Biventricular pacing in heart failure

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Optimal pharmacological therapy for heart failure improves patients' prognosis and symptoms. Despite this, the long-term prognosis for these patients is very poor and symptoms are debilitating. Biventricular pacing, or resynchronization therapy, should be considered for patients who remain symptomatic despite optimal therapy and have evidence of dyssynchrony.

The worldwide prevalence of heart failure is increasing as the population ages. In developed countries the prevalence of heart failure in the general population is 1–2% (Chow et al, 2003). In the UK heart failure is the commonest cause of hospital admission, accounting for 5% of all adult admissions (Varma and Camm, 2001). It is estimated that 0.2% of the population are admitted to hospital with this condition each year.

In the developed world the majority of patients with heart failure have impaired left ventricular function secondary to ischaemic heart disease or as a result of idiopathic dilated cardiomyopathy. Patients with progressive heart failure (New York Heart Association (NYHA) class III/IV) have not only a worsening quality of life, but also a poor prognosis. Death for such patients is usually the result of progressive heart failure or less commonly sudden death as a result of tachyarrhythmias.

In recent years there have been many therapeutic advances in the treatment of heart failure, with the use of angiotensin-converting enzyme (ACE) inhibitors (Flather et al, 2000), angiotensin II-receptor blockers (Pitt et al, 2000), beta-blockers (Bristow, 2000) and spironolactone (Pitt et al, 1999); however, the prognosis for patients with chronic heart failure remains extremely poor. Within the first year of diagnosis there is a reported mortality of up to 40%, with an additional 10% per year after this. Patients refractory to the maximum drug regimen have an annual mortality in excess of 40% per year, and remain highly symptomatic with frequent hospital admissions. The extent of this problem has huge implications both clinically and economically.

Until relatively recently the only non-pharmacological treatments available were heart transplantation and the use of left ventricular assist devices, but there are obvious availability and financial issues associated with these options.

For over a decade pacing has been considered for patients with heart failure with variable results. However, recent randomized clinical trials have produced unequivocal support for the use of biventricular pacing in patients with refractory heart failure with evidence of intraventricular conduction delay, most commonly seen as left bundle–branch block on the 12-lead electrocardiogram (ECG), with resulting ventricular dyssynchrony.

THE ROLE OF PACING IN HEART FAILURE

Controversy exists regarding the impact of right-sided pacing techniques on the development of heart failure in patients with conventional arrhythmia indications. Over the last 3 decades, conventional wisdom has suggested that optimizing atrioventricular (AV) synchrony by dual chamber pacing was associated with a lower incidence of heart failure and atrial fibrillation (AF) than ventricular pacing alone (Alpert et al, 1986).

Hochleitner et al (1990) reported that dual-chamber pacing with a short AV interval was of benefit in patients with heart failure and no conventional indication for pacing. They described a significant reduction in NYHA class, a fall in cardiothoracic ratio and increase in systolic and diastolic blood pressures. The proposed mechanism was thought to be an improvement in left ventricular filling. Further studies failed to confirm these benefits (Linde et al, 1995). Later studies sought to find the best position for placement of the right ventricular wire, some finding additional benefit haemodynamically in the right ventricular outflow tract (Gold et al, 1997) and more recently pacing from the His bundle (Deshmukh et al, 2000), although there are no randomized studies of these approaches.

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More recently the Dual Chamber and VVI Implantable Defibrillator (DAVID) study (Wilkoff et al, 2002) and the Mode Selection (MOST) study (Sweeney et al, 2003) have suggested that right ventricular pacing itself may increase the incidence of heart failure. This is believed to relate to the abnormal left ventricular electrical activation and consequent dyssynchronous mechanical activity. The negative effect of abnormal ventricular activity, despite the benefits of restoring AV synchrony, may account for the inconsistent results seen with right-sided pacing alone for heart failure.

Biventricular pacing for heart failure was first undertaken by Bakker in 1993. Since then numerous acute haemodynamic studies have been undertaken comparing the efficacy of biventricular, right ventricular and left ventricular temporary pacing (Leclercq et al, 1998). These have consistently shown an improvement in left ventricular filling and systolic contraction with reduction in mitral regurgitation and pulmonary pressures. Nelson et al (2000) reported that the improved systolic contraction was associated with a reduction in myocardial oxygen consumption implying improved myocardial efficiency. Optimal left ventricular pacing sites have also been studied (Blanc et al, 1997).

