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Treatment of Heart Failure – Role of Biventricular Pacing for Heart Failure Not Responding Well to Drug Therapy

W S Teo, R Kam, L F Hsu

ABSTRACT

Objective: Patients with heart failure may have conduction abnormalities in up to 30%, further aggravating cardiac output. Drugs worsen these abnormalities and resynchronisation therapy with biventricular pacing improves cardiac function by effecting a more coordinated and efficient ventricular contraction. We report here the technique of biventricular pacing and its results.

Methodology: Patients with NYHA Class III to IV heart failure, widened QRS (≥130 ms) complex on the ECG and impaired LVEF ≤40% were enrolled.

Results: Biventricular pacing was performed in 29 patients (26 males, three females) from August 1999 to December 2001. The mean age of the patients was 59.6 ± 12.8 years and 62% had underlying ischemic heart disease. All were in NYHA class III or more. Twenty-three had LBBB, four RBBB and two had widened paced QRS complex. The QRS duration was 161 ± 21 ms and LVEF was 22 ± 8%. All the left ventricular leads were implanted successfully. The procedure time was 167.0 ± 79.6 mins and the fluoroscopy time was 43.8 ± 41.4 mins. There were no significant complications. The NYHA class improved from a mean of 3.1 to 2.0 and exercise time from 252 ± 95 seconds to 392 ± 152 seconds at six months post implant (p=0.049). On follow-up (one month to 28 months), 25 (86%) patients had improvement in heart failure symptoms and 26 (90%) of the patients remained alive.

Conclusion: Biventricular pacing can be safely performed and results in improvement in symptoms and exercise tolerance in heart failure patients with ventricular dyssynchrony not responding to drug therapy.

Keywords: biventricular pacing, pacemaker, defibrillator, heart failure, arrhythmia

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INTRODUCTION

Heart failure results in severe symptoms and poor quality of life. It is becoming an increasingly common problem and in the United States of America, it has been estimated to occur in about 1.5% of the population[1]. In the Framingham study, the annual age adjusted incidence of heart failure among persons aged ≥45 years was 7.2 cases/1,000 in men and 4.7 cases/1,000 women, whereas the age adjusted prevalence of overt heart failure was 24/1,000 in men and 25/1,000 in women[2].

The treatment of patients with heart failure is predominantly with drugs such as diuretics and inotropes for acute treatment of heart failure while angiotensin converting enzyme inhibitors, angiotensin receptor blockers, beta blockers and vasodilators are useful for chronic treatment of heart failure.

In up to 30% of patients with advanced heart failure however, conduction abnormalities may occur. P wave abnormalities reflecting intra-atrial or inter-atrial conduction abnormality, abnormal PR interval and intraventricular conduction block especially left bundle branch block may occur[3]. A particular combination consists of a normal or slightly prolonged P wave, mildly abnormal PR interval and a very wide QRS complex usually associated with left bundle branch block and left superior axis deviation.

The conduction abnormalities have adverse haemodynamic effects resulting in impaired atrioventricular filling, ventricular dyssynchrony and hence impaired cardiac output and function. The increased QRS duration results in abnormal interventricular septal wall motion, reduced rate of rise in intracavitary pressure (dP/dt), reduced diastolic filling times and prolonged mitral regurgitation duration. The wider the QRS complex, the longer the left ventricular (LV) contraction and relaxation times with poorer LV systolic performance. This conduction abnormality may be progressive and is a marker of a poor outcome[4-7]. Drugs cannot correct the conduction abnormality or electrical dyssynchrony and in fact many antiarrhythmic drugs may aggravate it.

