Review

Pacing in congestive heart failure

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Abstract

Despite the major advances in medical drug therapy, heart failure remains a syndrome associated with high mortality and morbidity. Biventricular or left ventricular (LV) short atrioventricular (AV) delay pacing is being tested in congestive heart failure patients with left bundle branch block. The aim is to resynchronise the dyscoordinate LV contraction. A number of studies are underway, but it is clear that while some patients respond remarkably, this is highly variable. Accurate identification of patients likely to benefit will be crucial. The mechanism of benefit is unclear. A greater understanding of the physiological consequences of pacing will be necessary to accurately identify these patients.

Keywords: bundle branch block, haemodynamics, heart failure, pacing

Introduction

During the past two decades there have been major advances in the pharmacological treatment of chronic heart failure. Despite this, severe heart failure remains a syndrome associated with very high mortality, profound reduction in quality of life, and frequent hospitalisation. Cardiac transplantation can be an extremely effective therapy in such cases, but its provision is severely rationed by the lack of available donor organs. This rationing will remain unless xenotransplantation becomes a reality. Other cardiac surgical interventions including revascularisation, dynamic cardiomyoplasty and myocardial reduction surgery have been employed, but are currently of unproven value. It is in this context that pacemaker therapy is currently being intensively evaluated as a therapy for such patients.

Short atrioventricular delay right-sided pacing

Initial interest in the role of pacing as a potential treatment for congestive heart failure (CHF) focused on prolonging diastolic filling time by reducing or abolishing presystolic AV valve regurgitation.

Rutishauser *et al* first reported the phenomenon of presystolic AV valve regurgitation in patients with CHF and complete heart block [1]. It became apparent with the advent of Doppler echocardiography that such presystolic regurgitation of the mitral and/or tricuspid valves is common in

AV = atrioventricular; CHF = congestive heart failure; ICD = implantable cardioverter defibrillator; LBBB = left bundle branch block; LVEDP = left ventricular end diastolic pressure; MR = mitral regurgitation; RV = right ventricular; TR = tricuspid regurgitation.

patients with first-degree AV or complete heart block [2–4]. Presystolic regurgitation has also been reported in CHF patients with normal AV conduction times if left ventricular end diastolic pressure (LVEDP) is markedly increased [5,6]. The AV pressure gradient, when LVEDP is high and the conduction time is prolonged, is thought to reverse before the onset of ventricular systole. Although this promotes valve closure, there is incomplete closure, resulting in valvular regurgitation and reduced ventricular filling time. In the context of a ventricle that is abnormally stiff (and therefore highly dependent on filling time, especially on exercise), this can have considerable adverse haemodynamic consequences. The presence of interventricular conduction prolongation (wide QRS complex) further shortens the left ventricular filling period [7].

Hochleitner *et al* first reported beneficial effects from dual-chamber short AV delay (100 ms) pacing in patients on a transplantation waiting list, but did not establish the mechanism of benefit [8]. Brecker *et al* subsequently reported improved exercise capacity and haemodynamics in 12 CHF patients with short AV delay pacing. Pacing with a short AV interval eliminated the presystolic component of AV valve regurgitation and increased ventricular diastolic filling times [5]. These observations were supported by smaller uncontrolled studies [9,10]. Since then, further reports of unselected patients have shown no overall short- or medium-term benefits; while individual patients have improved, others have deteriorated [11–13].

These mixed results may be explained by the fact that benefits from the reduction in presystolic AV valve regurgitation may be offset by the electromechanical dyssynchrony of right ventricular (RV) pacing. Right-sided pacing results in paradoxical motion of the interventricular septum (as seen in left bundle branch block [LBBB]). This may adversely affect LV performance as it may reduce LV diastolic filling time, result in dyssynchronous (and inefficient) LV contraction and reverse the normal base–apex activation sequence.

