MECHANISMS BY WHICH CARDIAC RESYNCHRONISATION THERAPY IMPROVES CARDIAC PERFORMANCE IN HEART FAILURE

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ABSTRACT

This thesis assesses the mechanisms by which biventricular and left ventricular pacing improves cardiac performance in patients with heart failure. We demonstrated for the first time that CRT results in an improvement in acute haemodynamic variables in heart failure patients with a narrow QRS duration that is comparable to the effects seen in heart failure patients with a broad QRS duration. In addition, we have shown that both biventricular (BIVP) and left ventricular pacing (LVP) significantly reduce external constraint to left ventricular filling, resulting in an increase in effective filling pressure. In heart failure patients with evidence of external constraint at rest, the acute haemodynamic benefits of both BIVP and LVP were principally due to the relief of external constraint and preload recruitment. However, in those patients with evidence of electrical dyssynchrony and a broad QRS duration, a significant haemodynamic benefit was derived from an enhancement in left ventricular contractility, presumably as a result of a reduction in left ventricular dyssynchrony. Patients with external constraint appear to derive a greater haemodynamic benefit from pacing due to the significant increase in stroke work that is associated with relief of external constraint and preload recruitment, in addition to the increase in stroke work derived from enhanced contractility due to a reduction in dyssynchrony. These findings will inform better patient selection for this therapy and also optimisation of pacing strategy in individual patients.

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STATEMENT OF CONTRIBUTION

I undertook screening (with echocardiography, ECG and metabolic exercise testing) and recruitment of potential participants with a narrow QRS duration, as well as recruiting patients undergoing implantation of a biventricular pacemaker with a broad QRS duration.

I undertook the acquisition of the invasive haemodynamic data in 85% of all patients, and completed analysis of the data in all cases recruited. I was also involved in the collection and analysis of all echocardiographic data included in this thesis.

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CHAPTER 1

INTRODUCTION, LITERATURE REVIEW AND HYPOTHESES

INTRODUCTION

The worldwide prevalence of heart failure is increasing in part due to an ageing population. In the developed world, heart failure affects 1-2% of the general population (1), causing about 5% of all adult hospital admissions, and complicating a further 10-15% (2). It is estimated that 0.2% of the population are admitted to hospital with this condition each year. In the developed world, the major aetiological factors are ischaemic heart disease, hypertensive heart disease, idiopathic dilated cardiomyopathy and valvular heart disease. Patients with advanced heart failure (New York Heart Association (NYHA) class III-IV), have both a poor quality of life and a poor prognosis, with one third or more of patients dying within 6 months of diagnosis. The annual mortality amongst those surviving beyond six months is 10-15% (2). Death for patients with advanced heart failure is usually due to disease progression, or less commonly is sudden.

There have been several therapeutic advances in the treatment of heart failure over recent years, with the use of beta-blockers, Angiotensin-converting enzyme (ACE) inhibitors, Angiotensin II-receptor blockers and mineralocorticoid receptor blockers. However the prognosis remains extremely poor and there is probably limited potential for therapeutic benefit from additional neurohumoral blockade.

For more than a decade several pacing modalities have been considered for patients with severe drug refractory heart failure, with varying results. More recently randomized clinical trials, observational studies and mechanistic studies have produced unequivocal support for the use of biventricular pacing in patients with NYHA III-IV refractory heart failure and evidence of ventricular conduction delay, most commonly seen as left bundle branch block on the electrocardiogram (ECG). These studies have consistently demonstrated an improvement in functional status, quality of life and exercise capacity in these patients.

THE ROLE OF PACING IN HEART FAILURE AND THE DEVELOPMENT OF CARDIAC RESYNCHRONISATION THERAPY

Hochleitner *et* al (3) first described the use of conventional sequential AV pacing for the treatment of congestive heart failure. The authors initially reported that right-sided dual chamber pacing with a short programmed atrio-ventricular (AV) interval was of benefit in patients with heart failure who had no conventional indication for pacing, and demonstrated a reduction in NYHA class, fall in cardiothoracic ratio on chest X-ray, and an increase in both systolic and diastolic blood pressure. The benefit was due to a reduction in pre-systolic mitral regurgitation, and hence an increase in left ventricular filling period. Pre-systolic mitral regurgitation is pronounced in those patients with prolongation of the AV interval and an elevated left ventricular end diastolic pressure. The acute haemodynamic results in this and other studies (4;5) were impressive, however subsequent studies assessing effects on haemodynamic variables, symptoms and clinical outcomes in heart failure did not demonstrate significant benefits (6-8). More recently the 'Dual Chamber and VVI Implantable Defibrillator' (DAVID) study (9) and the 'Mode Selection' (MOST) study(10) have suggested that right ventricular pacing per se may increase the

incidence of heart failure. It is believed that despite restoring AV synchrony, the attendant abnormal left ventricular electrical activation pattern results in dyssynchronous mechanical activity.

Over the past decade an emerging body of evidence has shown the utility of both biventricular (BIVP) and left ventricular (LVP) pacing. The concept of biventricular stimulation was first tested clinically by Bakker et al, who demonstrated that BIVP improved functional capacity in patients with severe NYHA Class IV heart failure and left bundle branch block (LBBB) (11). The selection of patients with LBBB was based on the known adverse effects of LBBB, which results in late activation of the left ventricle (especially the left ventricular free wall) from the right ventricle via the septum, and subsequently a delay between the onset of left and right ventricular mechanical contraction. The presence of LBBB also results in abnormal ventricular septal motion, which in turn is related to interventricular dyssynchrony and an abnormal pressure differential between the right and left ventricle. The abnormal septal motion results in an increase in the left ventricular end systolic diameter and reduction in the left ventricular ejection fraction, cardiac output, mean arterial pressure and dP/dt_{MAX}. LBBB is associated with more severe symptoms of heart failure and also a higher mortality in heart failure patients (12;13).

In the mid-1990's there was considerable controversy as to whether the restoration of AV synchrony, sequential RV stimulation, or biventricular pacing might play a role in the treatment of patients with heart failure and conduction disturbances. The PATH-CHF study was designed to prospectively address these questions. This multicentre trial tested the hypothesis that acutely optimised, chronic atrial–synchronous biventricular stimulation in

patients with Class III-IV heart failure and conduction disturbances would lessen symptoms, increase exercise capacity, and improve quality of life. Results demonstrated a significant increase in functional capacity and quality of life, as well as a significant increase in anaerobic threshold and oxygen consumption at peak exercise (14). The initial clinical studies of long term biventricular pacing reported high peri-operative mortality figures, related to the early invasive epicardial lead placement procedure, involving thoracotomy under a general anaesthetic. Daubert *et al*, described the first transvenous approach for placing the left ventricular lead via the coronary sinus (15).

Several long term studies, of differing study design, have reported impressive results with biventricular pacing in heart failure patients with a prolonged QRS duration (>130ms) who are severely symptomatic (NYHA III-IV) despite optimal medication. The InSync study (16) reported significant improvements in exercise capacity, NYHA class and quality of life; the Multisite Stimulation in Cardiomyopathy (MUSTIC) study (17) reported a significant improvement in exercise tolerance, NYHA score, peak oxygen uptake and cardiac ejection fraction; the Multicentre InSync Randomized Clinical Evaluation study (MIRACLE) (18) reported a significant improvement in exercise capacity and quality of life, and a 50% reduction in hospitalisation in the first 6 months. Core centre analysis of the echocardiography data from the MIRACLE study also provides evidence of reverse remodeling of the left ventricle.

These studies were not powered to address mortality or morbidity as primary endpoints. However a meta-analysis of four studies (Contak CD, MUSTIC, MIRACLE, InSync ICD) with a total of 1634 patients reported a 51% reduction in progressive heart failure mortality from 3.5% to 1.7%, and a 21% reduction in hospitalization (19). The Comparison of

Medical Therapy, Pacing and Defibrillation in Heart Failure (COMPANION) study was a comparison of no pacing, biventricular pacing and biventricular pacing with ICD. It was halted prematurely because the ICD limb showed a 40% reduction in the combined end-point of death from or hospitalisation for heart failure, compared with a 34% reduction in the biventricular limb (20). This resulted in biventricular pacing being granted a class IIA indication by ACC/AHA/NASPE.

The results of CARE-HF have since been published. The trial was designed to evaluate the long-term effects of cardiac resynchronisation on the mortality and morbidity of patients with heart failure due to left ventricular systolic dysfunction with a QRS duration > 120msec who were already receiving optimal medical therapy. A total of 813 patients were randomised to device therapy or control and followed up for a mean of 29.4 months. The trial reported a 37% reduction in combined all-cause mortality (death) or unplanned cardiovascular hospitalisation, and a 36% reduction in all-cause mortality (21).

TABLE 1.1. Major trials of Cardiac Resynchronisation Therapy in heart failure

	MUSTIC	INSYNC	MIRACLE	COMPANION	CARE-HF
Number	n=131	n=103	n=453	n=1520	n=813
Design	Randomised Controlled	Prospective Observational	Double-Blind, Randomised Controlled	Randomised Controlled	Randomised Controlled
Criteria	NYHA III EF < 35% QRS > 150	NYHA III/IV EF < 35% QRS > 150	NYHA III/IV EF < 35% QRS > 130	NYHA III/IV EF < 35% QRS > 120	NYHA III/IV EF < 35% QRS > 120
Outcome	↑ QOL ↑ EF ↑ 6MWD ↓ NYHA Class ↑ Peak VO2 max	↑ QOL ↑ EF ↑ 6MWD ↓ NYHA Class ↑ Peak VO2 max	↑ QOL ↑ EF ↑ 6MWD ↓ NYHA Class ↑ Peak VO2 max	34% ↓ (CRT) 40% ↓ (CRT-ICD) in death or hospitalisation due to CHF 24% ↓ (CRT) 36% ↓ (CRT-ICD) in death	37% ↓ in death / unplanned hospitalisation for a CVS event 39% ↓ in unplanned hospitalisation for a CVS event

MECHANISMS OF BENEFIT IN RESPONSE TO CARDIAC RESYNCHRONISATION THERAPY (CRT)

Several mechanisms are thought to be responsible for the benefit seen in response to CRT in patients with heart failure.

ELECTRICAL AND MECHANICAL RESYNCHRONISATION

Dilatation of the left ventricle and associated fibrosis frequently induces intracardiac conduction delays resulting in dyssynchronous left ventricular motion. This often manifests as LBBB on the surface ECG. Biventricular pacing is currently advocated for patients with NYHA III and IV Class symptoms despite optimal medical therapy who have prolonged QRS durations (>120 ms). The latter is based on the original rationale that biventricular pacing acts via an improvement in cardiac 'electrical synchrony', hence the frequently used term "resynchronisation therapy". The phenomenon of dyssynchrony is a consequence of a progressive, global, or focal disorder of the myocardium, leading to heterogeneous propagation of cardiac electrical and mechanical activity. There are at least three components to dyssynchrony that may impair cardiac function by affecting the systolic and diastolic properties of the heart.

(a) Prolongation of the atrio-ventricular (AV) conduction time leading to AV dyssynchrony is common in patients with heart failure (22). The delay in the onset of ventricular systole following passive and active ventricular filling gives rise to pre-systolic mitral regurgitation (23). This results in a lower left ventricular preload, higher pulmonary capillary wedge pressure, and a decreased cardiac output.

(b) Interventricular dyssynchrony occurs when the left and right ventricles fail to contract simultaneously. This is usually as a result of right or left bundle branch block, and often leads to septal contraction which is out of phase with one or other ventricular free wall.

(c) Intraventricular dyssynchrony occurs when there is marked heterogeneity in the timing of mechanical events between different segments of the left ventricle. As a consequence the ventricle expends a great deal of energy changing its shape but not ejecting blood. This dyssynchrony commonly extends to the papillary muscles resulting in mitral regurgitation. Although partly due to electrical dyssynchrony, other factors appear to contribute to mechanical dyssynchrony (24;25).

There is increasing evidence that there is only a weak correlation between electrical (QRS duration) and mechanical dyssynchrony and the benefit of CRT therapy (17;18;25;26). A substantial proportion of patients with a prolonged QRS duration (up to a third) do not exhibit inter- or intraventricular dyssynchrony (26;27), which may at least partly explain why up to a third of heart failure patients with prolonged QRS duration derive no benefit. Furthermore, dyssynchrony is common even in heart failure patients with narrow QRS complexes (28), a group currently excluded from biventricular pacing treatment guidelines.

There is as yet no gold standard technique for quantifying intraventricular mechanical dyssynchrony. The QRS width on surface ECG is a simple method often used as a surrogate for mechanical dyssynchrony, but the sensitivity for predicting the benefit from CRT is low (29;30). MRI can also detect areas of dyssynchrony, but this technique is expensive and cannot be repeated for follow-up after device implantation. Echocardiographic tools are the most useful for the assessment of dyssynchrony. Studies have shown that measuring time to peak tissue velocity (Ts) from myocardial velocity curves using Tissue Doppler Imaging (TDI) is useful for quantitative assessment of systolic dyssynchrony. In particular, the dyssynchrony index (Ts-SD), or standard deviation of Ts in a 12-segment model, was a powerful predictor of LV reverse remodeling

after CRT therapy (31). Tissue Synchronisation Imaging (TSI) is a technological advancement in the assessment of systolic dyssynchrony by transforming the Ts into different colour-coding. It has the advantage of providing a visual aid for quick identification or regional delay within the LV wall. Yu *et al* have shown a good correlation between Ts or Ts-SD derived from both TDI and TSI (31). However, recent evidence suggests that conventional measures of dyssynchrony have high inter-observer variability (32) and may also underestimate the magnitude of dyssynchrony because they ignore radial dyssynchrony. Current dyssynchrony analysis is based on echo-Doppler methods which are largely derived from longitudinal motion data. This choice of orientation is mainly based on practical grounds given the available echocardiographic windows for transducer positioning. However, due to epicardial and subendocardial fiber orientation, cardiac contraction is principally radial. Helm and colleagues have demonstrated in a failing heart that dyssynchrony assessed by longitudinal motion is much less sensitive (33), suggesting that longitudinal motion data may not provide the most accurate and comprehensive means of assessing left ventricular dyssynchrony.

REDUCTION IN MITRAL REGURGITATION

Three mechanisms are responsible for mitral regurgitation in congestive heart failure.

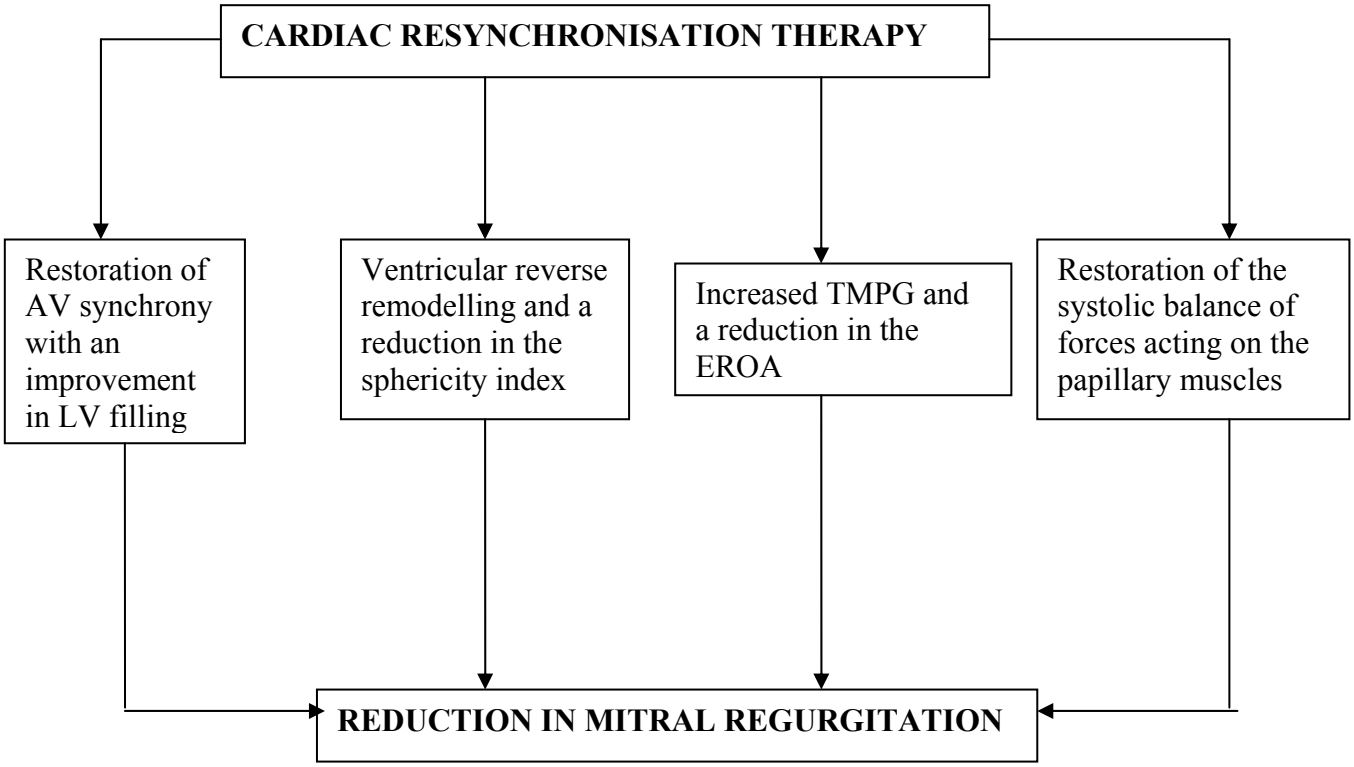
(a) As mentioned earlier, prolongation of the AV interval generates pre-systolic mitral regurgitation by generating a diastolic ventricular-atrial pressure gradient. This is because the end of atrial contraction occurs much earlier than the onset of the rise in intraventricular pressure. Because of the altered geometry within a dilated left ventricle, appropriate mitral or tricuspid closure is probably not complete until the start of ventricular contraction. This can lead to early systolic or late-diastolic

mitral regurgitation. Brecker et al (4) showed that pacing with short AV intervals can reduce or abolish diastolic mitral regurgitation.

(b) 'Functional' systolic mitral regurgitation in dilated cardiomyopathy is a result of ventricular dilatation and increased chamber sphericity. The resultant increase in distance between the papillary muscles to the enlarged mitral annulus, as well as to each other, restricts leaflet motion and increases the force needed for effective valve closure (34-36). The mitral valve closing force is determined by the systolic left ventricle-left atrium pressure difference (or transmitral pressure gradient). Increasing this pressure gradient can decrease the effective regurgitant orifice area (EROA). Studies have shown that CRT (by re-coordinating LV contraction) acutely increases the maximal rate of LV systolic pressure rise (dP/dt_{MAX}) and thus the transmitral pressure gradient (37;38). Breithardt *et al* (39) studied 24 consecutive patients with severely impaired LV function, LBBB, and functional mitral regurgitation. CRT acutely reduced the severity of mitral regurgitation by decreasing the effective regurgitant orifice area (EROA). This effect was directly related to an improvement in LV systolic function causing an accelerated rise in the transmitral pressure gradient (TMPG). The acute effect was independent of geometrical changes (reverse remodelling).

(c) Kanzaki *et al* (40) have described a further mechanism for the reduction in mitral regurgitation seen with CRT. Mitral regurgitation in patients with a LBBB relates to an altered systolic balance of forces acting on the papillary muscles due to uncoordinated regional LV contraction. Utilising strain imaging on echocardiography, they demonstrated a delay in peak strain at the mid-lateral segment adjacent to the anterolateral papillary muscle (implying tethering of the mitral leaflet), which was improved immediately after CRT.

FIGURE 1.1. Mechanisms of Improvement in Mitral Regurgitation



LEFT VENTRICULAR REVERSE REMODELLING

Biventricular pacing has been shown to have a beneficial effect on left ventricular remodelling. Enhanced ventricular ejection efficiency resulting from coordinate contraction, a reduction in mitral regurgitation, and a reduction in sympathetic/parasympathetic imbalance may contribute to chronically unload both ventricles and initiate reverse remodelling.

(a) Effects on left ventricular chamber geometry and dimensions

In a non-randomised study, Yu *et al* evaluated 25 NYHA class III-IV patients with an ejection fraction <40% and a QRS duration >140ms, who received biventricular pacing. Continued pacing at 3 months in these patients resulted in significant improvements in ejection fraction, left ventricular volumes, dP/dt_{MAX}, myocardial performance index and the degree of mitral regurgitation, as well as a decrease in the

sphericity index. Withholding pacing for a 4 week period resulted in a progressive, but not immediate, loss of effect. It was concluded that the improvement in left ventricular mechanical dyssynchrony was the mechanism for this (41). Data from several randomised trials consistently shows that CRT is able to induce reverse remodeling in the vast majority of patients. Stellbrink *et al* analysed 25 patients included in the PATH-CHF trial, focusing on changes in LV volumes after CRT. Left ventricular end diastolic (LVEDD) and end-systolic dimensions (LVEDS) were significantly reduced after 6 months, as were LV volumes (42). These findings are supported by data from the MIRACLE, CONTAK-CD, Vigor-CHF and INSYNC-ICD trials.

(b) *Effects on neurohumoral pathways*

Sympathetic activity is increased in patients with congestive heart failure, as demonstrated by elevated levels of circulating noradrenaline and an increase in adrenergic nerve outflow, as measured with microneurography. The cause of this increase is thought to be in part due to abnormal baroreflex control of adrenergic flow from the central nervous system. Although initially compensatory, chronic adrenergic activation promotes disease progression. Saxon *et al* recently reported no significant alteration in noradrenalin levels during three months of biventricular pacing (43). However, Hamdan and colleagues compared BV pacing with single-site pacing in patients with LV dysfunction. Results demonstrated that both acute BV and LV pacing reduced sympathetic activity compared with RV pacing regardless of the QRS duration (44), and Braun *et al* demonstrated significant decreases in noradrenalin and NT-proBNP after short-term CRT in patients with congestive heart failure and conduction delay, although this effect was attenuated after 24 months of long-term follow-up (45).

IMPROVEMENT IN LEFT VENTRICULAR FILLING

Cardiac resynchronisation therapy may improve the diastolic filling time of the left ventricle in several ways:

1. Reducing pre-systolic mitral regurgitation
2. Improving ventricular synchrony during active relaxation, biventricular pacing might theoretically improve diastolic filling, although two studies have reported no improvement in Tau (25;38)
3. Reducing external constraint to left ventricular filling

EXTERNAL CONSTRAINT AND DIASTOLIC VENTRICULAR INTERACTION

In 1895, Otto Frank (46) observed that as the left ventricle was stretched its force of contraction increased. Subsequently, Starling (47) reported that the force of ventricular contraction increased with increasing atrial pressure (the Starling relation), and later proposed a descending limb of the Starling curve (i.e. indicating a reduction in myocardial contraction at very high filling pressures). In an editorial in 1965, Katz (48) concluded that a descending limb of the Starling curve did indeed exist in severe heart failure, and had serious prognostic consequences. Data that have emerged since that time suggest that this descending limb relates to DVI in heart failure. Dupuis *et al* (49) reported a sustained haemodynamic benefit in some patients with severe chronic heart failure from a 72 h infusion of nitroglycerine. Among patients whose stroke volume increased, a tendency towards an increased LVEDV was noted, despite a fall in pulmonary capillary wedge pressure. Among patients in whom the stroke volume fell, however, LVEDV generally dropped.

Atherton *et al* (50) and Dauterman *et al* (51) have shown that in many heart failure patients the filling of the left ventricle may be impeded by external constraint from the raised pressure in the

stretched pericardium (pericardial constraint) and from the right ventricle via the interventricular septum (diastolic ventricular interaction). In these circumstances reducing central blood volume may acutely increase left ventricular diastolic volume despite reducing LV diastolic pressure. This is because the reduction in external constraint from the right ventricle and pericardium increases the true left ventricular distending pressure. LV pacing induces a phase shift such that LV contraction and filling both occur before they do in the RV (52-54). Because pericardial stretch (and therefore pericardial pressure) depends on total cardiac volume, a smaller RV volume during LV filling would result in less constraint to LV filling, a greater LV end-diastolic volume, and (by the Frank Starling mechanism) a greater LV stroke work. Bleasdale and colleagues (55) recently showed that LV pacing reduced this external constraint, effectively recruiting preload, presumably by causing the LV to fill relatively earlier, and therefore reducing the external constraint acting on the left ventricle at mid-diastole.

PATIENT SELECTION FOR CARDIAC RESYNCHRONISATION THERAPY

The present guidelines for patient selection for CRT are based largely on the entry criteria for the aforementioned larger clinical trials. The present criteria, as published by the National Institute for Clinical Excellence (NICE, 2003) are: drug refractory symptoms, NYHA III-IV, ejection fraction <35%, QRS duration >120ms, non-reversible cause, left ventricular end diastolic dimension >6cm. Despite the positive results of CRT trials, more than a third of patients receiving CRT therapy are non-responders. As mentioned earlier, echocardiographic markers of mechanical dyssynchrony show considerable variation in patients with broad QRS duration, and marked mechanical dyssynchrony may be present in heart failure patients with narrow QRS duration (25;28). Biventricular pacing (which reduces QRS duration) reduces indices of mechanical dyssynchrony, but curiously, despite increasing QRS duration, LV pacing also reduces mechanical dyssynchrony (25).

Furthermore, the BELIEVE study reported comparable clinical benefit from left ventricular and biventricular pacing (56). Nevertheless, several studies, using a variety of techniques have shown that biventricular pacing produces the greatest echocardiographic, haemodynamic and clinical benefit in those patients with the greatest mechanical dyssynchrony at baseline and reductions in dyssynchrony with pacing also predict these benefits (41;57;58). Some patients with narrow QRS complexes (who do not fulfill current criteria) may benefit. A better understanding of the mechanisms of benefit of biventricular and left ventricular pacing may lead to improved patient selection and optimisation of pacing strategy in individual patients.

TABLE 1.2. Current Guidelines for CRT Therapy

NICE GUIDELINES	•Drug-refractory, NYHA Class III-IV •LVEF < 35% •Sinus rhythm •QRS Duration >150ms OR QRS >120ms and mechanical dyssynchrony on echocardiography •LVEDD > 6cm •Non-reversible cause
ACC/AHA/NASPE GUIDELINES – CLASS IIA INDICATION	•Drug-refractory, NYHA Class III-IV •Dilated or ischaemic cardiomyopathy •QRS duration >130ms •LVEDD ≥ 55mm •LVEF ≤ 35%

SPECIFIC QUESTIONS TO BE ANSWERED

Aside from the haemodynamic benefits from cardiac resynchronisation therapy, many questions still remain:

(a) CRT in Patients with Heart Failure who have a Narrow QRS Duration

Previous small studies in patients with a narrow QRS duration have focused on clinical and echocardiographic end-points. Although these have shown a benefit from CRT based on clinical and echocardiographic parameters, these studies included QRS durations of < 150ms as 'narrow' and were limited to patients with evidence of dyssynchrony on echocardiography. In a study by Achilli *et al* (59), the authors report the efficacy of CRT in such a group of patients, with 14 of the 56 patients having a QRS duration of < 120ms. These findings were supported by those of Gasparini and colleagues (60), who reported an improvement in clinical and echocardiographic parameters in patients with a narrow QRS (13 of whom had a QRS < 120ms). The studies by Bleeker *et al* (61) and Yu *et al* (62) included 33 and 51 patients respectively with a QRS < 120ms. They showed an improvement in clinical parameters and evidence of left ventricular reverse remodeling, but in addition the study by Yu *et al* showed an improvement in exercise capacity as evidenced by an improvement in maximal metabolic equivalent achieved on treadmill testing (62).

However, a recent much larger study (RETHINQ) in an ICD population who all met conventional dyssynchrony criteria for CRT but had QRS duration <130msec did not report a significant improvement in exercise capacity or evidence of reverse remodeling (63).

(b) Biventricular (BIVP) Versus Left Ventricular Pacing (LVP)

Despite marked differences in ventricular pacing-induced QRS widths, BIVP and LVP pacing have proved equally effective in enhancing cardiac function in failing human hearts with LV dyssynchrony (37;38;64;65). This similar haemodynamic improvement despite striking differences in QRS duration supports the concept that mechanical rather than electrical resynchronisation is likely to be the most important phenomenon in achieving benefit from pacing therapy.