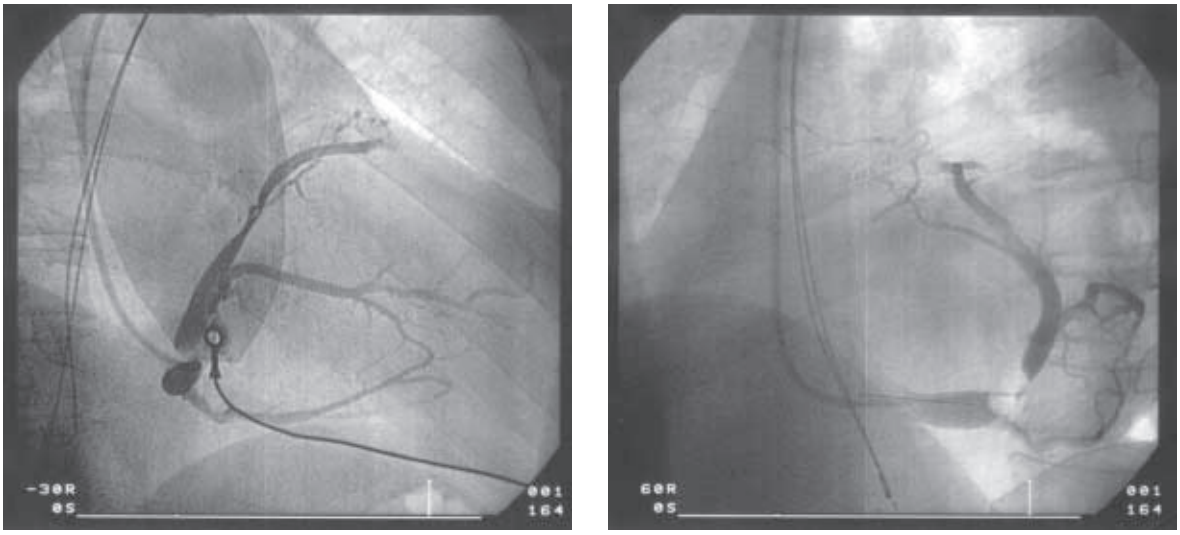

Fig. 1 Coronary sinus angiograms show branches of the coronary sinus. Left panel Right anterior oblique 30 degree view. Right panel Left anterior oblique 60 degree view.

Biventricular pacemakers have been proposed to improve the cardiac electrical synchronisation and improve cardiac function. The ventricular resynchronisation therapy is used not to increase the heart rate but to help the heart pump more efficiently without increasing myocardial oxygen demand on the failing heart. We report here our initial experience in the use of biventricular pacing for patients with medically refractory heart failure.

METHODS

Selection of patients

Patients were considered for biventricular pacing if they met the following criteria:

- Symptomatic heart failure, NYHA Class III, IV
- Widened QRS ≥130 ms
- LVEF ≤40%
- Already on optimum medical therapy
- Not candidate for or refused heart transplant

The following patients were excluded:

- Patients with myocarditis
- Patients with unstable coronary syndromes or coronary artery disease where revascularisation may be more appropriate
- Patients with Class IV heart failure who are candidates for cardiac transplantation

Informed written consent was obtained. The patients were explained that this was a new form of therapy for patients with symptomatic heart failure with bundle branch block. The risk of the procedure was estimated at about 1%. The procedures were performed in the cardiac catheterisation laboratory, National Heart Centre, Singapore in 22 patients, Mt Elizabeth Hospital, Singapore in four patients, Harapan Kita Heart Hospital in Jakarta, Indonesia in two patients and at Chulalongkorn Hospital, Bangkok, Thailand in one patient.

Technique of biventricular pacing

The patients were fasted for at least six hours prior to the procedure. Sedation was done with midazolam and fentanyl. The left chest was cleaned and draped. Venous access was obtained using either the cephalic vein cut-down or subclavian puncture techniques. The coronary sinus was then cannulated using an electrophysiological catheter and a long guiding sheath. Once the coronary sinus was cannulated, the sheath was advanced into the coronary sinus. The electrophysiological catheter was then removed and a balloon tipped Swan-Ganz catheter inserted via the sheath into the coronary sinus. The balloon was inflated and contrast injected into the coronary sinus to obtain a coronary sinus angiogram to visualise the branches of the coronary sinus (Fig. 1). The Swan-Ganz catheter was then removed and the left ventricular lead advanced into the coronary sinus. The lead may be introduced directly using a curved stylet as in the Medtronic Attain leads or using an over-the-wire system as in the Guidant system which uses a 0.014 inch wire and an EASYTRAK lead, which slides along the wire. The lead is then introduced into the most distal portion of the coronary sinus. Soft tines at the tip of the lead enable successful passive fixation in the coronary sinus. The optimal site for left ventricular pacing is in the lateral or posterolateral cardiac vein. This is because pacing from the mid lateral wall or posterior wall results in the best percentage increase in pulse pressure and left ventricular dP/dt[8]. However at times they are too small for the lead to enter or does not result in a

