Cardiac resynchronization therapy

This article provides an overview of cardiac resynchronization therapy. At the end of the article, the reader should be familiar with the indications, risks and complications of cardiac resynchronization therapy and important areas of debate.

Heart failure is defined as the inability of the heart to pump sufficient oxygenated blood for the metabolic needs of tissues, despite an adequate filling pressure. Most cases of chronic heart failure are caused by left ventricular systolic dysfunction, characterized by breathlessness, fatigue and fluid retention. A feature of this condition is left ventricular remodelling, which is an adverse progressive change in left ventricular structure and physiology.

Chronic heart failure is increasing in prevalence as a result of higher life expectancy and improved treatment of medical conditions such as ischaemic heart disease. It is responsible for considerable morbidity and mortality (Cowie et al, 1997; Berry et al, 2001). An estimated 900 000 people in the UK have chronic heart failure, of which coronary heart disease is the most common cause (Fox et al, 2007). Approximately 40% die within 1 year of diagnosis (Cowie et al, 2000) and total annual mortality rates are roughly 30% (National Institute for Cardiovascular Outcomes Research, 2012).

Management of chronic heart failure

Chronic heart failure is managed with treatment of the underlying cause, lifestyle changes and pharmacological therapies. The key first-line medications are angiotensin-converting enzyme inhibitors and beta blockers. Angiotensin-receptor blockers can be used in cases of angiotensin-converting enzyme inhibitor intolerance (usually as a result of the side effect of cough with angiotensin-converting enzyme inhibitors). The beta blockers of choice with evidence base for use in heart failure are bisoprolol, carvedilol, metoprolol and nebivolol. Diuretics are used in cases of pulmonary congestion or peripheral oedema. Aldosterone antagonists (spironolactone and eplerenone) are added in patients with New York Heart Association (NYHA) class III or IV symptoms. Other second-line drug treatment options are available.

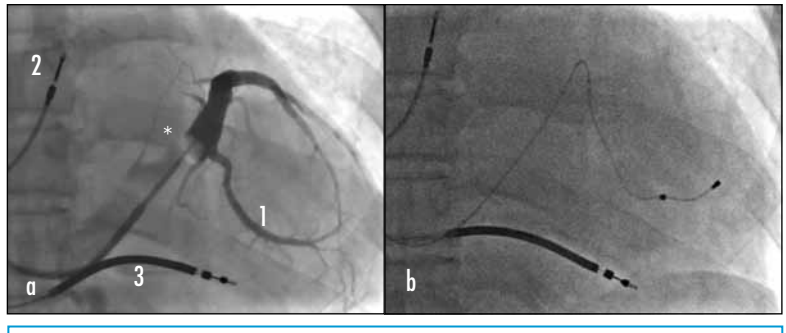
Cardiac resynchronization therapy should be considered a therapy to be offered once a patient is established on optimal medical therapy and provides additional support in selected patients with advanced heart failure.

What is cardiac resynchronization therapy?

A common feature of left ventricular systolic dysfunction is dyssynchronous contraction of the cardiac chambers, which exacerbates cardiac dysfunction. The rationale behind the development of cardiac resynchronization therapy was to improve cardiac mechanical efficiency by restoring synchrony. Atrioventricular dyssynchrony occurs when synchrony is lost between atrial and left ventricular contraction, leading to reduced ventricular filling and presystolic mitral regurgitation (mitral regurgitation occurring in late diastole). Dyssynchrony can also occur between ventricles (interventricular) and between segments within the left ventricle (intraventricular). Loss of coordination between right and left ventricles and within the left ventricle reduces the efficiency of systolic ejection of blood and can contribute to worsening of mitral regurgitation.

Cardiac resynchronization therapy involves implantation of a specialized pacemaker with usually an atrial lead and two ventricular leads (biventricular = right and left ventricle). Venous access is obtained by the cephalic, subclavian or axillary veins, typically using the Seldinger technique. The atrial and right ventricular leads are placed endocardially using standard methods. The left ventricular lead is placed epicardially into a tributary of the coronary sinus, which is accessed via the right atrium. Left ventricular lead placement is often the most challenging part of the procedure. There are a number of venous tributaries feeding into the coronary sinus. The optimal vein is usually a lateral or posterolateral tributary (*Figure 1*).

