Pacing in heart failure: patient and pacing mode selection

Tushar V. Salukhe*, Michael Y. Henein, Richard Sutton

Royal Brompton Hospital, London, UK

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Introduction

Pharmacological therapy in the management of heart failure has been proven and is well established. In the last decade ACE inhibitors,1,2 beta-blockers,3,4 spironolactone5 and digoxin6 have contributed to a reduction in mortality of nearly 50%, a reduced frequency of hospital admissions and improvement in quality of life.7–9 However, congestive heart failure still endures a high overall annual mortality of about 10%, with a 50% incidence of sudden death. Furthermore, many patients remain symptomatic and have a poor functional status (classified as NYHA III and IV) despite optimal medical therapy. It is in such patients in whom cardiac haemodynamics may be improved through appropriate pacing modalities with reasonable expectation of a better functional status.

Conventional Dual Chamber (DDD) Pacing

In the late 1980s Hochleitner et al. experimented using dual-chamber pacing in patients with drug-resistant end-stage heart failure.10 Permanent dual-chamber systems were implanted in 16 critically ill patients with idiopathic dilated cardiomyopathy and angiography confirming absence of coronary artery disease. All 16 had PR intervals >160 ms, seven with PR interval >220 ms and seven with left bundle branch block (LBBB). Atrioventricular delay was set at 100 ms at a lower rate of 50 bpm. All patients exhibited a normalization of heart rate during pacing, in that heart rate reduction was seen in tachycardic patients and rate increase in bradycardia patients. DDD pacing resulted in significant clinical improvement, manifest as resolution of dyspnoea and pulmonary oedema, reduced NYHA functional class and cardiothoracic ratio on X-ray. Echocardiographic studies showed increased left ventricular ejection fraction (EF) and reduction in grade of mitral regurgitation. Furthermore, the clinical improvement resulted in a decline in number of hospital admissions and three of...
the eight patients were removed from transplant lists. The physiology behind the results of these pioneering investigations was not fully elucidated at the time.

**LV filling dynamics in DCM**

In patients with severe ventricular disease, short ventricular filling times can often occur as a result of functional atrio-ventricular valve regurgitation of a long duration occupying not only ‘isovolumic’ contraction and relaxation but also a significant part of late diastole. Filling times may be so abbreviated as to reduce stroke volume severely, impair cardiac output and hence exercise capacity. Such atrio-ventricular regurgitation typically has a pre-systolic component and is particularly evident in patients with a long PR interval and LV disease. This pre-systolic (or late diastolic) component of regurgitation encroaches into and thereby reduces the duration of ventricular filling time, particularly at high heart rates. The presystolic component of regurgitation can even occur with a normal PR interval in patients with severe ventricular disease and broad QRS. Intraventricular conduction abnormalities, also common in these patients, can further prolong total regurgitation time. When assessed with pulse wave Doppler echocardiography, presystolic regurgitation can have two effects; it can eliminate the late atrial component (A wave) of filling. Secondly, the shortened filling time, particularly in the presence of tachycardia, may force the two normal components of ventricular filling, early diastolic (E wave) and atrial (A wave) to become superimposed into a single summation wave, manifest clinically as a summation sound.

The theory behind the beneficial effect of DDD pacing in dilated cardiomyopathy was described by Brecker and Gibson. With DDD pacing the overall duration of atrio-ventricular regurgitation is reduced and the presystolic component eliminated altogether, simply by appropriate shortening of the A-V delay (75–100 ms). Successful elimination of the presystolic regurgitation, results in extending the diastolic LV filling time and this augments stroke volume. (Fig. 1). Optimum A-V delay is important as too short a delay could synchronize atrial and ventricular contraction causing the atria to contract against a closed atrio-ventricular valve. By convention A-V delay is optimized under Doppler echocardiographic guidance to maximize LV filling and ejection time.

**Patient selection for DDD pacing in DCM**

DDD pacing with A-V delay optimization, has beneficial functional and clinical effects when applied to the appropriate patients, namely, symptomatic patients in sinus rhythm with a long PR interval, prolonged functional mitral regurgitation (>450 ms) and a ventricular filling time of less than 200 ms at rest. In these patients, however, it may be difficult to differentiate a summation LV filling pattern due to fusion of the E and A waves, which can be improved by DDD pacing, from an isolated E wave in a non-compliant (restrictive) ventricle which will not necessarily benefit from DDD pacing. Accurate methods of distinguishing these have yet to be established.