In order to clarify the respective mechanisms of BIVP and LVP responsible for similar haemodynamic improvement despite differing electrical activation, Bordachar *et al* (38;66) conducted an acute echocardiographic study in 33 severe heart failure patients to compare haemodynamic and dyssynchrony parameters during the two modes of pacing. Results showed that although LVP and BIVP produced similar haemodynamic improvements, LVP was associated with a substantial reduction of intra-LV dyssynchrony. However, it was also associated with a shortened LV filling time and a longer aortic pre-ejection delay (time to onset of aortic flow on continuous wave Doppler), as well as worsened interventricular dyssynchrony. However, to date only intraventricular and not interventricular dyssynchrony has been associated with an adverse outcome in patients with heart failure (38;67;68).

As mentioned earlier, one of the mechanisms of improvement with CRT in heart failure is a reduction in external constraint. LVP induces a phase shift such that LV contraction and filling both occur before they do in the RV. Whether BIVP may similarly reduce external constraint is uncertain. Because it would be expected to produce a lesser phase shift in the time of ventricular filling, the benefit may not be as great.

HYPOTHESES

(1) The acute haemodynamic benefits of LVP and BIVP are similar in patients with heart failure and narrow QRS complexes to those seen in patients with broad QRS complexes.

(2) The acute haemodynamic benefits of LVP are principally due to a reduction in diastolic ventricular interaction.

(3) BIVP reduces diastolic ventricular interaction (in those in whom it is present) in patients with broad QRS complexes but not in those with narrow QRS complexes.

AIMS OF THE STUDY

Despite the wealth of data available on the effects of Cardiac Resynchronisation Therapy in congestive heart failure, a number of important questions remain. This study will assess the mechanisms by which biventricular and left ventricular pacing improves cardiac performance in patients with heart failure. It will assess the relative contributions of reduced diastolic ventricular interaction, enhanced contractility, and a reduction in mitral regurgitation to the acute benefit of each pacing modality in heart failure patients with both narrow and broad QRS complexes. The findings will better inform patient selection and also allow optimisation of pacing strategy in individual patients according to underlying physiology.

CHAPTER 2

METHODOLOGY AND STUDY PROTOCOL

ASSESSMENT OF CARDIAC PERFORMANCE BY PRESSURE-VOLUME LOOPS

Assessment of left ventricular systolic and diastolic pump properties is fundamental to advancing our understanding of cardiac pathophysiology and assessing the effects of both pharmacologic and non-pharmacologic therapies, particularly in heart failure. The use of the ventricular pressure-volume relation began as far back as 1895, when Otto Frank first described the relationship between filling volume and strength of myocardial contraction (46). However, the technique proceeded at a slow pace thereafter due to difficulties with assessing ventricular volumes in the intact human or animal heart(69;70).

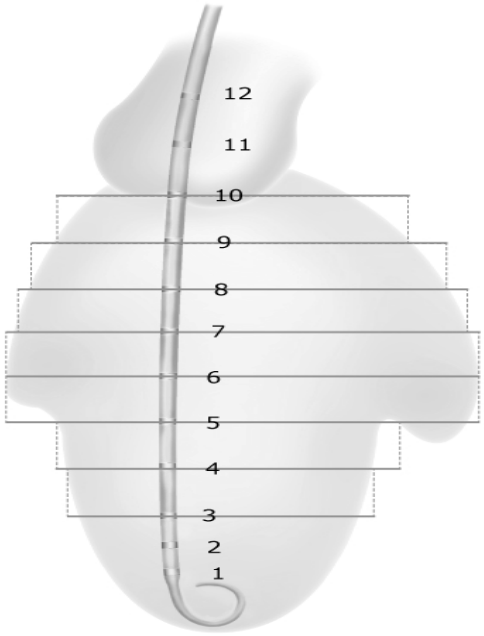
With the development of the isolated blood-perfused canine heart model there was a resurgence of activity in the 1970's and 1980's (71;72). This led to a series of pivotal studies detailing the use of end-systolic and end-diastolic pressure-volume relations (ESPVR and EDPVR) as a measure of intrinsic myocardial pump properties (72;73). Further studies have described the characteristics of these relationships in detail, and have validated techniques for measuring ventricular volume (74), allowing these techniques to be applied to basic and clinical research. In addition, the physiological significance of the ESPVR and EDPVR has been demonstrated by their correlation with myocardial energy demand (75;76). Because the technique is applicable to the hearts of all species, pressure-volume analysis has become a standard technique in studies of both humans and animals of all sizes.

When assessing cardiac performance, it is important to remember that two distinct properties of cardiac function, that are intimately interrelated, are being assessed. One is assessment of the properties of the ventricle as a haemodynamic pump (both systolic and diastolic), and the second intrinsic properties of the myocardium itself. However, pump function is dependent on intrinsic myocardial properties such as muscle mass, myocardial architecture, and chamber geometry. The pressure-volume relation is used mainly to assess ventricular pump function, but some parameters derived from this relation yield information about intrinsic myocardial properties.

THE CONDUCTANCE CATHETER TECHNIQUE

The conductance catheter technique developed by Baan et al (74;77) enables continuous real-time measurements of left ventricular (LV) volume and pressure. The method has been described extensively as a method of assessment of global systolic and diastolic ventricular function. The conductance methodology is based on the measurement of electrical conductance of the blood within the left ventricle. The catheter contains multiple electrodes which when positioned along the long axis of the left ventricle generate an intra-cavitary electric field (utilising the two most distal and two most proximal electrodes) and sense the resulting voltage gradients. The remaining electrodes measure segmental conductance signals which represent the instantaneous volumes or corresponding slices of the left ventricle (Figure 2.1).

FIGURE 2.1. Positioning of conductance catheter in the left ventricle



The measured conductance (applied current divided by the measured voltage gradient) is subsequently converted to an absolute volume by taking into account the specific conductivity of the blood and the electrode spacing. Parallel conductance (the offset in volume due to structures surrounding the left ventricular cavity i.e. the right ventricle) is determined by the hypertonic saline dilution method (74;78), and subsequently subtracted.

The conductance-derived stroke volume and cardiac output are generally an underestimation of actual stroke volume and cardiac output due to electrical field inhomogeneity and because the segments do not fully cover the LV long axis.

This is corrected by using a slope factor (α) which is calculated by comparing the catheter-derived cardiac output, and the cardiac output determined using the Fick equation:

$$\textit{Fick cardiac output} = \frac{\textit{O}_2\textit{ consumption}}{\textit{((arterial sats) – (mixed venous sats)) x Hb x 1.34 x 10}}$$

Hence:

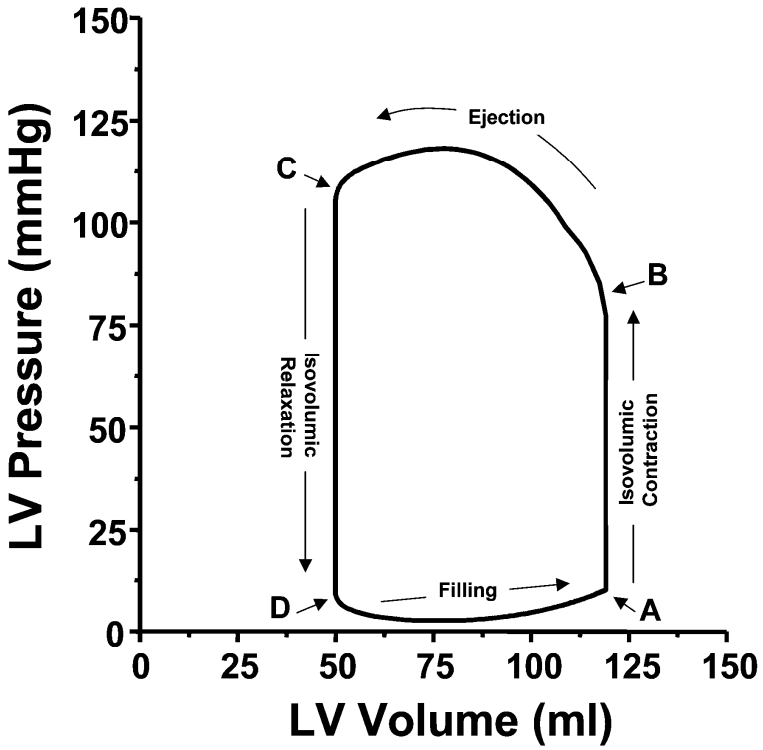
$$\textit{Slope factor (α)} = \textit{Catheter derived cardiac output / Fick cardiac output}$$

The catheter also contains a solid-state, high-fidelity pressure sensor to measure instantaneous left ventricular pressure. Currently most pressure-volume studies performed in humans use combined pressure-conductance catheters. These catheters are typically 7-French, over-the-wire, pigtail catheters which are connected to a dedicated patients module to allow generation of an electric field, measurement of resting voltages, and the acquisition of pressure, volume and ECG signals.

GENERATED PRESSURE-VOLUME SIGNALS, LOOPS AND RELATIONS

When positioned in the long-axis of the LV, the combined pressure-conductance catheter yields real-time segmental volume signals and an LV pressure signal with a temporal resolution of 4ms. The total LV volume is then calculated as the instantaneous sum of the segmental volumes. In order to assess ventricular pump function, pressure and volume signals are combined to construct a pressure volume loop, with each loop representing one cardiac cycle. The distinct cardiac phases are shown in Figure 2.2. Important parameters of both systolic and diastolic ventricular function can be determined either directly from the pressure-volume loop, or from the pressure and volume time curves and their derivatives.

FIGURE 2.2. A representative pressure-volume loop. Cardiac phases and timing of aortic and mitral valve opening and closure are depicted

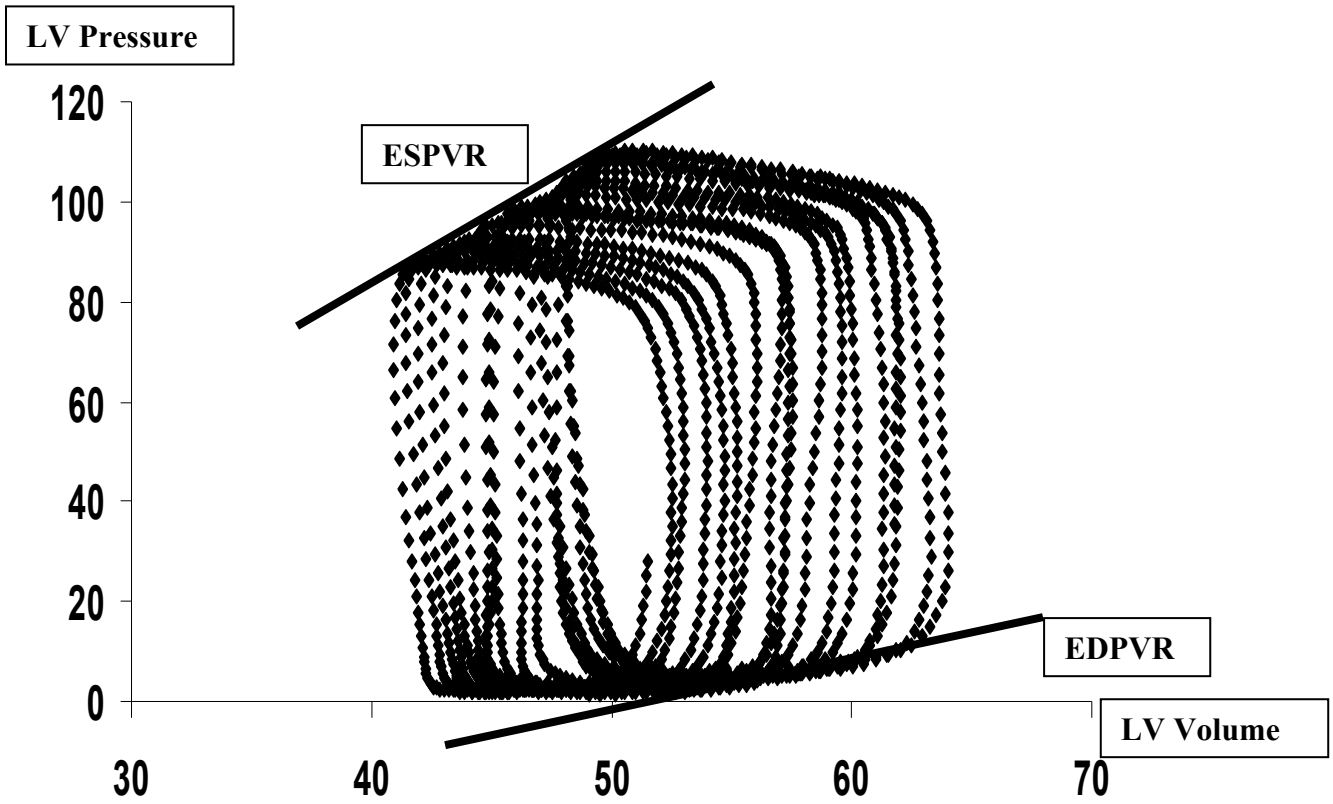


A. Mitral valve closure; B. Aortic valve opening;

B. C. Aortic valve closure; D. Mitral valve opening

Many of these parameters are to a large extent load-dependent, and in order to overcome this problem it is possible to construct pressure-volume relations which are much less load-dependent. This requires the acquisition of a series of pressure-volume loops over a range of loading conditions, which must be achieved by an intervention that has minimal effect on intrinsic myocardial function. This can be achieved utilising inferior vena caval balloon occlusion, which results in a rapid, purely mechanical, reduction in preload which is easily and rapidly reversible. A typical example is shown in Figure 2.3.

<u>FIGURE 2.3.</u> Pressure-volume loops acquired during preload reduction by means of inferior vena caval occlusion.



ESPVR – End-systolic pressure-volume relation

EDPVR – End-diastolic pressure-volume relation

ASSESSMENT OF SYSTOLIC FUNCTION

INDICES OF CARDIAC CONTRACTILE FUNCTION

Important parameters characterising left ventricular contractile function can be determined directly from the pressure-volume loop without the need for construction of curves or relations between variables. These include stroke volume, cardiac output, stroke work, and $dP/dt_{MAX.}$ An important limitation of all of these indices is their relative load-dependence.

END-SYSTOLIC PRESSURE VOLUME RELATION (ESPVR)

As demonstrated by Figure 2.3, the ESPVR is constructed by connecting the pressure-volume points of each loop acquired during IVC occlusion. The ESPVR characterises the properties of the left ventricle at the point of maximal activation, and was initially thought to be a reasonably linear relation with a slope (E_{ES} – end-systolic elastance) and an intercept on the volume axis (V_O). Inotropic agents that increase contractile state have been shown to increase E_{ES} with relatively little change in V_O (i.e. an increase in the slope of the ESPVR), while negative inotropes decrease the E_{ES} with little effect on V_O (79). Similarly, increases in heart rate result in an increase in E_{ES} via the force-frequency relationship.

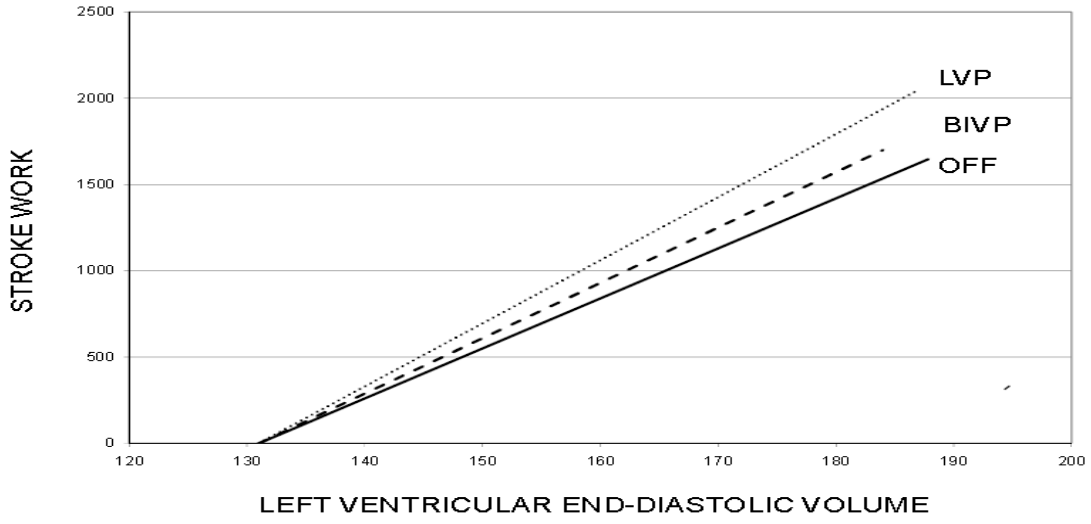
In the latter studies the end-systolic pressure volume relation (ESPVR) was determined using the single-beat method (E_{ES}) adopted from Takeuchi *et al* (80). There are several limitations to the assessment of ESPVR. Firstly, the ESPVR has been shown to be influenced by afterload impedance, but this effect is relatively small and can generally be ignored in most in-vivo studies as afterload conditions do not vary over very wide ranges. Secondly, the ESPVR is in reality non-linear over the entire range of pressures, and becomes convex in situations of enhanced inotropic state and concave with depressed inotropic state (81). Thirdly, ESPVR is dependent on muscle mass and geometry, but this

effect can be ignored in acute studies which assess an intervention and these variables are fixed over the various interventions.

PRELOAD RECRUITABLE STROKE WORK RELATION (PRSWR)

The PRSW relation is generated by plotting stroke work against end-diastolic volume during preload-reduction, resulting in a slope (M_w) and an axis intercept value (which is represented by the theoretical unstressed volume of the heart at a point when stroke work is equal to zero) (Figure 2.4). The theoretical unstressed volume of the heart is calculated using the equation LVEDV multiplied by a constant value k=0.72 for hearts with an end diastolic volume ≥ 95.7ml (82). This relation has many advantages over assessment of the ESPVR, including linearity, afterload independence, heart rate independence, and an independence of heart size, and presents the gold-standard for assessing changes in myocardial contractile performance.

FIGURE 2.4. Preload recruitable stroke work relation from a study patient during no pacing (OFF), biventricular pacing (BIVP) and left ventricular pacing (LVP)



ASSESSMENT OF DIASTOLIC FUNCTION

INDICES OF ACTIVE RELAXATION AND LEFT VENTRICULAR FILLING

Important parameters characterising left ventricular relaxation and filling can be determined directly from the pressure data, although these too are limited by their dependence on load. These include dP/dt_{MIN} (minimal rate of pressure change) and Tau (τ), the relaxation time constant.

END DIASTOLIC PRESSURE VOLUME RELATION (EDPVR)

The EDPVR is intrinsically non-linear due to different types of structural fibres being stretched in different pressure-volume ranges (83). In the low pressure-volume range compliant elastin fibres and myocytes with sarcomeric titin molecules account for diastolic stiffness (84), resulting in only a small increase in pressure for any given increase in volume. As volume is increased further, pressure rises more steeply as the slack lengths of collagen fibres and titin molecules are exceeded and further stretch is strongly resisted by these stiffer elements. Therefore chamber stiffness increases as end diastolic pressure or volume is increased. Nonlinear regression analysis may be applied to EDPVR data in order to develop simple indices of left ventricular chamber stiffness or compliance. Shifts of the EDPVR may reflect changes in myocardial properties (fibrosis, ischaemia or oedema) or pathological remodelling (with hypertrophy and chamber dilatation in heart failure), but take into account the net effects of changes in myocardial properties, chamber structural properties, and changes in the extracellular matrix.

The slope of the EDPVR can be determined using a single-beat method to calculate the E_{ED} (a measure of end diastolic chamber stiffness which is derived from a linear fit of the filling phase trajectory of the pressure-volume loop). Similarly the end-diastolic stiffness

constant KV_{ED} can be derived by fitting an exponential curve to the diastolic trajectory of the pressure-volume loop as previously described by Steendijk *et al* (85).

ASSESSMENT OF EXTERNAL CONSTRAINT TO LV FILLING

External constraint (EC) to LV filling can be determined using a modified static equilibrium technique whereby external constraint is quantified as the difference in LVEDP before and after removal of the pericardium while a constant LVEDV is maintained. This technique can only be used when the chest is open. However, a modification can be applied by continuous measurement of LV pressure and volume during occlusion of the IVC to acutely reduce RV volume and pressure (51). This acute reduction in RV volume removes external constraint to LV filling from the RV and pericardium. During this intervention, LVEDP is progressively reduced over several beats. For each beat, the relation between LVEDP and LVEDV is assessed. In the absence of external constraint, IVC occlusion gradually reduces both LVEDP and LVEDV, with the values progressing downward and leftward along a single end-diastolic pressure-volume relation. In contrast, in severe heart failure, when marked external constraint is present, LVEDV initially (for a few beats) increases as LVEDP falls. Only after the external constraint has been removed do the pressure-volume values move down and to the left (Figure 2.5). The magnitude of external constraint is then calculated as shown in Figure 2.6.

FIGURE 2.5. **Response to inferior vena caval occlusion in a patient with congestive cardiac failure and significant external constraint (left panel) and a healthy control (right panel)**

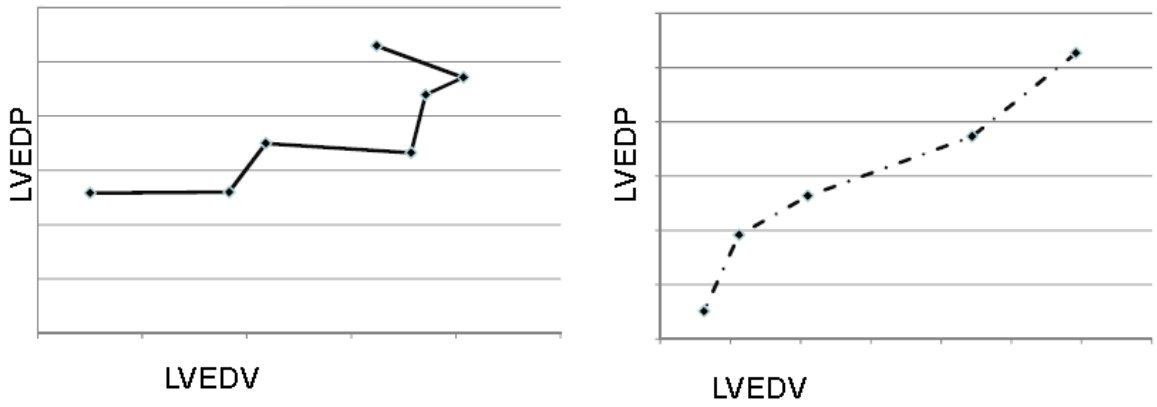
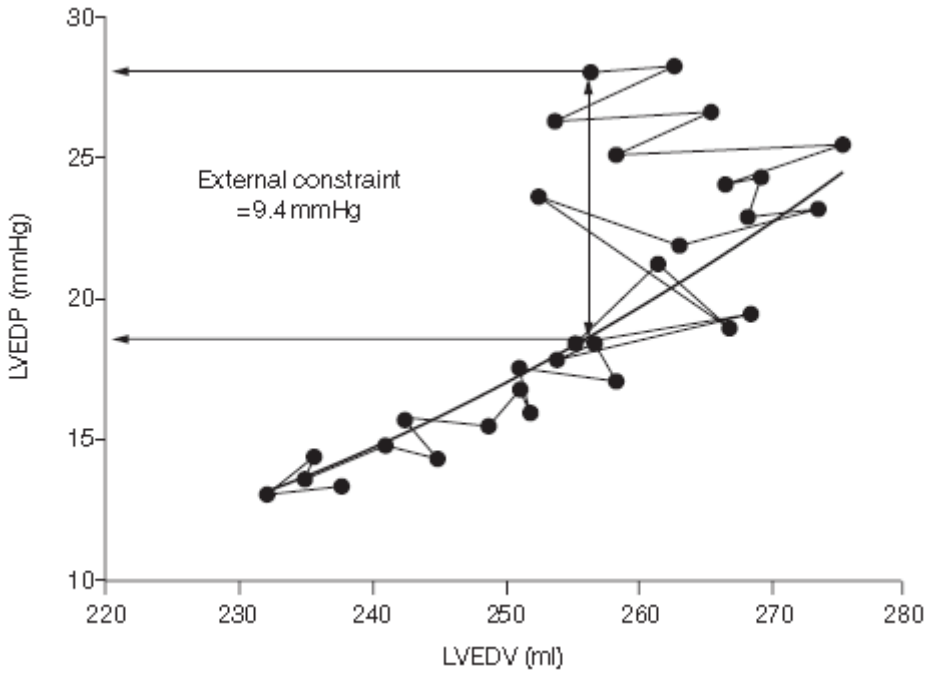


FIGURE 2.6. **Quantification of external constraint after inferior vena caval occlusion in a patient with congestive cardiac failure and significant external constraint**



ASSESSMENT OF LEFT VENTRICULAR SUCTION

PRESSURE-VOLUME LOOP ANALYSIS

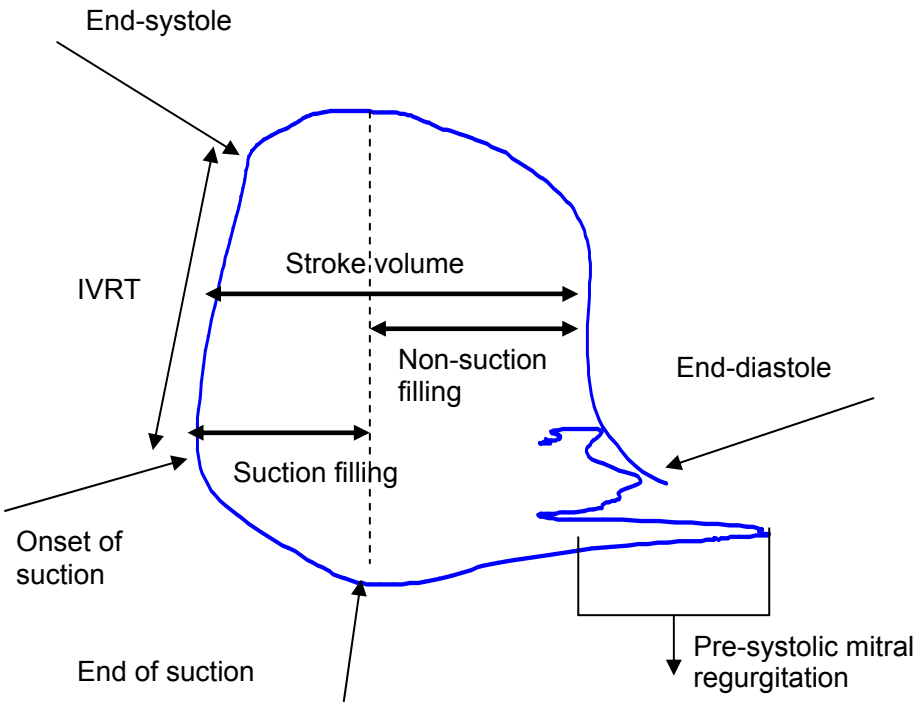
The term 'suction filling' has been defined by Katz as the phenomenon whereby the left ventricle relaxes faster than it can fill (86), resulting in a fall in pressure as the left ventricle enlarges. Suction filling is therefore the period of filling which occurs during the period of pressure decline to minimum pressure after the mitral valve has opened. This can be calculated from the pressure-volume loop by the following equations:

$$Vsuction = V@Pmin - Vmin$$

$$\%\ Suction\ filling = \frac{Vsuction}{Stroke\ volume}$$

where Vsuction is the total volume of filling occurring between mitral valve opening (Vmin or minimum volume) and the point of minimum pressure (V@Pmin or volume at minimum pressure), and the percentage of suction filling is equal to Vsuction divided by stroke volume (see Figure 2.7).

FIGURE 2.7. Representative pressure-volume loop from a patient with congestive heart failure



ECHOCARDIOGRAPHY

Echocardiography was used to compare time intervals related to left ventricular filling with those obtained from the pressure volume loops. These recordings were obtained with the patients lying in a supine position at rest at identical heart rates to those during the pressure volume loop studies. Transmitral flow was recorded in the standard apical four-chamber view with the sample volume positioned between the tips of the mitral leaflets. The isovolaemic relaxation time (IVRT) was derived by subtracting the time interval from Peak R-Wave of the ECG to mitral valve opening (onset of E wave) from the time interval from Peak R-wave to aortic valve closure. This method incorporating the use of the ECG complex eliminates the possibility of measurement error caused by valve artifact when measuring small time durations using continuous or pulsed wave Doppler imaging. The time interval from the Peak R-Wave of the ECG to the peak of the E wave on transmitral flow (T-Peak E) was also measured. The IVRT and T-Peak E time intervals derived from echocardiography was compared with the IVRT and T-Pmin derived from the pressure volume loops.