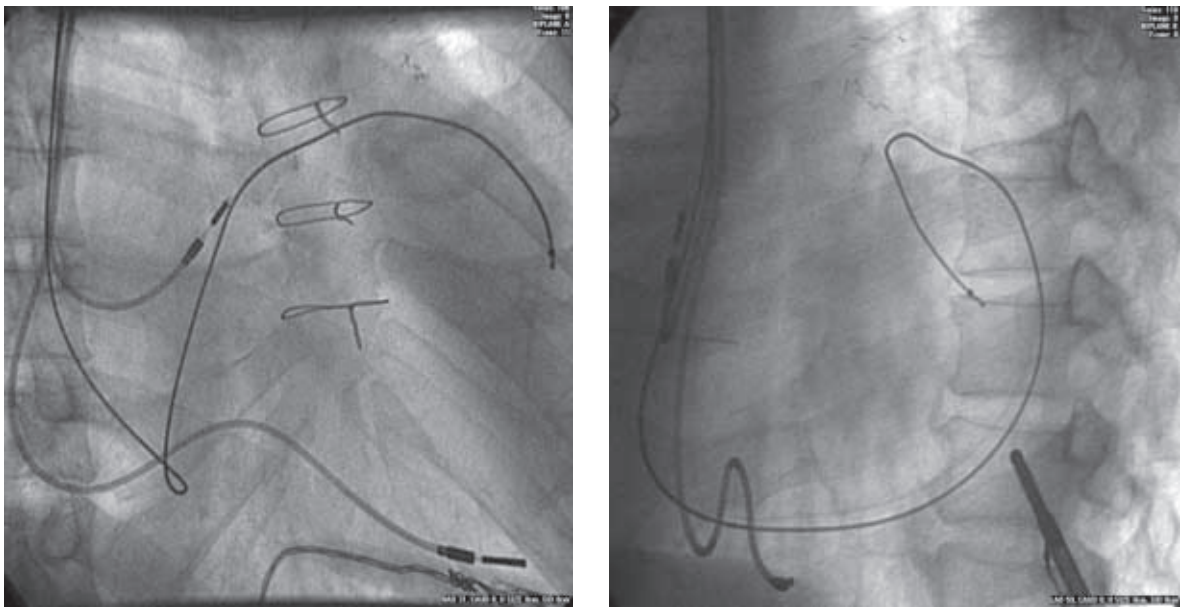

Fig. 2 Radiographs show the position of the leads in right anterior oblique view (30 degrees) and left anterior oblique view (60 degrees).

stable position and the lead is then positioned in the anterior great cardiac vein.

Once the left ventricular lead was secured, the right ventricular apex lead and right atrial lead were then implanted in the usual manner for a dual chamber pacemaker. Where possible, the RV and LV lead should however be anatomically as far apart as possible (Fig. 2). The three leads were then connected to the pulse generator device and the whole system placed in the subcutaneous pocket just above the pectoralis major muscle. We used either the Guidant Contak TR/CD or the Medtronic Insync devices. The ECG with biventricular pacing usually shows a narrowing of the QRS complex (Fig. 3).

Statistics

Continuous variables are expressed as mean +/- one standard deviation. Chi-square, paired and unpaired t-tests using the Statistical Package for Social Sciences version 9.0 (SPSS, Chicago, Illinois) software were used and a p value of <0.05 was taken to be significant.

RESULTS

Table I summarises the baseline characteristics and clinical outcome of our study population. Twenty-nine patients underwent biventricular pacing at National Heart Centre, Singapore, Mount Elizabeth Hospital, Singapore, Harapan Kita Cardiac Hospital, Indonesia and Chulalongkorn Hospital, Bangkok during the period between August 1999 and December 2001.

There were 26 males and three females. The mean age of the patients was 59.6 ± 12.8 years (range 28 - 79 years). Sixty-two percent of the patients had underlying ischemic heart disease, with 38% having previous myocardial infarction. All patients were in NYHA class III or more and had an LVEF of ≤40%. The mean LVEF for the whole group was 22 ± 8% (range 10 - 40%). Twenty-three patients had LBBB, four patients had RBBB and two patients had markedly widened QRS with right ventricular apical pacing. The mean QRS duration preoperatively was 161 ± 21 ms (range 130 - 240 ms).

Six patients had the Medtronic Insync device and 18 patients had the Guidant Contak TR. Five patients had concomitant ventricular tachycardia or fibrillation and had biventricular devices with additional implantable cardioverter defibrillator capability as well. Two patients had the Medtronic Insyn ICD while three patients had the Guidant Contak CD devices. All the left ventricular leads were implanted successfully. Seven LV leads were in the anterior great cardiac vein while the rest were in the lateral, anterolateral or posterolateral cardiac vein. The mean left ventricular R wave was 13.8 ± 6.6 mV (range 5.6 - 30.2 mV) and mean left ventricular threshold was 1.8 ± 1.1 V (range 0.3 - 5.1 V). The mean procedure time was 167.0 ± 79.6 mins and ranged from 95 mins to 391 mins. The mean fluoroscopy time was 43.8 ± 41.4 mins (ranged 15 - 211 minutes).

