Advanced pacing techniques in congestive heart failure

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Abstract

Heart failure is an increasingly common condition for which device therapy, including the advanced pacing technique cardiac resynchronisation therapy, is becoming an accepted treatment. In this review we discuss the rationale, evidence base, indications, limitations and implant technique of this maturing treatment modality and speculate on expansion of its role in the near future.

Key words: heart failure, cardiac resynchronisation therapy, dyssynchrony.

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Introduction

Heart failure is a common condition which causes significant morbidity and mortality in the developed world.[1] Treatment of the condition through diuresis and manipulation of neurohormonal factors, especially the renin-angiotensin-aldosterone[2,3] and catecholamine[4-6] axes, has yielded symptomatic and prognostic benefit. In recent years a ceiling phenomenon appears to have been reached with pharmacological therapy,[7] and an electromechanical approach (through pacing) is becoming accepted as a useful adjunct to optimal medical therapy in certain patients.[8,9]

Electrical dyssynchrony in heart failure

Three broad categories of dyssynchrony are of interest: atrioventricular delay, interventricular delay and intraventricular delay.

First-degree heart block (with a PR interval > 120 ms) is common in, and contributes to,[10] heart failure and is a reliable indicator of atrioventricular conduction delay. The precise site of the block (whether intra-atrial, interatrial, His bundle or fascicular) is not detected by the surface ECG but is comparatively unimportant as the haemodynamic impact is independent of the level of block.

Interventricular delay may be defined as the time interval between right ventricular (RV) and left ventricular (LV) contraction. In most cases this is an LV delay as the common conduction defect in ischaemic and cardiomyopathic ventricles resembles left bundle branch block both electrically and mechanically.[11,12] In a less well-studied minority, including some patients with congenital heart defects, it may also be RV delay.[13]

Intraventricular conduction defect refers to the regional differences in time of maximum wall motion between areas of the left ventricle. This is most often assessed between the LV free wall and septum but it may also be expressed in the antero-posterior axis.

Dyssynchrony is assessed by scrutiny of the surface ECG, although many now feel this to be a blunt tool lacking both sensitivity and specificity in predicting responders to pacing therapies for chronic heart failure (CHF).[14]

Rationale for correcting dyssynchrony

There are a number of sequelae of dyssynchrony that may be deleterious to the impaired ventricle. Prolonged atrioventricular (AV) intervals result in loss of cardiac output due to reduced ventricular filling time and pressure and increased mitral regurgitation.[10] This can be addressed by dual chamber pacing with a programmed short PR interval. Although early results appeared promising,[15] two large trials failed to demonstrate any benefit.[16,17] It is now known that RV pacing (with the inevitable consequence of shortening AV delay) is both less efficient than physiologically conducted contraction and has an adverse impact long-term on ventricular function.[18] RV pacing generates gross interventricular dyssynchrony with the left ventricle activated by slowed intramyocardial conduction, in a manner analogous to left bundle branch block. When left ventricular activation is delayed due to pathological change in the intraventricular conduction system, benefit from modern cardiac resynchronisation therapy (CRT) may be observed.

Intraventricular and interventricular asynchrony lengthen systole and consequently shorten diastole, thereby reducing the proportion of the cardiac cycle during which myocardium is perfused. This has obvious implications in ischaemic patients but may also significantly reduce contractility in patients without coronary artery disease.

If dyssynchrony is present, myocardial areas that are not actively contracting are deformed by the increased chamber pressure generated by contracting regions. Energy is wasted by this phenomenon, and the effect is compounded by the same process occurring in reverse as electrical activation spreads: previously contracting segments relax and energy is wasted, deforming the now contracting (previously non-contractile) segments. This process may be particularly pronounced in interven-

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Table 1. Major randomised trials in cardiac resynchronisation therapy (CRT)