PATIENT RECRUITMENT

Patients were recruited from the heart failure clinics at the Queen Elizabeth Hospital (Birmingham), Good Hope Hospital (Sutton Coldfield), Sandwell Hospital (West Bromwich), and St Peter's Hospital (Chertsey). Inclusion and exclusion criteria are detailed below:

Inclusion Criteria

Congestive heart failure due to ischaemic or dilated cardiomyopathy

Sinus rhythm

NYHA III or IV breathlessness despite optimal tolerated medical therapy

Exclusion Criteria

Atrial fibrillation

Structural valve disease

Previous cardiac surgery

Structural pericardial disease

Patient Groups

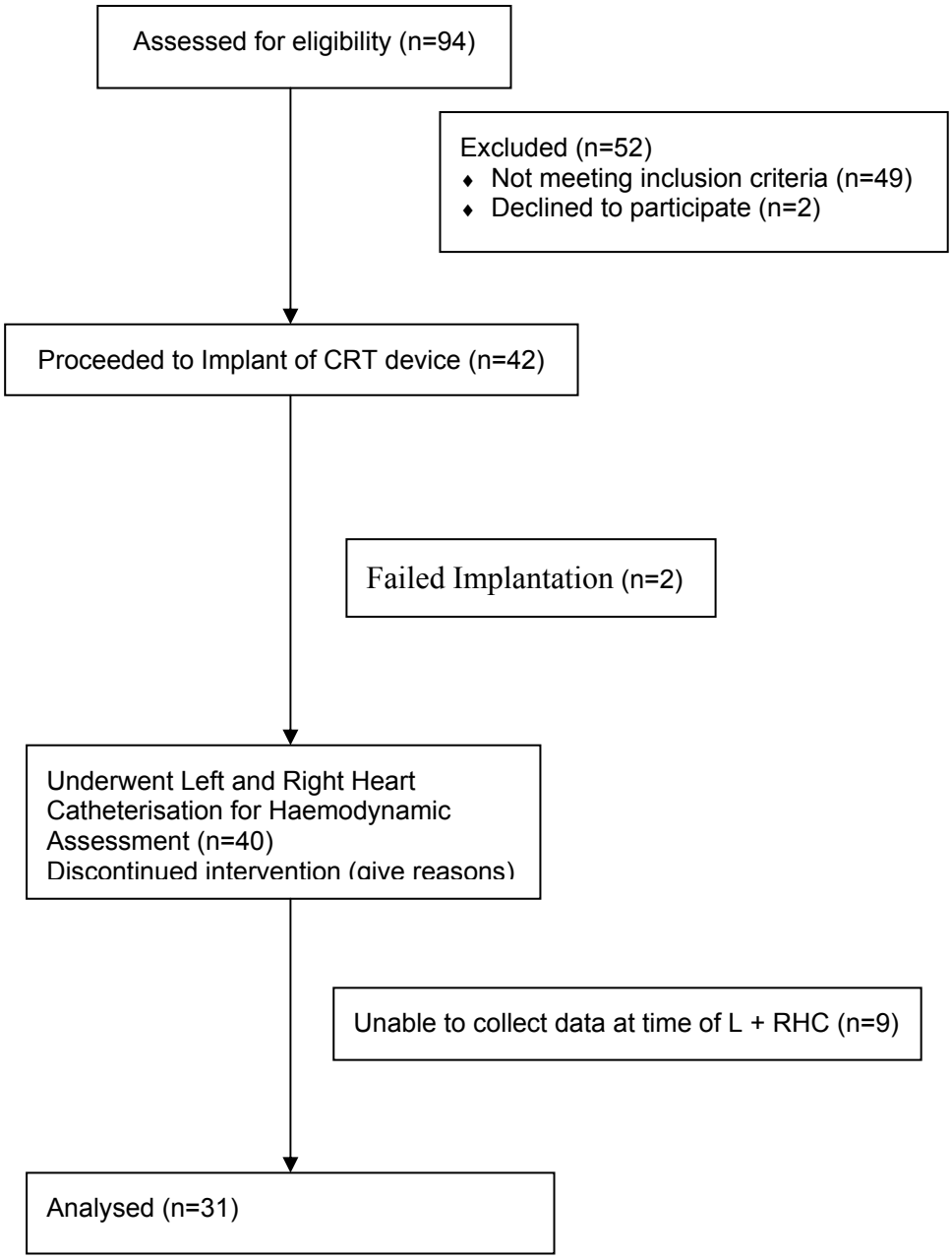
(1) Narrow QRS duration with no evidence of inter or intraventricular dyssynchrony

(2) Broad QRS duration (unselected for dyssynchrony)

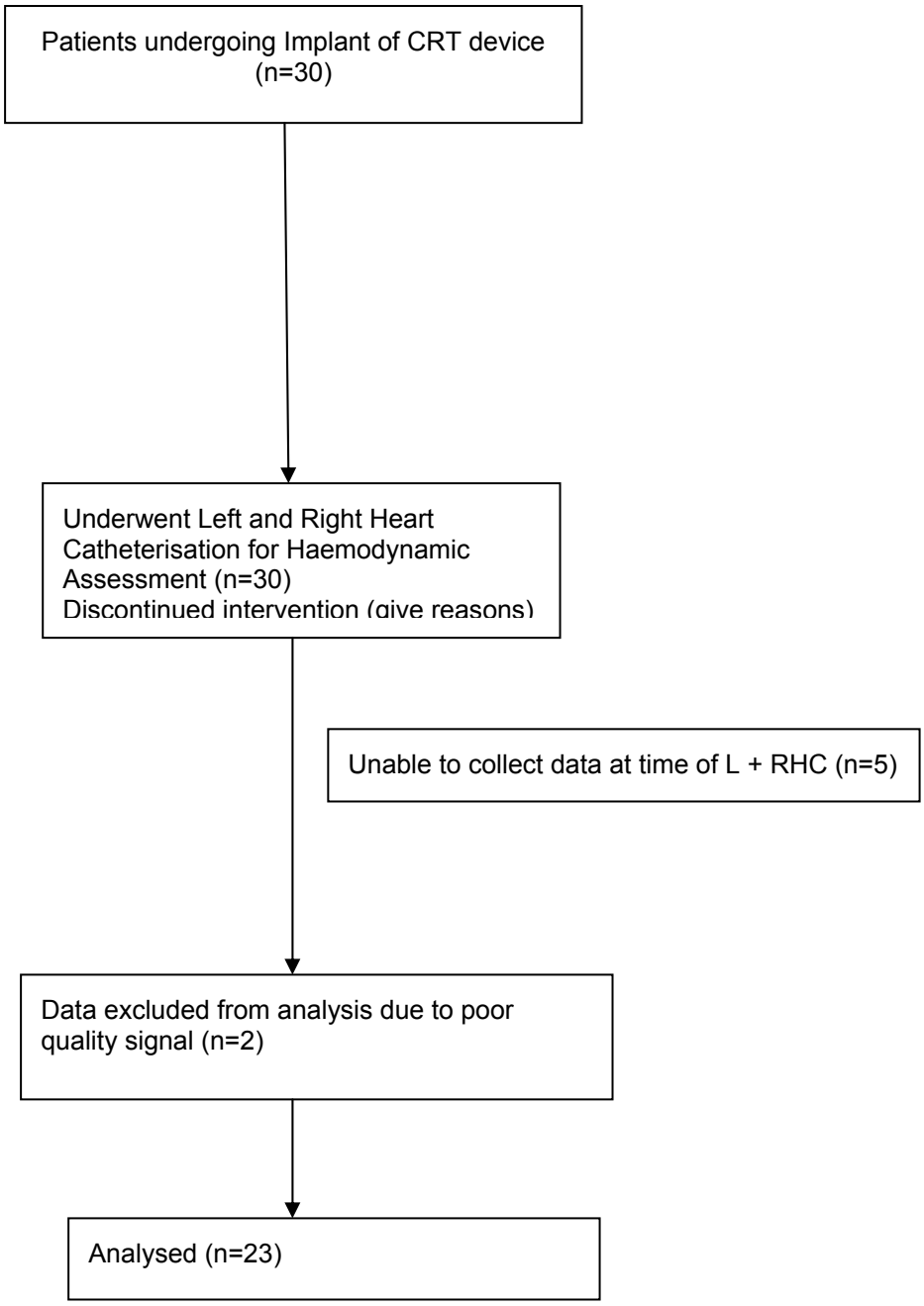
(3) Control group with structurally normal heart undergoing EPS and ablation

Details of patient recruitment are detailed in the following flow charts:

NARROW QRS PATIENT GROUP



BROAD QRS PATIENT GROUP



STATISTICAL ANALYSIS

All data are expressed as the mean value ± SD. For continuous variables that were not normally distributed, the median and range are expressed.

A repeated measure ANOVA was used to assess changes for paired samples if the data was normally distributed based on a Kolmogorov-Smirnov test. For data that was not normally distributed, a Kruskal-Wallis test was used and medians reported. If the repeated measure ANOVA was statistically significant then pairwise comparisons were performed.

For comparison of data between patients groups (independent samples) a non-parametric Mann-Whitney test was performed.

Statistical significance was assumed at $p<0.05$.

CHAPTER 3

ACUTE HAEMODYNAMIC EFFECTS OF CARDIAC RESYNCHRONISATION THERAPY ON SYSTOLIC AND DIASTOLIC FUNCTION

INTRODUCTION

The effects of cardiac resynchronization therapy (CRT) in patients with heart failure and a QRS duration ≥ 120ms are well established (20;21). In the Cardiac Resynchronization Therapy Heart Failure (CARE-HF) study, CRT was associated with a 40% reduction in all-cause mortality (21). This and other studies have also shown that CRT leads to an improvement in symptoms and a reduction in hospitalization. The predominant mechanism of benefit has been considered to be improvement in both inter and intra-ventricular (LV) dyssynchrony. However, additional mechanisms independent of resynchronisation contribute to the benefit derived from CRT.

Hemodynamic studies have previously demonstrated the acute (37;38;65;87;88) effects of CRT in patients with heart failure and a broad QRS duration. Data from studies by Kass *et al* (38) and Auricchio *et al* (37) demonstrated an acute 15% increase in LV dP/dt_{MAX} in response to biventricular pacing. Steendijk *et al* performed pressure-volume loop studies at 6 months in patients who had undergone biventricular pacing, and demonstrated a 34% increase in LV stroke work and an 18% increase in LV dP/dt_{MAX} in response to pacing (89). We previously showed that LV pacing produces an acute haemodynamic benefit (reduced pulmonary capillary wedge pressure, increased stroke volume) in patients with

heart failure and a QRS<120 ms (25), although these patients had not undergone any prior assessment for the presence or absence of dyssynchrony. Even patients with narrow QRS complexes who do not have dyssynchrony might be expected to benefit from LV and potentially biventricular pacing by relief of diastolic ventricular interaction if present.

In this study we assess the acute haemodynamic effects of both biventricular (BIVP) and left ventricular only pacing (LVP) in symptomatic heart failure patients with a QRS duration<120ms who did not meet the 'conventional' criteria for dyssynchrony and compared these effects with those demonstrated in symptomatic heart failure patients with a broad QRS duration who were unselected for the presence or absence of dyssynchrony.

METHODS

Patients. Thirty one patients with narrow QRS duration and 23 with broad QRS duration heart failure were recruited into the study. All patients had an LVEF≤35% as determined by echocardiography. Patients were in NYHA class III or IV despite optimal tolerated medical therapy that included diuretics and Angiotensin-converting enzyme (ACE) inhibitors. In addition, all patients with a narrow QRS ≤ 120ms had no evidence of inter- or intraventricular dyssynchrony. The former was defined as a Qp-Qa time delay > 40ms, whereas the latter was defined as a septal-posterior wall motion delay > 130ms, or an intraventricular septal-lateral wall delay > 40ms. Patients with a narrow QRS who met two or more of the above criteria were excluded. Baseline patient characteristics for the two groups are shown in Table 3.1.

TABLE 3.1. Baseline patient characteristics

	Narrow QRS (n=31)	Broad QRS (n=23)
Age	62 ± 14 years	69 ± 10 years
Male	28/31 (90%)	19/23 (83%)
Ischaemic cardiomyopathy	17/31 (55%)	14/23 (61%)
NYHA Class III	29/31 (94%)	21/23 (91%)
NYHA Class IV	2/31 (6%)	2/23 (9%)
LVEF	26 ± 5%	24 ± 7%
Beta-blockers	25/31 (81%)	16/23 (70%)
ACE-inhibitors / ARB	29/31(94%)	23/23 (100%)
Spironolactone	25/31 (81%)	17/23 (74%)
Diuretics	30/31 (97%)	23/23 (100%)
Qp-Qa interval	15 ± 9ms	N/A
Septal-posterior wall delay	126 ± 54ms	N/A
Yu-dyssynchrony index	22 ± 7	N/A

Acute Haemodynamic Studies. Acute haemodynamic studies were performed in the cardiac catheterization laboratory at the time of CRT device implantation with patients in the non-sedated and supine state. Catheterisation of the left ventricle was performed by a standard over-the-wire technique. The dual-field conductance catheter (CA-71103-PL catheter, CD Leycom, The Netherlands) was then positioned in the apex of the ventricle. We applied a modified parallel conductance calibration via a right atrial injection(78) to avoid catheterisation of the right ventricle or pulmonary artery.

All data were acquired during an unforced end-expiratory breath hold. From each acquisition run, the derivatives of pressure and volume were calculated as the mean of the 10 to 15 consecutive beats free from atrial or ventricular ectopic activity. Pressure-volume analysis was also performed during an inferior vena caval (IVC) occlusion, which reduced central blood volume and RV pressure acutely, achieved with a 40-mm IVC occlusion balloon catheter (Meditec, Boston Scientific International). Data were acquired with a CFL-512 system (CD Leycom), which allows further offline analysis (CircLab, Leiden University, The Netherlands). The haemodynamic measurements were undertaken during no pacing (OFF), in biventricular (BIVP) and in left ventricular only pacing (LVP) modes with AV intervals set at 100msec, and interventions applied in a random order, each with a run-in (stabilization) period of 5 minutes.

The following parameters were derived from the pressure volume loops (PVL) at baseline (OFF), during inferior vena cava occlusion (IVCO), and in both BIVP and LVP pacing modes: dP/dt_{MAX} and dP/dt_{MIN}, absolute left ventricular stroke work (LVSW), cardiac output (CO) and left ventricular end-diastolic volume (LVEDV). A plot was constructed of beat-by-beat LV end-diastolic volume versus LVSW before and during IVC occlusion in

all pacing modes (the Preload Recruitable Stroke Work Relation or PRSWR). The end-systolic pressure volume relation (ESPVR) was determined using the single-beat method (E_{ES}), the end-diastolic pressure-volume relation (EDPVR) was determined using the single-beat method to calculate the E_{ED} and the end-diastolic stiffness constant KV_{ED} as described in Chapter 2.

In order to negate the effect of any change in heart rate on systolic function (via the force-frequency relation), a tracking VDD pacing mode was utilised to ensure a stable mean heart rate across all interventions (as shown in Table 3.2), with no statistically significant difference in heart rate between pacing modes.

TABLE 3.2. Mean heart rate (beats per minute) during different pacing modes

PACING MODE	Narrow QRS (n=31)	Broad QRS (n=23)
OFF	73 bpm	70 bpm
BIVP	76 bpm	70 bpm
LVP	76 bpm	72 bpm

Statistical Analysis. All data are expressed as the mean value ± SD. The Mann-Whitney rank-sum test was used to compare independent samples between the two groups. A repeated measure ANOVA was used to assess the effect of vena caval occlusion and pacing if the data was normally distributed based on a Kolmogorov-Smirnov test. For data that was not normally distributed, a Kruskal-Wallis test was used and medians reported. Statistical significance was assumed at $p < 0.05$.

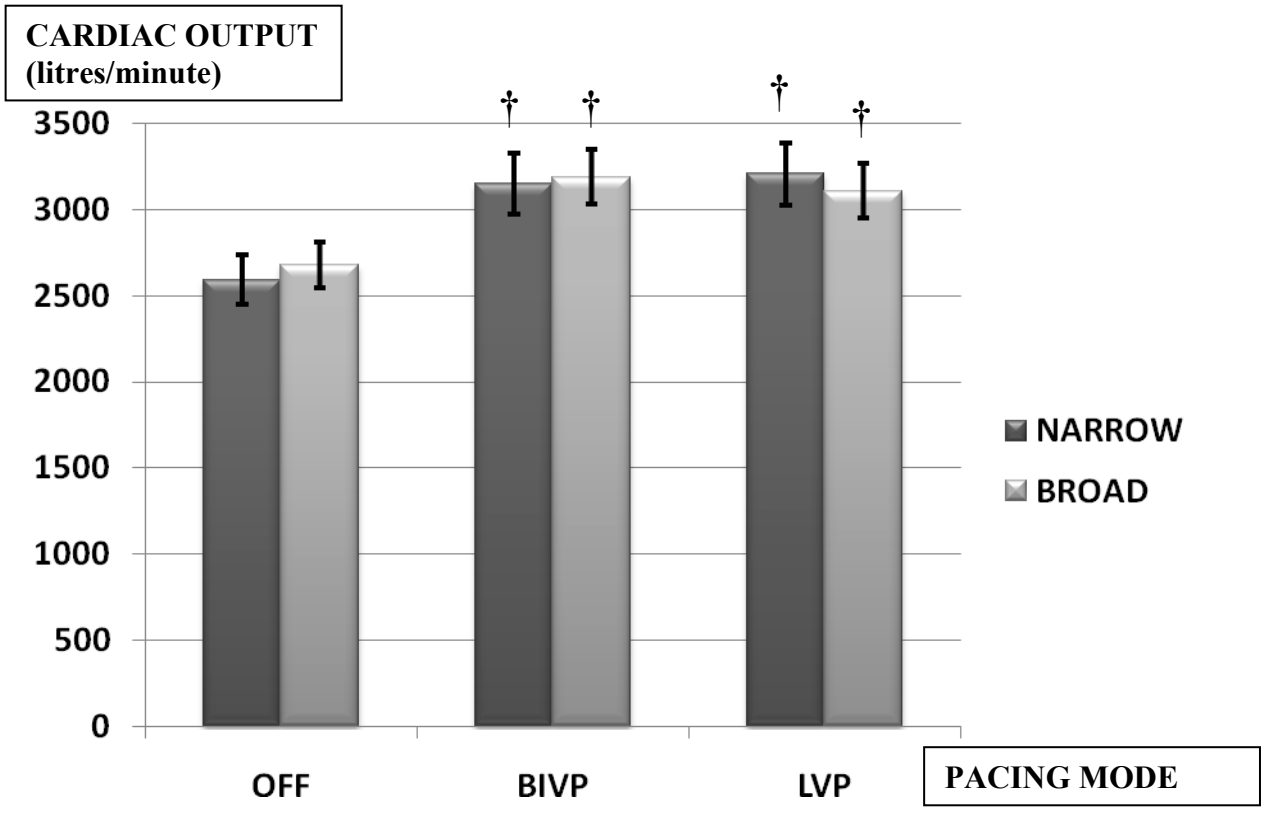
RESULTS

Indices of left ventricular contractility and systolic function

Cardiac Output

Cardiac output was similar at baseline for the narrow and broad QRS groups (2.6 ± 0.8 vs. 2.7 ± 0.6 l/min respectively; p=0.92). Cardiac output increased by 25% in response to both BIVP and LVP in the narrow QRS group (p=0.02) and by 19% in the broad QRS group (p=0.04). There was no significant difference between BIVP and LVP in either group, or between the two groups.

FIGURE 3.1. The effect of biventricular (BIVP) and left ventricular pacing (LVP) on cardiac output (in l/min) compared with baseline values (OFF)

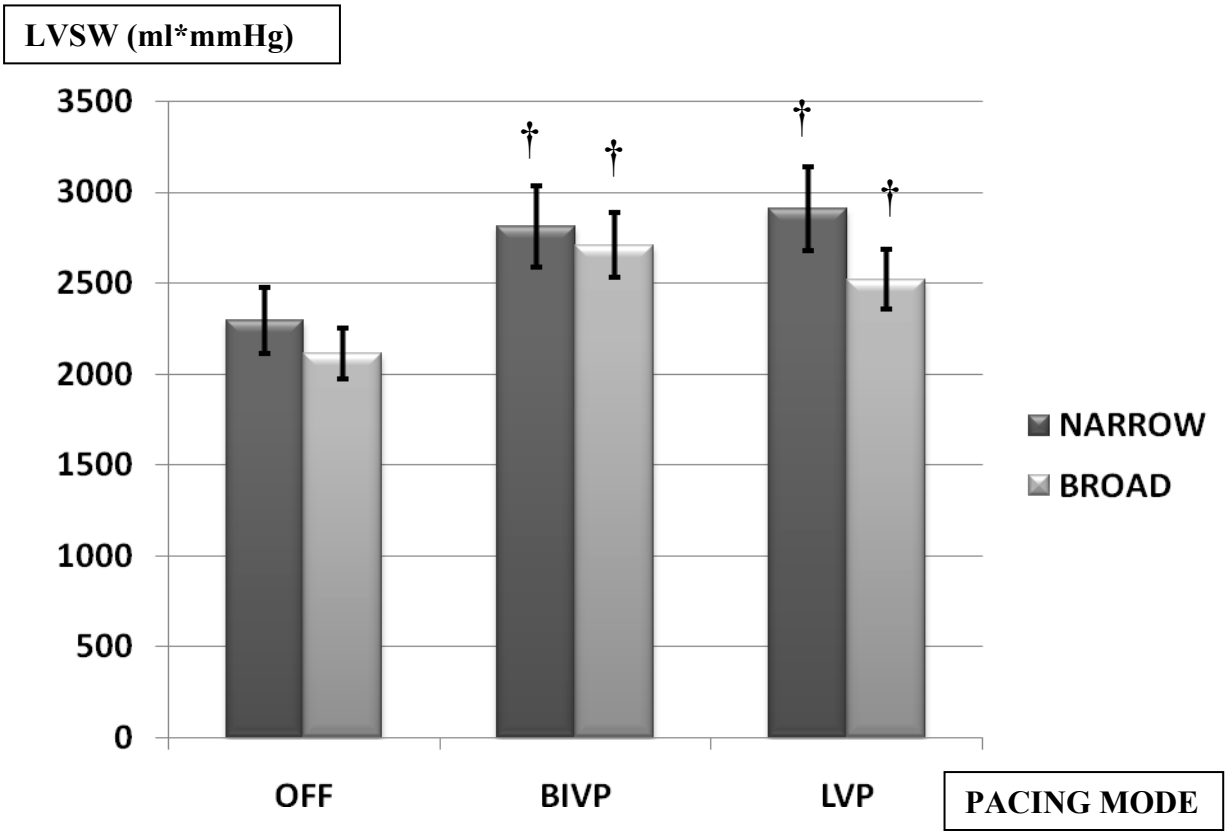


Error bars indicate ± 1 SEM; †indicates a statistically significant increase from OFF ($p<0.05$)

Left ventricular stroke work (LVSW)

LVSW was similar at baseline for the narrow and broad QRS groups (2292 ± 1060 vs. 2110 ± 629 ml*mmHg respectively; p=0.87). LVSW increased by 26% in response to BIVP and 31% in response to LVP in the narrow QRS group (p=0.04) and by 32% and 26% in the broad QRS group in response to BIVP and LVP respectively (p=0.03).

FIGURE 3.2. The effect of biventricular (BIVP) and left ventricular pacing (LVP) on LVSW (in ml*mmHg) compared with baseline values (OFF)

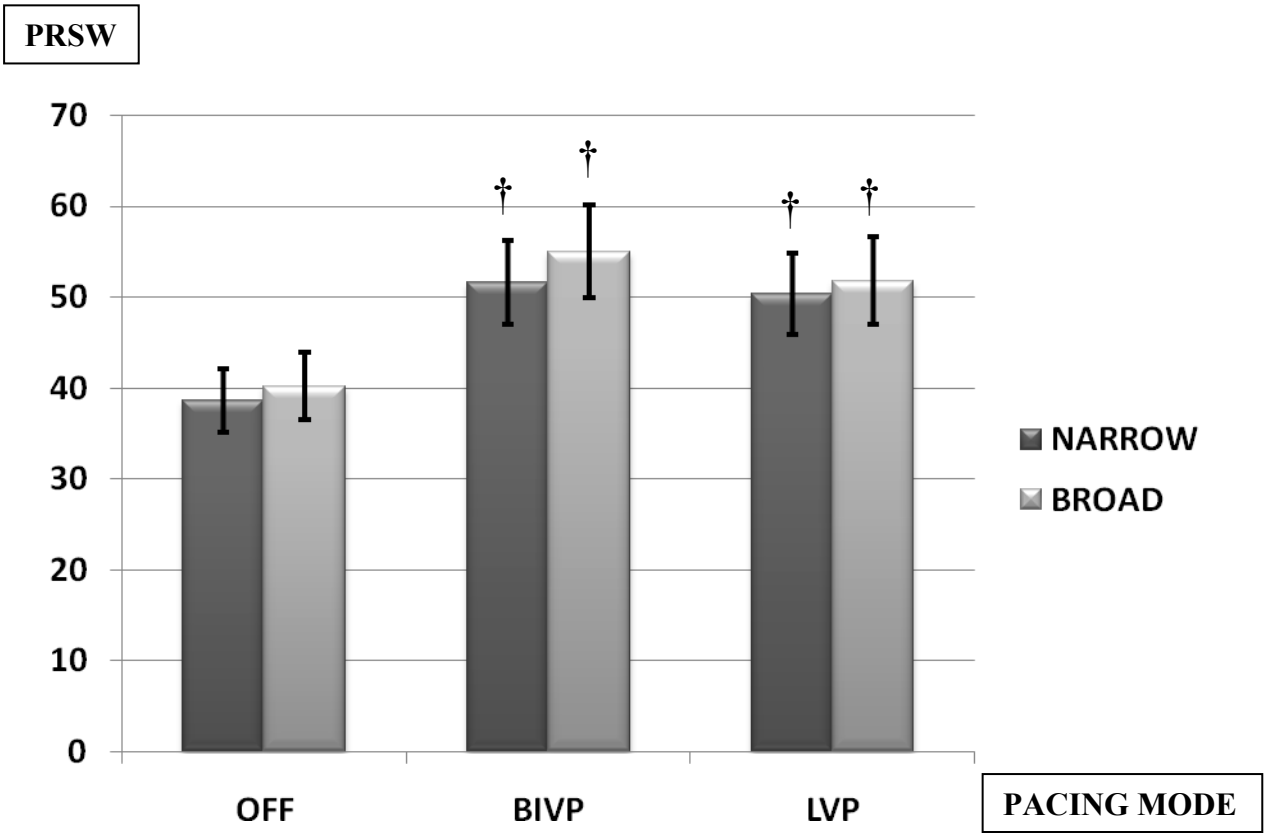


Error bars indicate ± 1 SEM; † indicates a statistically significant increase from OFF (p<0.05)

Preload recruitable stroke work (PRSW)

PRSW was similar at baseline for the narrow and broad QRS groups (38.6 ± 20 vs. 40.2 ± 13.4 respectively; p=0.45). PRSW increased by 34% in response to BIVP and 30% in response to LVP in the narrow QRS group (p=0.03) and by 37% and 29% in the broad QRS group in response to BIVP and LVP respectively (p=0.04). There was no significant difference between BIVP and LVP in either group, or between the two groups.