There were no major complications during the implant although one patient had a haematoma over the pacemaker site and another had transient worsening of his heart failure symptoms immediately after the implant and required inotropic support but recovered within a few hours after the procedure.

Acutely, in the cardiovascular laboratory, the AV delay which produced the greatest increase in pulse pressure was chosen. In Fig. 4, the improvement

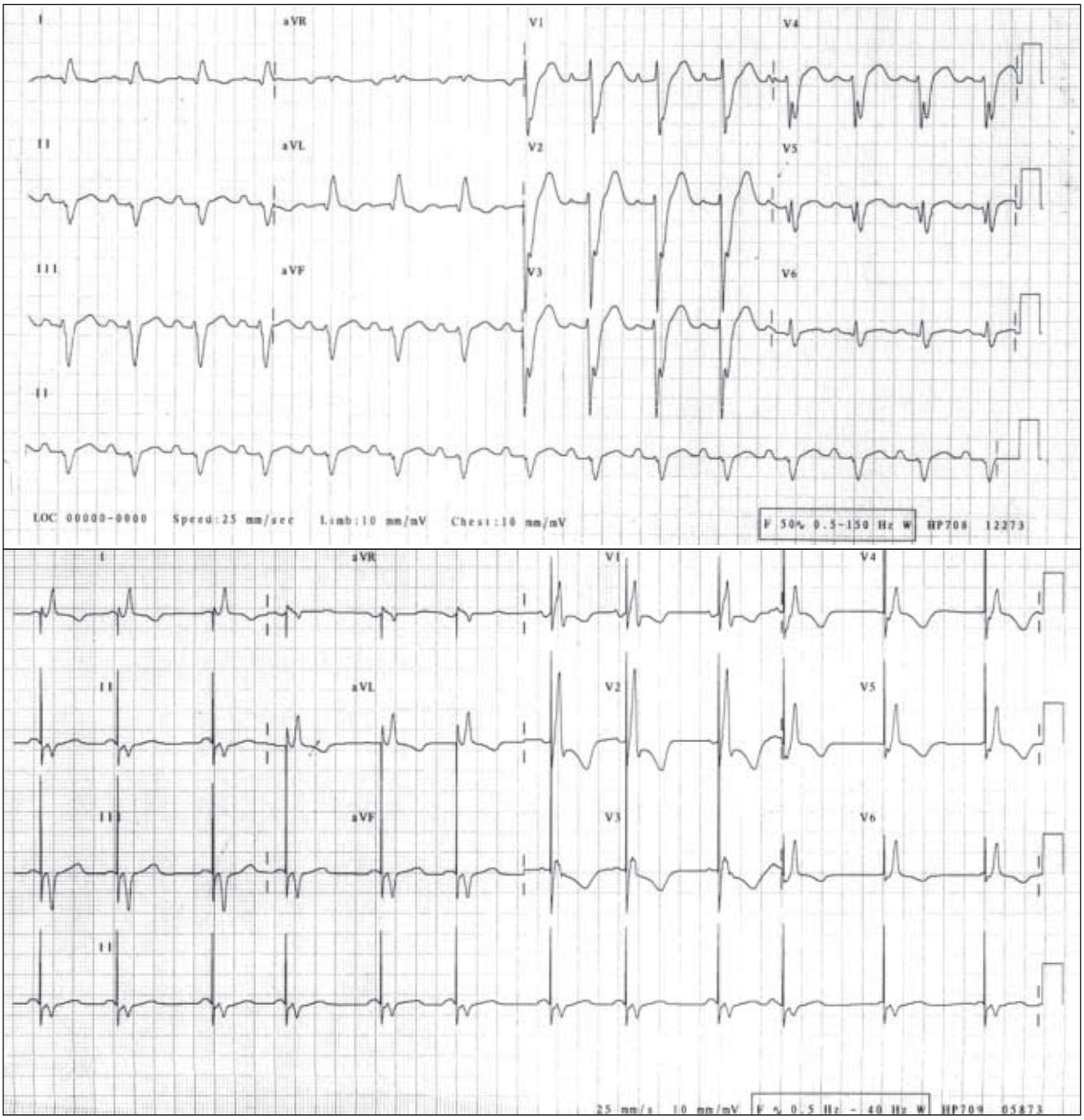

Fig. 3 Top panel: 12 lead ECG of patient with widened QRS showing LBBB.
Bottom panel: 12 lead ECG of patient with narrower biventricular paced QRS.

in systolic blood pressure and pulse pressure is evident immediately when biventricular pacing is switched on. Echocardiography was performed pre-discharge and the optimal AV delay was derived from the Doppler signal of the transmitral flow, using Ritter's formula[9]. Echocardiography was performed pre-implant and six months post-implant to assess left ventricular function by using the modified Quinone's method as well as visual estimation.