In a study of patients with coronary heart disease but without CHF, Betocchi *et al* demonstrated that right-sided AV sequential pacing caused an upward shift in the LV diastolic pressure–volume relation. There was also a reduction in LV peak filling rate, an increase in the time constant of isovolumic relaxation (tau), and a reduction in cardiac index [14]. Rosenqvist *et al* used radionuclide ventriculography to assess exercise responses in 12 patients without CHF. Cardiac output measured on exercise (with similar heart rates) was higher during atria pacing than during either dual chamber pacing or ventricular pacing. Paradoxical septal motion was apparent during ventricular pacing and dual chamber pacing, with a 25% impairment of regional septal ejection fraction [15]. There is, therefore, clear evidence that RV pacing impairs both systolic and diastolic function of the LV in patients without CHF.

Attempts to normalise the base–apex electromechanical sequence have produced conflicting results. Several studies in normal dogs and in patients without CHF have suggested that pacing from the RV outflow tract or interventricular septum may be superior to RV apical pacing [16–19]. Both acute haemodynamic and long-term studies in patients with CHF, however, have not shown any benefit [13,20,21].

Further evidence against RV pacing for CHF comes from the observation that it results in an increase in plasma norepinephrine levels [22] (a powerful adverse prognostic marker in CHF [23]).

The response to right-sided AV sequential pacing in CHF may depend on a balance between beneficial alleviation of presystolic mitral regurgitation (MR) and tricuspid regurgitation (TR) (in those patients with AV conduction delay and elevated LVEDP), and adverse consequences of dyssynchrony of left ventricular contraction and filling. Consistent with this, Nishimura *et al* reported that benefit was confined to those patients with presystolic MR and prolonged AV conduction, whereas other patients showed a worsening of haemodynamics [10]. It has been suggested, on this basis, that the decision to implant such a pacemaker should be based on the haemodynamic response to an acute pacing study [24]. However, enthusiasm for right-sided short AV delay pacing as a treatment for CHF has waned.

Biventricular and left ventricular pacing

In much the same way that RV pacing induces LV dysfunction, a similar dysfunction may arise from LBBB in patients with CHF. This conduction abnormality is present in 10–53% of patients with CHF and, when present, is associated with a worse prognosis [25]. 'Resynchronisation' of RV and LV contraction, by simultaneous (biventricular) pacing, would therefore appear logical. The technical feasibility of such an approach was reported by two groups in 1994 [26,27]; in these reports, lead implantation was performed at thoracotomy. Cazeau *et al* subsequently reported acute haemodynamic benefit from temporary AV sequential biventricular pacing in eight patients with severe CHF [28]. Further support came from two larger acute studies of patients with severe CHF. The first of these was from Blanc *et al*, in which CHF patients with first-degree AV block and/or LBBB, and a pulmonary capillary wedge pressure >15 mmHg were paced with a short AV delay and either biventricular, LV or RV pacing. Both LV and biventricular configurations were haemodynamically superior to baseline or to RV pacing [29]. Leclercq *et al*, in a similar patient group, also observed an equal magnitude of benefit from LV and biventricular pacing, comparing biventricular pacing with baseline or RV pacing (dual chamber pacing) in this study [30].

The long-term results of the 'Resynchronisation for Heart Failure' (In Sync) Trial were recently reported. This was an open study of biventricular pacing in patients with medically refractory NYHA III/IV heart failure with QRS duration >150 ms and left ventricular ejection fraction <35%. The predetermined end points were 6 min walk distance, NYHA functional class and quality of life at 1, 3, 6 and 12 months versus baseline. There were significant improvements in all three parameters at each time point when compared with baseline [31].