FIGURE 3.3. The effect of BIVP and LVP on PRSW compared with baseline (OFF)

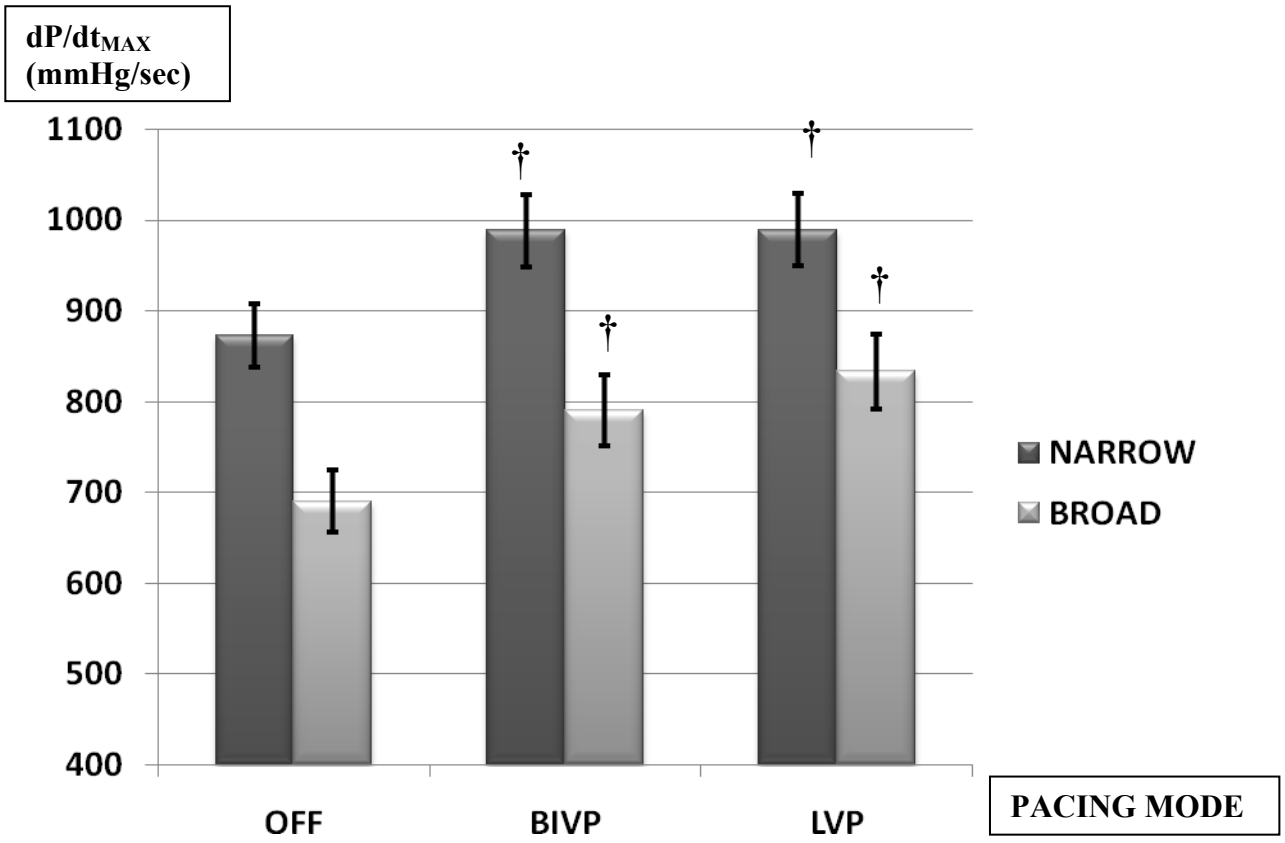


Error bars indicate ± 1 SEM; † indicates a statistically significant increase from OFF ($p<0.05$)

dP/dt$_{MAX}$

dP/dt$_{MAX}$ was significantly higher at baseline in the narrow compared with the broad QRS group (872 ± 189 vs. 690 ± 179 respectively; p<0.01). dP/dt$_{MAX}$ increased by 15% in response to BIVP and by 21% in response to LVP in the broad QRS group (p=0.03) and by 13% in the narrow QRS group in response to both BIVP and LVP (p=0.04).

FIGURE 3.4. Effect of BIVP and LVP on dP/dt$_{MAX}$ compared with baseline (OFF)

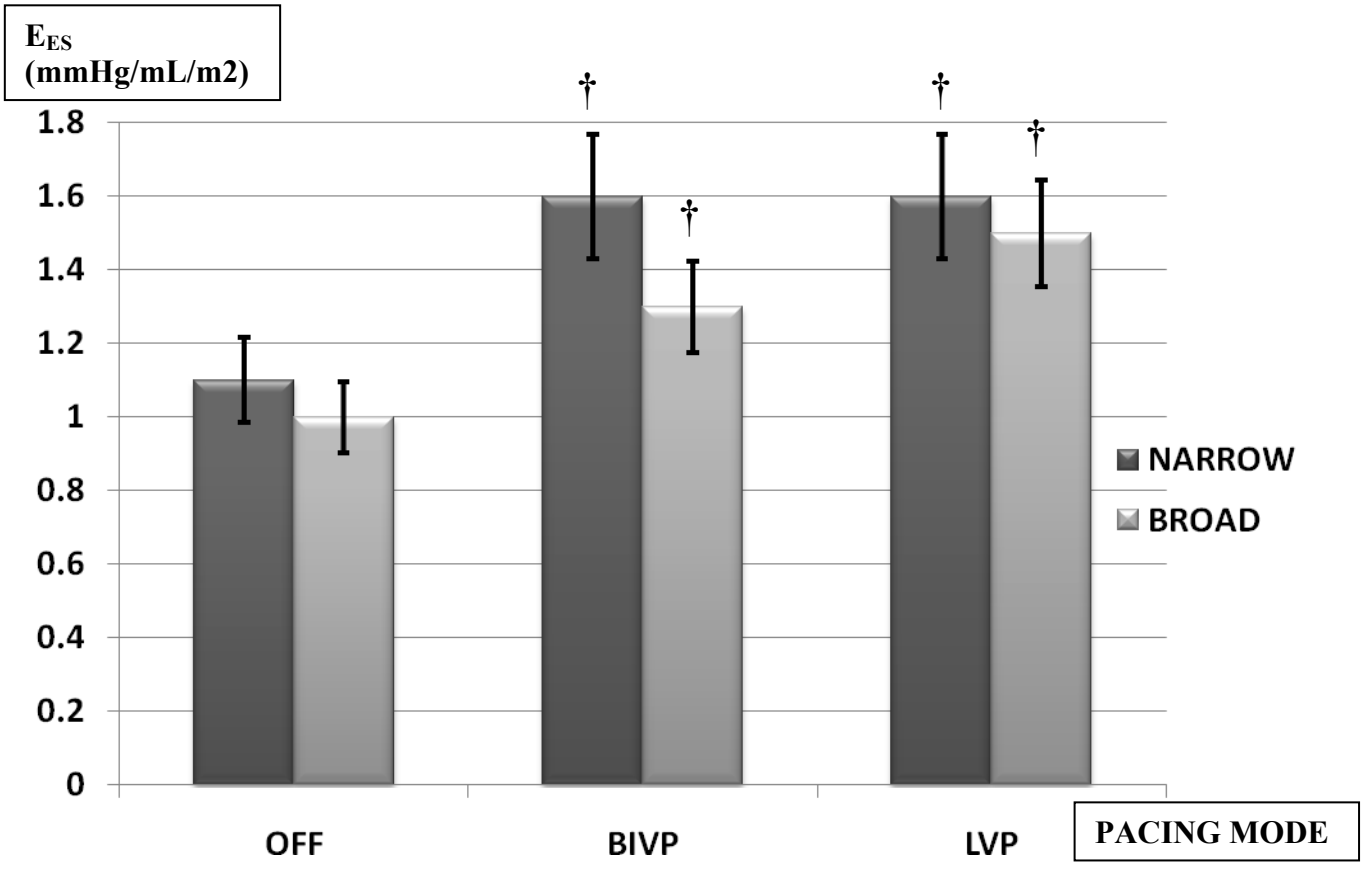


Error bars indicate ± 1 SEM; †indicates a statistically significant increase from OFF (P<0.05)

ESPVR (E$_{ES}$)

There was no significant difference in the slope of the ESPVR (E_{ES}) at baseline between the two groups (1.1 ± 0.4 vs. 1.0 ± 0.5; p=0.45). The slope of the ESPVR (E_{ES}) increased by 45% in the narrow QRS group in response to both BIVP and LVP (p=0.03), and by 30% in response to BIVP and by 50% in response to LVP in the broad QRS group (p=0.02).

FIGURE 3.5. The effect of BIVP and LVP on E_{ES} compared with baseline (OFF)



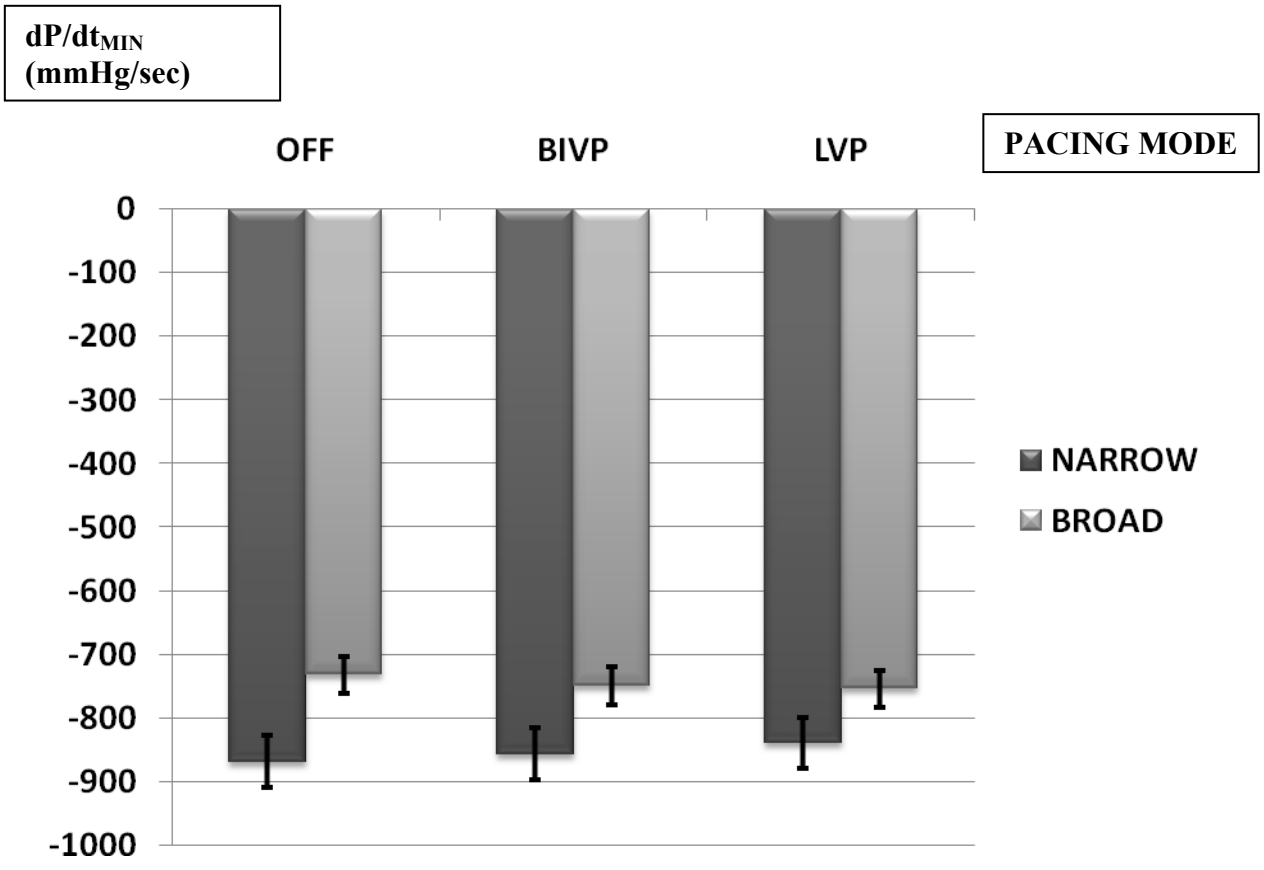
Error bars indicate ± 1 SEM; † indicates a statistically significant increase from OFF (p<0.05)

Indices of left ventricular diastolic function

dP/dt$_{MIN}$

dP/dt$_{MIN}$ was significantly higher at baseline in the narrow compared with the broad QRS group (-868 ± 217 vs. -732 ± 145 respectively; p=0.04). There was no significant change in dP/dt$_{MIN}$ in response to BIVP or LVP in either the narrow QRS (p=0.92) or the broad QRS group (p=0.87).

FIGURE 3.6. The effect of BIVP and LVP on dP/dt$_{MIN}$ compared with baseline (OFF)

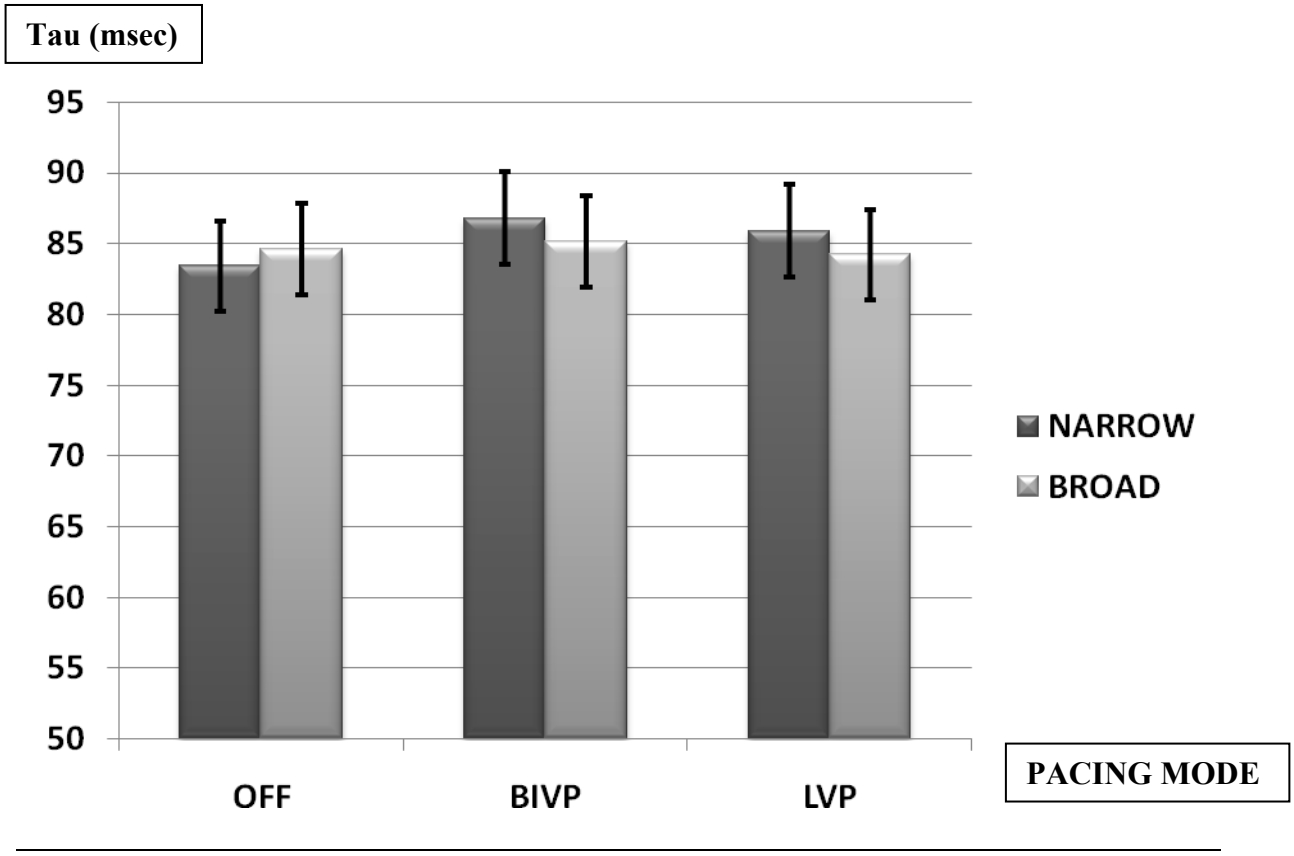


Error bars indicate ± 1 SEM

Tau

There was no significant difference in Tau at baseline between the two groups (83.4 ± 15 vs. 84.6 ± 15; p=0.84). There was no significant change in Tau in response to BIVP or LVP in either the narrow QRS (p=0.73) or the broad QRS group (p=0.98).

FIGURE 3.7. The effect of BIVP and LVP on Tau compared with baseline (OFF)

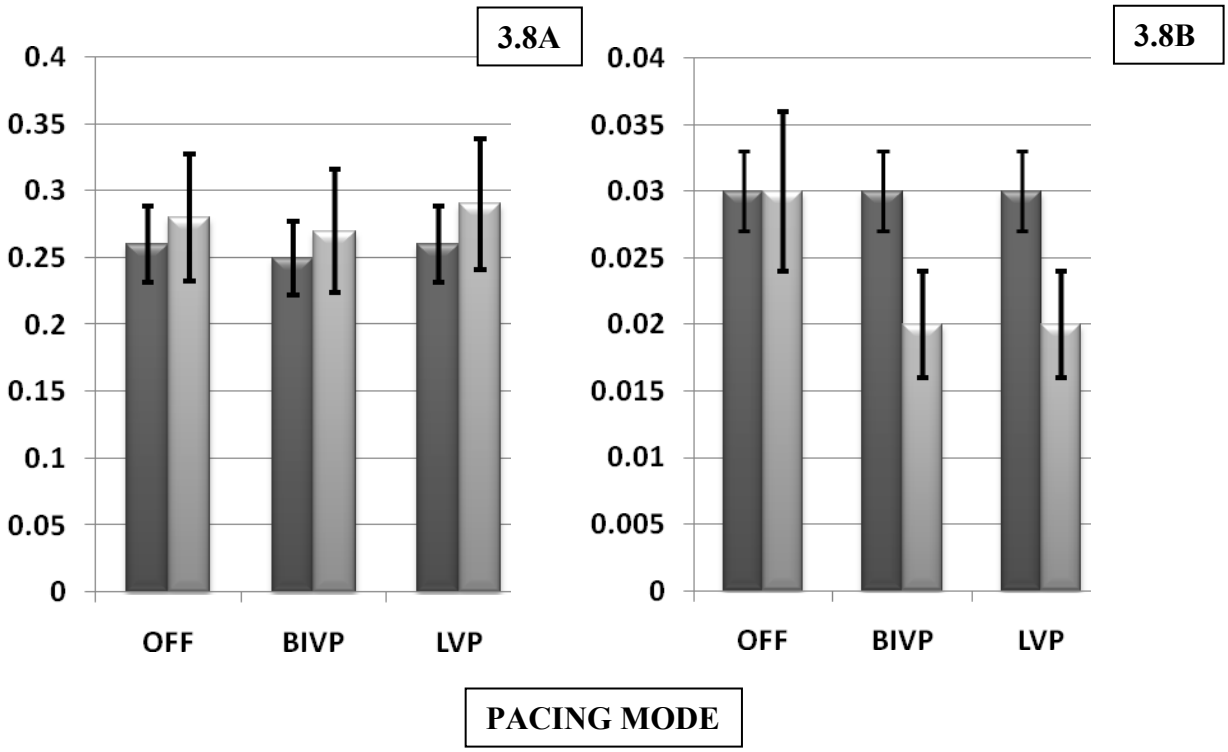


Error bars indicate ± 1 SEM

EDPVR (E_{ED} and KV_{ED})

There was no significant difference in either E_{ED} (p=0.60) or KV_{ED} (p=0.29) at baseline between the two groups. There was no significant change in either parameter in response to BIVP or LVP in either the narrow QRS (p=0.92) or the broad QRS group (p=0.77).

FIGURE 3.8. The effect of BIVP and LVP on E_{ED} (Figure A) and KV_{ED} (Figure B) compared with baseline (OFF)



Error bars indicate ± 1 SEM

DISCUSSION

The important findings of this study are significant acute increases in LV stroke work, cardiac output, and dP/dt_{MAX} in these symptomatic patients with a narrow QRS duration and no conventional measures of mechanical dyssynchrony in response to both BIVP and LVP. Haemodynamic studies have previously demonstrated the acute effects of CRT in patients with heart failure and a broad QRS duration. In this study we have shown that CRT results in comparable acute haemodynamic improvements in patients with a narrow QRS duration to those with a broad QRS duration, amounting to as much as a 25% improvement in cardiac output and a 25 to 30% increase in absolute left ventricular stroke work.

Data from studies by Kass *et al* (38) and Auricchio *et al* (37) demonstrated an acute 15% increase in dP/dt_{MAX} in response to BIVP in patients with heart failure and a broad QRS duration, in comparison with the 13% and 15% increase we have demonstrated in the broad QRS and narrow QRS group of patients respectively. Steendijk *et al* (90) performed pressure-volume loop studies at 6 months in patients who had undergone CRT implantation and demonstrated a 34% increase in LV stroke work and an 18% increase in dP/dt_{MAX} in response to pacing. Prior studies have concentrated on measuring the effect of pacing on $dP/dt_{MAX,}$ but in the present study we have assessed the effect of pacing on several haemodynamic measures, including the effect on the slope of the preload recruitable stroke work relation, a far more robust measure of left ventricular contractile function as discussed in Chapter 2.

Given the narrow QRS duration and the absence of conventional measures of dyssynchrony, these findings may at first glance be surprising. Recent evidence suggests that conventional measures of dyssynchrony have high inter-observer variability (32) and may underestimate

the magnitude of dyssynchrony because they ignore radial dyssynchrony. Current measures of dyssynchrony are based on echocardiographic Doppler parameters that are derived largely from longitudinal motion data (91). This choice of orientation is based mainly on practical grounds given the available echocardiographic windows for transducer positioning. However, because of epicardial and subendocardial fibre orientation, cardiac contraction is principally radial. Helm and colleagues (33) have demonstrated in a failing heart that dyssynchrony assessed by longitudinal motion is much less sensitive, suggesting that longitudinal motion data may not provide the most accurate and comprehensive means of assessing left ventricular dyssynchrony. Therefore, a possible explanation for the benefit observed is an improvement in 'occult' dyssynchrony. Consistent with this, there was a substantial improvement in the PRSWR, a load-independent and robust measure of LV contractile function. Whilst increases in left ventricular compliance result in a move upwards along the same preload recruitable stroke work relation (thereby increasing stroke work) they do not alter the slope of this relation, therefore an increase in the slope of this relation reflects an increase in left ventricular contractility.

Although CRT has been shown to result in chronic symptomatic benefit and reverse remodelling in heart failure patients with a broad QRS duration, it is yet to be determined whether the acute haemodynamic benefits we have demonstrated in the patient group with a narrow QRS duration will translate into similar long-term benefits. Previous small studies in patients with a narrow QRS duration have focused on clinical and echocardiographic end-points. Although these have shown a benefit from CRT, these studies defined a QRS duration of less than 150ms as 'narrow' and were limited to patients with evidence of dyssynchrony on echocardiography. In a study by Achilli *et al* (59) the authors report the efficacy of CRT in such a group of patients, with 14 of the 56 patients included having a QRS duration less than

120ms. These findings were supported by those of Gasparini *et al* (60), who reported an improvement in clinical and echocardiographic parameters in patients with a narrow QRS duration (13 of whom had a QRS of less than 120ms). The studies by Bleeker *et al* (61) and Yu *et al* (62) included 33 and 51 patients respectively with a QRS duration of less than 120ms. Both studies demonstrated an improvement in clinical parameters and evidence of left ventricular reverse remodelling, but in addition the Yu study showed an improvement in exercise capacity as evidenced by an improvement in maximal metabolic equivalent achieved on treadmill testing(62).

However, a recent and much larger study (RETHINQ) studied an implantable cardioverter defibrillator population who fulfilled conventional criteria for the implantation of a CRT device but who had a narrow QRS duration of less than 130ms (63). This study failed to demonstrate an improvement in exercise capacity or evidence of reverse remodelling of the left ventricle. The patient population in the RETHINQ study is indistinguishable from our patient group with regards to demographics, aetiology of heart failure, and baseline left ventricular function and exercise capacity. However, it is important to bear in mind that this patient population were an ischaemic cardiomyopathy group who primarily had an indication for ICD therapy, and as such were more likely to have left ventricular scar related to prior infarction which may have a resulted in a significant non-responder rate depending on positioning of the left ventricular pacing lead. It will be interesting to see whether the acute haemodynamic benefits we have demonstrated in the narrow QRS patient population in this study will translate into a long-term improvement in symptoms, quality of life, and left ventricular function.

STUDY LIMITATIONS

Patients with a narrow QRS duration were assessed for the presence or absence of inter- and intraventricular dyssynchrony using tissue Doppler imaging (TDI). Recent evidence suggests that conventional measures of dyssynchrony have high inter-observer variability and may also underestimate the magnitude of dyssynchrony because they ignore radial dyssynchrony. However, the limitation of this form of dyssynchrony analysis is that it is based on echocardiographic Doppler parameters which are largely derived from longitudinal motion data; hence the presence of radial dyssynchrony was not specifically excluded in this group of patients.

The calibration method of the conductance catheter was not based on assessment of absolute volume, but this would have little effect on the results which depend entirely on relative changes within in each patient in response to the pacing mode.

As an increase in heart rate is known to result in enhancement of systolic function via the force-frequency relation, an augmentation in systolic indices in the acute setting may be a result of an increase in heart rate alone. For this reason we used a tracking pacing mode (VDD) to ensure that no statistically significant differences in heart rate occurred between pacing modes.

There was a difference in the median age of patients in the narrow versus broad QRS group, with the patients in the narrow QRS group being on average 7 years younger. As haemodynamic variables decline with age, this may account for the slightly lower indices of

systolic function at baseline in the broad QRS patients. However, as each patient acted as their own control with respect to changes in both systolic and diastolic function in response to the varying pacing modes, age would have no effect on the changes seen with pacing.

Because of the invasive nature of the study, only a small sample of patients was studied in the short term, hence these results may not predict the medium and long-term effects of CRT on cardiac function.

CONCLUSION

In the present we demonstrate that CRT results in an improvement in acute haemodynamic variables in heart failure patients with a narrow QRS duration that is comparable to the effects seen in heart failure patients with a broad QRS duration. Detailed invasive haemodynamic studies (including analysis of pressure volume loop data) have previously been published reporting both the acute and chronic effects of CRT in patients with heart failure and a broad QRS duration. Although Bleasdale *et al* have previously demonstrated the beneficial effects of left ventricular pacing in narrow QRS heart failure patients with a raised pulmonary capillary wedge pressure, to the best of our knowledge this is the first study to assess the haemodynamic effects of both BIVP and LVP in a group of patients with both a narrow QRS duration and no evidence of significant inter- or intraventricular dyssynchrony.

CHAPTER 4

EFFECTS OF CARDIAC RESYNCHRONISATION THERAPY ON EXTERNAL CONSTRAINT

INTRODUCTION

The ventricles share a common interventricular septum and, therefore, the compliance of one ventricle is influenced by changes in the volume, pressure or compliance of the other. This phenomenon has been termed diastolic ventricular interaction (DVI). The relatively non distensible pericardium further substantially increases ventricular interaction, since a rise in pressure within one ventricle will be transmitted to the other ventricle. In the resting state in healthy individuals, pericardial pressure is close to zero, but as the pericardium becomes stretched by enlargement of the ventricles it can exert a significant restraining effect on left ventricular filling (pericardial constraint).

In heart failure patients with high pulmonary capillary wedge pressures, LV filling has been shown to be markedly impeded by external constraint from the right ventricle via the shared interventricular septum (50) and from the stretched pericardium. The application of lower body negative pressure (as a means of reducing venous return and preload) resulted in a reduction in right ventricular (RV) volume but increased left ventricular (LV) volume and stroke volume. This was concluded to be due to a greater reduction in external constraint from the RV and pericardium than the reduction in LVEDP, resulting in an increase in the effective filling pressure (the trans-mural gradient). Invasive haemodynamic studies by Dauterman *et al* (51) and Bleasdale *et al* (55) also support the presence of marked DVI in

patients with chronically high intra-cavitary LVEDP's. In patients with chronic heart failure and a high LVEDP, balloon occlusion of the inferior vena cava removed external constraint to LV filling, resulting in an initial increase in LVEDV despite a fall in LVEDP (55). In a subsequent study by Moore *et al*, in a rapid pacing model of heart failure, LV volume increased as LVEDP was lowered, but these changes were explained entirely by a larger fall in external pressures, causing a rise in the trans-septal and trans-mural pressure associated with a rightward shift of the septum (92).