Studies which did not use such stringent criteria for application of conventional DDD pacing, not surprisingly showed only minimal acute, and no long term benefits. Fifteen patients selected purely on the basis of poor ejection fraction, irrespective of PR interval, LV filling and MR duration, demonstrated no immediate improvement in cardiac output and only marginal improvement in LV filling time with DDD pacing and AV delay of 60 ms. In another study, ten patients were selected for DDD pacing only on the basis of NYHA functional class III or IV and being in sinus rhythm with EF<35%. AV delay was optimized using Doppler echocardiography and after 6 months patients showed no significant change in stroke volume, cardiac output, or NYHA class. A randomized cross-over trial with twelve male patients with dilated cardiomyopathy (33% idiopathic and 67% ischaemic), EF<35% and NYHA class III or IV, were assigned either DDD pacing with AV optimization (100 ms at lower rate 40 bpm) or VVI pacing (40 bpm), the two groups were switched to the alternate mode at 4–6 weeks. Baseline PR interval was 214±45 ms and QRS duration 130±41 ms. Ejection fraction, cardiac output and NYHA functional class did not improve with DDD pacing and short AV delay.

When patients are selected appropriately results are more positive. In one study, twelve patients with dilated cardiomyopathy (three ischaemic, eight idiopathic and one muscular dystrophy) and in sinus rhythm were paced in DDD mode with AV delay optimized to maximise left or right ventricular filling time. The patients selected all had left or right ventricular filling times below 200 ms due to functional mitral or tricuspid regurgitation of long duration. After AV delay optimization, pre-systolic and hence total atrio-ventricular regurgitation durations were significantly reduced...
(mean reduction: 85 ms mitral, 110 ms tricuspid) with consequent increase in left and right ventricular filling times (mean increase: 65 ms LV and 90 ms RV). Although five patients died during 12 month follow-up, all patients demonstrated improvement in exercise duration (mean 3.9 min vs 6.1 min at one month) and maximal oxygen uptake (MVO₂) (mean 9.2 vs 11.9 ml/kg/min).22

Right ventricular DDD pacing, however, is at a cost; as pacing the right ventricle can result in a relative delay in left ventricular activation, and may in itself induce ventricular asynchrony,
possibly due to a site of activation being distant from the LV. For similar reasons pacing the right side of the heart in patients with dilated cardiomyopathy and grossly inco-ordinate ventricular contraction due to left-sided conduction abnormalities for example, can do little to improve co-ordination. In such patients direct left ventricular pacing appears to be the best approach.

**Ventricular asynchrony**

Functional haemodynamic abnormalities in patients with asynchronous ventricular contraction have been well documented, particularly those with depressed systolic function and delayed inter-and intra-ventricular conduction. Indeed QRS duration exceeds 140 ms in almost 30% of symptomatic patients and mortality from heart failure increases dramatically with QRS duration greater than 170 ms. The sum of PR interval and QRS duration (sinus rhythm) is also of significant prognostic importance in dilated cardiomyopathy, with values of 375 ms correlating with end-points of death or need for conventional DDD pacing. Such conduction delays are associated with atrioventricular asynchrony, right and left interventricular asynchrony, and left ventricular septal to free wall intraventricular delay. These patterns can result in prolonged isovolumic time, compromised diastolic filling time and ineffective atrial contribution to LV filling.

The isovolumic times within the cardiac cycle are periods of haemodynamic stasis. When times are abnormally prolonged, for example in conduction abnormalities, it can be considered to be time wasted and the cycle becomes 'inefficient'. This phenomenon is well illustrated by a demonstrable reduction in the useful time of the cardiac cycle expressed as a reduced Z ratio (the ratio of the sum of ejection time and filling time to the total R-R interval) in patients with isolated left bundle branch block even in the absence of ventricular disease. The electromechanical delay as a result of conduction abnormalities delays the onset of ventricular contraction and wall tension development, this in turn delays the onset and shortens duration of ventricular ejection. The delayed ventricular tension development as a result of delayed activation can result in continued wall tension and intraventricular pressure development beyond ejection and into early diastole thus impeding the early phases of ventricular filling. In addition, delayed and inco-ordinate ventricular relaxation also contributes to the abbreviation of ventricular filling times. The shortened filling and ejection times reduce the Z ratio. The aim of biventricular (BIV) pacing or ventricular resynchronization therapy is to optimize segmental electrical excitation, timing of contraction and relaxation, and consequently cycle efficiency.