Several randomised and non-randomised studies of biventricular pacing are currently in progress or planned. Table 1 summarises the design (and where available results) of studies that are either completed or due to finish soon, whereas Table 2 lists the studies that have yet to commence or are in the early phases. Most of these studies are now assessing clinically important end points such as exercise capacity and quality of life in patients with severe CHF and LBBB. The Multisite Stimulation in Cardiomyopathy (MUSTIC) study [32] is the first single-blind, randomised, cross-over study of ventricular resynchronisation therapy in CHF. The cross-over design enabled patients to act as their own control, being paced for 3 months in each mode (ie biventricular/no ventricular stimulation). The MUSTIC study contained two patient groups: one in sinus rhythm and one in atrial fibrillation post-atrioventricular nodal ablation. This is based on the previous demonstration that, among patients with CHF and poorly controlled atrial fibrillation, AV nodal ablation and right ventricular pacing can result in symptomatic improvement [33,34]. The inclusion criteria for all patients were NYHA class III or IV, an ejection fraction <35% and significant ventricular conduction delay. The results of the sinus rhythm group have now been reported [35–37]. Biventricular pacing significantly improved both primary end points (VO_2 max and 6 min walk distance). There were significant improvements in quality of life (Minnesota questionnaire) and also in rehospitalisation (both prespecified secondary end points). At the end of the cross-over phase, 86% of patients chose (blind) biventricular pacing as their preferred mode for the longitudinal phase. Although further studies will need to address the question of mortality benefit, the availability of a non-pharmacological treatment that improves exercise capacity and quality of life would be a major advance. The quality-of-life issue is particularly pertinent as the baseline data in MUSTIC confirms the profound impairment of quality of life in NYHA class III and IV heart failure. The only concern is that some deaths occurred very soon after changes in pacemaker programming (ie soon after the cross-over from atria pacing to biventricular pacing or at the onset of biventricular pacing), raising the possibility that patients' biventricular pacing may be arrhythmogenic, perhaps because of the presence of two ventricular activation wave fronts. The timing of these few early deaths in a small subset may be a chance finding but requires clarification. One study has conversely shown a reduction in ventricular ectopic activity by biventricular pacing [38].

Preliminary results from the acute and chronic phases of the Pacing Therapies for Congestive Heart Failure (PATH-CHF) study have also been reported recently. The acute results emphasised the importance of optimising AV delay, and showed that LV pacing was superior to both RV pacing and biventricular pacing [39]. In the chronic study, significant improvements in VO_2 max, quality of life, 6 minute walk distance, NYHA class and ejection fraction were observed, with a progressive increment of benefit over the first 6 months. This benefit remained stable between 6 and 12 months [40].

Results of VIGOR CHF will be reported shortly. Patients with severe CHF due to dilated cardiomyopathy in sinus rhythm with intraventricular conduction delay underwent biventricular pacemaker insertion at thoracotomy. A single-blind, cross-over phase of biventricular pacing or no ventricular stimulation (6 weeks in each phase) followed by a 12 week longitudinal paced phase is present. The primary end point is the measurement of VO_2 max. Many patients with CHF meet the criteria for an implantable cardioverter defibrillator (ICD) [41]. Patients in VENTAK CHF with severe drug refractory CHF, a QRS duration >120 ms and indications for ICD implantation will undergo implantation of a biventricular pacemaker/ICD. The study is otherwise similar to VIGOR CHF [22]. The end points of the two studies are the same except that antitachycardia and defibrillator efficacy and safety are included as additional secondary end points. The feasibility of combined trans-venous biventricular pacing/automatic implantable cardioverter defibrillator implantation has recently been reported [42], leading to the addition of an ICD/pacing limb to the MUSTIC study.

There are several studies in the 'design and recruitment' stage, some of which now address the issue of mortality and healthcare cost issues; for example, Cardiac Resynchronisation in Heart Failure (CARE-HF). This study aims to assess mortality in a controlled patient group by randomising patients to biventricular pacing and optimal therapy, or optimal therapy alone. All-cause mortality and hospital admissions for decompensated CHF will be evaluated together with an assessment of a 6 minute walk distance and VO_2 max. The second end points of this study will be NYHA status, mortality, quality of life, neurohormone levels and echocardiographic indices.

Table 2 summarises the design of other important studies planned or in the early phases, including PACMAN, MIRACLE, COMPANION and RELEVANT.

