improved exercise capacity, functional status and quality of life, little difference between biventricular pacing *vs* left ventricular pacing alone
PATH-CHF II (Auricchio et al, 2003)	NYHA class II–IV; LVEF≤30%; QRS≥120 ms optimal therapy for heart failure, implantable cardioverter defibrillator patients may be included	89	Improved exercise tolerance and quality of life
Multisite stimulation in cardiomyopathy sinus rhythm (MUSTIC SR) (Cazeau et al, 2001)	NYHA class III; LVEF<35% LVEDD>60 mm QRS≥150 ms; 6-min walk<450 m	67 Follow up: 12 months	Improved 6-min walk, peak oxygen consumption, quality of life, and NYHA class, reduced hospitalizations, active pacing preferred in 85% of patients, decreased mitral regurgitation
Multisite stimulation in cardiomyopathy atrial fibrillation (MUSTIC AF) (Leclercq et al, 2002)	NYHA class III; LVEF<35%; LVEDD>60 mm slow ventricular rate necessitating ventricular pacing; QRS≥ 200 ms during ventricular pacing; 6-min walk<450 m	59 Follow up: 12 months	Improved 6-min walk, peak oxygen consumption, quality of life, and NYHA class, reduced hospitalizations, decreased mitral regurgitation
Multicentre InSync randomized clinical evaluation (MIRACLE) (Abraham et al, 2002)	NYHA class III–IV; LVEF≤35% LVEDD ≥55 mm; QRS≥130 ms stable optimal medical therapy	453 Follow up: 6 months	Improved NYHA class, 6-min walk, quality of life, LVEF, ventricular volumes, mitral regurgitation, peak oxygen consumption, reduced hospitalizations
Cardiac resynchronization in heart failure (CARE-HF) (Cleland et al, 2005)	NYHA class III–IV; LVEF≤35% LVEDD ≥30 mm/m (height); QRS≥150 ms or QRS≥120 ms+ echocardiographic criteria of dyssynchrony Stable optimal medical therapy	813 Follow up: mean 29.4 months	CRT reduced intra-ventricular mechanical delay, end systolic volume index, area of mitral regurgitant jet, increased LVEF, improved symptoms and quality of life and reduced risk of death
Post AV nodal ablation evaluation (PAVE) (Doshi et al, 2005)	NYHA class I–III; post atrioventricular nodal ablation for atrial fibrillation; 3 months of stable medical therapy; capable of 6-min walk but not distance >450 m	652 Follow up: 6 months	Improved LVEF and 6-min walk with biventricular pacing, improvement more in those with impaired systolic function
Muticentre InSync randomized clinical evaluation-implantable cardioverter defibrillator (MIRACLE ICD) (Young et al, 2003)	NYHA class III–IV LVEF ≤35% QRS ≥130 ms implantable cardioverter defibrillator indication	364 Follow up: 6 months	Improved quality of life, NYHA class and exercise capacity, CRT-D safe to use
VENTAK CHF/ CONTAK CD (Lozano et al, 2000)	NYHA class II–IV; LVEF ≤35% QRS ≥120 ms; implantable cardioverter defibrillator indication stable optimal medical therapy	490 Follow up: 6 months	Primary end point not met, improvement in peak oxygen consumption, 6-min walk; changes in quality of life and functional class in NHYA class III–IV patients; improvement in LVEF and reduction in LVEDD/ LVESD dimensions
Comparison of medical therapy pacing and defibrillation in heart failure (COMPANION) Trial (Bristow et al, 2004)	NYHA class III–IV; LVEF <35% QRS >120 ms; PR >150 ms no indication for pacemaker or implantable cardioverter defibrillator	1120	Stopped early because of reduced all-cause mortality and hospitalization with CRT, reduced all-cause mortality with CRT-D

CRT = cardiac resynchronization therapy; CRT-D = cardiac resynchronization therapy with internal defibrillator; LVEDD = left ventricular end diastolic dimension; LVEF = left ventricular ejection fraction; LVESD = left ventricular end systolic dimension; NYHA = New York Heart Association.