All patients were on stable doses of medication prior to implantation. Since this was not a randomised study, post implantation, treatment of heart failure was left to the discretion of the primary cardiologist and medication doses were adjusted as the patient's clinical condition permitted.

All patients had improvement in clinical symptoms initially. There was marked symptomatic improvement with an improvement of at least one NYHA classification. The NYHA class improved from a mean of 3.1 to 1.96 in the first month and to 1.8 in the third month. The duration of exercise on the Modified Bruce protocol improved from a mean of 252 ± 95 seconds before biventricular pacing to 392 ± 152 seconds at six months post implant (p=0.049). In patients with paired LVEF measurements, the mean LVEF at baseline was 22 ± 9% (range

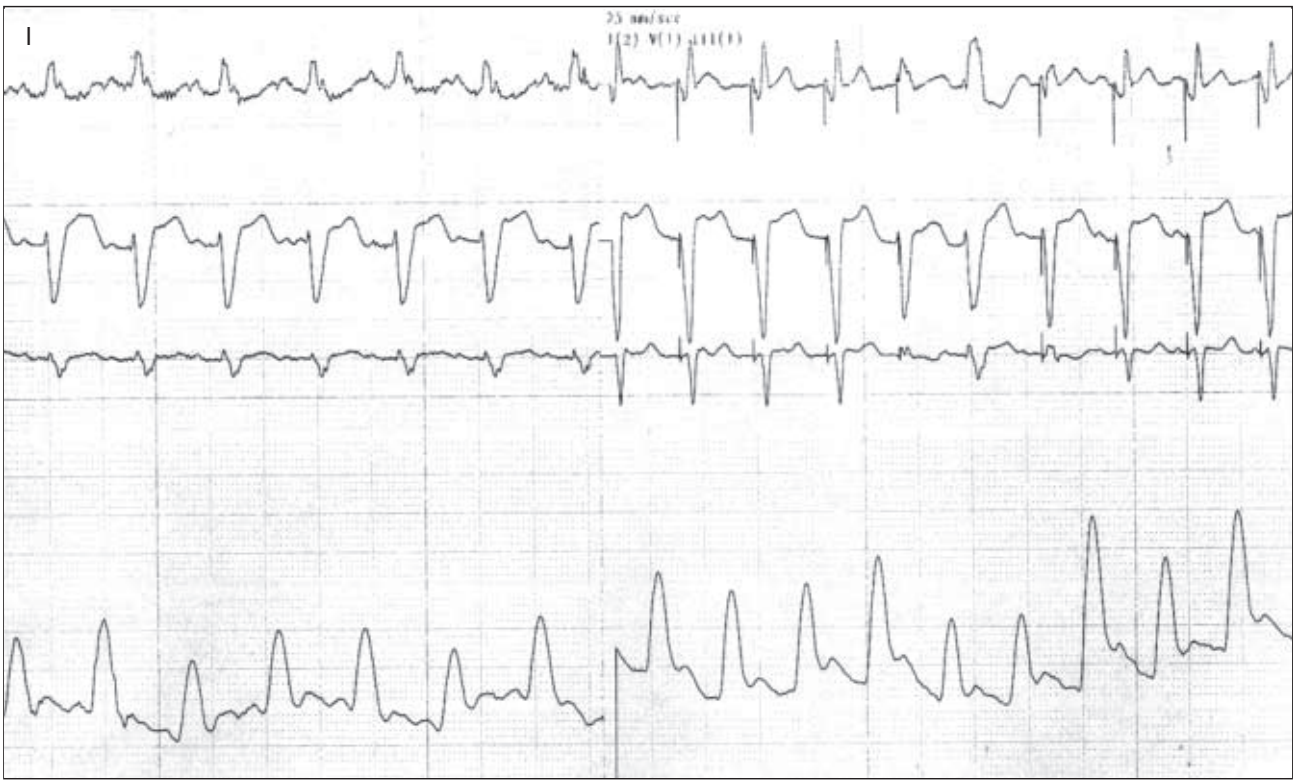

Fig. 4 Acute hemodynamic study showing improvement in pulse pressure and systolic blood pressure with biventricular pacing.

10 - 40%) and at six months post implant the mean LVEF was 27 ± 7% (p=0.2).

Four patients had recurrence of heart failure symptoms after about four to six weeks. In two of them, there was evidence of lead dislodgement. Repositioning of the lead in one patient immediately improved his symptoms considerably. The other patient declined to have a reoperation. Thus on follow-up, 25 (86%) of the patients had persistent improvement in heart failure symptoms.