Table 1

Studies completed or well advanced

Study	Lead implant	Inclusion criteria	Design	Primary endpoint	Secondary endpoint	Expected completion/outcome if known
VIGOR CHF [22]	Thoracotomy	Severe CHF due to DCM sinus rhythm intraventricular conduction delay	Randomised single-blind active versus no pacing for 6 weeks then VDD for a further 12 weeks	VO_2 max	6 min walk distance Quality of life questionnaire Plasma norepinephrine	Study will be reported shortly
VENTAK					Echocardiographic assessment	Completion Spring 2001
PATH CHF [40]	Thoracotomy	NYHA III/IV CHF Sinus rhythm > 55/min QRS > 120 ms PR > 150 ms; 42 patients	(1) Acute phase: acute haemodynamic study at time of implant to evaluate optimal pacing site and AV delay	Haemodynamics	–	(1) LV pacing superior to biventricular; both superior to RV pacing; optimisation of AV delay important
			(2) Chronic phase: single-blind, cross-over study biventricular pacing versus best unventricular pacing site assessed in acute study	VO_2 max 6 min walk distance	Quality of life questionnaire Echocardiographic assessment	(2) Significant improvement in all end points
InSYNC	Transvenous	NYHA III / IV (48% IHD) EF < 35% LVEDD > 60 mm QRS > 150 ms 103 patients on optimal therapy	Non-randomised trial Patients were implanted with biventricular pacer and assessed at 1, 3, 6 and 12 months	6 min walk distance QRS duration	NYHA class Quality of life	Completed Improvement in QOL, 6 min walk, reduction in QRS, symptoms irrespective of aetiology
MUSTIC [35]	Transvenous	NYHA III, EF < 35% QRS ≥ 150 or 180 for AF group Group I: sinus rhythm Group II: AF with AV node ablation	Single-blind, randomised, cross-over 12 weeks of biventricular versus no ventricular stimulation followed by a longitudinal phase in the patients preferred mode	6 min walk distance VO_2 max	Mortality or need for transplant/LVAD QOL Rehospitalisation and/or changes in drug therapy for decompensated CHF	Results in sinus rhythm group → improved 6 min walk distance, VO_2 max and QOL AF data to be presented late 2000

AF, atrial fibrillation; AV, atrioventricular; CHF, congestive heart failure; DCM, dilated cardiomyopathy; EF, ejection fraction; IHD, ischaemic heart disease; LVAD, left ventricular assist device; LVEDD, left ventricular end-diastolic diameter; QOL, quality of life; RV, right ventricular.

Table 2

Studies planned or in an early phase

Study	Lead implant	Inclusion criteria	Design	Primary endpoint	Secondary endpoint	Expected completion/outcome if known
PACMAN	Transvenous	NYHA III EF < 35% QRS > 150 ms (NYHA I + II data recorded in registry) 300 patients	Two patient groups (1) NYHA III + indication for AICD (2) NYHA III with no indication for AICD Biventricular pacing ON or OFF for 6 months	6 min walk	Quality of life Rehospitalisation	Estimated completion 2002/2003
MIRACLE	Transvenous	NYHA III/IV CHF Sinus rhythm QRS duration ≥ 130 ms EF ≤ 35%	Randomised double-blind biventricular pacing or no pacing for 6/12 months, then active pacing for long-term follow-up	6 min walk distance QOL NYHA	Neurohormones Echo indices VO_2 max	Recruitment completed 2000 Early results Spring 2001
COMPANION	Transvenous	NYHA III / IV for > 6/12 months QRS > 120 EF < 35% > 1 hospital admission in past year 2200 patients	Three treatment arms: (1) Biventricular + AICD + OT (2) OT (3) Biventricular + OT	All-cause mortality and hospitalisation	Total mortality and morbidity Symptoms and function	Estimated completion Dec 2002
RELEVENT	Transvenous	NYHA II–IV EF < 35% QRS > 140 ms LVEDD > 55 mm 400 patients	Two groups (1) 50% of patients; optimal medical therapy only (OT) (2) OT + LV based pacing (BiV or LV) Studied at 1 and 6 months, then every 6/12 months for 2 years	Safety and mortality	QOL Echo indicies Total mortality	Not yet started 2.5 year study
CARE HF	Transvenous	CHF with EF < 35% QRS ≥ 150 ms NYHA III/IV	Randomised biventricular pacing + optimal therapy Optimal therapy and no implant	All-cause mortality or hospital admissions CHF VO_2 max 6 min walk	NYHA status QOL Neurohormones Echocardiographic assessment	Not yet started Estimated completion 2003

AICD, automatic implantable cardioverter defibrillator; CHF, congestive heart failure; EF, ejection fraction; LVEDD, left ventricular end-diastolic diameter; OT, optimal therapy; QOL, quality of life.