Acronym	No. included	CRT duration	Design	Blinding	QRS (ms)	NYHAC	Primary end points	Secondary end points	Comments
MUSTIC[8]	67	3 months	Cross-over	Single	> 150	III	6MWT	QoL, V_{O2}max, hospitalisation, mortality, LVEF, patient preference	
MUSTIC AF[49]	59	3 months	Cross-over	Single	> 150	III	6MWT	QoL, V_{O2}max, hospitalisation, mortality, LVEF, patient preference	Failed to reach statistical significance; several patients included with low pacing percentages
MIRACLE[9]	453	6 months	Parallel	Double	> 130	III-IV	NYHAC, QoL, 6MWT	V_{O2}max, LVEF, LVEDD, MR, QRS duration, patient response	
MIRACLE ICD[50]	284	6 months	Parallel	Double	> 130	III-IV	NYHAC, QoL, 6MWT	V_{O2}max, LVEF, LVEDD, MR, QRS duration, patient response	
COMPANION[34]	~1,600	24 months	Parallel	Open	> 120	III-IV	Death or hospitalisation	All-cause mortality	3 way randomisation: Control; CRT; CRT+ICD. Stopped early due to 40% reduction in mortality in CRT+ICD arm
PACMAN[51]	~350	6 months	Parallel	Single	> 150	III	6MWT	Death, hospitalisation, QoL, NYHAC, arrhythmias	
CARE-HF[44]	~800	12 months	Parallel	Open	> 120	III-IV	Death or hospitalisation	Mortality, clinical deterioration, health economic factors	

Key: NYHAC = New York Heart Association class; 6MWT = 6-minute walk test; QoL = Quality of Life; LVEF = left ventricular ejection fraction; LVEDD = left ventricular end-diastolic diameter; ICD = implantable cardioverter defibrillator

tricular dyssynchrony as the septum bows alternately into left and right ventricles instead of being splinted by simultaneous increases in left and right interventricular pressures.

The phenomenon of mitral regurgitation in the dilated heart with a structurally near-normal valve apparatus is partly due to a loss of apposition of the valve leaflets.[19] This may be due to dilation of the annulus or to dyssynchronous leaflet motion. Correction of annular stretch would require a process of reverse remodelling but improving synchrony of muscular contraction might be expected to have an immediate impact on apposition. Avoiding the retrograde flow that occurs with mitral regurgitation would represent an efficiency saving by the left ventricle; it also reduces the risk of raised pulmonary venous pressure and hence pulmonary oedema.

History of resynchronisation

After something of a false start with attempts at AV delay optimisation, CRT as we would now recognise it began in 1994 as a last-ditch treatment in moribund patients with New York Heart Association (NYHA) class IV heart failure.[20] Following initial successful cases, early workers trialled atrial-biventricular pacing systems with promising results but the acceptability of the technique was limited by the requirement for a thoracotomy to place the epicardial LV lead. Development of techniques for percutaneous transvenous LV stimulation via the coronary venous system led to an increase in acceptability to patients and clinicians.[21] A further positive influence was the availability of implantable cardioverter defibrillators (ICDs) capable of offering CRT functions.[22,23]

Current indications

Internationally recognised guidelines make CRT a class IIA recommendation in patients meeting all the following criteria: NYHA class III-IV heart failure, established optimal medical therapy (including beta blockers and ACE inhibitors), QRS duration > 130 ms, LV ejection fraction < 36% and LV end-systolic diameter > 54 mm.[24]

Grey areas include patients in atrial fibrillation,[25] patients with mechanical evidence of asynchrony but QRS < 130 ms[14] and patients with NYHA class II symptoms. In the UK, whilst ICDs have attracted specific funding, CRT provision has been made from general resources. In other developed countries reimbursement for CRT implants has not generally been resisted.

Clinical and trial outcomes

The main trials in the field are summarised in table 1. End points of interest in CRT may be divided into early and intermediate (there are no long-term randomised data) or into func-

Table 2. CRT manufacturers and devices

Manufacturer	Device type	Name
Biotronik	PPM	Stratos LV
	ICD	Tupos
ELA Medical	PPM	Talent MSP AF
	ICD	Alto MSP
Guidant	PPM	Contak TR
	ICD	Renewal 2
Medtronic	PPM	InSync
	ICD	InSync ICD
St Jude	ICD	Epic
Vitatron	PPM	CRT 800

Key: PPM = permanent pacemaker; ICD = implantable cardioverter defibrillator

Table 3. Left ventricle stimulation leads

Manufacturer	Model	Placement	Fixation	Sensing
Biotronik	Corox LV-H BP	Stylet	Helix	Bipolar
	Corox LV-H	Stylet	Helix	Unipolar
	Corox LV-P	Stylet	Curve	Unipolar
	Corox LV-H	Stylet	Silicone thread	Unipolar
ELA Medical	Situs OTW	OTW	Silicone screw	Unipolar
	Situs LV	Stylet	Dual curve	Unipolar
Guidant	Easytrack	OTW	Tines	Unipolar
	Easytrack 2	OTW	Tines	Bipolar
Medtronic	Attain 2187	Stylet	Curve	Unipolar
	Attain 2188	Stylet	Curve	Bipolar

Key: OTW = over the wire

tional, symptomatic, mortality, physiological and health economic.