The presence of DVI is likely to have important implications for the mechanism of exercise limitation in heart failure, since it prevents utilisation of the Starling mechanism to increase cardiac output (93). We hypothesized that at least part of the acute haemodynamic benefit from cardiac resynchronisation therapy may be due to a reduction in external constraint to LV filling by inducing a phase shift such that LV contraction and filling occur before they do in the RV. Because pericardial stretch (and therefore pericardial pressure) depends on total cardiac volume, a smaller RV volume during LV filling would result in less constraint to filling, a greater LV end-diastolic volume, and (by the Frank Starling mechanism) a greater LV stroke work.

METHODS

Patients. Thirty one patients with narrow QRS duration and 23 with broad QRS duration heart failure were recruited into the study. All patients had LVEF≤35% as determined by echocardiography. Patients were in NYHA class III or IV despite optimal tolerated medical therapy that included diuretics and Angiotensin-converting enzyme (ACE) inhibitors. In addition, all patients with a narrow QRS ≤ 120ms had no evidence of inter- or intraventricular dyssynchrony. Baseline patient characteristics for the two groups are shown in Table 4.1.

Table 4.1. Baseline patient characteristics

	Narrow QRS (n=31)	Broad QRS (n=23)
Age	62 ± 14 years	69 ± 10 years
Male	28/31 (90%)	19/23 (83%)
Ischaemic cardiomyopathy	17/31 (55%)	14/23 (61%)
NYHA Class III	29/31 (94%)	21/23 (91%)
NYHA Class IV	2/31 (6%)	2/23 (9%)
LVEF	26 ± 5%	24 ± 7%
LVEDP	18 ± 8mmHg	19 ± 7mmHg
IVRT	123 ± 27ms	130 ± 27ms

Acute Haemodynamic Studies. Acute haemodynamic studies were performed in the cardiac catheterization laboratory at the time of CRT device implantation with patients in the non-sedated and supine state. Catheterisation of the left ventricle was performed by a standard over-the-wire technique. The dual-field conductance catheter (CA-71103-PL catheter, CD Leycom, The Netherlands) was then positioned in the apex of the ventricle. We applied a modified parallel conductance calibration via a right atrial injection (78) to avoid catheterisation of the right ventricle.

All data were acquired during an unforced end-expiratory breath hold. From each acquisition run, the derivatives of pressure and volume were calculated as the mean of the 10 to 15 consecutive beats free from atrial or ventricular ectopic activity. Pressure-volume analysis was also performed during an inferior vena caval (IVC) occlusion, which reduced central blood volume and RV pressure acutely, achieved with a 40-mm IVC occlusion balloon catheter (Meditec, Boston Scientific International). Data were acquired with a CFL-512 system (CD Leycom), which allows further offline analysis (CircLab, Leiden University, The Netherlands). The haemodynamic measurements were undertaken during no pacing (OFF), in biventricular (BIVP) and in left ventricular only pacing (LVP) modes with AV intervals set at 100msec, and interventions applied in a random order, each with a run-in (stabilization) period of 5 minutes.

The following parameters were derived from the pressure volume loops (PVL) at baseline (OFF), during inferior vena cava occlusion (IVCO), and in both BIVP and LVP pacing modes: dP/dt_{MAX}, absolute left ventricular stroke work (LVSW), cardiac output (CO) and left ventricular end-diastolic volume (LVEDV). A plot was constructed of beat-by-beat LV end-

diastolic volume versus LVSW before and during IVC occlusion in all pacing modes (the Preload Recruitable Stroke Work Relation or PRSWR). External constraint (EC) to LV filling was determined using a modified static equilibrium technique whereby external constraint is quantified as the difference in LVEDP before and after removal of the pericardium while a constant LVEDV is maintained. The static equilibrium technique can only be used when the chest is open. However, a modification was applied by continuous measurement of LV pressure and volume during occlusion of the IVC to acutely reduce RV volume and pressure(51). The magnitude of external constraint was determined as described in Chapter 2.

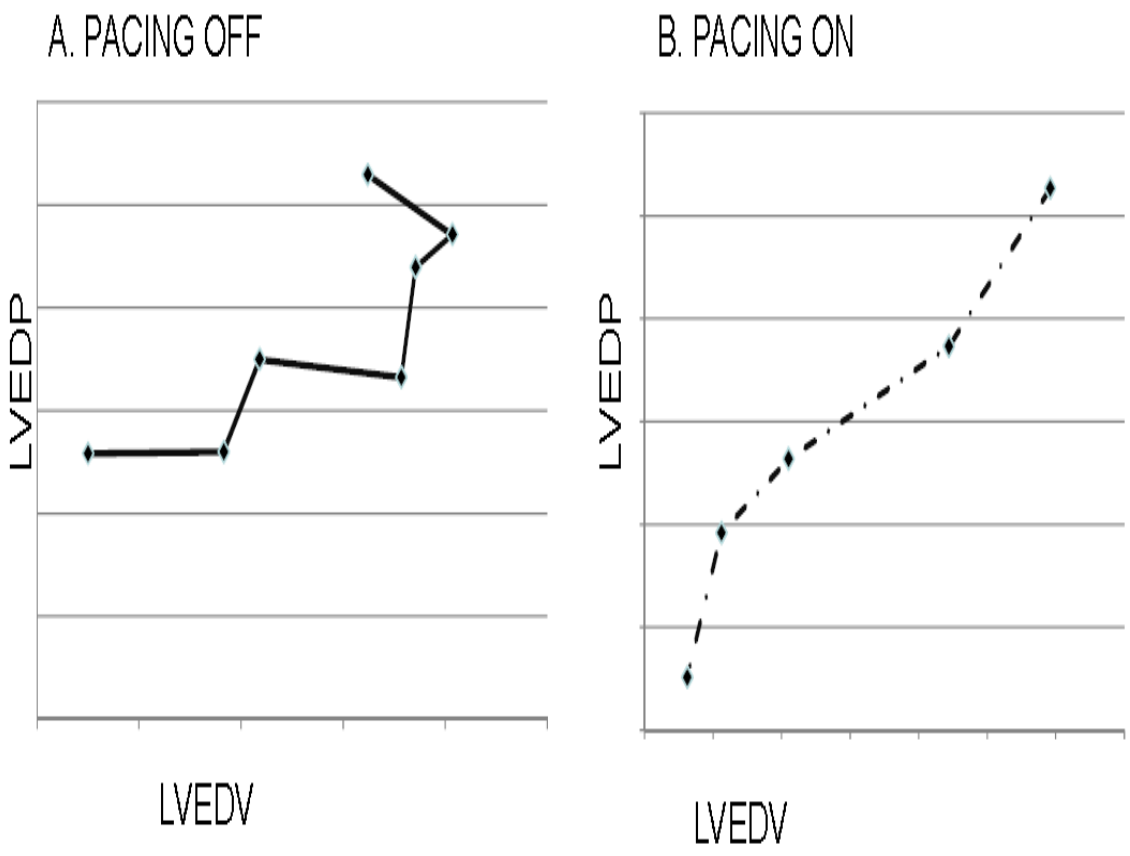
Statistical Analysis. All data are expressed as the mean value ± SD. The Mann-Whitney rank-sum test was used to compare independent samples between the two groups. A one-way ANOVA was used to assess the effect of vena caval occlusion and pacing if the data was normally distributed based on a Kolmogorov-Smirnov test. For data that was not normally distributed, a Kruskal-Wallis test was used. Statistical significance was assumed at $p < 0.05$.

RESULTS

Effects of Pacing on External Constraint (EC)

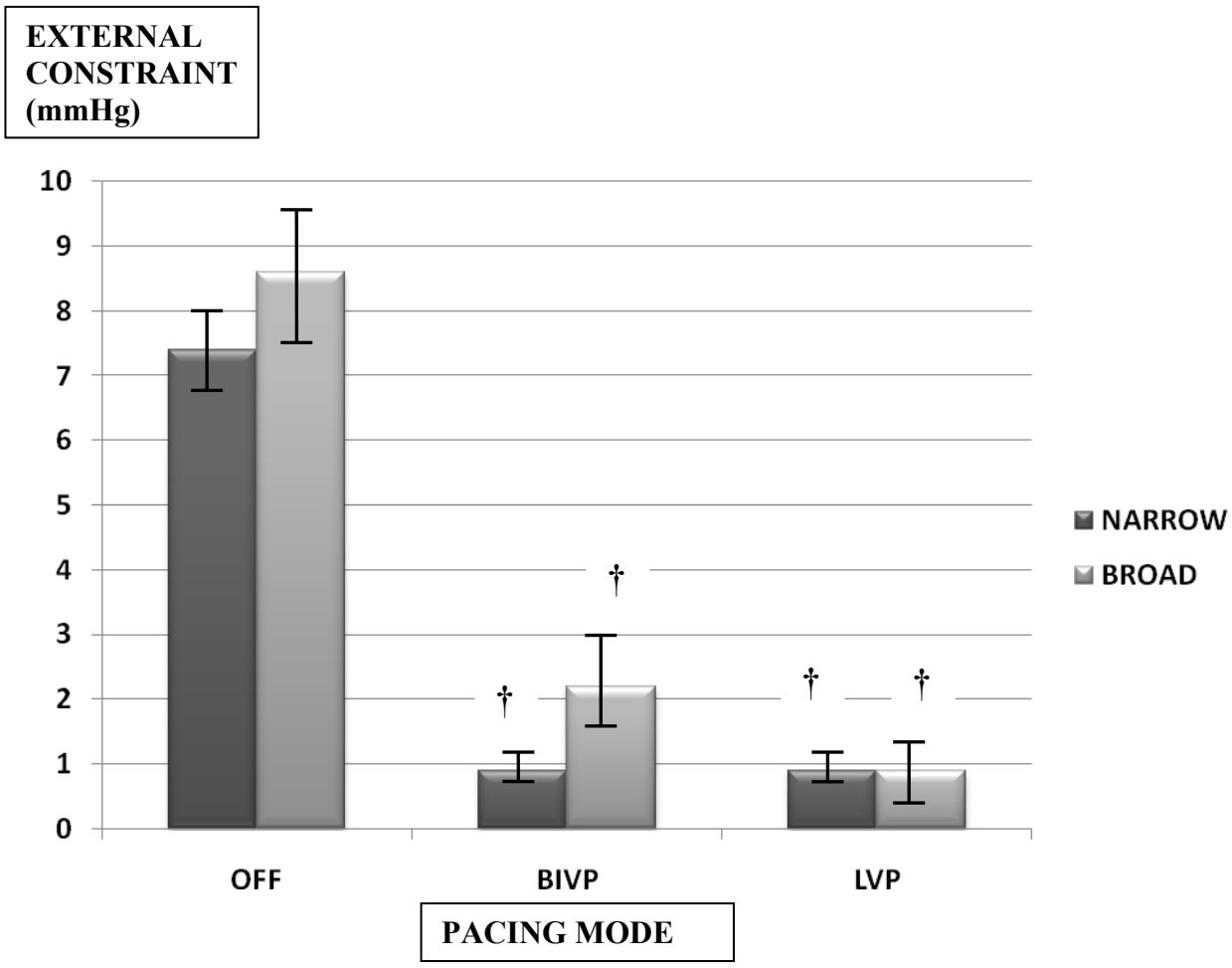
Figure 4.1 demonstrated the response to BIVP in a patient with evidence of external constraint at baseline.

FIGURE 4.1. The effect of BIVP on external constraint in a representative patient



External constraint was present in 15 of the 31 patients with a narrow QRS duration, and was reduced from 7.4 ± 2.8mmHg to 0.9 ± 1.2 mmHg with BIVP, and to 0.9 ± 1.4mmHg with LVP ($p<0.01$) (Figure 4.2). In those patients with a broad QRS duration, external constraint was present in 14 of the 23 patients, and was reduced from 8.6 ± 3.0mmHg to 2.2 ± 3.2 mmHg with BIVP, and to 0.9 ± 1.6mmHg with LVP ($p<0.01$) (Figure 4.2). There was no significant difference between BIVP and LVP in either patient group.

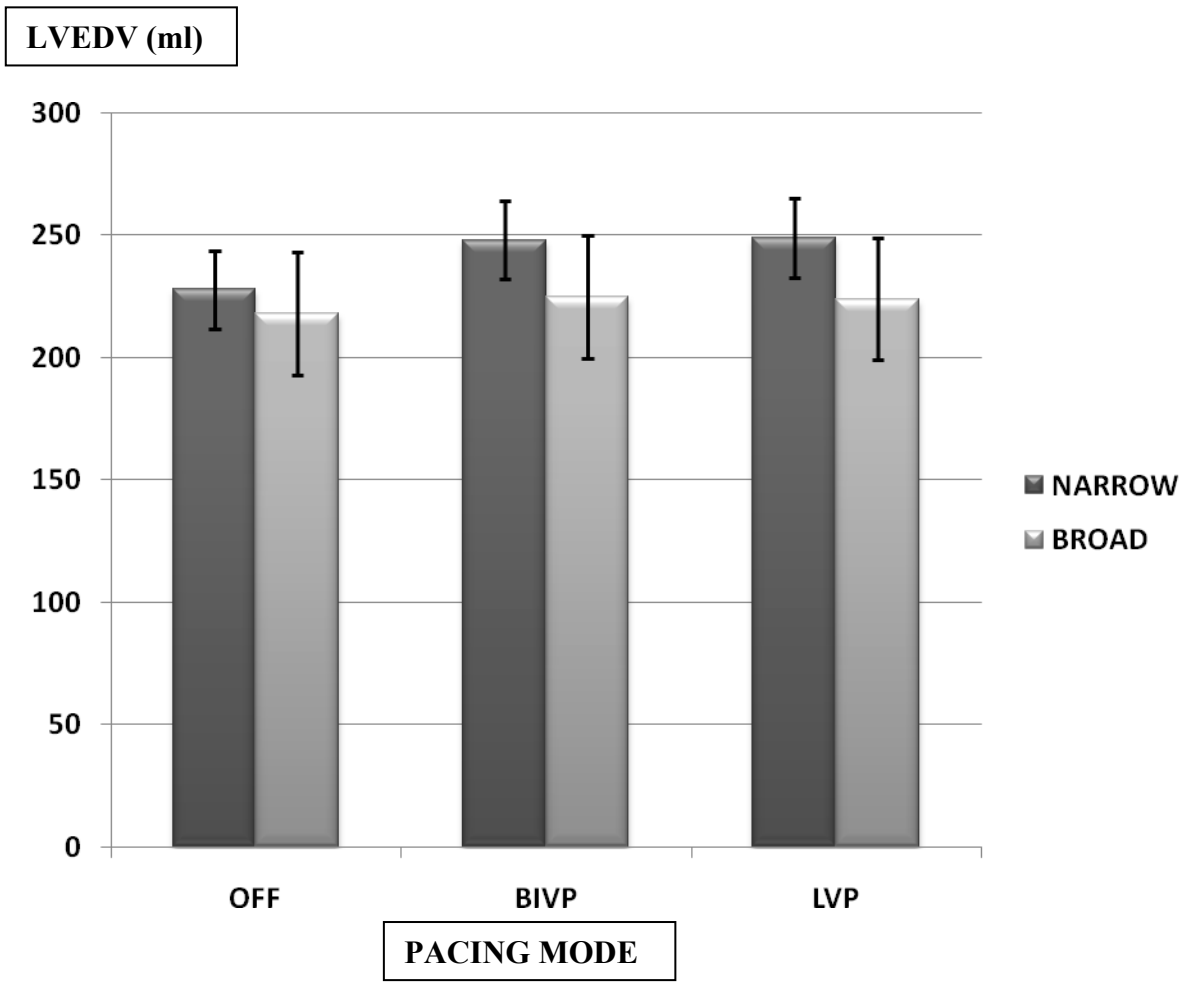
<u>FIGURE 4.2.</u> The effect of pacing on external constraint in the narrow QRS broad QRS patient group respectively



Error bars indicate ± 1 SEM; † indicates a significant change from OFF ($p<0.05$)

In those patients with evidence of external constraint and a narrow QRS duration (n=15), left ventricular end-diastolic volume increased from 228 ± 53ml to 248 ± 55ml in response to BIVP (p=NS), and to 249 ± 56ml with LVP (p=NS). In those patients with a broad QRS duration (n=14), left ventricular end-diastolic volume increased from 218 ± 71ml to 225 ± 71ml in response to BIVP (p=NS), and to 224 ± 71ml with LVP (p=NS) (Figure 4.3).

FIGURE 4.3. The effect of pacing on left ventricular end-diastolic volume (LVEDV) in the narrow QRS and broad QRS patient group respectively



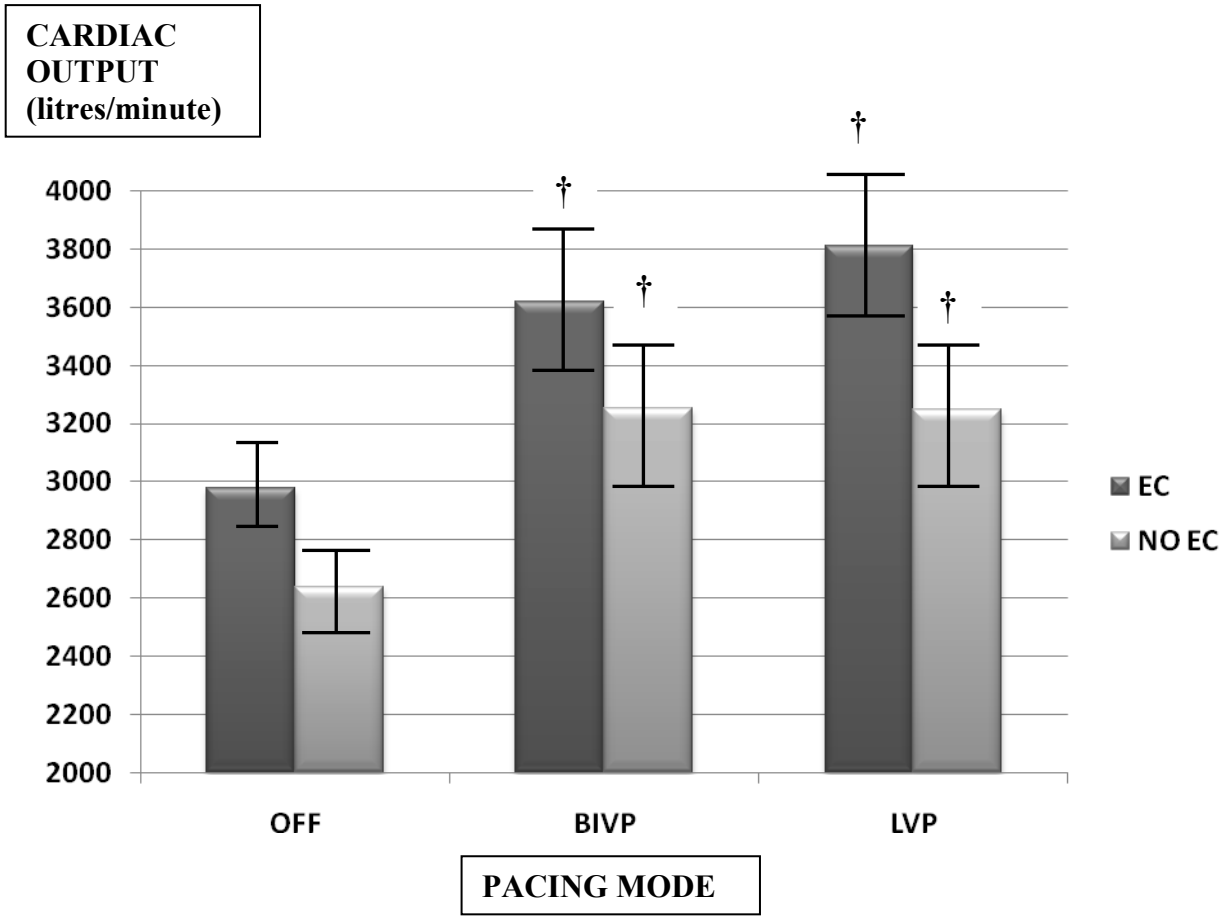
Error bars indicate ± 1 SEM

Indices of systolic function in patients with and without external constraint (EC)

Cardiac Output

In those patients with evidence of external constraint and a narrow QRS duration (n=15), cardiac output increased from 2976 ± 476ml/min to 3618 ± 727ml/min in response to BIVP (22% increase), and to 3811 ± 717ml/min with LVP (28% increase; p=0.01). In those patients without evidence of external constraint and a narrow QRS duration (n=16), cardiac output increased from 2637 ± 628ml/min to 3253 ± 825ml/min in response to BIVP (23% increase), and to 3247 ± 1084ml/min with LVP (23% increase; p=0.05) (Figure 4.4A). There was no significant difference between BIVP and LVP in either group.

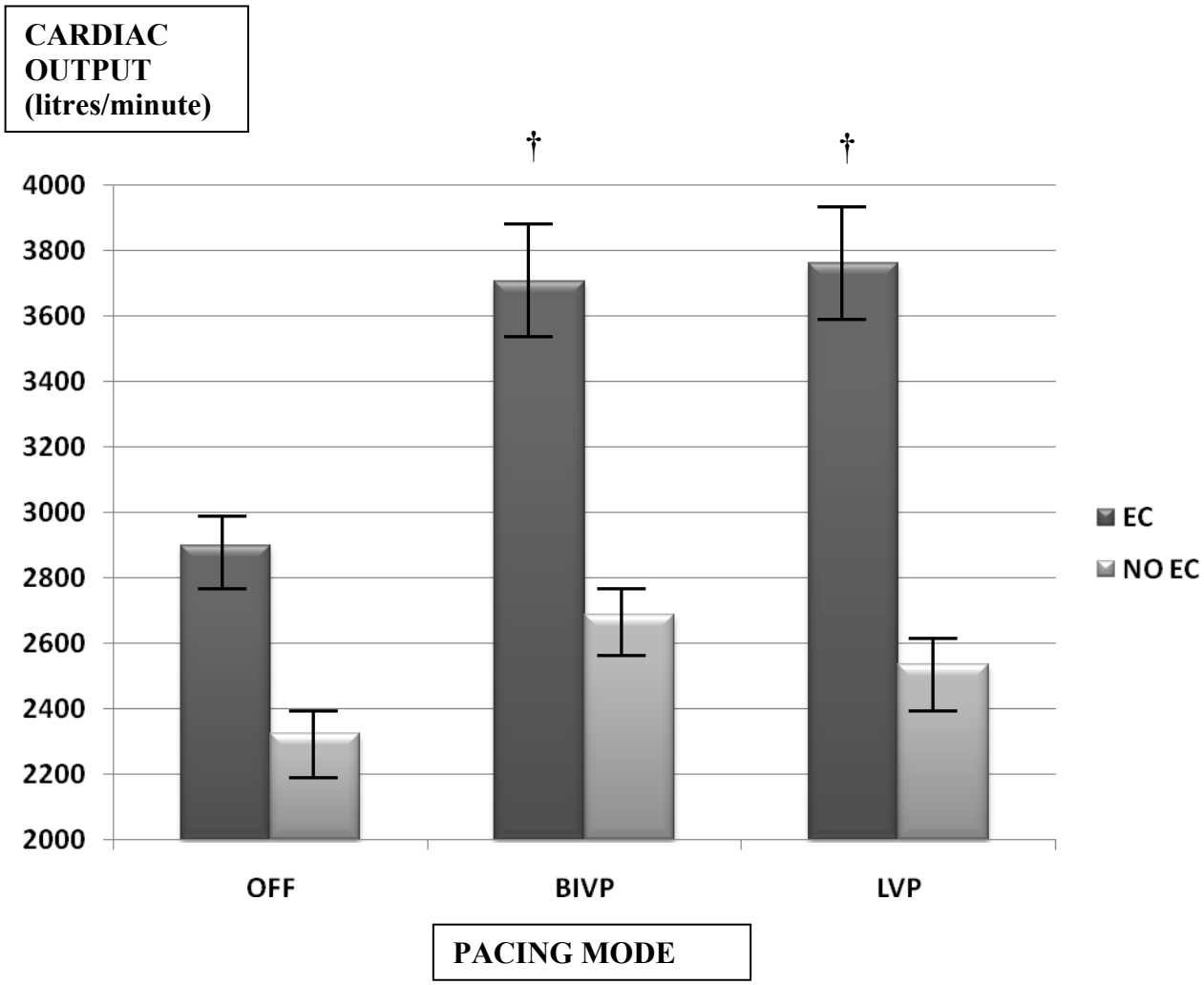
FIGURE 4.4A. The effect of pacing on cardiac output (CO) in the narrow QRS patients with (EC) and without external constraint (NO EC)



Error bars indicate ± 1 SEM; † indicates a significant change from OFF (p<0.05)

In those patients with a broad QRS duration and external constraint (n=14), cardiac output increased from 2898 ± 496ml/min to 3706 ± 710ml/min in response to BIVP (28% increase), and to 3760 ± 652ml/min with LVP (30% increase; $p<0.01$). In those patients without evidence of external constraint and a broad QRS duration (n=9), cardiac output increased from 2324 ± 330ml/min to 2686 ± 333ml/min in response to BIVP (16% increase), and to 2535 ± 457ml/min with LVP (9% increase; p=NS) (Figure 4.4B). There was no significant difference between BIVP and LVP in either group.

FIGURE 4.4B. The effect of pacing on cardiac output (CO) in the broad QRS patients with (EC) and without external constraint (NO EC)

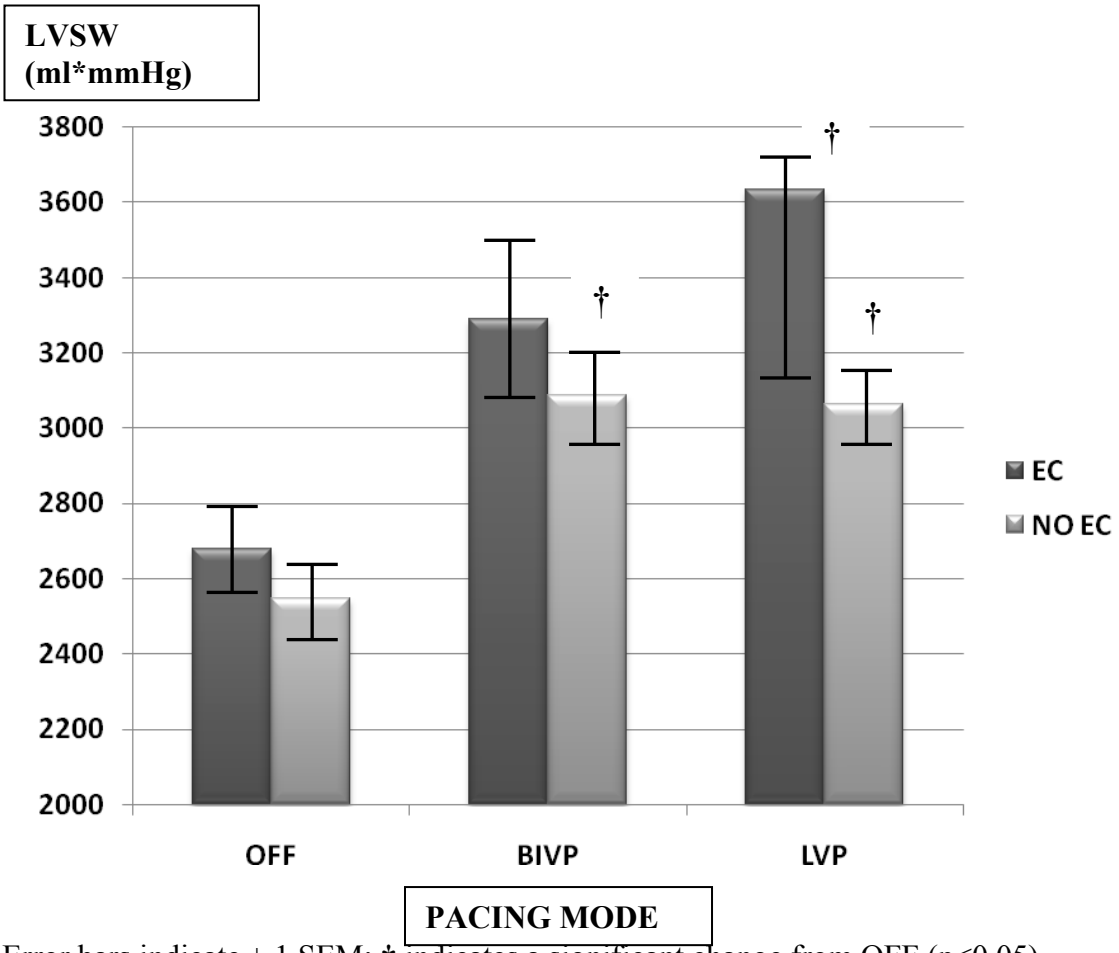


Error bars indicate ± 1 SEM; † indicates a significant change from OFF ($p<0.05$)

Left Ventricular Stroke Work (LVSW)

In those patients with evidence of external constraint and a narrow QRS duration (n=15), LVSW increased from 2678 ± 565ml*mmHg to 3291 ± 746ml*mmHg in response to BIVP (23% increase; p=NS), and to 3633 ± 1008ml*mmHg with LVP (36% increase; p=0.02). In those patients without evidence of external constraint and a narrow QRS duration (n=16), LVSW increased from 2547 ± 731ml*mmHg to 3087 ± 538ml*mmHg in response to BIVP (21% increase), and to 3064 ± 529ml*mmHg with LVP (20% increase; p=0.01) (Figure 4.5A). There was no significant difference between BIVP and LVP for either group on pairwise comparisons.