of patients with chronic heart failure and a prolonged QRS duration fail to respond to treatment. It is now recognized that one of the prime reasons behind lack of response to cardiac resynchronization therapy resides in the fact that a prolonged QRS duration may not reflect mechanical left ventricular dyssynchrony in a significant minority of patients (Kass, 2003). Evaluation of the relationship between QRS duration and intraventricular dyssynchrony using echocardiographic tissue Doppler imaging, has shown an absence of significant dyssynchrony in 30–40% of patients with QRS duration ≥120 msec (Ghio et al, 2004). Conversely, about 30–50% of patients with chronic heart failure and a narrow QRS complex may have evidence of mechanical dyssynchrony (Ghio et al, 2004). Consequently, the surface ECG may not be the optimal marker to select candidates for cardiac resynchronization therapy and non-invasive imaging techniques to directly assess dyssynchrony might be superior both for clinical purposes and future research. This notion is supported by the fact that many studies have shown that echocardiographic criteria for left ventricular dyssynchrony predict response to cardiac resynchronization therapy more consistently than QRS duration (Bax et al, 2005). Indeed, there is often no significant difference in baseline QRS duration in responders *vs* non-responders to cardiac resynchronization therapy. Furthermore, the only study to show a significant reduction in the end point of all-cause death (CARE-HF) (Leclercq et al, 2002) used not only QRS duration, but also echocardiographic criteria of mechanical dyssynchrony to enhance patient selection.

Besides the presence of left ventricular dyssynchrony, other important factors contribute to the response to cardiac resynchronization therapy. Studies using tissue Doppler imaging have shown that the site of latest mechanical activity varies considerably among individuals and therefore appropriate pre-procedural echocardiographic selection of the pacing site may be expected to maximize the beneficial effect of cardiac resynchronization therapy. In practice, however, it is often not possible to place the left ventricular lead in the optimal position for reasons that relate to variations in coronary venous anatomy and technical aspects of the procedure.

Another factor that seems to be associated with non-response to cardiac resynchronization therapy is the lack of myocardial viability in the target region for left ventricular lead placement. A study showed that cardiac resynchronization therapy did not reduce left ventricular dyssynchrony in patients with transmural posterolateral scar tissue and therefore did not provide a beneficial therapeutic effect (Bleeker et al, 2006). A further study showed that the extent of myocardial viability assessed by perfusion scores derived from myocardial contrast echocardiography predicted the response to cardiac resynchronization therapy in ischaemic cardiomyopathy over and above the assessment of dyssynchrony by tissue Doppler imaging (Hummel et al, 2005). Finally, following insertion of the biventricular pacing device, programmable pacemaker parameters are often left at default settings. They may, however, be customized to provide the best haemodynamic response to cardiac resynchronization therapy on an individual basis. This optimization can be readily performed by determining the V–V offset (time interval between right and left ventricular pacing stimuli) associated with the highest stroke volume derived by echocardiography. In selected patients, this may offer a better chance of a successful therapeutic response to cardiac resynchronization therapy.

Future directions

In view of the invasive nature of cardiac resynchronization therapy, and the potential for complications related to implantation, the issue of non-response is of both clinical and economic importance. Clinical studies suggest that echocardiographic criteria for left ventricular dyssynchrony are good predictors of response to cardiac resynchronization therapy. The predictors of response to CRT (PROSPECT) trial has assessed the role of a variety of echocardiographic measures in the prediction of response to cardiac resynchronization therapy, and is due to report shortly.

Atrial fibrillation is common in patients with heart failure, but there is little data regarding the efficacy of cardiac resynchronization therapy in these patients. Limited data suggest that benefit does exist, provided heart rate is closely controlled to optimize the use of biventricular pacing (Delnoy et al, 2007). Ablation for atrial fibrillation has been shown to improve cardiac function in patients with heart failure (Hsu et al, 2004), and may be combined with cardiac resynchronization therapy in the future to optimize left ventricular performance in selected patients.

Advances in pacing technology are anticipated, including multi-polar pacing leads which allow pacing to be initiated from one of several electrodes, providing a wider range of options for optimization of pacing parameters. Biological pacemakers have been produced in animal models, either by transplant of cells with intrinsic pacemaker activity directly into the heart, or by genetic manipulation of existing cardiac cells to produce intrinsic pacemaker activity. This technology is likely to expand further into the field of cardiac resynchronization.

KEY POINTS

- Cardiac resynchronization therapy can provide symptomatic and prognostic benefit in addition to standard medical therapy in a selected subset of heart failure patients.
- The 12-lead electrocardiogram has traditionally been used to assess for the presence of dyssynchrony.
- QRS duration does not necessarily correlate with the presence or absence of mechanical dyssynchrony.
- In the future more refined measures of dyssynchrony may enable better selection of patients to receive cardiac resynchronization.