In the initial clinical studies of long-term biventricular pacing perioperative mortality figures were high, presumably related to the thoracotomy used for left ventricular lead placement and the associated anaesthetic risk (Cazeau et al, 1994). Daubert et al (1998) described a fully transvenous approach to the left ventricle via the coronary sinus using both conventional and, subsequently, specifically designed pacing leads.

STUDIES OF BIVENTRICULAR PACING

The Insync study (Kuhlkamp, 2002) was a prospective, non-randomized investigation of biventricular pacing in patients with class III/IV drug refractory heart failure. Significant improvements, compared to baseline, were seen in the end points of exercise capacity (6-minute walk test), NYHA class and quality of life.

The multisite stimulation in cardiomyopathy studies (MUSTIC) (Linde et al, 2002) enrolled 68 patients in a single blinded, randomized, cross-over trial of biventricular pacing. Biventricular pacing produced significant improvements in exercise tolerance, NYHA class, quality of life scores, peak oxygen uptake and cardiac ejection fraction during pacing.

In the multicentre Insync randomized clinical evaluation (MIRACLE) (Abraham, 2000) 524 patients were enrolled and randomized, after successful implantation, to therapy on or off. Both the patient and the assessing heart failure physician were blinded to the modality of pacing. Again, there was significant improvement in the primary end points of exercise capacity and quality of life. In addition there was a 50% reduction in hospital admissions during the 6 months, and a 77% reduction in total hospital days saved for treating heart failure in the group receiving biventricular pacing.

Although these trials have not addressed mortality or morbidity as a primary end point, the meta-analysis of four trials (Contak CD (Guidant, Basingstoke, Hampshire), MUSTIC, MIRACLE, Insync Implantable Cardioverter-Defibrillator (InSync ICD)) involving 1634 patients, published in *JAMA* (Bradley et al, 2003), reported a 51% reduction (confidence interval (CI)= 0.25–0.93) in progressive heart failure mortality from 3.5% to 1.7% and a 29% reduction in hospitalization. Core centre analysis of the echocardiography data from the MIRACLE study provides exciting evidence of reverse remodelling of the left ventricle (Abraham, 2000).

In the Comparison of Medical Therapy, Pacing and Defibrillation in Heart Failure (COMPANION) study patients were randomized to receive optimal medical therapy alone, a biventricular pacemaker or a biventricular implantable cardioverter-defibrillator (ICD). The study was halted prematurely with 1600 of the planned 2200 patients enrolled because the requisite event rate had been reached. The ICD limb showed a significant 40% reduction in all-cause mortality while the biventricular limb showed a non-significant reduction of 20%. On the basis of this study it has been suggested that all biventricular devices should have ICD capabilities but this concept remains contentious. Interestingly the combined end points of death and heart failure hospitalization were similar in both device limbs, and significantly reduced compared to medical therapy alone. This suggests that the ICD patients might have increased hospitalization (Bristow et al, 2000; Cleland et al, 2001).

The Cardiac Resynchronisation in Heart Failure (CARE-HF) study compares optimal medical therapy alone to a combination with a biventricular pacemaker. Recuitment is now complete at 800 patients and is due to be presented at the end of 2004.

HOW DOES BIVENTRICULAR PACING WORK?

Conduction changes in heart failure include impaired atrioventricular conduction and intraventricular conduction. These electrical changes are associated with incoordinate ventricular contraction and regional delay in activation. In extreme circumstances there may be regional systolic contraction of the lateral left ventricle after closure of the aortic valve.

Biventricular pacing has the potential to improve atrioventricular, intraventricular and interventricular synchrony. Additional potential benefits of left ventricular activation may include reduction in diastolic ventricular interaction.

WHO SHOULD BE CONSIDERED FOR BIVENTRICULAR PACING?