Functional end points assessed include 6-minute walk tests, peak V_{O2}, treadmill testing and NYHA class.

Symptomatic factors also influence NYHA class but are often more precisely assessed by the Minnesota living with heart failure questionnaire (MLHFQ), a 21-stem assessment in which responders are asked to rate the effect of their heart failure symptoms on their quality of life.[26]

Mortality data may be assessed as total, cardiovascular or heart failure-related mortality.

Physiological end points used may be structural (echocardiographic measurements are commonly used), arrhythmic (prevalence of atrial fibrillation [AF] and life-threatening ventricular arrhythmias may be affected) or less direct such as haemoglobin or renal function. Health economic data are usually assessed by hospitalisations but ability to work (and pay tax) is also relevant in a minority of cases.

Currently, there are data to support an early effect on mitral regurgitation and ejection fraction, and an intermediate effect on functional and symptomatic parameters.[8,9,27] There is also good evidence for a reverse remodelling effect on the left ventricle,[27-29] with patients who have undergone a period of CRT maintaining an improved ejection fraction even with their CRT turned off. Evidence of reduction in hospitalisation has been published but remains contentious.[8,9,30] These data are important because they influence cost-efficacy assessment.

Other end points are unproven or unstudied. There are reports of both anti-[31] and pro-arrhythmic potential;[32] systemic parameters such as haemoglobin and renal function have not been rigorously assessed.

Mortality requires particular discussion as an end point, and two salient observations warrant consideration. The first is that subgroup analysis from MADIT II[33] demonstrated that the greatest relative and absolute mortality reduction from ICD occurred in those with prolonged QRS intervals. The second is that COMPANION, the only completed CRT trial powered to demonstrate mortality benefit, was approaching statistical significance when it was stopped prematurely for predetermined criteria.[34] The trial had three arms; control, CRT and CRT-ICD (labelled CRT-P [pacing] and CRT-D [defibrillation] respectively), having been designed before MADIT II reported. Predetermined criteria for trial termination included a clear mortality benefit in any arm.

The rationale for stopping the trial early was a significant 40% mortality reduction in the CRT-D arm, but CRT-P was also tending to show a 19% mortality reduction at the time of termination. Had the MADIT II results been available at the time the trial was designed, the more interesting comparison of ICD vs. CRT-ICD might have been made. Nevertheless, when published in full, COMPANION is likely to add to the evidence base: it extends the threshold for QRS duration in CRT down to 120 ms in patients with PR intervals > 120 ms and extends evidence for primary prevention ICD into the dyssynchronous, non-ischaemic cardiomyopathy population. Data from COMPANION have already been used in a meta-analysis that suggests a reduction in heart failure mortality with CRT.[35] It is unlikely that all-cause mortality reduction with CRT will now be demonstrated from a single trial, although as yet unpublished data from CARE-HF and PACMAN may add power to future meta-analyses.

System considerations

There are currently six manufacturers active in the field of CRT devices and leads (tables 2 and 3). The main determinant of device choice is the requirement for adjunctive defibrillation therapy. An increasing proportion of CRT devices are ICDs as published trial data have extended their role into heart failure-targeted primary prevention of sudden cardiac death.[33,36,37] Secondary considerations are separately programmable LV and RV outputs (allowing easier threshold checks and LV-RV offset manipulation for CRT optimisation) and monitoring applications (such as heart rate variability assessment).

Leads are predominantly selected according to whether a stylet-driven or 'over the wire' coronary venous lead is more appropriate in the operator's preference or for the patient's