**Bi-ventricular pacing — acute haemodynamic studies**

The acute haemodynamic effects of pacing the free wall of the left ventricle in heart failure patients were examined by cardiac catheter studies showing immediate changes in cardiac performance before and during multi-site (single- and bi-ventricular) pacing. Significant falls in pulmonary capillary wedge pressure, V-wave amplitude, improved systolic blood pressure and cardiac index have been demonstrated during left ventricular (LV) and BIV pacing. Systolic performance, as represented by maximum LV pressure derivatives (LV dP/dtmax) and aortic pulse pressure, also improves. These studies almost unanimously favoured LV and BIV pacing over right ventricular (RV) pacing alone. Optimization of AV-delay has been shown to improve pulse pressure and LV dP/dtmax when pacing in the VDD mode; in this study AV-delay optimized to fit the equation 0.5×AV-delay (baseline). This formula was used in the COMPANION trial—a mortality and morbidity trial of atrio-biventricular pacing in congestive heart failure. Resynchronization with LV pacing causes a drop in coronary sinus O₂ difference as well as reduced myocardial oxygen consumption and improves parameters of cardiac performance at a reduced energy cost in patients with dilated cardiomyopathy and left bundle branch block.

It has become evident in most of these investigations that not all patients with heart failure respond to LV or BIV pacing, indeed some reported a deterioration of haemodynamic parameters during these pacing modes. Moreover, this was despite there being no significant clinical or demographic differences at baseline, hence highlighting the importance of responder identification. Nelson et al. suggested that baseline measurements of LV dP/dtmax (values ≤700 mmHg/s) and QRS duration (values ≥155 ms) were useful when combined, as predictors of early haemodynamic improvement which correlated with the degree of mechanical resynchronization.

**Bi-ventricular pacing — clinical studies**

The studies of acute haemodynamics, although useful, did not delineate long-term effects or clinical
improvement. In one of the earliest clinical studies, 50 patients with severe drug-resistant dilated cardiomyopathy, intraventricular conduction delay and poor NYHA functional class (III/IV) were implanted with biventricular pacemakers and were assessed over a mean follow-up period of 15.4 months. Mortality was lower in class III patients (12.5%) than class IV patients (52.5%). In survivors, significant improvements were seen in functional class (NYHA 2.2 vs 3.7 at baseline) and exercise capacity (peak VO₂ 15.5 vs 11.1 mL/min/kg at baseline). Fifty-five percent of patients remained free from transplant or LV assist devices.  

More recently, small clinical trials have shown significant beneficial effects of BIV pacing in patients with congestive cardiac failure. PATH-CHF was a randomized crossover trial in which 42 patients of functional class NYHA III with prolonged QRS duration (173±32 ms) and reduced EF (23±7%) received either uni-ventricular (VDD-LV or VDD-RV) or biventricular (VDD-BIV) pacing. In 80% of patients, acute measurements of dP/dt and pulse pressure showed similar improvements in function during univentricular LV and BIV pacing modes over RV pacing, by 28% and 16% respectively. Chronic improvement was documented in Peak VO₂ and 6-min walk which both improved by 23% and 60 m respectively. Fifty-five percent of patients remained free from transplant or LV assist devices.  

During the MUSTIC trial 41 48 patients with NYHA III heart failure, QRS duration ≥150 ms, EF ≤35% and LV end-diastolic diameter (LVEDD) ≥60 mm were randomly assigned to BIV pacing or no pacing (VVI 30 bpm). All were crossed over at 12 weeks. AV-delay optimization was guided by Doppler echocardiography. End points were wholly clinical-during condition during pacing, again suggesting imperfect inclusion criteria. This study also demonstrated a significant reduction in hospitalizations with resynchronization from 15% in controls to 8% in BIV paced patients. As only six-month data were available, implications on survival or mortality cannot be made, particularly in a study size of less than 500. Nevertheless, the magnitudes of the differences in the primary end-points between the paced and un-paced groups, though statistically significant, were surprisingly small and were not influenced by pre-medication, aetiology of heart failure, nor baseline QRS duration or configuration. This was partly due to a large placebo effect, but again indicates the need for more discriminating methods of identifying optimal responders.  