Figure 1. a. Balloon occlusive venography. Contrast has been injected into the coronary veins through a balloon-tipped catheter in the coronary sinus. The balloon (*) prevents contrast flushing back into the right atrium while the image is acquired. The target lateral vein is marked (1). An active fixation atrial lead (2) and right ventricular lead (3) are shown. b. Left ventricular lead in position. The left ventricular lead has successfully been placed in the target vein.



Dr V Cobb *is Cardiology Research Fellow and* **Dr M Thomas** *is Consultant Cardiologist at The Heart Hospital, UCLH, London W1G 8PH*

Correspondence to: Dr M Thomas (martin.thomas@uclh.nhs.uk)

The atrial and right ventricular leads are fixed to the endocardium either with the use of a helical screw-in mechanism ('active fixation', *Figure 2*) or with the use of projections at the tip of the lead that snag into irregularities on the endocardial surface ('passive fixation', *Figure 3*). There are advantages and disadvantages to both types of fixation and the choice usually depends on operator preference. Most left ventricular leads do not have an active fixation mechanism. Instead, the distal part of the lead has a selection of designs to enable passage and fixation of the lead into the chosen tributary. These include corkscrew and spiral shapes (*Figure 4*), low profile leads for smaller vessels and steerable tips.

Generators are produced in a variety of shapes and sizes (*Figure 5*). Generators with implantable cardioverter defibrillator capability tend to be a larger size (around 40 cc). The generator can be placed subcutaneously or (especially in very thin patients) under the pectoral muscle.

Figure 2. Active fixation mechanism at the lead tip. The helix is extended to screw in to the myocardium.

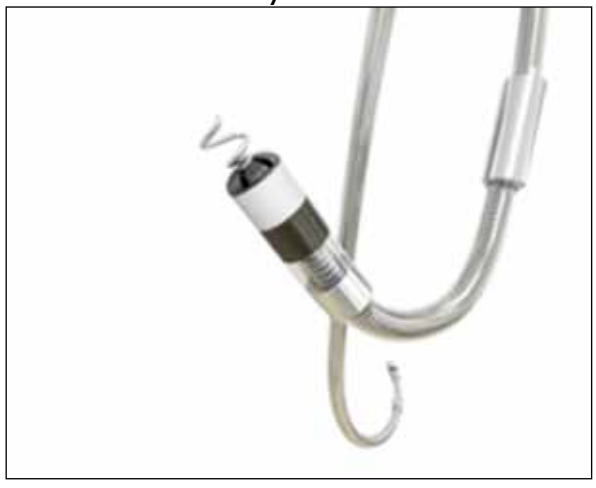


Figure 3. Lead tip showing projections at the lead tip (tines) for passive fixation to the endocardium.

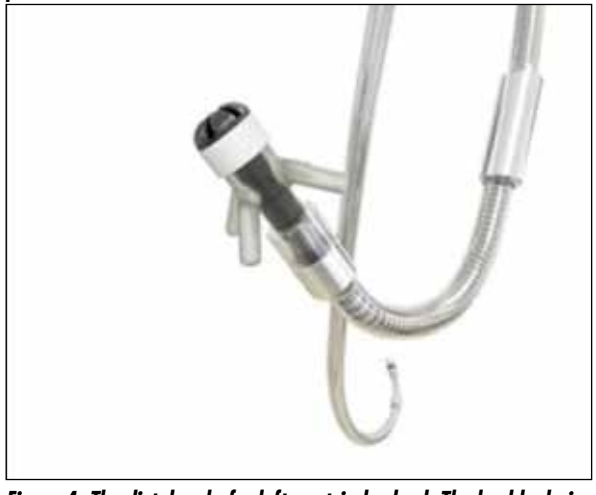


Figure 4. The distal end of a left ventricular lead. The lead body is shaped to a spiral to maintain stability once in the target vessel. This is one of several different designs.

What is the evidence for cardiac resynchronization therapy?

The evidence for cardiac resynchronization therapy is supported by large randomized controlled prospective trials. Cardiac resynchronization therapy improves cardiac function (Cleland et al, 2005), exercise capacity (Linde et al, 2002), heart failure symptoms and quality of life (Abraham et al, 2002). It has been shown to reverse deleterious ventricular remodelling (Yu et al, 2005; Ypenburg et al, 2008), reduce heart failure-related hospitalizations (Bristow et al, 2004) and prolong survival (Bristow et al, 2004; Cleland et al, 2005) and is now an established treatment for selected patients with chronic heart failure.