Figure 1. Venogram, right anterior oblique (RAO) view

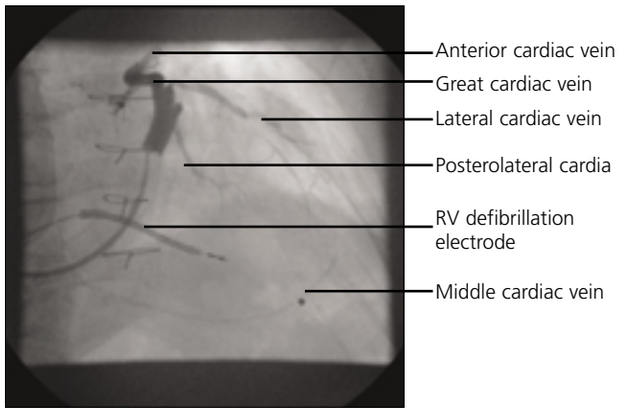


Figure 2. Venogram, left anterior oblique (LAO) view

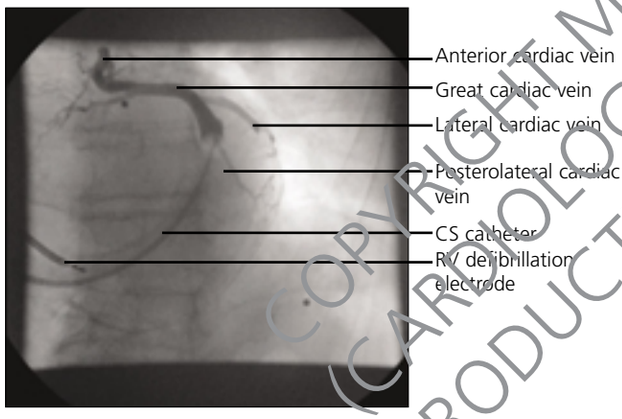


Figure 3. Guide wire in place, LAO view

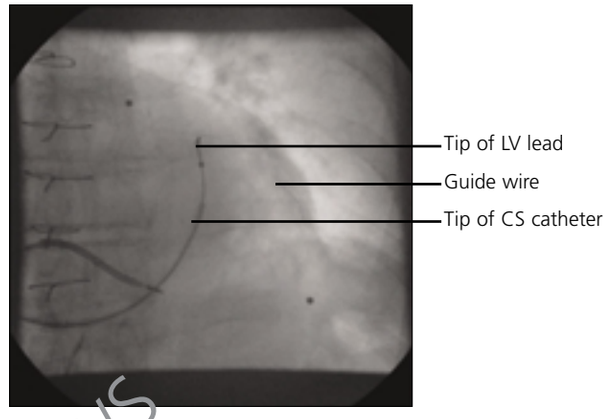
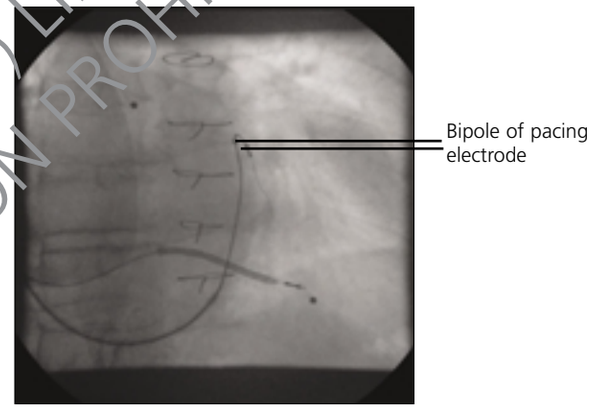


Figure 4. Lead advanced over wire, RAO view



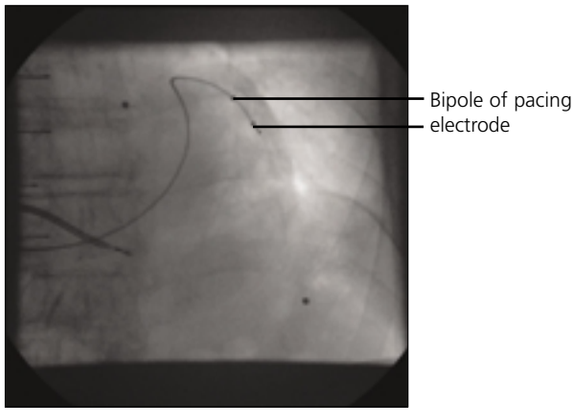
venous anatomy. Other considerations are use of bipolar or unipolar leads and the method of fixation used.

Implant techniques

Usual practice is to fashion a right subcutaneous pectoral pocket for CRT pacemakers and a left submuscular pocket for ICD. The right side offers easier access to the coronary sinus but in ICDs the device housing forms an electrode and defibrillation is more effective with this electrode on the left chest.[38] ICDs are considerably larger than pacemakers and many patients find subcutaneous implants uncomfortable.[39]

The coronary sinus (CS) transvenous approach is the preferred implant route for LV stimulation electrodes. The subclavian or cephalic vein is accessed and the atrial and RV leads sited in the usual fashion. An additional sheath is required and the CS is cannulated with an 8–10F catheter; a variety of catheter shapes is available to allow for anatomical variation. The CS is usually cannulated in the LAO projection and occluded with a balloon. This facilitates retrograde venography of the coronary venous system. Frames are acquired in the LAO and RAO projections, (figures 1 and 2), and from these images a vein supplying the lateral LV myocardium is selected. A pacing lead is advanced into this vein, either directly or after a guide wire has first been advanced (figures 3–5). If a guide wire is used, selection of the appropriate vein may be aided by passing a 6F catheter through the main catheter to engage the desired branch selectively. An ideal position is about half way from the AV groove to the apex in a true lateral vein:[29,40] In practice, however, accessibility, stability and pacing characteristics dictate both the vein used and the site within it.

