EDITORIAL

Optimisation of cardiac resynchronisation therapy: addressing the problem of "non-responders"

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Cardiac resynchronisation therapy has become firmly established as a treatment for patients with symptomatic heart failure. Several randomised controlled trials and numerous observational studies have demonstrated improvements in exercise capacity and quality of life. Despite these advances it is clear that approximately 25% of patients who meet current criteria for implantation of such a device do not show objective evidence of clinical benefit. Implantation of a CRT device is expensive, time consuming and involves some risk so it is important to accurately identify patients who are likely to respond and to optimise pacing lead placement and device programming to maximise the benefit in these selected patients.

Disruption of the usual sequence of ventricular activation is now recognised as a major factor in the development of symptomatic heart failure in patients with ischaemic and non-ischaemic cardiomyopathy. Delayed and dyssynchronous left ventricular (LV) contraction reduces myocardial efficiency, causes abnormal diastolic interactions between the ventricles,¹ and increases mitral regurgitation.² Biventricular pacing, also known as cardiac resynchronisation therapy (CRT), is designed to reduce symptoms of breathlessness and fatigue in these patients by restoration of a more physiological sequence of cardiac activation.

Early clinical trials of CRT were carried out in the USA and Europe from 1995 to 1998 using a thoracoscopic procedure for lead placement on the epicardial surface of the lateral wall of the left ventricle.³⁻⁴ In 1998 Daubert and colleagues⁵ reported a technique of transvenous lead implantation with manipulation of a lead into a cardiac vein via the coronary sinus to enable pacing of the epicardial surface of the left ventricle. However, despite further developments, this technique remains challenging and time consuming with average procedure times in large clinical trials of between 2-4 hours. Although implantation success rates for LV leads have risen with greater experience, in most series they do not exceed 90%.⁶ Moreover, this is a relatively expensive treatment which carries significant risks when performed in patients with heart failure and incipient pulmonary oedema.⁷

THE PROBLEM OF "NON-RESPONDERS"

Important effects on the functional status of the patient are difficult to quantify objectively and very significant placebo effects can be seen with this type of intervention. The functional assessments therefore need to be performed in conjunction with less subjective measurements of ventricular performance and exercise capacity, including serial echocardiography and maximal oxygen uptake (VO₂max) pre- and post-CRT. Most patients who receive CRT will have an improvement in their symptomatic status. Trial data have demonstrated an overall mean increase in VO₂max of approximately 1-2 ml/kg/min, in exercise duration of 30-60 seconds, and in six minute walk test distances of 20-40 m.⁶ Echocardiographic data demonstrate reductions in LV dimensions and reduced severity of mitral regurgitation.⁸ However, the dramatic treatment effect seen in many patients in the clinical trials has consistently been diluted by the 20-30% of patients who have no objective clinical benefit following implantation of a CRT device.⁹⁻¹⁰

At this stage in the development of CRT it is important to identify these "non-responders" and to consider the possible underlying reasons. The patient could then be spared an ineffective intervention or the therapy could be optimised to ensure maximal benefit, thus using limited healthcare resources more efficiently. In practice this process will involve:

- improvement in the assessment of patients before to CRT
- optimisation of pacing lead positions
- optimisation of device programming.

PATIENT SELECTION

Entry criteria for clinical trials of CRT

The accepted criteria of patient selection for CRT are:

- New York Heart Association (NYHA) class III/IV symptomatic heart failure
- LV ejection fraction < 35%
- LV end diastolic diameter > 55 mm
- QRS duration > 120 ms*
- sinus rhythm
- stable optimal medical treatment.

Abbreviations: AV, atrioventricular; CRT, cardiac resynchronisation therapy; LBBB, left bundle branch block; LV, left ventricular; NYHA, New York Heart Association; RBBB, right bundle branch block; TDI, tissue Doppler imaging; VO₂max, maximal oxygen uptake

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Viability of myocardium

When heart failure is related to ischaemic heart disease, viability of LV myocardium is likely to be a crucial determinant of the response to CRT and patients with extensive LV scarring are unlikely to benefit. This is supported by a study demonstrating that patients with severe resting myocardial perfusion defects had no objective evidence of augmented ventricular function following CRT, in contrast with the improvements seen in patients without resting defects and despite an apparent symptomatic improvement in both groups.¹⁵ Present practice does not generally include an assessment of LV viability before CRT and further studies are required to determine the role of such assessments in patient selection.

Electrical versus mechanical assessment of dyssynchrony

An important limitation of initial CRT trials is the use of QRS prolongation (in particular left bundle branch block (LBBB)) on the standard ECG as the sole marker of ventricular dyssynchrony. The trials have included a relatively small number of patients with right bundle branch block (RBBB). In both the MIRACLE and CONTAK CD¹⁶ trials small groups of patients with RBBB appeared to respond as well as those with LBBB. Garrigue and colleagues¹⁷ also demonstrated that patients with RBBB respond to CRT, but only when associated with intraventricular dyssynchrony. The presence of RBBB can mask significant ventricular conduction delay in the left ventricle and echocardiography is required to assess ventricular dyssynchrony pre-implantation. The surface ECG provides a relatively crude assessment of myocardial activation and may not show localised delays which have important mechanical consequences. Several studies have shown that QRS duration is a relatively poor predictor of the symptomatic response to CRT in an individual patient,^{18–19} and there is increasing evidence that patients with ventricular dysfunction and “normal” QRS duration can benefit.²⁰ More detailed analysis of ventricular activation with vector cardiography, signal averaged ECG, or non-contact endocardial mapping²¹ may have a role in patient selection.