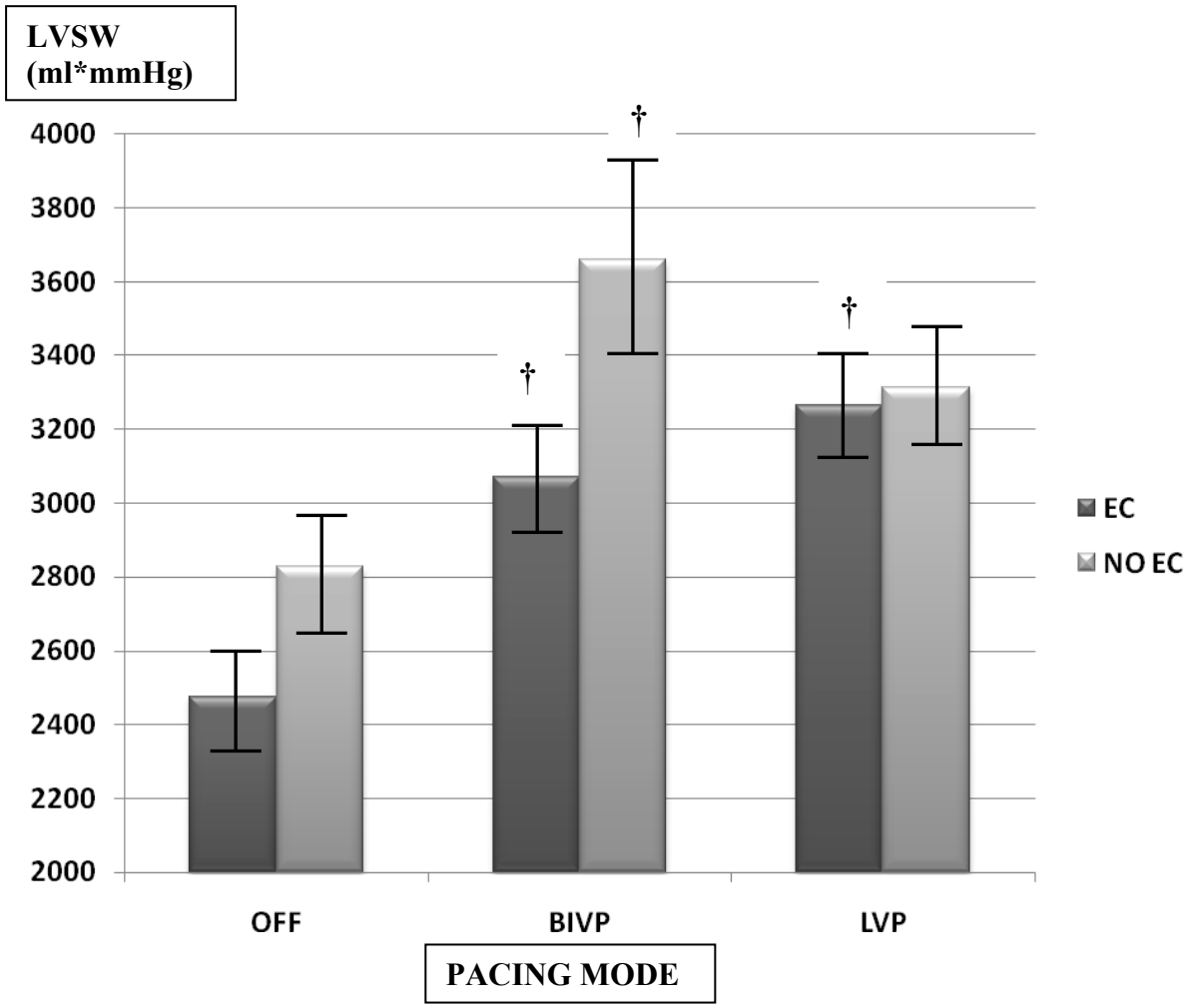
FIGURE 4.5A. The effect of pacing on left ventricular stroke work (LVSW) in the narrow QRS patients with (EC) and without external constraint (NO EC)



Error bars indicate ± 1 SEM; † indicates a significant change from OFF ($p<0.05$)

In those patients with evidence of external constraint and a broad QRS duration (n=14), LVSW increased from 2474 ± 557ml*mmHg to 3072 ± 464ml*mmHg in response to BIVP (24% increase), and to 3265 ± 458ml*mmHg with LVP (32% increase; p<0.01). In those patients without evidence of external constraint and a narrow QRS duration (n=9), LVSW increased from 2827 ± 578ml*mmHg to 3661 ± 795ml*mmHg in response to BIVP (30% increase; p=0.02), and to 3312 ± 506ml*mmHg with LVP (17% increase; p=NS) (Figure 4.5B). There was no significant difference between BIVP and LVP in either group.

<u>FIGURE 4.5B.</u> The effect of pacing on left ventricular stroke work (LVSW) in the broad QRS patients with (EC) and without external constraint (NO EC)

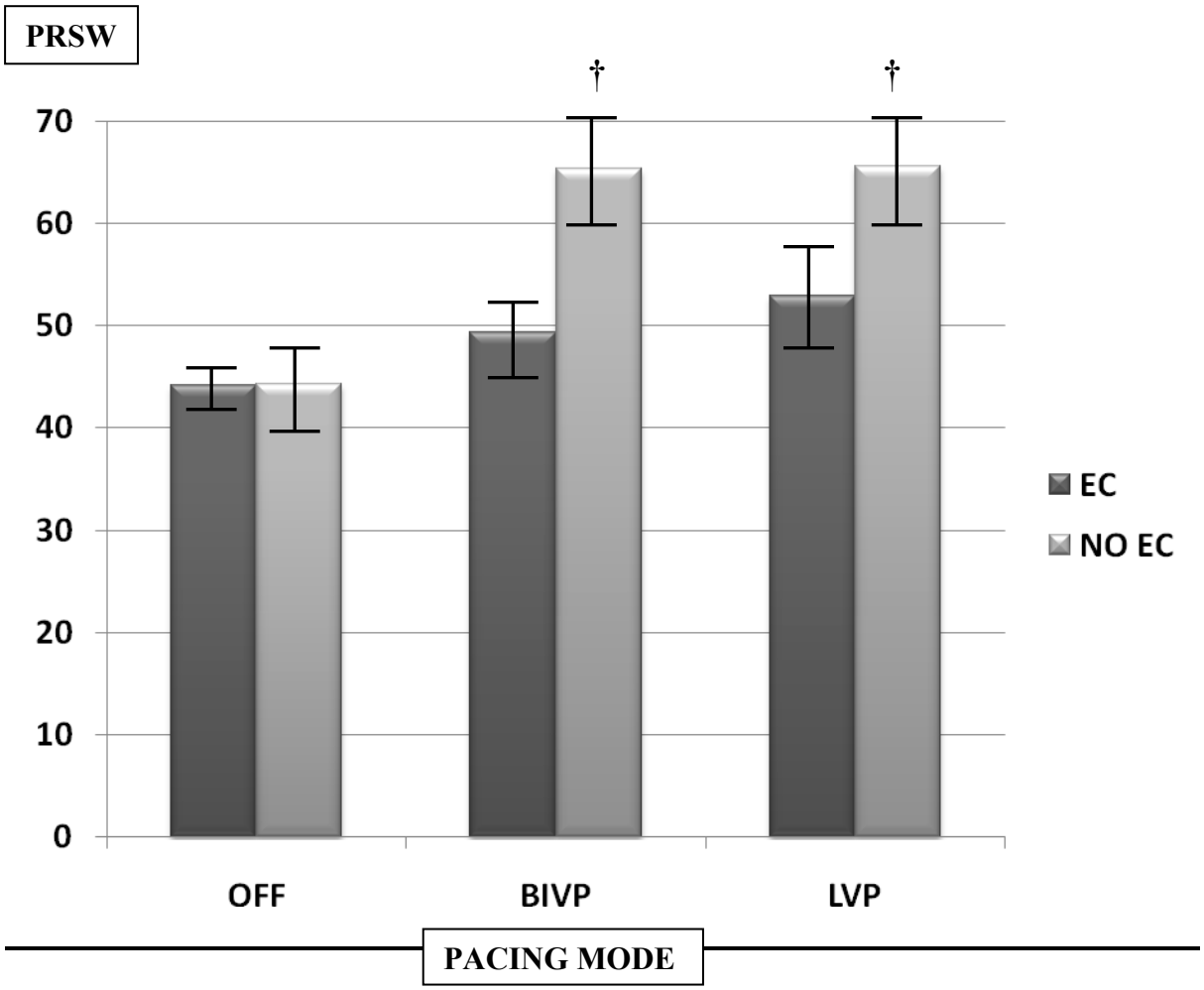


Error bars indicate ± 1 SEM; † indicates a significant change from OFF (p<0.05)

Preload Recruitable Stroke Work

In those patients with evidence of external constraint and a narrow QRS duration (n=15), PRSW increased from 44.2 ±11.7 to 49.3 ±11.6 in response to BIVP (12%), and to 52.9 ± 14.6 (20%) with LVP, without reaching statistical significance. In those patients without evidence of external constraint and a narrow QRS duration (n=16), PRSW increased from 44.3 ± 18.9 to 65.3 ± 20.7 in response to BIVP (47%), and to 65.6 ± 21.5 with LVP (48%; $p<0.01$) (Figure 4.6A).

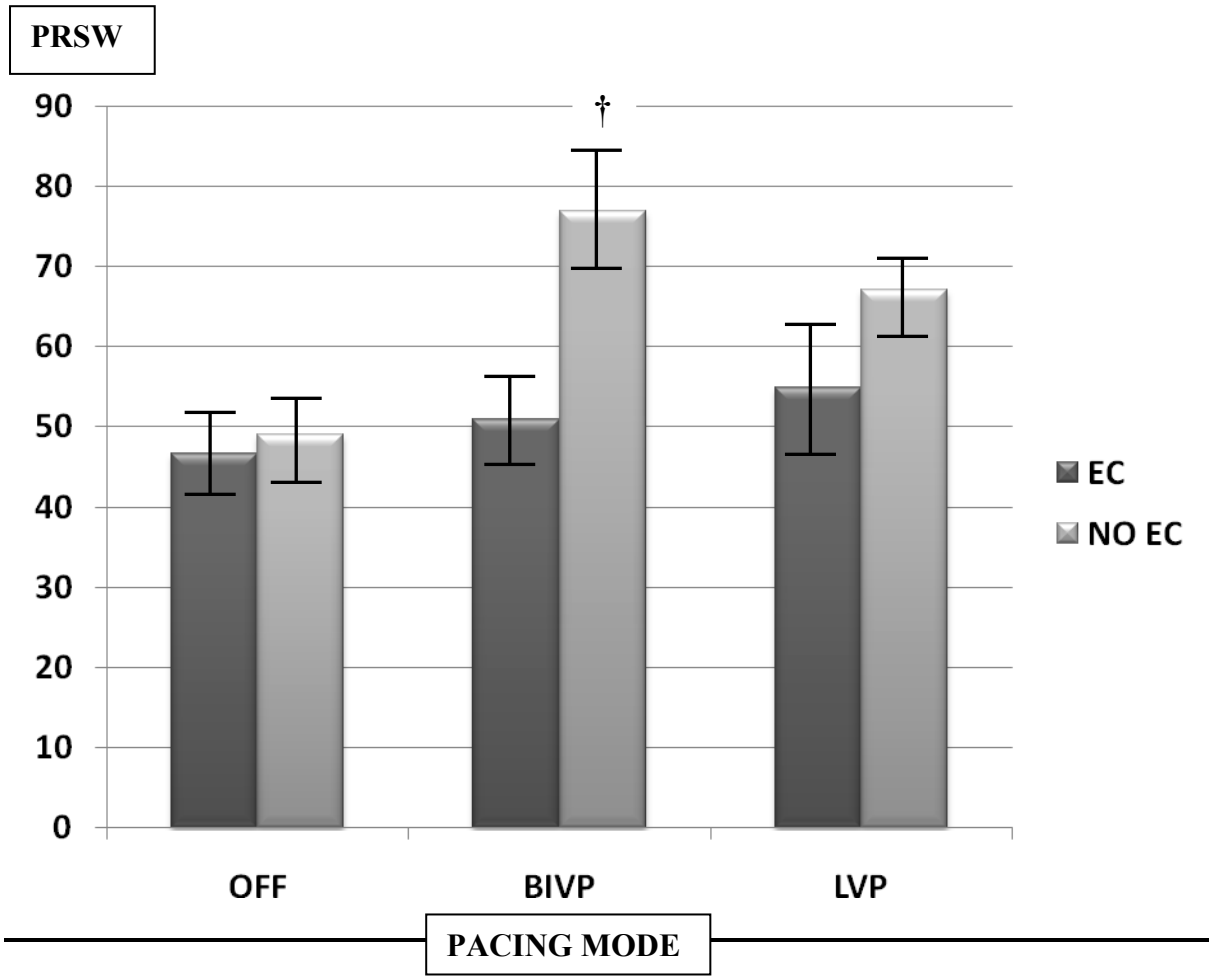
FIGURE 4.6A. The effect of pacing on preload recruitable stroke work (PRSW) in the narrow QRS patients with (EC) and without external constraint (NO EC)



Error bars indicate ± 1 SEM; † indicates a significant change from OFF ($p<0.05$)

In those patients with evidence of external constraint and a broad QRS duration (n=14), PRSW increased from 46.6 ± 10.6 to 51.0 ± 9.9 in response to BIVP (9%) and to 54.9 ± 14.3(18%) with LVP, although neither change reach statistical significance. In those patients without evidence of external constraint and a narrow QRS duration (n=9), PRSW increased from 49.1 ± 15.8 to 76.9 ± 25.3 in response to BIVP (57%; p=0.04), and to 67.1 ± 16.5 with LVP (37%; p=NS) (Figure 4.6B). There was no significant difference between BIVP and LVP in either group.

<u>FIGURE 4.6B.</u> The effect of pacing on preload recruitable stroke work (PRSW) in the broad QRS patients with (EC) and without external constraint (NO EC)

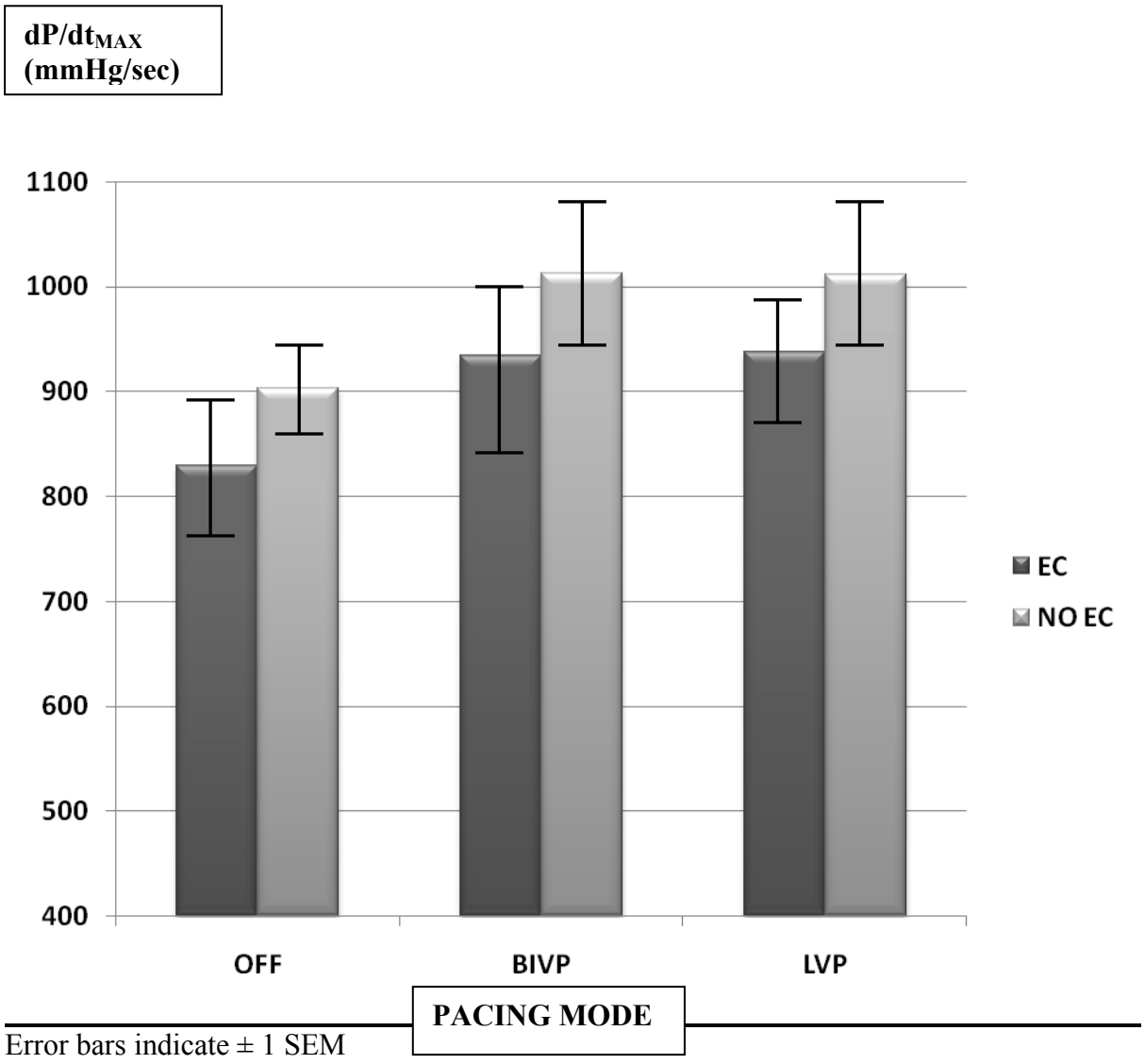


Error bars indicate ± 1 SEM; † indicates a significant change from OFF ($p<0.05$)

dP/dt$_{MAX}$

In those patients with evidence of external constraint and a narrow QRS duration (n=15), dP/dt$_{MAX}$ increased from 829 ± 211 to 934 ± 193mmHg/s in response to BIVP (13%) and to 938 ±198mmHg/s with LVP (13%), without reaching statistical significance. In those patients without evidence of external constraint and a narrow QRS duration (n=16), dP/dt$_{MAX}$ increased from 903 ± 171 to 1013 ± 216mmHg/s in response to BIVP (12%), and to 1011 ± 199mmHg/s with LVP (12%), again without reaching statistical significance (Figure 4.7A).

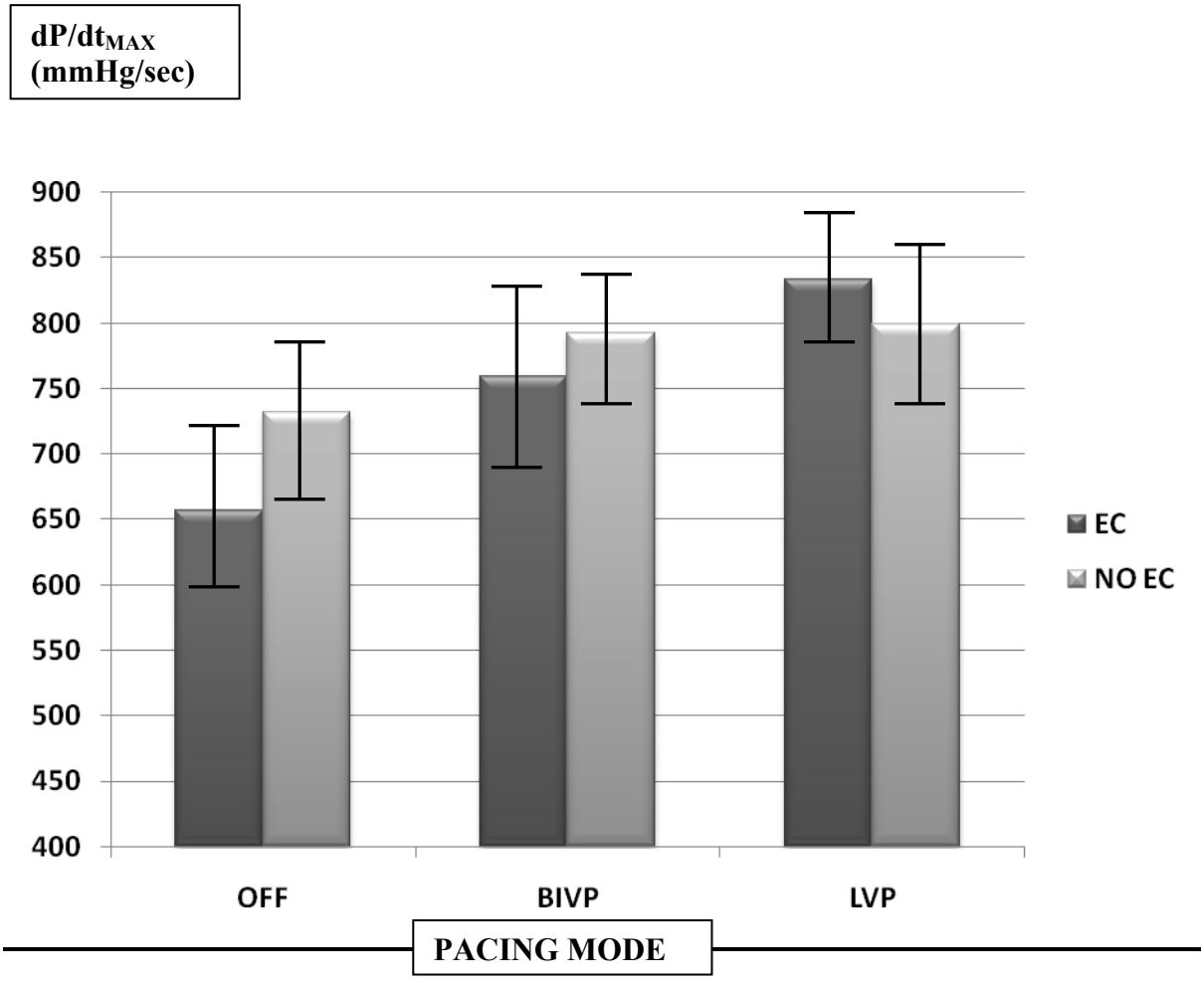
FIGURE 4.7A. The effect of pacing on dP/dt$_{MAX}$ in the narrow QRS patients with (EC) and without external constraint (NO EC)



Error bars indicate ± 1 SEM

In those patients with evidence of external constraint and a broad QRS duration (n=14), dP/dt_{MAX} increased from 657 ± 197 to 759 ± 233mmHg/s in response to BIVP (16%) and to 833 ±163mmHg/s with LVP (27%), without reaching statistical significance. In those patients without evidence of external constraint and a broad QRS duration (n=9), dP/dt_{MAX} increased from 732 ± 211 to 792 ± 180mmHg/s in response to BIVP (8%), and to 799 ± 189mmHg/s with LVP (9%), again without reaching statistical significance (Figure 4.7A).

FIGURE 4.7B. The effect of pacing on dP/dt_{MAX} in the broad QRS patients with (EC) and without external constraint (NO EC)



Error bars indicate ± 1 SEM

DISCUSSION

In the present study we have demonstrated that half of the heart failure patients had evidence of external constraint to left ventricular filling at baseline, with a similar frequency in patients regardless of baseline QRS duration. This is similar to the previously reported prevalence of external constraint in a heart failure population using a radionuclide measurement of ventricular volumes during application of lower body negative pressure (50). The present data shows that in this heart failure population both BIVP and LVP resulted in a similar significant reduction in external constraint in both the broad and narrow QRS heart failure patients.

Bleasdale *et al* have recently demonstrated that LV pacing ameliorated external constraint to LV filling by the right ventricle through the interventricular septum (diastolic ventricular interaction – DVI), and by the pericardium (pericardial constraint) (the combined impact of which is referred to as external constraint) (55). This was a more conventional patient group in whom the authors exclusively studied LV pacing and reported a reduction in external constraint. Relief of external constraint causes an acute increase in LV diastolic volume despite a similar LVEDP, thereby increasing stroke work by the Starling mechanism. Static equilibrium analysis has been used to quantify the external constraint to LV filling in animal models (94;95). With this technique, external constraint is quantified as the difference in LVEDP before and after removal of the pericardium while a constant LVEDV is maintained. This technique can only be used when the chest is open. However, in the present study we applied a modified approach by continuously measuring LV pressure and volume during occlusion of the IVC to acutely reduce RV volume and pressure (51). This acute reduction in RV volume removes external constraint to LV filling from the RV and pericardium. The

mechanism for the reduction in external constraint is probably related to the induction of a phase shift in the timing of LV filling relative to RV filling resulting in the timing of events being brought forward in time in the left ventricle, as previously demonstrated in a canine pacing model (54). Pericardial stretch, and, therefore, pericardial pressure, thus depend on total cardiac volume; therefore, a reduced right ventricular volume during left ventricular filling would be expected to result in less constraint, a greater LVEDV, and (by the Frank–Starling mechanism) greater left ventricular stroke work.

In those patients with evidence of external constraint at baseline there was trend towards a greater haemodynamic benefit from left ventricular pacing compared with simultaneous biventricular pacing, with a greater percentage increase in cardiac output, absolute left ventricular stroke work, preload recruitable stroke work, and dp/dt_{MAX} in both the narrow and broad QRS groups. This is not unexpected, as left ventricular pacing would result in a more pronounced shift in the timing of events in the left ventricle relative to those occurring in the right ventricle than simultaneous biventricular pacing. In comparison, in those patients without evidence of external constraint at rest, an equivalent haemodynamic benefit was seen with both biventricular and left ventricular pacing, although the increase in absolute left ventricular stroke work and preload recruitable stroke work was greater with biventricular pacing.

The presence of external constraint is likely to have important implications for the mechanisms of exercise limitation in heart failure, since it prevents utilization of the Starling mechanism to increase cardiac output. External constraint may help to explain why exercise tolerance is limited in patients with heart failure, since it prevents utilisation of the Starling mechanism to increase cardiac output (93). There is indirect evidence to suggest that

ventricular interaction may limit the stroke volume response to exercise even in health. Higginbotham et al reported that in the early stages of upright exercise in man, the increase in cardiac output was due to an increase in both heart rate and stroke volume (mainly due to an increase in LVEDV with a modest increase in ejection fraction) (96). Above approximately 50% of maximal oxygen consumption, the increase in cardiac output was due entirely to an increase in heart rate. There was no further increase in LVEDV, indeed in some subjects it fell despite an increase in PCWP. These observations may either be a consequence of DVI or due to the effects of a reduced diastolic filling time at higher levels of exercise but the latter seems unlikely because in the normal heart, the left ventricular end diastolic pressure-volume relation is only affected at heart rates above 170bpm (97). The failure of LVEDV to rise despite an increase in PCWP began at much lower heart rates. Furthermore, the observations of Robinson *et al* (98) imply that by peak exercise, the Starling mechanism cannot be utilised because of external constraint to filling. Consistent with this, Stray-Gundersen *et al* showed that in greyhounds pericardiectomy resulted in an increased cardiac output during the later stages of exercise (and also increased maximal oxygen consumption) via a greater increase in LVEDV (99). Venoconstriction, with an associated translocation of blood to the central compartment during exercise, with the resulting increase in right atrial pressure and right ventricular end-diastolic volume, would be expected to result in an increase in external constraint to left ventricular filling and a subsequent inability to augment cardiac output. Relief of external constraint might be expected to have a significant role in the improvement in exercise capacity seen in patients who respond to cardiac resynchronisation therapy.