On follow-up, one patient (3%) had sudden death two months after the implant. The first recorded rhythm by the ambulance officer was asystole with pacing and no capture. Two patients (7%) died from progressive heart failure. Thus in this group of very sick patients in NYHA Class III to IV not responding well to drug therapy, 26 (90%) of the patients remain alive, with follow-up ranging from one month to 28 months.

DISCUSSION

Biventricular pacing involves pacing from the coronary sinus, right ventricular apex and preferably sensing rather than pacing from the right atrium. The main therapeutic intent of cardiac resynchronisation therapy using atrio-biventricular pacing is to optimise AV conduction and activate both ventricles simultaneously, thus improving the mechanical efficiency of the ventricles without an increase in workload on the heart, Our initial experience with biventricular pacing shows that it can be safely performed with no significant complications. The procedure time is however much longer compared with conventional dual chamber pacing, requiring on average an additional hour. There are also technical difficulties especially in cannulating the coronary sinus in the dilated hearts. The second major problem is in positioning the left ventricular lead in the optimum position in a branch of the coronary sinus. However, as with all procedures, there is a learning curve and once the learning curve is over the success rate and procedure time will improve.

Initial studies of pacing for heart failure

The potential mechanisms for improvement by pacing in congestive heart failure patients include:

- Decreasing mitral regurgitation
- Increasing diastolic filling time
- Augmenting cardiac output by increasing heart rate at rest and during exercise
- Decreasing left ventricular filling pressure and left ventricular size
- Improving efficiency of left ventricular myofibril contraction through better alignment and ventricular resynchronisation
- Maintaining and/or establishing atrioventricular (AV) synchrony with optimal AV delay
- Overdrive suppression of arrhythmias

- Allowing more aggressive medical management with drugs such as beta-blockers, digitalis or amiodarone

Initial studies by Iskandrian et al suggested that increasing the atrial rate might decrease left ventricular end-diastolic volume and improve cardiac performance[10]. However, in patients with associated ischemic heart disease, this may aggravate the ischemia and worsen myocardial function. Acute and long term studies with conventional dual chamber (DDD) pacing in patients with congestive heart failure due to various etiologies have yielded conflicting results. The initial enthusiasm generated by Hochleitner decreased considerably after subsequent studies showed unfavourable and even contradictory results[11]. Hochleitner et al had showed that in 16 severely symptomatic patients, dual chamber pacing with a short AV delay of 100 ms resulted in marked symptomatic improvement in New York Heart Association (NYHA) classification and an increased ejection fraction. Brecker et al and Aurricchio et al demonstrated similar good results[12,13]. However, subsequent randomised controlled trials showed no improvement in cardiac output or benefit of VDD pacing in patients with congestive heart failure[14,15]. Two major long-term studies were also disappointing[16,17]. Subgroup analysis of DDD pacing suggested however that it may be useful in patients with prolonged PR interval. Nishimura et al noted that in patients with a prolonged PR interval (mean 280 ms), an optimal AV delay increased diastolic filling and decreased mitral regurgitation with a significant 38% increase in cardiac output (P=0.005)[18]. The consensus at present is that conventional DDD pacing may benefit only a small group of patients with prolonged PR interval and congestive heart failure but it is difficult to predict accurately who are the patients that can benefit. Conventional DDD pacing is classified as a Class IIB indication in congestive heart failure patients with concomitant PR prolongation[19].

One reason why conventional DDD pacing may not be beneficial could be that right ventricular pacing alone may be detrimental. This is because right ventricular (RV) apical pacing is associated with alteration of the normal ventricular activation sequence, resulting in an artificial left bundle branch block. By delaying LV activation and reversing the ventricular activation sequence, pacing in the RV apex induces substantial asynchronous ventricular contraction and relaxation resulting in a variety of detrimental chronic haemodynamic consequences.

Table I. Patient characteristics, procedural details and clinical outcome.