One retrospective study 44 attempted to identify predictors of responders to BIV pacing. 26 patients implanted with BIV were analyzed—nineteen who responded and seven did not. The degree of shortening of the QRS duration after pacing was much greater in responders. Similarly there was also a tendency for the QRS axis to normalize in the responders during pacing. However, practically, QRS shortening and axis changes do not serve as useful 'predictors' if the differences are seen only after pacing is instituted. Though there was no significant difference between the LV lead position sites between the responders and non-responders, there was a trend towards a greater number of lateral and anterior LV sites in patients whose symptoms and exercise tolerance improved.

Clinical improvement after BIV pacing has recently been shown to be paralleled by structural and functional improvement in LV dynamics as evidence by tissue Doppler echocardiography. 45 In 25 patients with DCM, functional class III-IV and QRS >140 ms, significant improvement in 6 min walk, quality of life score and NYHA functional class were
accompanied by significantly reduced LV end-diastolic (205±68 vs 168±67) and end-systolic volumes (162±54 vs 122±42 mLs) and reduced mitral regurgitation 3 months after BIV pacing. Moreover, when pacing was switched to sensing mode (ODO) increased in LV cavity volumes, prolongation of mitral regurgitation occurred within one week and deteriorated further after 4 weeks. This was again paralleled by clinical deterioration. This study demonstrated evidence of reversibility of LV remodelling in advanced heart failure with BIV pacing and suggested underlying mechanisms may include improved segmental LV synchrony, interventricular synchrony and reduced isovolumetric contraction time (‘wasted’ time).

Biventricular pacing — developmental directions

Patient selection

The identification of patients who will respond to ventricular resynchronization is the crux of appropriate and cost-effective utilization of BIV pacing therapy. It is most likely that the quality of resynchronization determines outcome, and as the evidence suggests this quality cannot be achieved simply by the assessment of ‘conventional’ parameters used to date, but rather by detailed documentation of ventricular asynchrony prior to therapeutic pacing. This may not only provide a predictor of resynchronization response but also a guide to optimal pacing site and pacing delay.

There is a reasonable correlation of the electrical (QRS axis and duration) with the mechanical parameters of ventricular synchrony, as indeed some studies have suggested using echocardiography\(^46\) and angioscintigraphy.\(^47,48\) Although current evidence suggest the surface ECG alone does not give enough information with respect to the degree and pattern of ventricular asynchrony hence response to resynchronization. Appropriate assessment may be achievable through alternative methods, the best of which is still unresolved.

Cardiovascular magnetic resonance is rapidly gaining credibility in the assessment of global and regional cardiac function.\(^49\) 3D-tagged magnetic resonance imaging can determine high resolution 3D wall motion imaging in patients with DCM and temporally display magnitude of asynchrony between ventricles in patients with conduction delay.\(^44,50\) However its role in the pre-assessment of patients for resynchronization therapy is yet to be established, particularly as it is not applicable after pacemaker implantation.

Echocardiography has therefore been widely exploited in an effort to demonstrate and quantify parameters of mechanical inter-ventricular asynchrony. In an echocardiographic study of 34 patients with idiopathic dilated cardiomyopathy who had biventricular pacemakers, investigators examined the magnitude of regional wall displacement during the cardiac cycle. When plotted over time, regional displacement curves or phase relationships were generated for the LV lateral wall and septum. The magnitude of asynchrony measured as dichotomy of phase relationship, was shown to correlate with improvement in the end-point of \%dP/dt after BIV pacing.\(^51\) In an earlier study, phase relationships between the RV and LV were calculated using similar algorithms with multiple gated equilibrium blood pool scintigraphy in patients with DCM before and after BIV pacing.\(^52\) This study demonstrated a significant negative correlation between interventricular asynchrony and LV EF calculated with scintigraphy. However, it was apparent in both these studies that QRS duration was quite closely related to degree of mechanical asynchrony and results did not demonstrate any superiority of ventricular phase relationships over QRS duration in predicting response to BIV pacing.