In the present study we used an invasive measure of the presence or absence of external constraint, namely inferior vena caval occlusion and left heart catheterisation. However, this method of assessment is not feasible in all heart failure patients. Similarly, assessing the

change in left ventricular end-diastolic volume in response to the application of lower body negative pressure to assess for external constraint remains a research tool and not widely clinically available.

Echocardiography provides the simplest and easily accessible method for assessing the volume and pressure of the right ventricle, right atrial pressure (an excellent surrogate for pericardial pressure), septal position, septal motion, and the transmitral filling pattern. As previously described, the presence of a restrictive transmitral filling pattern has both a high sensitivity and specificity for detecting diastolic ventricular interaction and external constraint.

In addition, the position of the interventricular septum at end-diastole provides valuable information relating to the trans-septal pressure gradient (LVEDP minus RVEDP). The normal interventricular septum is convex when viewed from the left ventricle, with the shape remaining the same in systole and diastole because the pressure in the left ventricle remains higher than in the right. The impact of right ventricular volume or pressure overload can lead to a reversal of the end-diastolic trans-septal pressure gradient, resulting in the septum becoming flattened or even concave at end-diastole (often in association with paradoxical septal motion as the septum moves rightward during systole as a result of restoration of the normal positive trans-septal pressure gradient). This is often seen as a delay in septal to posterior wall contraction on M-mode echocardiography of > 130ms. The echocardiographic assessment of ventricular interdependence could easily be incorporated into current protocols, in addition to non-invasive assessment of LVEDP using the E/E' ratio (transmitral E wave velocity / tissue Doppler E velocity derived at the mitral valve annulus), in order to identify patients more likely to derive a significant benefit from pacing.

STUDY LIMITATIONS

The calibration method of the conductance catheter was not based on an assessment of absolute volume, but this would not affect results, which depend entirely on relative changes within each patient in response to the pacing mode.

The catheter was calibrated during steady-state at the beginning of the study. Vena caval occlusion, which results in a fall in RV volume, could result in a decrease in parallel conductance which may result in a modest underestimation of LV volume. To estimate the effect of IVC occlusion we assessed parallel conductance at baseline and repeated the measurement during a caval occlusion in 3 patients. Results show that the decrease in parallel conductance was less than 5% in each patient, which would translate into an apparent (i.e. artificial) decrease of 10ml in absolute volume at most. Because of the invasive nature of the study, only a small sample of patients was studied in the short-term, hence these results may not predict the medium and long-term effects of CRT on cardiac function.

These studies were performed supine and at rest. The magnitude of ventricular interaction is variable; it is likely to decrease on adopting the upright posture as the RV volume decreases, and it is likely to increase on exercise, secondary to intestinal venoconstriction (100). Indeed, ventricular interaction may be an important mechanism contributing to stroke volume limitation and exercise intolerance in CHF (101). The present studies did not examine the effect of LV pacing on ventricular interaction during exercise.

CONCLUSIONS

This study suggests a potentially important mechanism by which cardiac resynchronisation therapy may produce haemodynamic benefit. Both BIVP and LVP significantly reduce external constraint to left ventricular filling, resulting in an increase in effective filling pressure; the consequent increase in LV end-diastolic volume increases stroke volume via the Starling mechanism. In those patients with evidence of external constraint at baseline there was a trend towards a greater haemodynamic benefit from left ventricular pacing compared with simultaneous biventricular pacing. The presence of external constraint is likely to have important implications for the mechanisms of exercise limitation in heart failure, since it prevents utilization of the Starling mechanism to increase cardiac output.

CHAPTER 5

OPTIMAL INTERVENTRICULAR TIMING DELAY BASED ON UNDERLYING PHYSIOLOGY AND QRS DURATION

INTRODUCTION

Invasive haemodynamic studies have previously demonstrated the acute beneficial effects of CRT in patients with heart failure and a broad QRS duration (37;38;65;87). In a recent study we have demonstrated comparable haemodynamic improvements in patients with heart failure and a narrow QRS duration (102), amounting to as much as a 25% increase in cardiac output and a 25-30% increase in left ventricular stroke work. Despite a marked difference in the QRS width induced by biventricular (BIVP) and left ventricular pacing (LVP), both modes of pacing have been shown to be equally efficacious at improving cardiac function in heart failure patients with left ventricular dyssynchrony (37;38;65;103), and indeed our study showed comparable benefits from BIVP and LVP in a patient group with a narrow QRS duration and no observable dyssynchrony (102). This similarity in acute haemodynamic effect suggests that mechanical rather than electrical resynchronization is responsible for the benefit from pacing therapy.

Bordachar *et al* have clarified the respective mechanisms by which BIVP and LVP result in a haemodynamic improvement despite differing effects on the surface ECG (66). They demonstrated that LVP resulted in a substantial reduction in intraventricular dyssynchrony, but was associated with a reduction in left ventricular filling time and a longer pre-aortic ejection delay, thereby worsening interventricular dyssynchrony. Although intraventricular

delay is known to be associated with a poor prognosis in heart failure, no such data exists for the effects of interventricular conduction delay on prognosis (67;68).

Although the predominant mechanism of improvement from CRT is thought to be a reduction in both inter- and intraventricular dyssynchrony, additional mechanisms independent of resychronisation contribute to the benefit derived. One of these mechanisms is a reduction in external constraint to left ventricular filling by the right ventricle and pericardium. In a previous study we exclusively studied LV pacing and reported a reduction in external constraint to left ventricular filling (55). Relief of external constraint caused an acute increase in LV diastolic volume despite a similar LVEDP, thereby increasing stroke work by the Starling mechanism. The mechanism for the reduction in external constraint is probably related to the induction of a phase shift in the timing of LV filling relative to RV filling (more pronounced with LVP compared to BIVP), resulting in the timing of events being brought forward in time in the left ventricle. This effectively results in LV filling occurring at a time when RV pressure and volume are lower; hence RV diastolic pressure and pericardial pressure are likely to be lower at any given LV diastolic volume. We have also shown that BIVP is as effective as LVP at reducing external restraint in a patient group with heart failure and a narrow QRS duration (102).

In the present study we evaluated the acute hemodynamic effects of various interventricular timing delays on cardiac performance in symptomatic heart failure patients with both a narrow and broad QRS duration.

METHODS

Patients. Twenty five heart failure patients (age 59 years ± 4; 21 to 79 years) with a QRS duration < 120ms and 12 heart failure patients (age 63 ± 4 years; 53 to 76 years) with a QRS duration > 120ms were studied. All patients had LVEF≤35% as determined by echocardiography. Patients were in NYHA class III or IV despite optimal tolerated medical therapy that included diuretics and Angiotensin-converting enzyme (ACE) inhibitors.

Acute Haemodynamic Studies. Acute hemodynamic studies were performed in the cardiac catheterization laboratory at the time of CRT device implantation with patients in the non-sedated and supine state. Catheterization of the left ventricle was performed by a standard over-the-wire technique. A dual-field conductance catheter (CA-71103-PL catheter, CD Leycom, The Netherlands) was then positioned in the apex of the ventricle. The conductance catheter method provides a continuous online beat-by-beat measurement of left ventricular pressure and volume (74). The conductance catheter calibration has been described elsewhere (78). We applied a modified parallel conductance calibration via a right atrial injection (78) to avoid catheterization of the right ventricle or pulmonary artery.

All data were acquired during an unforced end-expiratory breath hold. From each acquisition run, the derivatives of pressure and volume were calculated as the mean of the 10 to 15 consecutive beats free from atrial or ventricular ectopic activity. Pressure-volume analysis was also performed during an inferior vena caval (IVC) occlusion, which reduced central blood volume and RV pressure acutely, achieved with a 40-mm IVC occlusion balloon catheter (Meditec, Boston Scientific International). Data were acquired with a CFL-512 system (CD Leycom), which allows further offline analysis (CircLab, Leiden University, The Netherlands).

The hemodynamic measurements were undertaken during no pacing (VVI), in biventricular pacing mode (BIVP), in left ventricular pacing (LVP) mode, and over a range of

interventricular timing delays. Interventions were applied in the order shown in Table 1. Absolute left ventricular stroke work and dP/dt_{MAX} were determined at each interventricular delay. We quantified external constraint (EC) to LV filling using a modification of the static equilibrium technique as previously described by us (55).

Table 5.1. Interventricular timing delays

V-V INTERVAL	A-V INTERVAL	
Pacing OFF		
RV-LV 80ms	20ms	RV LEAD
RV-LV 40ms	60ms	
RV-LV 20ms	80ms	
RV-LV 12ms	90ms	SIMULTANEOUS
BIVP	100ms	
LV-RV 12ms	100ms	
LV-RV 20ms	100ms	LV LEAD
LV-RV 40ms	100ms	
LV-RV 80ms	100ms	
LVP	100ms	

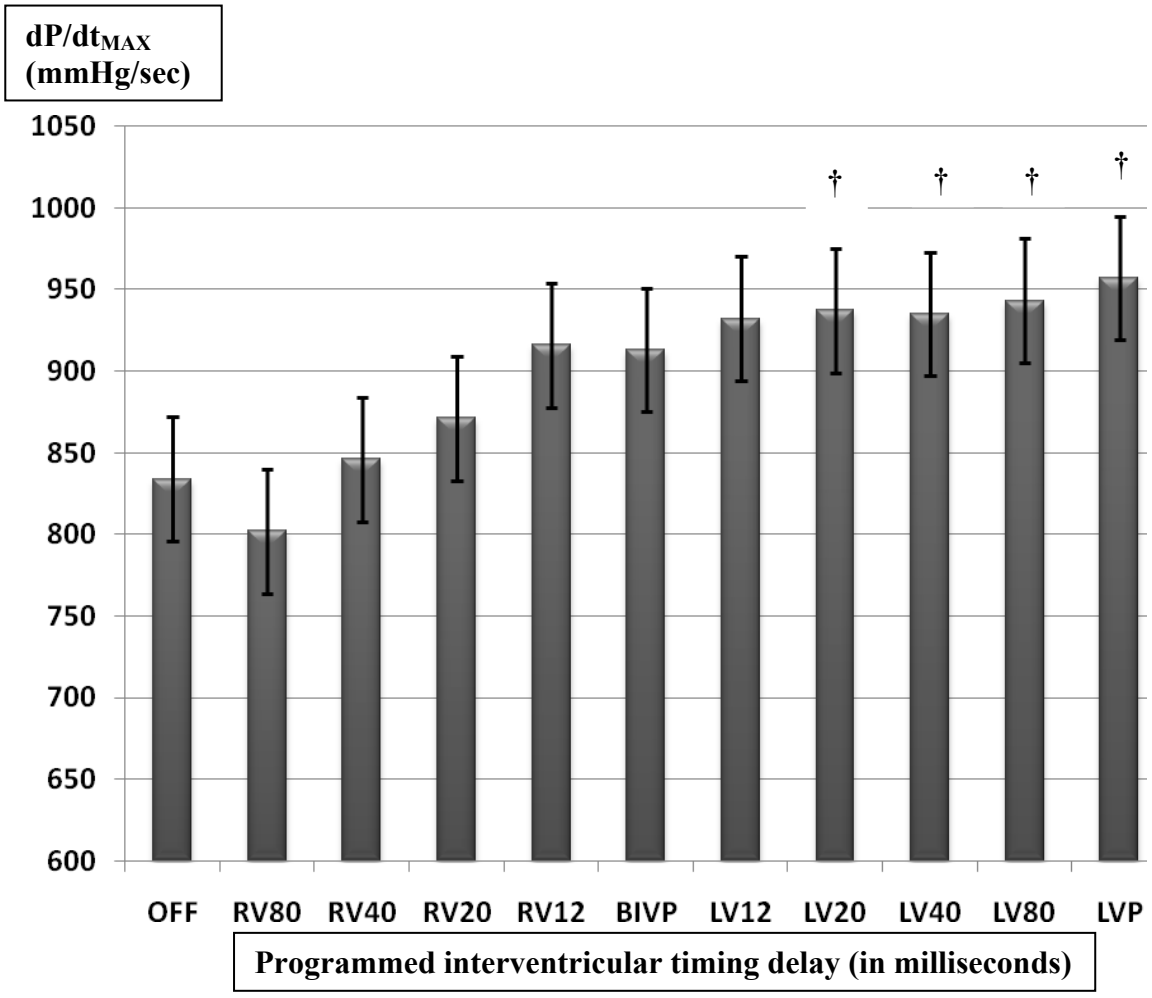
Statistical Analysis. All data are expressed as the mean value ± SD. A one-way ANOVA was used if the data was normally distributed based on a Kolmogorov-Smirnov test. For data that was not normally distributed, a Kruskal-Wallis test was used. Statistical significance was assumed at $p<0.05$.

RESULTS

Effect of interventricular timing delay on dP/dt_{MAX}

dP/dt_{MAX} decreased in response to pacing with a V-V delay of RV first by 80ms, but increased in response to all other programmed interventricular delays. However, only V-V delays in which the LV led by > 20ms resulted in a significant increase in dP/dt_{MAX} from baseline values ($p<0.05$) (Figure 5.1A.). Percentage changes from baseline and from simultaneous BIVP for all programmed V-V delays are shown in Figure 5.1B and 5.1C respectively.

Figure 5.1A. dP/dt_{MAX} at different V-V delays



Error bars indicate ± 1 SEM; † indicates a significant change from OFF ($p<0.05$)

Figure 5.1B. **Percentage change in dP/dt_{MAX} from OFF**

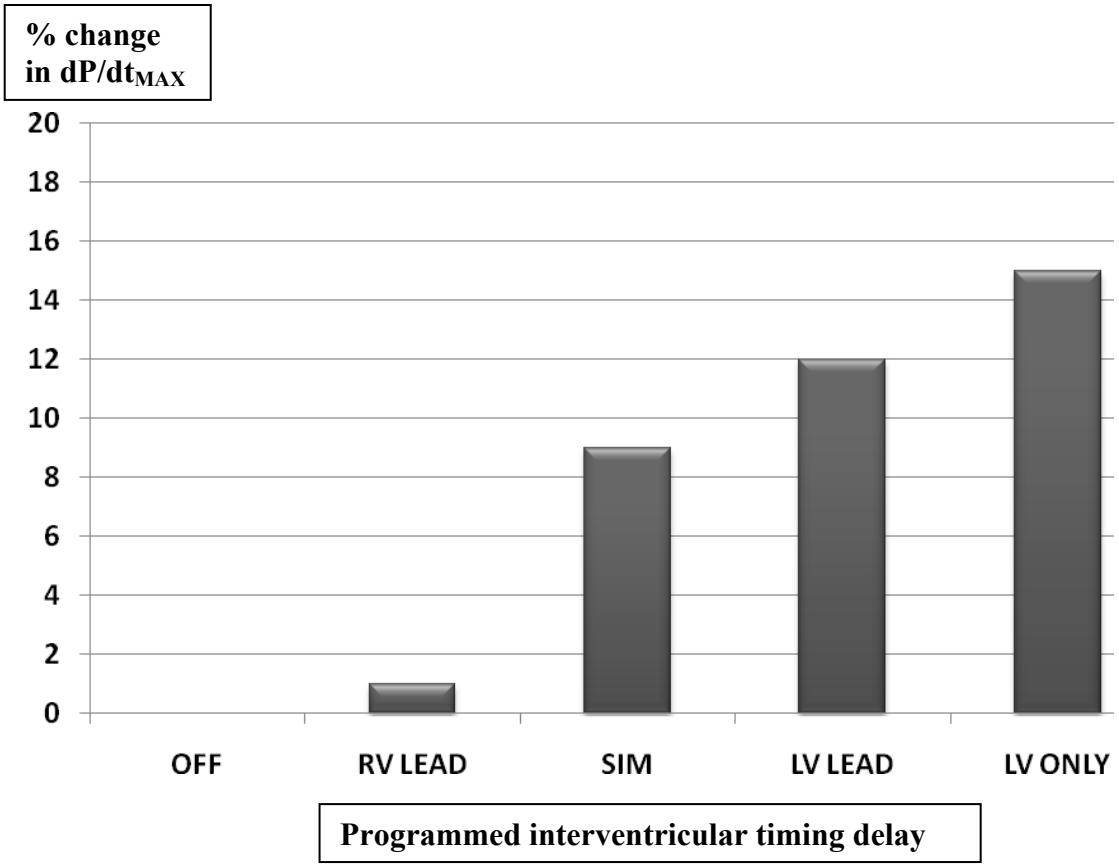
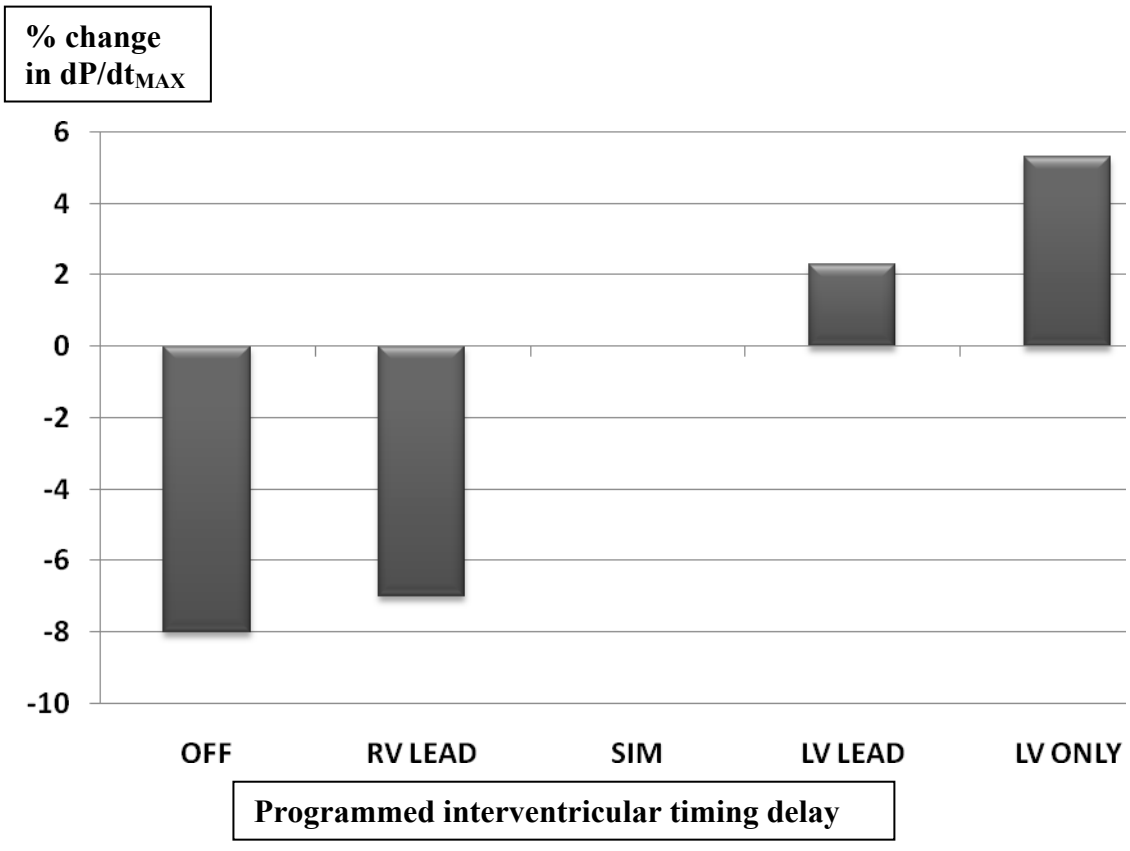


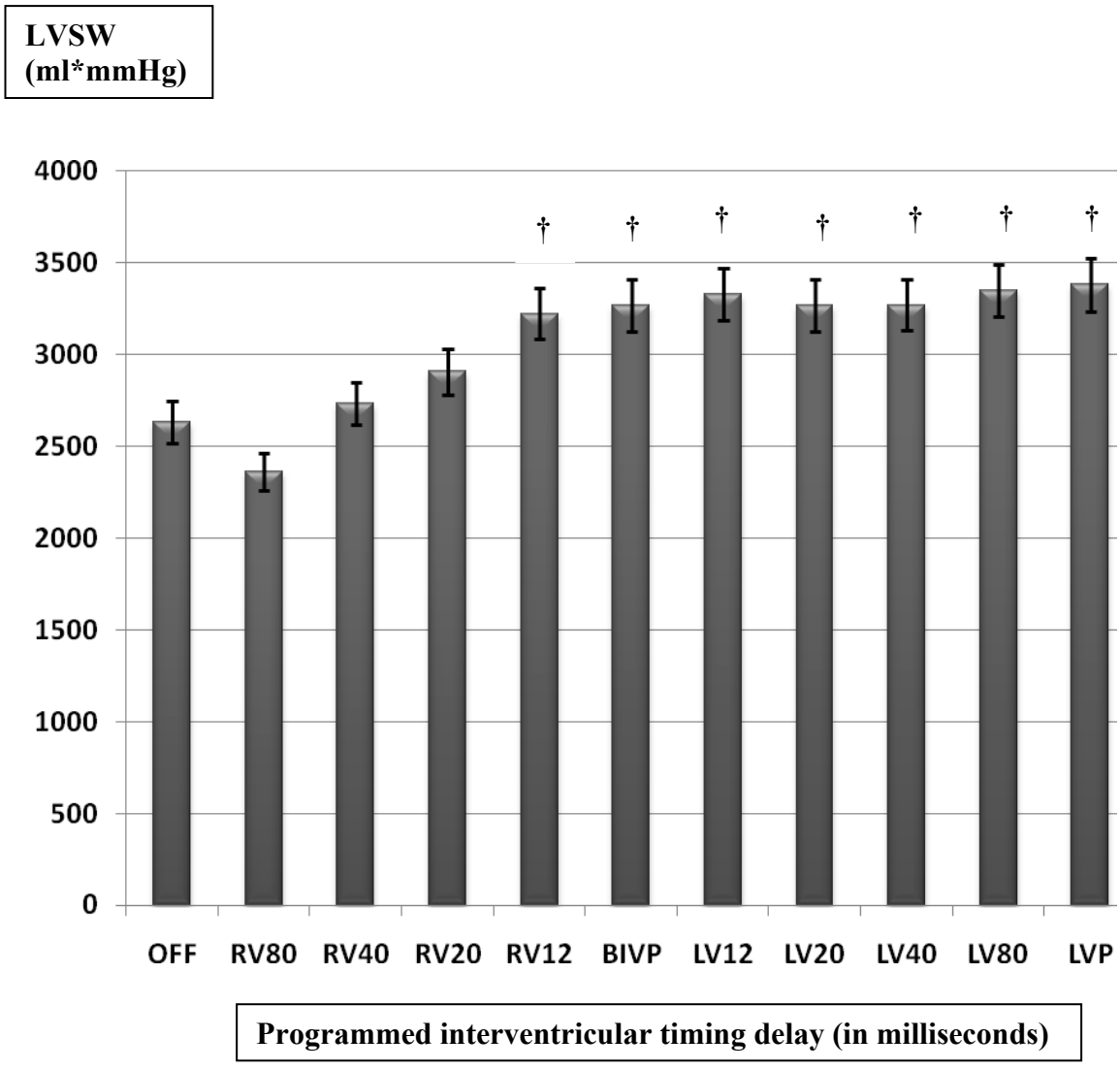
Figure 5.1C. **Percentage change in dP/dt_{MAX} using BIVP as a comparator**



Effect of interventricular timing delay on LVSW

LVSW decreased in response to pacing with a V-V delay of RV first by 80ms, but increased in response to all other programmed interventricular delays. All V-V delays ranging from RV first by 12ms through to LVP only resulted in a significant increase in LVSW from baseline values ($p<0.05$) (Figure 5.2A.). Percentage changes from baseline and simultaneous BIVP for all programmed V-V delays are shown in Figure 5.2B and 5.2C respectively.

Figure 5.2A. LVSW at different V-V delays



Error bars indicate ± 1 SEM; † indicates a significant change from OFF ($p<0.05$)

Figure 5.2B. **Percentage change in LVSW from OFF**

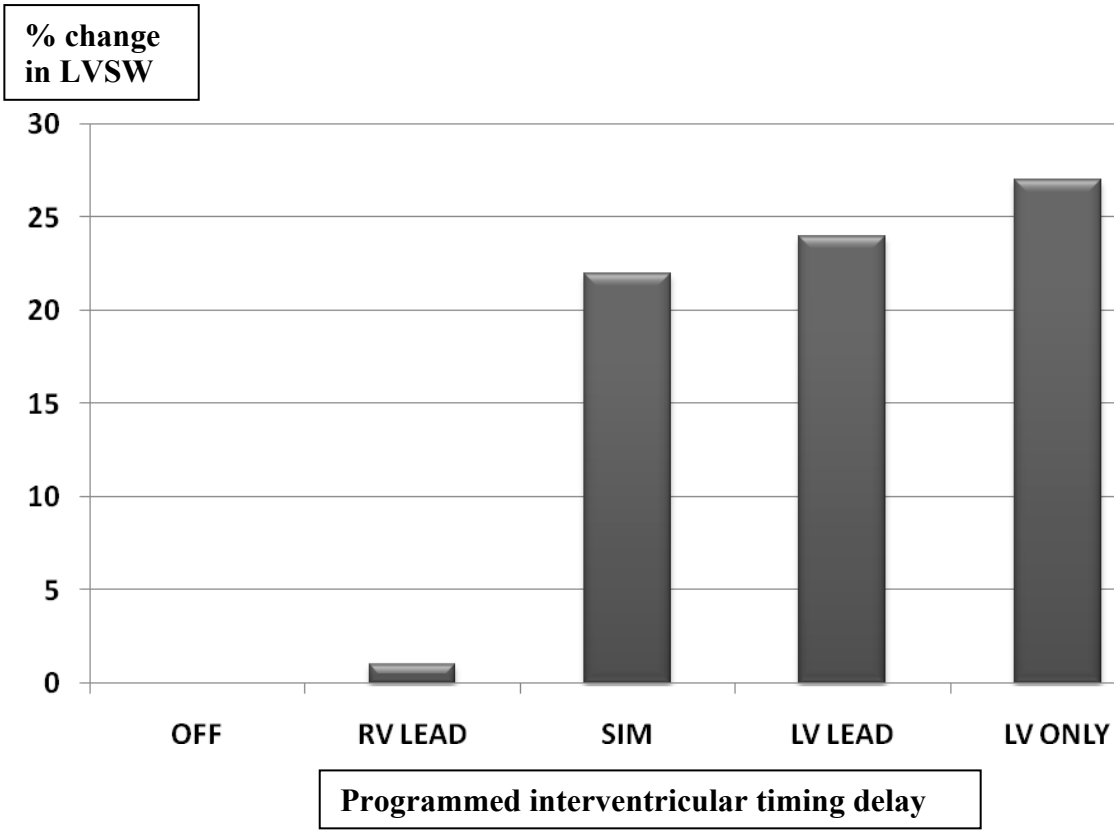
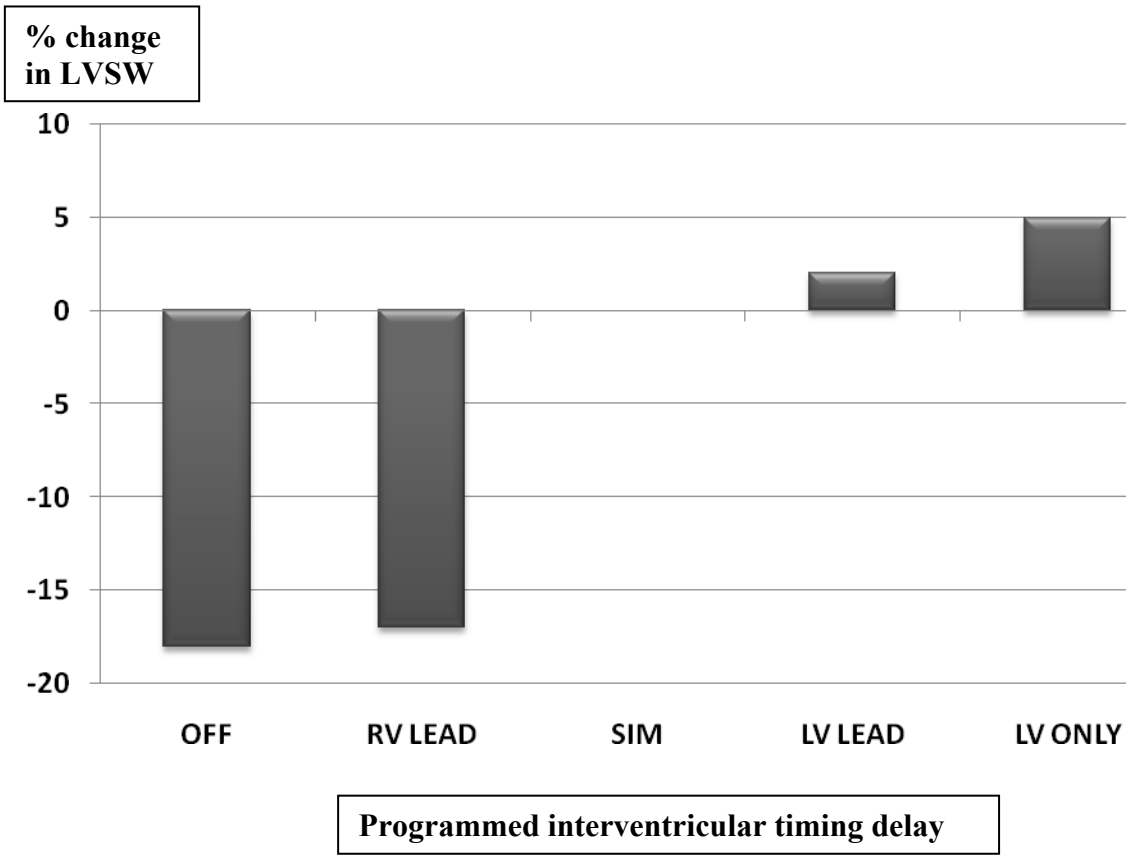