As cardiac resynchronization therapy evolves, selection criteria will be refined to target those most likely to benefit. The benefit of cardiac resynchronization therapy in patients with evidence of mechanical dyssynchrony but a normal QRS duration, and in those with stress-induced rather than resting mechanical dyssynchrony, are issues that will require specific investigation. **BJHM**

Conflict of interest: none.

Abraham WT, Fisher WG, Smith AL et al (2002) Cardiac resynchronisation in chronic heart failure. *N Engl J Med* **346:** 1845–53

Adamson PB, Kleckner KJ, van Hout WL et al (2003) Cardiac resynchronization therapy improves heart rate variability in patients with symptomatic heart failure. *Circulation* **108:** 266–9

Aurricchio A, Stellbrink C, Sack S et al (2002) Long term clinical effect of haemodynamically optimised cardiac resynchronisation therapy in patients with heart failure and ventricular conduction delay. *J Am Coll Cardiol* **39:** 2026–33

Aurricchio A, Stellbrink C, Butter C et al (2003) Clinical efficacy of cardiac resynchronisation therapy using left ventricular pacing in heart failure patients stratified by severity of ventricular conduction delay. *J Am Coll Cardiol* **42:** 2109–16

Aurricchio A, Fantoni C, Regoli F et al (2004) Characterization of left ventricular activation in patients with heart failure and left bundle-branch block. *Heart* **109:** 1133–9

Bax JJ, Abraham T, Barold SS et al (2005) Cardiac resynchronisation therapy: Part 1 – Issues before device implantation. *J Am Coll Cardiol* **46:** 2153–67

Bleeker GA, Kaandorp TA, Lamb HJ et al (2006) Effect of posterolateral scar tissue on clinical and echocardiographic improvement after cardiac resynchronisation therapy. *Circulation* **113:** 969–76

Bristow MR, Saxon LA, Boehmer J et al (2004) Cardiac resynchronization therapy with or without an implantable defibrillator in advanced chronic heart failure. *N Engl J Med* **350:** 2140–50

Butter C, Aurricchio A, Stellbrink C et al (2001) Effect of resynchronization therapy stimulation site on the systolic function of heart failure patients. *Circulation* **104:** 3026–9

Cazeau S, Leclercq C, Lavergne T et al for the Multisite Stimulation In Cardiomyopathies (MUSTIC) Study Investigators (2001) Effects of multisite biventricular pacing in patients with heart failure and intraventricular conduction delay. *N Engl J Med* **344:** 873–80

CIBIS-II Study Group (1999) The cardiac insufficiency bisoprolol study II (CIBIS – II): a randomised trial. *Lancet* **353:** 9–13

Cleland JGF, Daubert J-C, Erdmann E et al (2005) The effect of cardiac resynchronisation on morbidity and mortality in heart failure. *N Engl J Med* **352:** 1539–49

CONSENSUS Trial Study Group (1987) Effects of enalapril on mortality in severe congestive heart failure. *N Engl J Med* **316:** 1429–35

Delnoy PP, Ottervanger JP, Luttikhuis HO et al (2007) Comparison of usefulness of cardiac resynchronisation therapy in patients with atrial fibrillation and heart failure versus patients in sinus rhythm and heart failure. *Am J Cardiol* **99:** 1252–7

Doshi RN, Daoud EG, Fellows C et al (2005) Left ventricular-based cardiac stimulation post-AV nodal ablation evaluation (The PAVE Study). *J Cardiovasc Electrophysiol* **16:** 1–6

English M, Mastream M (1995) Chronic heart failure: public and private burden. *Crit Care Nurse* **18:** 1–6

Fung JWH, Yu CM, Yip G et al (2004) Variable left ventricular activation pattern in patients with heart failure and left bundle branch block. *Heart* **90:** 17–19

Gerber TC, Nishimura RA, Holmes Jr DR et al (2001) Left ventricular and biventricular pacing in chronic heart failure. *Mayo Clin Proc* **76:** 803–12

Ghio S, Constantin C, Klersy C et al (2004) Interventricular and intraventricular dyssynchrony are common in heart failure patients, regardless of QRS duration. *Eur Heart J* **25:** 571–8

Gottipaty VK, Krelis SP, Lu F et al (1999) The resting electrocardiogram provides a sensitive and inexpensive marker of prognosis in patients with congestive cardiac failure. *J Am Coll Cardiol* **33**(2): 145A Abstract 874–4