ASSESSMENT OF MECHANICAL DYSSYNCHRONY Echocardiography

There are two main echocardiographic predictors of benefit to CRT: firstly, the difference between the aortic pre-ejection period and the pulmonary pre-ejection period estimated by standard pulsed wave Doppler; and secondly, septal to lateral wall contraction delay, best assessed by tissue Doppler imaging.

The larger the difference between the aortic pre-ejection period and the pulmonary pre-ejection period, the greater the chance of response to CRT, which is independent of QRS duration. A delay of greater than 40 ms is considered compatible with significant dyssynchrony, the larger the delay the greater the chance of response to CRT.²²

The most widely used technique for identification of mechanical dyssynchrony uses tissue Doppler imaging (TDI), which involves measuring the time to peak myocardial sustained systolic (T_s) and diastolic velocity in different segments of myocardium. Typical appearances in patients with heart failure are of a notable regional variation, usually with the earliest activation in the basal anterior septum and the latest in the basal lateral segments. Yu and colleagues²³ demonstrated mechanical dyssynchrony using TDI in 75% of those with a QRS > 120 ms, but also in 40% of heart failure

patients with normal QRS duration, demonstrating the weakness of ECG criteria for the accurate detection of dyssynchrony. Three dimensional echocardiography has also been studied and is likely to have a role in these assessments.

Other methods

Other potential techniques to assess mechanical dyssynchrony include magnetic resonance imaging²⁴ and radionuclide studies, but clinical trials are needed to evaluate these prospectively. There may also be a role in patient selection for neurohormonal markers, such as brain natriuretic peptide, which is released predominantly from viable LV myocardium in response to increased LV wall tension.²⁵

LEAD POSITIONING AND OPTIMISATION OF PACING SITE

Butter and colleagues²⁶ showed that the LV pacing site was a crucial factor in determining the effects of CRT, with lateral (free wall) sites consistently producing better short term haemodynamic responses than anterior sites. This study showed that in 30% of patients, stimulation of the anterior left ventricle via tributaries of the great cardiac vein resulted in *worsening* of haemodynamic function. This can be explained by the fact that LV free wall sites are consistently the latest to be activated and stimulation at these sites reliably restores homogenous LV activation. Conversely anterior wall sites are usually activated early and pacing to advance their activation further will enhance regional dyssynchrony.^{27–28}

Pacing of the LV free wall usually means implanting the lead in either the posterolateral, lateral, or anterolateral veins, in the territory supplied by the circumflex or diagonal coronary arteries. With the transvenous approach the operator is constrained by the coronary venous anatomy, which shows considerable inter-individual variability, and the issue is complicated by the inconsistent nomenclature which is used for the veins. It is often difficult or impossible to deliver a lead to the most suitable site of the ventricle. The left phrenic nerve runs down the lateral LV wall and diaphragmatic stimulation can further limit pacing site options. With current lead delivery systems an LV free wall site cannot be achieved in 5–10% of cases. In the MUSTIC study¹⁴ a lateral position was achieved in only 80% of cases, and this may be one reason for the proportion of non-responders. Improved technology will facilitate lead delivery to a suitable site but in some cases this may be impossible and the above data suggest that it is better to abandon the procedure rather than deploy the lead in a site which may worsen cardiac function. There is a continuing role for surgical epicardial lead implantation when a lateral lead position cannot be achieved by the transvenous route.

DEVICE PROGRAMMING: ATRIOVENTRICULAR (AV) AND VENTRICULAR-VENTRICULAR (VV) DELAYS

For CRT to work as intended there should be a paced rhythm at all times so the atrioventricular (AV) delay on the pacemaker must be set below the intrinsic AV conduction time. Often the AV delay is programmed at a nominal low value of around 100 ms to ensure ventricular pacing, but this may excessively reduce the atrial contribution to LV filling and echocardiographic assessment may be required to optimise this setting. Indeed it may be that there are no “non-responders” as such, and providing that a suitable site for the LV lead is found optimal programming could ensure the vast majority of patients respond.

On more recent biventricular pacing devices, the output and timing of right and left ventricular stimulation are independently programmable and there is increasing interest in optimisation of the *inter*-ventricular delay. Sogaard and

*Many of the large multicentre trials (COMPANION, PATH CHF, MIRACLE, MUSTIC) adopted a policy of inclusion which ranged from > 120 ms to > 150 ms.^{11–14}

colleagues²⁹ looked at this issue in a group of 21 patients with LBBB and congestive heart failure. They concluded that while simultaneous biventricular pacing produced a predictable improvement in haemodynamic parameters, further refinement of ventricular "offset" achieved even greater benefits in systolic and diastolic performance as measured by TDI. Notably several patients in this study benefited from pre-activation of the right ventricle before the left ventricle and there was considerable inter-individual variability, suggesting that individual "fine tuning" of the V-V interval is required to gain maximal benefit. Several studies have assessed various invasive and non-invasive methods of optimising this aspect of CRT programming, including beat-beat analysis of cardiac output and haemodilutional techniques, but there are few data correlating these with long term clinical effects. Although large interventricular delays (up to 100 ms) can be programmed, the optimal settings in this study were in a relatively narrow range (12–20 ms).

CONCLUSION

Clinical trials of CRT have demonstrated considerable improvements in quality of life and exercise capacity, but a significant number of "non-responders" have diluted the overall benefits. The use of ECG criteria alone will result in selection of some patients who are unlikely to benefit and also exclusion of potential responders. Assessment of regional LV mechanical activation and viability with echocardiography should be considered before implantation of a biventricular pacing device and further studies are required to refine the selection process. Once a decision has been made to proceed with CRT then appropriate placement of the LV lead and optimal programming of the device will maximise the therapeutic effect. A combination of these measures will enable CRT to deliver even more impressive results in patients with heart failure.

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