In a small study if 20 patients, Tissue Doppler imaging (TDI) was demonstrated to be a better predictor than QRS duration of improvement in LV EF and reduction of LV end systolic and diastolic volumes after BIV pacing in patients with advanced idiopathic DCM.\(^53\) However, this study did not report clinical improvement in patients whose echocardiographic parameters improved. In a study of 31 patients, investigators were able to use TDI to evaluate patients who would successfully respond to BIV pacing and clinical improvement in NYHA class and 6-min walk also improved in all patients although in this study TDI was no better than QRS duration as an overall predictor. However, the authors highlighted the potential of TDI in the evaluation of regional LV delay and its implications on pacing site selection, as greater improvements in LV end-systolic volume and LV EF were observed in patients paced specifically at sited of greatest delayed contraction.\(^54\)

Other possible avenues of development in evaluation of patients for BIV pacing include the calculation of cardiac cycle efficiency or Z ratio\(^39\) and M-mode long-axis function.\(^36,53\) The CARE-HF study already employs echo inclusion criteria as part of evidence for ventricular asynchrony, these include (1) delayed aortic ejection >140 ms, (2) interventricular delay of >40 ms between aortic and pulmonary ejection, and (3) delayed inward motion of
the postero-lateral LV wall in M-mode or tissue Doppler, occurring later than the start of LV filling.56

**Lead placement**

Acute studies demonstrated significant haemodynamic improvement after BIV pacing over RV pacing, however, the overall difference between BIV pacing and LV pacing alone was not impressive. In fact, some even demonstrated superior effect of lone LV pacing.32,35,36 This may ultimately question the need for an RV pacing lead when left sided resynchronization may alone suffice. If indeed an RV lead is placed the issue of relative LV to RV timing i.e. the effect of inter-ventricular delay on overall cardiac performance is still to be investigated.

Results from the PATH-CHF study40 suggested that a mid-lateral LV lead position correlated with best acute haemodynamic response. Others have shown better results with apical and mid-anterior positions compared with basal positions of the LV lead.57 As methods of identifying patients who respond to resynchronization are refined, so might those of identifying optimum LV pacing sites. This will inevitably expose the technical difficulties in LV via coronary vein lead positioning, as optimal sites may not always be accessible, being limited by venous anatomy and current lead placement technology. Advances in lead placement technology adopting over-wire techniques employed in coronary angioplasty may help problems of accessibility. These developments are not discussed in detail here but emphasize their importance.

**Atrial fibrillation**

It is evident from the criteria for DDD pacing in dilated cardiomyopathy, that the shortening of A-V delay is the basis of physiological improvement, which renders this mode of pacing in patients in atrial fibrillation (AF) unsuitable. A-V delay optimization during BIV pacing is also a contributing factor to its beneficial effects in patients in sinus rhythm, but the application of BIV pacing in chronic AF is still unclear. A logical approach in such patients, is to ablate the AV node and program a rate-responsive mode to the ventricular leads. The MUSTIC study also included 58 patients in AF whose enrolment criteria were the same as those in sinus rhythm although patients with QRS duration of longer than 200 ms during RV pacing were enrolled as QRS duration is generally longer during RV pacing than native conduction.42 All patients had AV nodal ablation and were randomized to receive either RV or BIV pacing. The two groups were crossed over to the alternative-pacing mode after 3 months. Like the patients in sinus rhythm, end-points in the AF group were better during BIV pacing, although the magnitude of improvement was smaller. Six-minute walk improved by mean 9.3%, peak oxygen uptake by 13% and rate of hospitalizations reduced by 70% after BIV pacing. Quality of life score did not improve significantly. A high drop-out rate resulted in only 37 patients (42%) completing crossover.58 Further studies are needed to qualify this approach.