The future

We are at a crucial point with this series of large clinical trials in the adoption or otherwise of pacing for the treatment of severe CHF.

Current philosophy on the use of pacing in CHF assumes that the mechanism of benefit arises from resynchronisation of ventricular contraction in patients with LBBB. The major studies are therefore evaluating biventricular pacing in severe CHF associated with LBBB. The evidence in support of this mechanism is far from conclusive.

If the mechanism of benefit was due to a resynchronisation of both ventricles, then biventricular pacing (in which synchronous depolarisation occurs together with a narrowing of the QRS complex) would be expected to be superior to LV pacing (which is associated with a much broader QRS complex). In acute haemodynamic studies, however, LV pacing has been shown to be either equal to [29] or superior to [21,39,43,44] biventricular pacing. We are not aware of any study showing the converse. Kass *et al* reported that patients with the greatest QRS prolongation showed the greatest acute haemodynamic benefit, but there was no relationship between QRS narrowing associated with pacing and acute haemodynamic improvement. LV pacing was specifically superior to biventricular pacing despite a much broader paced QRS complex. It is certainly true that analysis of pressure–volume loops suggested that the mechanism of benefit was an improvement in LV contractile function, with no significant change in LV diastolic compliance [21]. Varma *et al*, in a recent study, assessed the impact of different pacing sites on LV coordination using LV pressure–dimension loops in patients with CHF and LBBB. Dyssynchrony of intraventricular conduction results in a low 'cycle efficiency', yet there was no consistency regarding the optimal pacing chamber or site to improve cycle efficiency [45]. This group conversely observed that LV pacing provided greater overall acute haemodynamic benefit than biventricular pacing [44]. Kerwin *et al* recently showed that biventricular pacing did not improve intraventricular dyssynchrony, but did improve interventricular dyssynchrony [46].

The mechanism(s) of acute haemodynamic benefit from biventricular pacing is therefore not understood. Although Kass *et al* did not find evidence to support it, the possibility of an improvement in diastolic filling cannot be excluded. Right ventricular pacing clearly worsens diastolic filling [14], so the converse with LV pacing is certainly possible. CHF patients with high LVEDPs have marked diastolic ventricular interaction; that is, the filling of the LV is constrained by the RV and by the pericardium [47]. Our preliminary data suggests that, by permitting the LV to fill before the RV, LV pacing may improve filling in these patients with diastolic ventricular interaction, whether or not they have underlying LBBB [48,49].

All of these factors serve to emphasise the need to understand the effects of pacing on pathophysiology, in order to design optimally larger clinical trials. It is unlikely, given the non-uniform nature of the pathophysiology and the multiple potential effects of pacing (reduction in presystolic MR, recoordination of intraventricular versus interventricular contraction sequence with improvement in both contractile and diastolic function), that a 'one size fits all' strategy is optimal. It is possible that benefit may not be confined to patients with LBBB, nor necessarily that all such patients will benefit. Furthermore, LV pacing may be superior to biventricular pacing. Previous experience of a dichotomy between symptomatic and prognostic effects with positive inotropic agents in CHF should sound a note of caution. Encouraging preliminary data in this regard suggest that the improvement in myocardial contractile performance with biventricular pacing is associated with a fall in myocardial O_2 consumption [50]. Furthermore, whereas RV pacing increases plasma norepinephrine, biventricular pacing is associated with a reduction [22].

We strive to practice 'evidence based medicine'. We must, however, remember that simply by virtue of their size, large 'clinical trials' will not always provide the answers for individual patients. Unless such studies are directed by a sound understanding of pathophysiology, of its non-uniformity, and of the effects of therapy on this pathophysiology, the wrong questions may be asked in the wrong patients. This may lead to inappropriate therapy for some patients and missed therapeutic opportunities for others.

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