The recently published National Institute For Clinical Excellence (NICE, 2003) guidelines concentrate on the current evidence base and recommend:

> **'Resynchronisation therapy should be considered in selected patients with left ventricular systolic dysfunction (left ventricular ejection fraction <35%), drug refractory symptoms, and a QRS duration >120 ms.'**

In addition to this patients should:

- Have a non-reversible cause
- Have NYHA class III/IV symptoms (6-minute walk <425 m)
- Have failed optimal medical therapy, including ACE inhibitor, beta-blocker, spironolactone, and in addition to these diuretics, angiotensin II receptor antagonist and digoxin
- Be able to lie flat for at least 2 hours
- Have a left ventricular end-diastolic dimension >6 cm.

Current trials have concentrated on QRS duration as an inclusion criteria and a marker for dyssynchrony. However, QRS duration does not necessarily predict dyssynchrony, which may account for the 30% non-responder rate reported in these studies. Current studies are examining whether techniques such as tissue Doppler echocardiography, enabling us to quantify the degree of dyssynchrony, are more accurate in predicting response to pacing.

Of those people with heart failure in the UK, how many would be suitable candidates for biventricular pacing? A study carried out in a large UK district general hospital audited patients admitted with severe heart failure (NYHA III/IV) and a QRS >120 ms, and estimated that approximately 10% might be suitable for biventricular pacing (Farwell et al, 2000).

IMPLANTATION

Typically implantation is done under local anaesthetic with sedation. Three leads are most commonly used, inserted via the cephalic or subclavian veins:

1. A standard transvenous pacing lead is inserted into the right atrium, for those patients in sinus rhythm, to sense the sinus node initiation of electrical activity
2. A standard transvenous or a transvenous defibrillation lead is inserted into the right ventricle. Many centres now advocate pacing from the right ventricular septum, providing a more physiological pattern
3. A specially designed transvenous left ventricular lead is inserted into a lateral branch of the coronary sinus into a cardiac vein (often visualized with the use of a coronary sinus venogram). The coronary sinus is initially entered using a purpose-designed guiding catheter.

Modern devices are now available which allow manipulation of the atrioventricular and the interventricular pacing intervals, enabling further individual optimization both functionally and haemodynamically.

Implantation time is operator dependent, as are the associated complications. However, even with the improved delivery systems for implantation, the position of the left ventricular lead is often dependent upon the patient's coronary venous anatomy. Failure to position the left ventricular lead is responsible for the majority of the reported 8% implant failures. Problems with deployment of the left ventricular lead include: inability to cross the coronary sinus or its venous tributary, coronary sinus dissection, left ventricular lead displacement and diaphragmatic stimulation.

In order to minimize complications it is essential to have an experienced operator, strict testing at implantation and careful programming post-implantation.

FUTURE DIRECTIONS

Further work is required to define more accurately who will benefit from biventricular pacing. The majority of the studies so far have concentrated on biventricular pacing in those patients with a widened QRS complex on their ECGs, together with a poor ejection fraction and NYHA class III/IV. Initial studies suggest that patients with narrow QRS complexes may also benefit haemodynamically from biventricular pacing. Synchronization of the ventricles seems not to be the only mechanism of improvement (Morris-Thurgood et al, 2000).

With the large longer term studies coming to an end it will soon become evident whether biventricular pacing has a big impact on mortality in patients with severe heart failure. The role of ICDs within this population has also to be established.

CONCLUSIONS

The evidence base for biventricular pacing in selected patients with heart failure continues to grow. It certainly seems that biventricular pacing can reduce symptoms of heart failure and potentially have a positive influence on both morbidity and mortality. Cost efficacy remains to be fully established and will probably depend on optimal patient selection. Similarly the role of combined ICD and biventricular pacing is yet to be established. HM

Conflict of interest: none.

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KEY POINTS

- Heart failure is increasing in prevalence with the ageing population.
- Heart failure is responsible for 5% of all adult hospital admissions in the UK.
- There is 40% mortality within the first year of diagnosis.
- National Institute for Clinical Excellence guidelines for treatment of chronic heart failure were introduced in July 2003.
- Biventricular pacing should be used for for patients with New York Heart Association (NYHA) class III–IV, wide QRS complexes (>120 ms) and left ventricular ejection fraction <35%.
- Biventricular pacing improves NYHA class, quality of life, and exercise tolerance.
- Recent studies suggest a reduction in all-cause and cardiac mortality with biventricular pacing.

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