**Mortality and Economy**

Though the clinical benefits of resynchronization therapy are clear, improved exercise capacity is a notoriously poor predictor of survival and so the long term effects on morbidity and mortality need to be established. Trials such as CARE-HF and COMPANION should help to answer this question. The CARE-HF study56 will recruit 800 patients in sinus rhythm with QRS duration of >150 ms and has recruited 560 patients to date. Patients will have stable heart failure of functional class III or IV on optimum medical therapy, LVEDD >30 mm height and EF <35%. In addition, all subjects will have echocardiographic evidence of ventricular asynchrony, the details of which were described above. Patients will be randomized, in open-label fashion, to receive atrio-biventricular pacing or no pacing therapy. In a minimum follow-up period of 18 months primary end-points will be all-cause mortality and unplanned cardiovascular admissions. The COMPANION trial59 was an open-label three-arm study which began recruiting heart failure patients with dilated cardiomyopathy with NYHA III or IV symptoms, EF <35% and QRS duration of 120 ms or more and a PR interval >150 ms. All patients had optimum medical therapy and were randomized to receive either no additional therapy, biventricular pacing alone or biventricular pacing with cardioverter-defibrillator capability, allocated in a 1:2:2 ratio. The COMPANION trial was terminated early after recruiting 1600 patients and after 950 of the anticipated 1000 end-points were reached, as combined biventricular pacemaker-defibrillators were found to reduce primary end-points of all-cause mortality and hospitalization.60 Total survival, cardiac morbidity and exercise performance were secondary end-points, the latter was investigated in a sub-study. Combined all-cause mortality and hospitalizations were 20% lower in the two device arms than in the no-device arm.61 This implies that defibrillator therapy conferred no additional benefit over BIV pacing alone on this
combined end-point. Total mortality however, was reduced from 19% in the no-device arm and 15% in the BIV pacing-only arm to 11% in the combined device arm, which represents a 40% reduction in total mortality from combined devices. The question of whether patients with a normal PR interval will show the same degree of benefit from BIV pacing still remains. This question addresses the issue whether benefit was gained from RV-LV resynchronization or atrio-ventricular resynchronization and ultimately has implications for the use of BIV pacing in AF. The official release of the COMPANION trial results are anticipated at the American College of Cardiology Congress in 2003.

Patients selected for BIV pacing invariably have significant ventricular disease and can also benefit from implantable cardioverter-defibrillators (ICD). The implantation of combined BIV pacemakers and ICD may ultimately have profound effects on survival if the initial results from current combined device trials like COMPANION support the evidence of smaller trial data in which patients with conventional indications for ICDs were implanted with combined devices. The results of such trials addressing issues of long-term survival and hospitalization will have implications on the cost-effectiveness for the use of such devices, alone or in combination. Though patients implanted with ICD for a conventional indication show improved survival, one may argue that since ICDs have not been shown to improve symptoms or quality of life, this therapy merely changes the mode of death from sudden cardiac death to progressive cardiac failure. However, there is still a case for reduced hospital admissions for conventional ICD therapy and for atrio-biventricular pacing when used independently, which when applied as combined devices may prove to have considerable positive economic implications.

Summary

The application of specific pacing therapies in heart failure needs to be directed at correcting specific electromechanical abnormalities resulting from abnormal activation. The application of dual chamber pacing with short AV delay has been described in patients with long PR intervals and short filling times of less than 200 ms and long atrioventricular regurgitation lasting more than 450 ms. The unspecified application of this pacing mode has invariably lead to unfavourable results. However, large trial data addressing long term clinical improvement and survival are lacking.

Though survival and mortality statistics after BIV pacing are still anticipated, using current application criteria based on symptom profile, basic echo parameters and QRS duration, the magnitude of the clinical improvement presented to date has been modest, perhaps reflecting the need for better means of measuring ventricular asynchrony and predictors of beneficial response to resynchronization. For this purpose studies selecting patients using echocardiographic techniques such as M-mode, tissue Doppler and long-axis function are in progress. As pacing only improves the timing of activation and not velocity or amplitude of myocardial contraction, the emphasis of these techniques in the identification of responders is based on timing of wall motion and useful versus wasted time within the cardiac cycle, rather than absolute dimensions and amplitude of myocardial motion.

In conclusion, to achieve their full potential pacing therapies must not be accepted as a universal last resort in refractory heart failure, but a specific therapy directed at correcting specific abnormalities of activation. This ethos may eventually open the therapy to use in the earlier stages of heart failure beyond its role in refractory disease when electromechanical abnormalities can be shown to predominate over those that may respond to medical therapy.

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