Granger CB, McMurray JJ, Yusuf S et al (2003) Effects of candesartan in patients with chronic heart failure and reduced left ventricular systolic function intolerant to angiotensin-converting-enzyme inhibitors: the CHARM-Alternative trial. *Lancet* **362:** 772–6

Gras D, Leclercq C, Tang A et al (2002) Cardiac resynchronisation therapy in advanced heart failure – the multicentre InSync clinical study. *Eur J Heart Fail* **4:** 311–20

Helm RH, Byrne M, Helm PA et al (2007) Three-dimensional mapping of optimal left ventricular pacing site for cardiac resynchronization. *Circulation* **115:** 953–61

Hsu LF, Jais P, Sanders P et al (2004) Catheter ablation for atrial fibrillation in congestive heart failure. *N Engl J Med* **351:** 2373–83

Hummel JP, Lindner JR, Todd Belcik J et al (2005) Extent of myocardial viability predicts response to biventricular pacing in ischaemic cardiomyopathy. *Heart Rhythm* **2:** 1211–17

Hunt SA, Abraham WT, Chin M et al (2005) ACC/AHA guideline update for the diagnosis and management of chronic heart failure in the adult – summary article; a report of the American College of Cardiology / American Heart Association Task Force on practice guidelines. *J Am Coll Cardiol* **46:** 1116–43

Kass DA (2003) Predicting cardiac resynchronisation response by QRS duration: the long and short of it. *J Am Coll Cardiol* **42:** 2125–7

Kass DA, Chen CH, Curry C et al (1999) Improved left ventricular mechanics from acute VDD pacing in patients with dilated cardiomyopathy and ventricular conduction delay. *Circulation* **99:** 1567–73

Lambiase PD, Rinaldi A, Hauck J et al (2004) Non-contact left ventricular mapping in cardiac resynchronisation therapy. *Heart* **90:** 44–51

Leclercq C, Walker S, Linde C et al (2002a) Comparable effects of permanent biventricular and right-univentricular pacing in heart failure patients with chronic atrial fibrillation. *Eur Heart J* **23:** 1780–7

Lozano I, Bocciardo M, Achtelik M et al (2000) Impact of biventricular pacing on mortality in a randomized crossover study of patients with heart failure and ventricular arrhythmias. *Pacing Clin Electrophysiol* **23:** 1711–12

Nelson GS, Berger RD, Fetics BJ et al (2000) Left ventricular or biventricular pacing improves cardiac function at diminished energy cost in patients with dilated cardiomyopathy and left bundle branch block. *Circulation* **102:** 3053–9

Pitt B, Zannad F, Remme WJ et al (1999) The effect of spironolactone on morbidity and mortality in patients with severe heart failure. *N Engl J Med* **341:** 709–19

St John Sutton MG, Plappert T, Abraham WT et al (2003) Effect of cardiac resynchronization therapy on left ventricular size and function in chronic heart failure. *Circulation* **107:** 1985–90

Swedberg K, Cleland J, Dargie H et al (2005) Guidelines for the diagnosis and treatment of chronic heart failure: executive summary (update 2005): The Task Force for the Diagnosis and Treatment of Chronic Heart Failure of the European Society of Cardiology. *Eur Heart J* **26:** 1115–40

Sweeney MO, Hellkamp AS, Ellenbogen KA et al (2003) Adverse effect of ventricular pacing on heart failure and atrial fibrillation among patients with normal baseline QRS duration in a clinical trial of pacemaker therapy for sinus node dysfunction. *Circulation* **107:** 2932–7

Tse HF, Yu C, Wong KK, Tsang V, Leung YL, Ho WY, Lau CP (2002) Functional abnormalities in patients with permanent right ventricular pacing. The effects of sites of electrical stimulation. *J Am Coll Cardiol* **40:** 1451–8

Weber KT, Brilla CG (1991) Pathological hypertrophy and cardiac interstitium: fibrosis and the renin-angiotensin – aldosterone system. *Circulation* **83:** 1849–65

Wilensky RL, Yudelman P, Cohen AI et al (1988) Serial electrocardiographic changes in idiopathic dilated cardiomyopathy confirmed at necropsy. *Am J Cardiol* **62:** 276–83

Young JB, Abraham WT, Smith AL et al (2003) Combined cardiac resynchronisation and implantable cardioversion defibrillation in advanced chronic heart failure. The MIRACLE ICD Trial. *JAMA* **289:** 2685–94