Figure 5. Final lead position, LAO view



Although the success rate of transvenous lead placement increases with experience of the operator,[29,41] there remain approximately 10% of patients in whom placement is not possible. Upgrades of dual or single chamber devices are particularly problematic. An option in such patients is surgical placement of epicardial LV electrodes; this may be performed by minimally invasive techniques.[42]

Complications

All the recognised complications of pacemaker/ICD implantation (e.g. pneumothorax, infection, haematoma) are at least as common in CRT systems. The specific complication rate for transvenous resynchronisation is low in experienced hands.[41] Coronary sinus dissection (5% cases approximately) less commonly leads to tamponade and even death.[5,9,41] The requirement for system revision due to unacceptable thresholds or diaphragmatic pacing should also be considered. Most importantly, on an intention-to-treat basis up to 40% (5–10% procedural failure[8,9] plus 20–30% non-response[8]) of patients will derive no benefit from undergoing an attempt to implant a transvenous CRT system.

Cost-benefit analyses

The large immediate cost of CRT arising from the implant procedure has been a barrier to acceptance by healthcare funders. Attempts have been made to ascribe a net cost to the therapy by deducting the monetary saving arising from reduced hospitalisation from the upfront implant costs;[43] it has even been suggested that there may be a net saving.[30] This is contentious: in a large series of CRT procedures the risk of early or late requirement for system revision in patients implanted after five years' experience at the centre was 29% (95% CI 21–39%).[41] Including data on procedure-related hospitalisation would clearly detract from any savings on heart failure hospitalisation. The CARE-HF study[44] will clarify hospitalisation and cost issues through its open label design.

Key messages

- Cardiac resynchronisation therapy (CRT) is indicated in patients on optimal medication with moderate to severe symptoms of systolic heart failure and prolonged QRS durations
- The therapy improves quality of life and exercise tolerance, reduces hospitalisations and induces reverse remodelling
- There is a large crossover in indications for CRT and ICDs; devices capable of delivering both modalities are available
- Left ventricular stimulation is achieved by transvenous insertion of a pacing lead into tributaries of the coronary sinus
- Indications are evolving as further trial data become available: QRS duration is likely to be replaced by echocardiographic measures of dyssynchrony in the near future

Programming considerations

There are various methods (electrical and echocardiographic) of optimising AV delay.[45,46] It is crucial that CRT stimulation overrides intrinsic conduction, or resynchronisation will not be effected. In AF, CRT must be above the spontaneous rate. This may only be achieved by AV node ablation or rate control drugs[25] in some patients, although devices are equipped with algorithms designed to maximise CRT pacing in the context of AF without recourse to AV node ablation.

Many devices now have the ability to deliver independent and temporally separated LV and RV stimulation. The default setting is simultaneous RV and LV stimulation but, based on echocardiographic evidence, the interval may be altered to optimise synchronisation.[47] There is no proven outcome benefit to this process although many authorities would recommend attempting this in patients who do not respond to empirically programmed CRT. Up to 30% of patients receiving CRT do not derive symptomatic improvement (non-responders) despite all attempts at optimisation.

Future directions

It is unlikely that patients with mild or absent symptoms who would not otherwise require any device implant will become candidates for CRT. An obvious direction in which CRT may extend its indications is in heart failure patients undergoing permanent pacing or ICD implant. Individuals requiring backup anti-bradycardia therapy will be rendered asynchronous during RV pacing even if their native rhythm is normally propagated through the ventricles. What pacing proportion would justify a CRT system and how this is to be predicted is unknown; trials are underway to evaluate these questions.[48]

Summary

It may be said with some confidence that CRT improves medium-term quality of life and functional capacity in patients with moderate to severe heart failure and ventricular conduction delay. As such it is a useful adjunct to optimal pharmacological treatment. There is also reason to believe that a long-term benefit may arise from the reverse remodelling it induces, although this remains unproven.

Patient selection algorithms are currently sub-optimal and it seems likely that the surface ECG will be replaced by echocardiographic assessments of dyssynchrony. How far accepted indications extend will depend on long-term outcome, cost-benefit analyses and whether a mortality reduction is demonstrated over and above ICD therapy alone.

Conflict of interest

JRP received a research grant from Ela Medical. JMM is a Consultant to Guidant.

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