Which patients should be offered cardiac resynchronization therapy?

The class 1 indications for cardiac resynchronization therapy as recommended by the American Heart

Figure 5. Example of a cardiac resynchronization therapy with defibrillator (CRT-D) generator. Leads are inserted at the top of the device.

Association/American College of Cardiology (Tracy et al, 2012) and European Society of Cardiology (McMurray et al, 2012) are shown in *Table 1*.

The greatest evidence of benefit with cardiac resynchronization therapy, supported by randomized prospective trials, is found in patients with prolonged QRS duration ≥150 ms and left bundle–branch block on electrocardiogram. The aetiology of heart failure also appears important in predicting a good response. Patients with ischaemic cardiomyopathy are less likely to derive benefit than those with dilated cardiomyopathy, although aetiology of heart failure is not used as a criterion in the guidelines.

The areas of debate include the following groups:

QRS <150 ms

Patients with left bundle–branch block and QRS duration 120–149 ms will usually be offered a biventricular device provided they fulfil the other criteria for cardiac resynchronization therapy. Additional supportive evidence of mechanical dyssynchrony may be sought to decide suitability for cardiac resynchronization therapy, particularly where QRS duration is <120 ms. However, currently available mechanical measures of dyssynchrony are less reliable predictors of response compared with QRS duration. Electrical dyssynchrony (measured by a prolonged QRS) does not always correlate with mechanical dyssynchrony (measured by imaging methods with good temporal resolution such as echocardiography and magnetic resonance imaging). Not all patients with broad QRS will show mechanical dyssynchrony and some patients with narrow QRS will show mechanical dyssynchrony. The RethinQ trial (Beshai et al, 2007) showed no benefit of cardiac resynchronization therapy in patients with NYHA class III symptoms, left ventricular ejection fraction ≤35% and narrow QRS (≤130 ms) despite echocardiographic evidence of mechanical dyssynchrony.

Non-left bundle–branch block morphologies

The RAFT (Tang et al, 2010) and MADIT-CRT (Moss et al, 2009) trials showed no benefit of cardiac resynchronization therapy in patients with non-left bundle–branch block morphology conduction delay. Even with significantly prolonged QRS, there is no robust evidence to support the implantation of biventricular devices in non-left bundle–branch block morphologies. However, patients fulfilling other criteria for cardiac resynchronization therapy who also require a standard pacemaker may still be considered for cardiac resynchronization therapy because chronic right ventricular pacing can have a deleterious effect on cardiac function.

Mild symptoms

Although no mortality benefit with cardiac resynchronization therapy was shown in patients with NYHA class I or II symptoms in the MADIT-CRT and REVERSE trials, some argue that long-term benefit is still to be gained by implanting a biventricular device before severe symptoms develop.

Table 1. Class 1 indications for cardiac resynchronization therapy

American Heart Association/ American College of Cardiology (Tracy et al, 2012)	On optimal medical therapy	
	NYHA class II–III or ambulatory class IV symptoms	
	Left ventricular ejection fraction ≤35%	
	In sinus rhythm	
	Left bundle–branch block morphology on electrocardiogram	
	QRS duration ≥150 ms on electrocardiogram	
European Society of Cardiology (McMurray et al, 2012)	For patients with NYHA class III or ambulatory class IV symptoms	On optimal medical therapy
		Left ventricular ejection fraction ≤35%
		In sinus rhythm
		Left bundle–branch block morphology on electrocardiogram
		QRS duration ≥120 ms on electrocardiogram
		Expected to survive with good functional status for >1 year
	For patients with NYHA class II symptoms	On optimal medical therapy
		Left ventricular ejection fraction ≤30%
		In sinus rhythm
		Left bundle–branch block morphology on electrocardiogram
		QRS duration of ≥130 ms on electrocardiogram
		Expected to survive with good functional status for >1 year

NYHA = New York Heart Association

Atrial fibrillation

Although a large proportion of people with heart failure have atrial fibrillation, most important cardiac resynchronization therapy trials have excluded them. Despite lack of strong trial evidence of benefit in this group, in real life many patients with atrial fibrillation are offered cardiac resynchronization therapy. Where cardiac resynchronization therapy is offered, it is important to ensure that rapidly conducted atrial fibrillation does not compromise biventricular pacing. In some cases atrioventricular node ablation is performed.