Number of patients	29 (26 male: 3 female)
Mean age	59.6 ± 12.8 years
Mean QRS duration	161 ± 21 ms (130 - 240 ms)
Device characteristics	
Medtronic Insync pacemaker	6
Guidant Contak TR pacemaker	18
Medtronic Insync ICD	2
Guidant Contak CD ICD	3
Implant Vein	
Anterior great cardiac vein	7
Lateral cardiac vein	17
Anterolateral cardiac vein	3
Posterolateral cardiac vein	2
Measurements at implant	
Mean left ventricular R wave	13 ± 6.6 mV (5.6 - 30.2 mV)
Mean left ventricular pacing threshold	1.8 ± 1.1 V (0.3 - 5.1 V)
Mean procedure time	167 ± 79.6 min (95 -391 min)
Mean fluoroscopy time	43.8 ± 41.1 min (15 - 211 min)
Complications	
Pocket haematoma	1
Transient worsening of heart failure immediately post implant	1
Lead dislodgement	2
Outcome	
Mean NYHA class (baseline)	3.1
Mean NYHA class (1 month)	1.96
Mean NYHA class (3 months)	1.8
Mean treadmill exercise time (baseline)	252 ± 95 sec
Mean treadmill exercise time (6 months)	392 ± 152 sec, p=0.049
Mean LVEF (baseline)	22 ± 9%
Mean LVEF (6 months)	27 ± 7%, p=0.2
Deaths	
Sudden death	1
Progressive heart failure	2
Total	3

The LV asynchrony during RV pacing is greatly aggravated in patients with structural heart disease and especially in ischemic patients with myocardial infarction scars. Vassallo et al using endocardial mapping studies during apical RV pacing have shown that patients with previous anterior myocardial infarction scarring had a significant prolongation of the earliest LV local activation time, total endocardial activation time and total duration of LV electrical activity[20].

Why is biventricular pacing potentially useful?

Biventricular pacing therapy may work primarily by correcting the electrical and mechanical asynchrony

in the left heart, which is characteristic of dilated cardiomyopathy. Bakker et al were the first to evaluate the potential role of permanent biventricular pacing in patients with poor LV function and intraventricular conduction block[21].

Resynchronisation therapy achieved via left ventricular or biventricular pacing works by shortening the AV conduction delay and potentially reducing mitral regurgitation. The synchronised contraction can result in improved fractional shortening. Blanc et al demonstrated that acute pacing in patients with left bundle branch block and dilated cardiomyopathy from the left ventricular free wall reduced the pulmonary capillary wedge pressure and degree of mitral regurgitation while increasing the systolic pressure[22]. Similarly, Kass et al reported that left ventricular pacing significantly increased left ventricular dP/dt and systolic blood pressure in patients with primarily left bundle branch block and congestive heart failure. These effects were associated with greater stroke work and stroke volume in the left ventricular pressure-volume relation, with a leftward and upward shift of the loop at end systole[23]. Auricchio et al demonstrated that the increase in left ventricular dP/dt and systolic pressure occurs immediately after initiation of left ventricular pacing and that the baseline QRS duration may predict which patients are most likely to gain haemodynamic benefits from this therapy[24].

Improvements in interventricular synchrony during biventricular pacing correlated with acute improvements in left ventricular ejection fraction (LVEF)[25]. Clinically biventricular pacing resulted in improved peak VO_2, improved exercise time, improvement in NYHA by one class and QRS width reduction. Preliminary data also suggest that patients who undergo biventricular pacing develop lower norepinephrine levels because of the favourable changes this pacing modality causes on the autonomic nervous system and this may contribute to reverse ventricular remodelling[26].

Potential number of patients who may benefit from biventricular pacing

It has been estimated that 3.7% of all patients with known coronary artery disease have left bundle branch block or right bundle branch block associated with a QRS $\geq$120 ms in combination with a LVEF $\leq$40%[27] and that approximately 10% of an unselected group of patients with heart failure would be appropriate candidates for resynchronisation therapy[28].

Clinical improvements after biventricular pacing

There was an improvement in clinical parameters (NYHA Class and exercise time) after biventricular pacing. Dislodgement of the lead as in one patient resulted in almost immediate worsening of heart failure, which improved rapidly once the lead, was repositioned. This is consistent with the short term studies that have shown acute haemodynamic and quality of life improvement with biventricular pacing[21,22].

The result of our study is supported by much larger clinical studies, which suggest long term benefit of biventricular pacing in patients with severe congestive heart failure symptoms. Leclercq in a single-centre study showed that biventricular pacing significantly improved symptoms (NYHA class 2.2 $\pm$ 0.5 at follow-up versus 3.7 $\pm$ 0.5 at baseline) and exercise tolerance (VO_2 peak 15.5 $\pm$ 3.4 mL/min per kilogram at follow-up versus 11.1 $\pm$ 3 mL/min per kilogram at baseline)[29]. The larger multicentre Insync trial showed that in patients with class III-IV heart failure with an LVEF <35% and QRS duration $\geq$150 ms, biventricular pacing resulted in improved quality of life, improvement in six minutes walk distance, improvement in NYHA class by 1 - 2 and an improved left ventricular ejection fraction[30]. Similarly the PATH-CHF trial was terminated early because of significant improvements in peak oxygen consumption (PVO_2), oxygen consumption at anaerobic threshold, quality of life (QOL Minnesota score) and the six minute walk test.