Defibrillator or pacemaker

The abbreviations CRT-P and CRT-D refer to the presence or absence of implantable cardioverter defibrillator capability in the biventricular system. CRT with implantable cardioverter defibrillator function is termed CRT-D (cardiac resynchronization therapy with defibrillator). CRT-P is the term used for devices with pacing function only (cardiac resynchronization therapy with pacemaker). Criteria for selection of patients for each type of device are beyond the scope of this article, but can be found in the American Heart Association and European Society of Cardiology guidelines (McMurray et al, 2012; Tracy et al, 2012).

Complications and risks of biventricular pacing

Biventricular pacing entails the same risks as conventional pacing, with additional risks associated with insertion of the left ventricular lead. The important or more frequent risks are shown in *Table 2*.

Table 2. Risks and complications of biventricular pacing

Periprocedural risks	Discomfort	
	Bleeding	
	Pneumothorax	
	Haemothorax	
	Pericardial effusion or tamponade	
	Arrhythmia	
	Renal failure	
	Complications associated with left ventricular lead placement	Coronary vein dissection
		Failure to implant the left ventricular lead
		Phrenic nerve pacing
Postprocedural risks	Venous thrombosis	
	Venous stenosis	
	Pocket haematoma	
	Infection	
	Lead displacement	
	Lead failure	
	Device migration	

Procedural complications include inadvertent puncture of lung, major vessels or the heart leading to pneumothorax, haemothorax and cardiac tamponade respectively. Manipulation of equipment within the heart can cause arrhythmia including asystole (caused by conduction system) trauma and ventricular tachycardia or ventricular fibrillation. When a biventricular device is implanted, many operators ensure that the right ventricular lead is implanted first so that the patient can be paced if he/she develops ventricular standstill during the procedure.

Pocket haematoma is more likely to occur in the short term after the procedure. It may be managed conservatively or in some cases require evacuation. Lead displacements occur in approximately 5% of cases and require either repositioning or replacement of the lead. The generator can also migrate and require repositioning. Infection is an important complication and usually mandates removal of the entire system, including the leads. Lead extraction is a technically difficult procedure with its own profile of serious risks and complications. Other important long-term risks are venous thrombosis or stenosis, which may lead to occlusion of the vessel and, in extreme cases, a superior vena cava syndrome. There are additional electrical complications associated with implanted devices that are beyond the scope of this article. Many of these can be resolved with tailored device programming.

With left ventricular lead implantation, coronary vein dissection is not uncommon. However, this usually results only in minor self-resolving tears or bleeds as the coronary venous system is at low pressure. Failure to place the left ventricular lead can occur even in experienced hands. Difficulties include inability to access the coronary sinus, venous tortuosity, venous narrowing and presence of valves. Options for lead placement are limited by the available venous tributaries to the coronary sinus and in some cases there are no suitable target veins. Even after successful lead placement in a target vessel, the operator may encounter further problems such as unacceptably high pacing thresholds, diaphragmatic stimulation from phrenic nerve pacing (the phrenic nerve passes over the left ventricle) or lead displacement. It is common for patients undergoing cardiac resynchronization therapy to have pre-existing renal impairment and large doses of iodinated contrast may be used for anatomical visualization during fluoroscopy to aid left ventricular lead implantation. In rare cases this will lead to requirement for temporary renal dialysis.

There are a number of options if left ventricular lead placement fails. In some cases a repeat attempt is successful. An alternative option is the surgical epicardial approach via thoracotomy. A transvenous endocardial approach is now also being explored, where the lead is placed inside the left ventricle. Some operators place two right ventricular leads with the aim of improving efficiency of contraction in the absence of a left ven-

tricular lead. There is some evidence to suggest that dual site or 'bifocal' right ventricular pacing can improve symptoms and may have a role in patients unsuitable for other cardiac resynchronization therapy strategies (Res et al, 2007).

A non-exhaustive summary of complications and risks is shown in *Table 2*.

Responders and non-responders

Cardiac resynchronization therapy is an expensive, invasive therapy associated with risks and complications described above. It is therefore particularly desirable from both a clinical and financial point of view for the maximum number of recipients to derive benefit. The 'non-responder rate' to this therapy is often quoted as being approximately 30%, although it may be greater than this because of a recognized placebo effect.

The concept of response *vs* non-response is problematic. There is no single, reliable outcome measure to define response and a patient may respond in one measure and not in another. Furthermore, it is not possible to predict with certainty what the trajectory of the patient's condition would have been without the device. A patient with stable symptoms may have otherwise deteriorated without the device, yet be considered a non-responder because the symptoms did not improve.

There are many studies investigating ways to improve the responder rate and these include refining selection of candidates for cardiac resynchronization therapy, targeting left ventricular lead placement more effectively and optimizing device function after implantation.

Cardiac resynchronization device programming

After implantation of a cardiac resynchronization device, programming is tailored to each patient's requirements. The aim is to achieve as close to 100% ventricular pacing as possible to gain most benefit. *Figure 6* compares three electrocardiogram samples recorded in a single patient with a biventricular device at different programmed settings. There is clear QRS narrowing with biventricular pacing in this patient.

Modern devices can be programmed to control timing of both the atrioventricular delay and interventricular delay, with a view to optimizing the respective timing of contractions between different chambers and achieve the best haemodynamic response. This form of fine-tuning is not routinely performed in many centres. Robust evidence for offering this intervention to all patients with biventricular devices is lacking, although it may benefit some patients with suboptimal response to cardiac resynchronization. Echo-guided optimization is considered the gold standard method and requires staff trained in cardiac sonography and device programming. Multiple echocardiographic measurements are performed at different settings and the device programmed according to the atrioventricular and interventricular delays that achieve the optimum result. Details of the variables measured are beyond the scope of this article but include Doppler-derived surrogates of cardiac output and assessment of transmitral flow.

Conclusions

Cardiac resynchronization therapy is a proven therapy for selected patients with chronic heart failure on optimal medical therapy. Although associated with some risks and complications, they are reduced in experienced hands and serious sequelae are rare.

Optimal candidate selection, strategies and targets for lead implantation and methods for optimal device programming remain under investigation. **BJHM**

Figures 2–5 *are reproduced courtesy of Boston Scientific Incorporated.*
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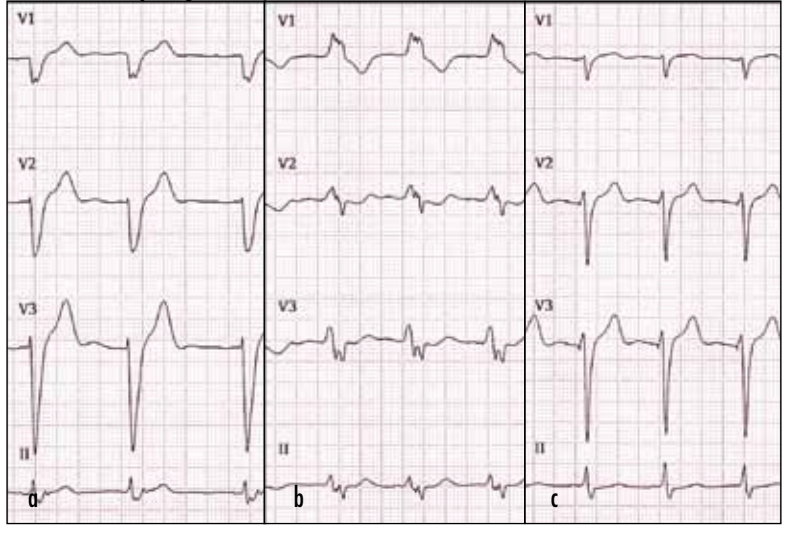
Figure 6. Leads V1-3 and II selected from 12 lead electrocardiograms performed in a single patient. The cardiac resynchronization device is programmed to pace in different configurations. a. No pacing (the patient's intrinsic rhythm). b. Left ventricular pacing. c. Biventricular pacing.



KEY POINTS

- Cardiac resynchronization therapy is a treatment offered to selected patients with heart failure on optimal pharmacological therapy.
- Although associated with some risks and complications, cardiac resynchronization therapy is a safe and effective therapy.
- Methods of maximizing responder rate are a current focus for research.

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