The recently published MUSTIC study which was a single-blind, controlled, randomised crossover study also showed that in patients with severe congestive heart failure and intraventricular conduction defects, biventricular pacing was associated with a 23% increase in six minute walk distance (399 versus 326 meters, $p<0.001$), increase in peak VO_2 and quality of life score. The frequency of hospitalisations (both for heart failure and non-heart failure indications) significantly decreased by two-thirds during active biventricular pacing and this pacing mode was preferred in most patients[31].

The recently presented MIRACLE (Multicenter InSync Randomised Clinical Evaluation trial) study also showed that the primary end points of the study – improvement in NYHA functional class, six minute walk test and quality of life indicators all improved significantly. The study also suggested that cardiac resynchronisation therapy promoted reverse remodelling as the echocardiographic studies showed significant reduction in mitral regurgitation jet and a decline in LV mass, both signs of reverse remodelling in heart failure, in contrast to the usual progressive increase in LV mass in patients with progressive heart failure.

Selection of patients who will benefit from biventricular pacing

Resynchronisation therapy is a promising treatment for patients with heart failure and ventricular dyssynchrony and the question is not whether biventricular pacing therapy will work but in whom it will work. The difficulty is in determining precisely who will benefit from the treatment and how long this benefit will last remains unanswered. Our short-term study shows that 86% of the patients have symptomatic improvement.

The classical indications for biventricular pacing are patients in NYHA class III or IV with an LVEF <35% and a QRS duration >120 ms and not responding to optimum heart failure drug therapy. The Pacing Therapies for Congestive Heart Failure (PATH-CHF) study suggests that acute haemodynamic improvement is best observed when the QRS duration is >150 ms[23]. Additionally patients with a prolonged PR interval will be expected to benefit more. Presently the data are most convincing for patients with left bundle branch block but patients with right bundle branch and even patients with atrial fibrillation and a widened QRS or preexisting pacemaker patients with a very wide QRS (>160 ms) are being studied.

Current data, mainly from the lnsync trial indicate that clinical parameters are poor predictors of response. Neither age, etiology nor NYHA class is useful to predict a response to pacing. Although a QRS duration of >160 ms indicated an acute haemodynamic response in the PATH-CHF trial, this was not a predictor of a short-term clinical response to pacing in the lnsync trial. Instead a significant narrowing of the QRS complex by biventricular pacing was found to predict responders. Whether the benefits of biventricular pacing may be extended to patients with less severe forms of intraventricular conduction delay awaits further investigation.

Biventricular pacing and influence on prognosis and long term survival

All the biventricular pacing trials have consistently showed sustained improvements in symptoms and quality of life[32,33]. The important question now is whether biventricular pacing will improve survival in this group of patients who have a very high mortality. The overall survival in our initial experience is 90% but the follow-up is still relatively short. Historically these patients have mortality rates of almost 50%, with almost 50% due to sudden death[34]. There is evidence from retrospective studies that DDD pacing as opposed to VVI pacing may reduce mortality in pacemaker patients with congestive heart failure[36]. Similarly, although the PATH-CHF trial did not measure survival as its primary endpoint, 80% of the patients who received biventricular pacing were alive after two years, suggesting an improvement when compared with historical controls.

In addition, some evidence indicates that the frequency of ventricular arrhythmias is decreased. Zagrodzky et al reported that biventricular pacing decreased the inducibility of ventricular tachycardia in patients with ischemic cardiomyopathy[35]. An interesting study from Higgins et al suggests that biventricular pacing diminishes the need for implantable defibrillator use as only 16% had at least one tachyarrhythmic episode while programmed to biventricular pacing, whereas 34% had at least one episode while programmed to no pacing[37]. However, whether the addition of a defibrillator to the biventricular pacemaker will improve survival remains to be determined and the results of ongoing studies such as the lnsync ICD, Contak CD and COMPANION Trial (Comparison of Medical Therapy, Pacing and Defibrillation in Chronic Heart Failure) studies.

CONCLUSION

In conclusion, biventricular pacing can be safely performed and results in significant improvement of heart failure symptoms. The evidence remains preliminary but suggest that cardiac resynchronisation therapy with biventricular pacing should be considered for symptomatic improvement of patients with heart failure associated with AV and ventricular conduction abnormalities when medical therapy with drugs alone fails to improve the patient's functional status and quality of life. It is possible that with the addition of the implantable defibrillator, prognosis may also be improved.

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