Figure 5.2C. **Percentage change in LVSW using BIVP as a comparator**

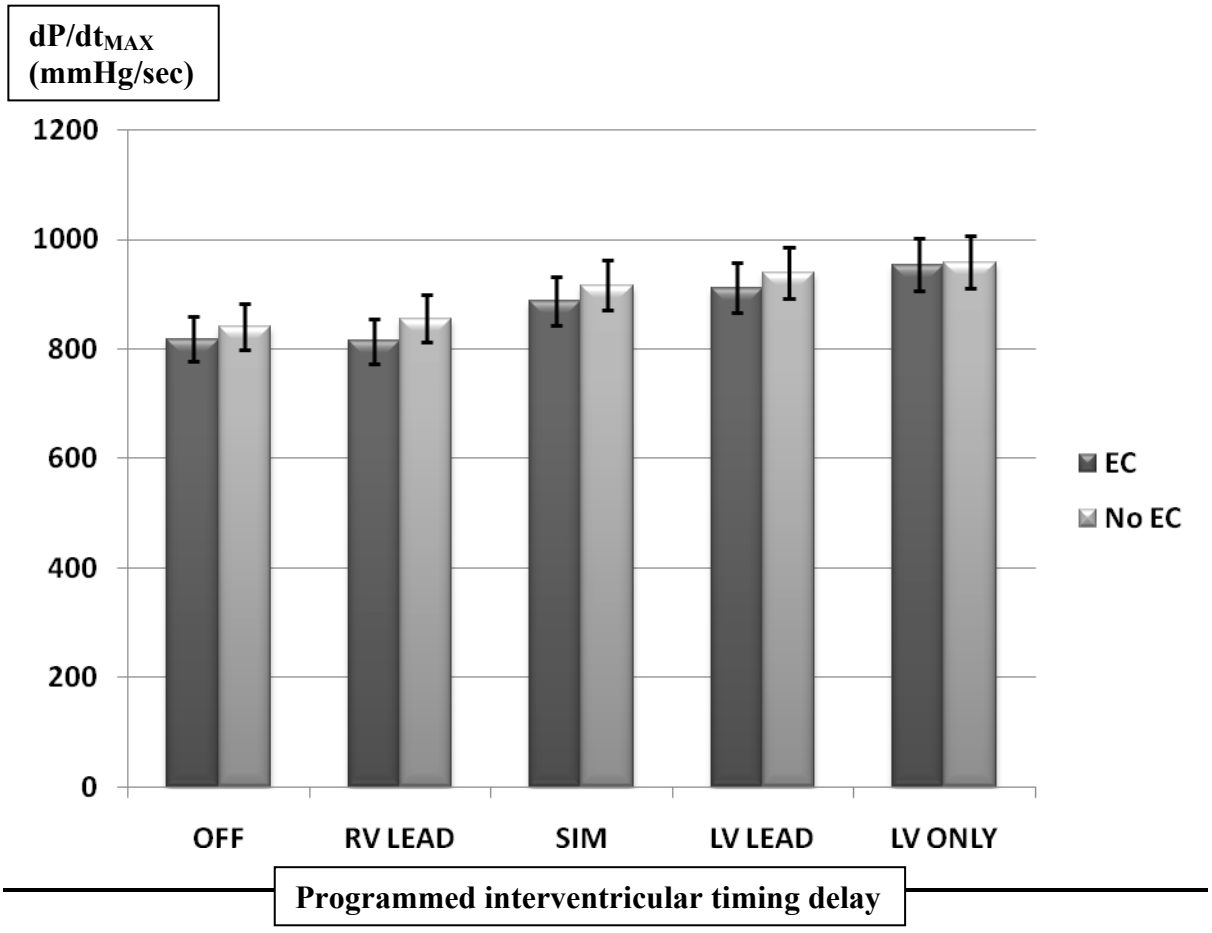


Optimal interventricular timing delay in patients with and without external constraint

Effect on dP/dt$_{MAX}$

dP/dt$_{MAX}$ decreased in response to pacing with a V-V delay of RV first by 80ms, but increased in response to all other programmed interventricular delays in both groups. There was a trend towards a greater increase in dP/dt$_{MAX}$ with those parameters were the LV was the first chamber paced, although it did not reach statistical significance (Figure 5.3A). Percentage changes from OFF and simultaneous BIVP for all programmed V-V delays are shown in Figure 5.3B and 5.3C respectively.

<u>Figure 5.3A.</u> dP/dt$_{MAX}$ at various V-V delays in those patients with (EC) and without external constraint (NO EC)



Error bars indicate ± 1 SEM

Figure 5.3B. **Percentage change in dP/dt_{MAX} from OFF in patients with (EC) and without external constraint (NO EC)**

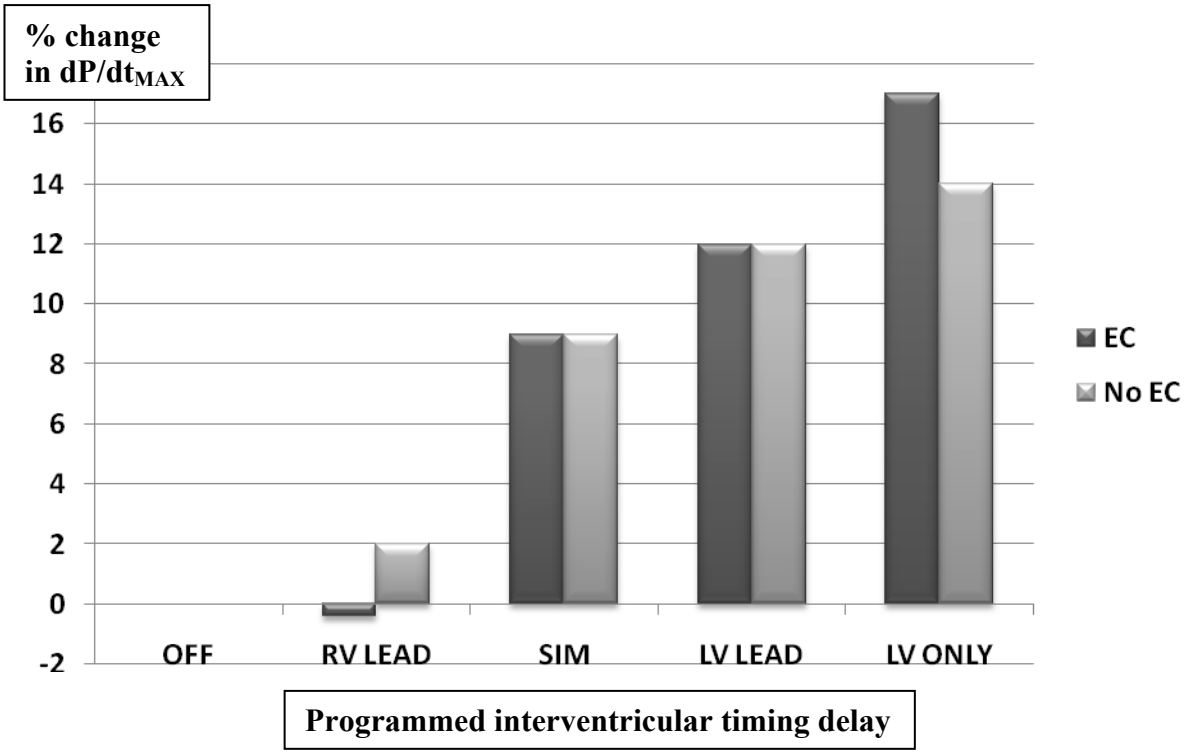
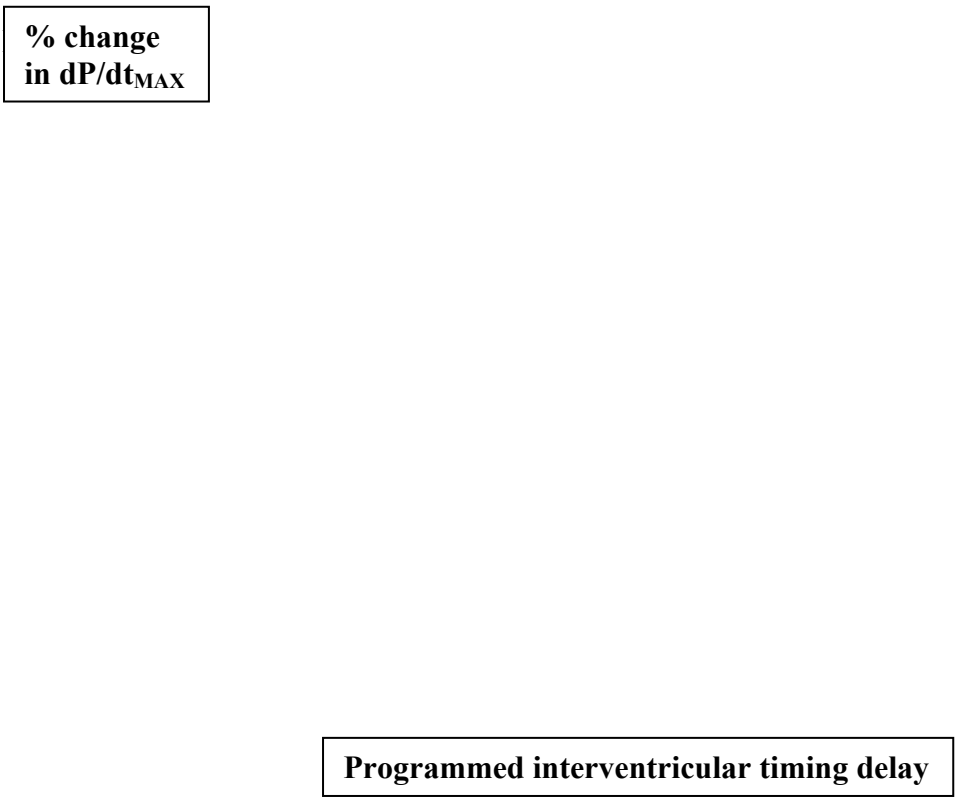
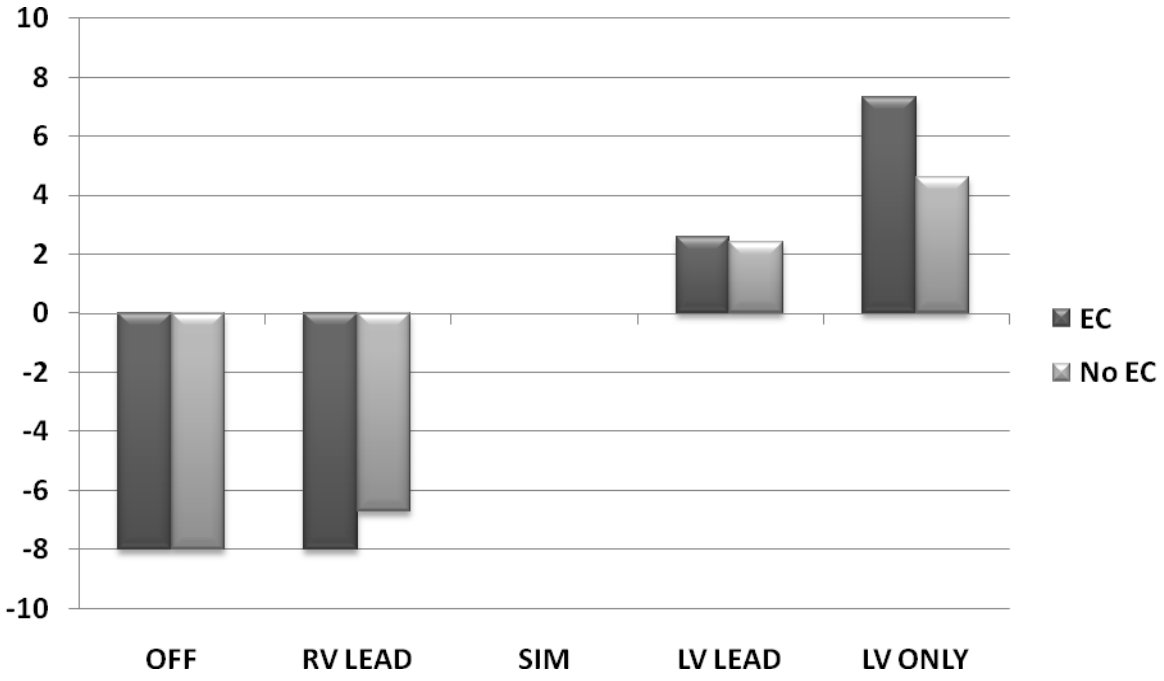


Figure 5.3C. **Percentage change in dP/dt_{MAX} using BIVP as a comparator in patients with (EC) and without external constraint (NO**



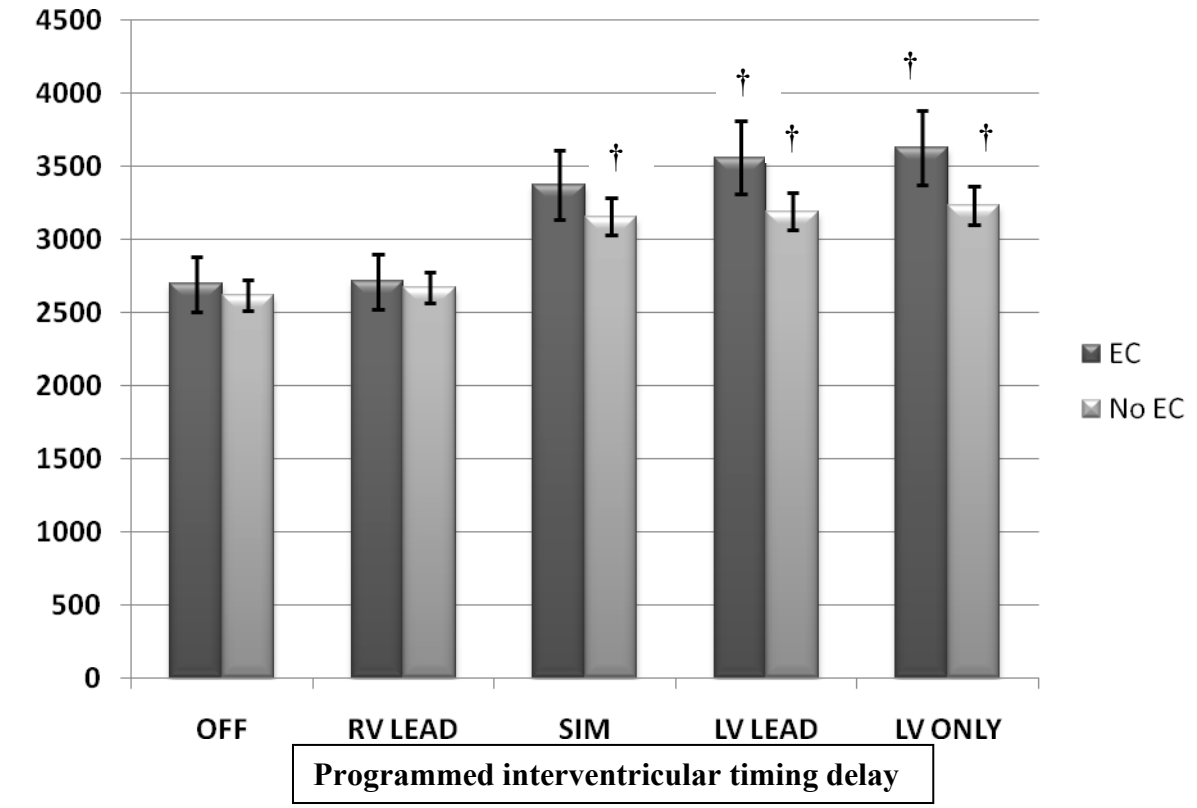


Effect on LVSW

LVSW decreased in response to pacing with a V-V delay of RV first by 80ms, but increased in response to all other programmed interventricular delays in both groups. The data for grouped V-V timing delays is shown below. In the patients with external constraint, there was a trend towards a greater increase in LVSW with those interventricular delays where the LV was the first chamber paced (Figure 5.4A). In those patients without external constraint, interventricular delays ranging from the RV leading by 12ms to the LV leading my 20ms appeared to be optimal. Percentage changes from baseline and simultaneous BIVP for all programmed V-V delays are shown in Figure 5.4B and 5.4C respectively.

<u>Figure 5.4A.</u> LVSW at various grouped V-V delays in those patients with (EC) and without external constraint (NO EC)

LVSW (ml*mmHg)



Error bars indicate ± 1 SEM; † indicates a significant change from OFF ($p<0.05$)

<u>Figure 5.4B.</u> Percentage change in LVSW from OFF in patients with (EC) and without external constraint (NO EC)

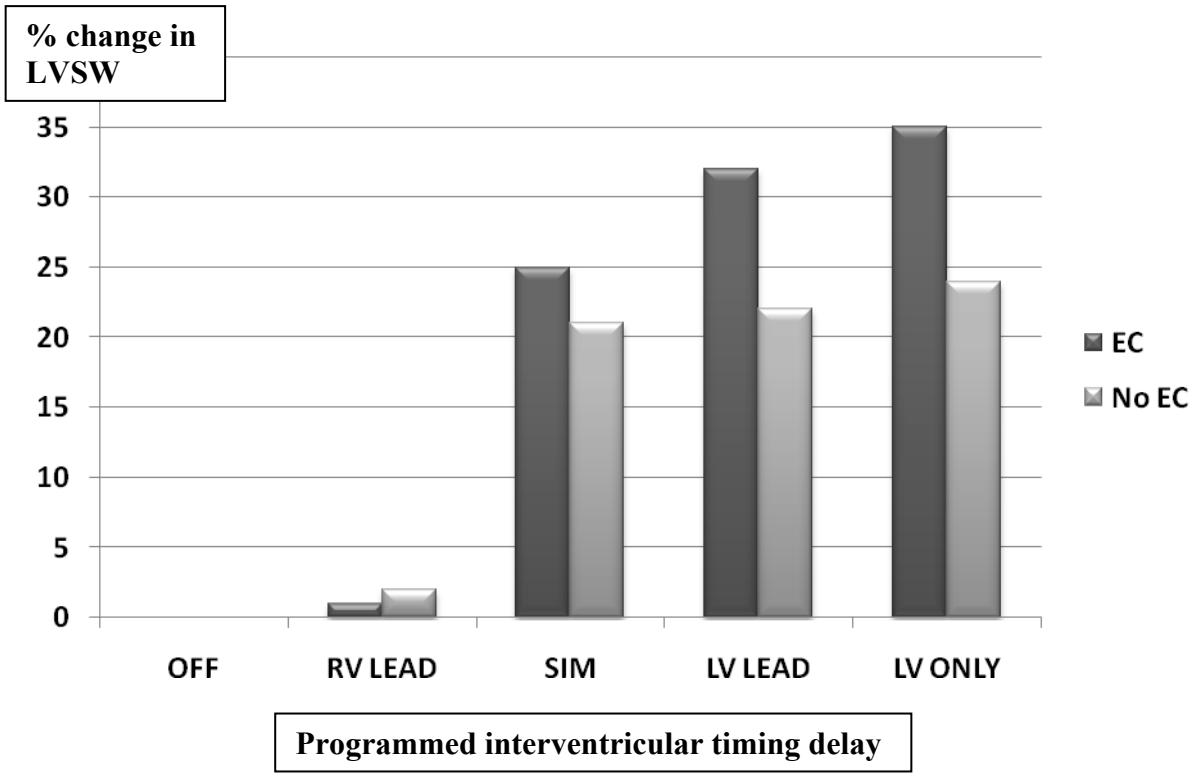
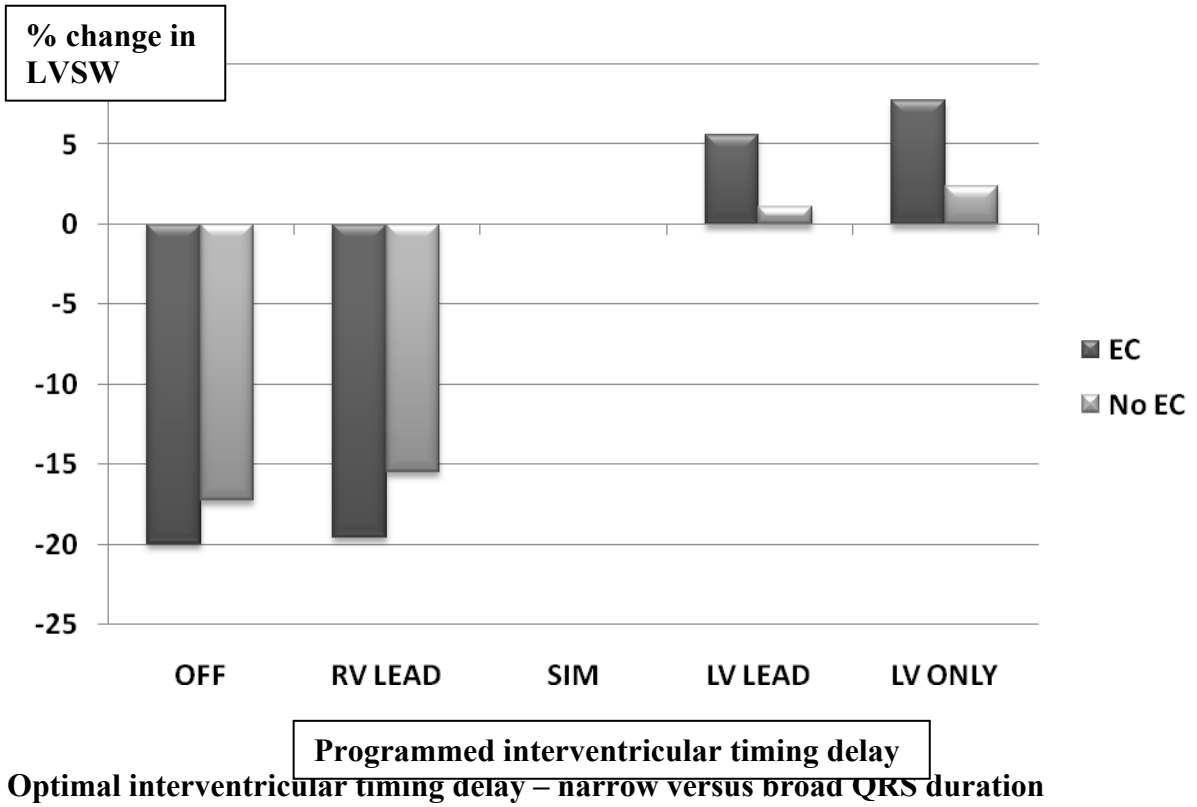


Figure 5.4C. Percentage change in LVSW using BIVP as a comparator in patients with (EC) and without external constraint (NO EC)



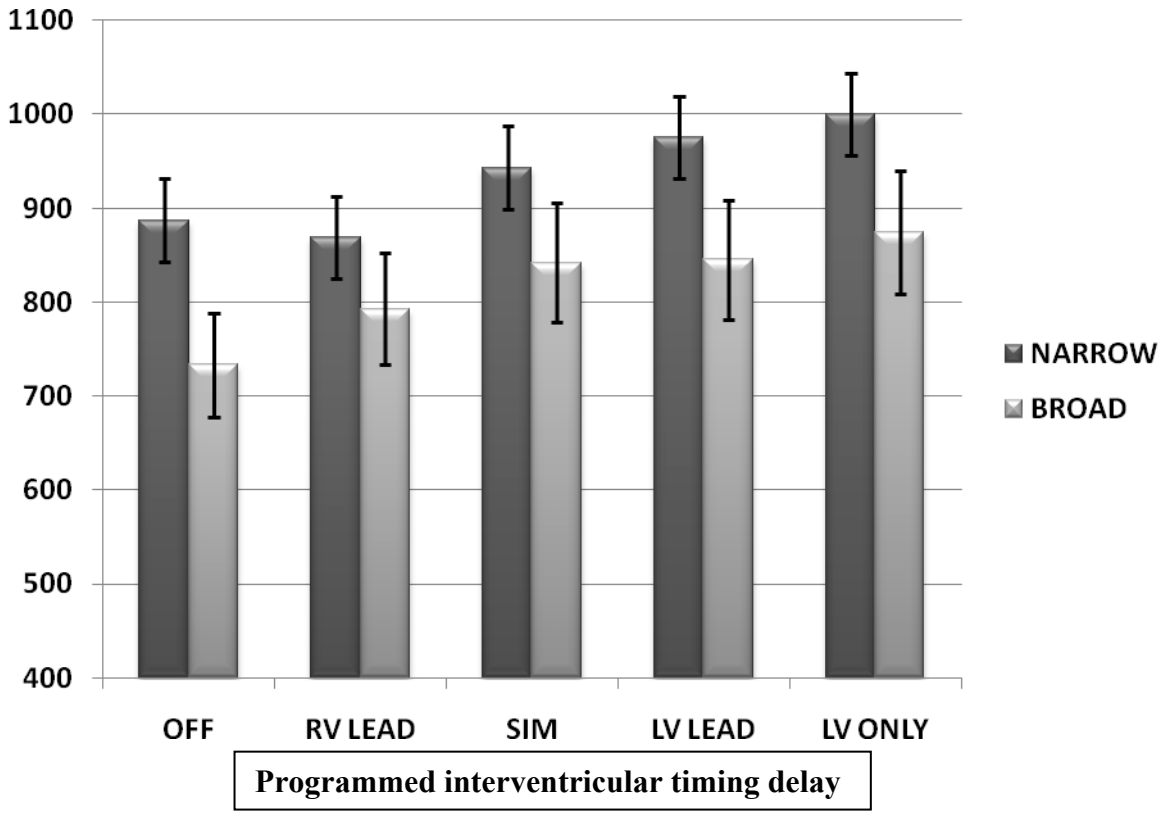
Optimal interventricular timing delay – narrow versus broad QRS duration

Effect on dP/dt$_{MAX}$

dP/dt$_{MAX}$ decreased in response to pacing with a V-V delay of RV first by 80ms, but increased in response to all other programmed interventricular delays in both groups. The data for grouped V-V delays is shown below. There was a trend towards a greater increase in dP/dt$_{MAX}$ with those parameters were the LV was the first chamber paced, although this did not reach statistical significance (Figure 5.5A). Percentage changes from baseline and simultaneous BIVP for all programmed V-V delays are shown in Figure 5.5B and 5.5C respectively.

Figure 5.5A. dP/dt$_{MAX}$ at various V-V delays according to baseline QRS duration

dP/dt$_{MAX}$ (mmHg/sec)



Error bars indicate ± 1 SEM

Figure 5.5B. Percentage change in dP/dt_{MAX} from OFF according to baseline QRS

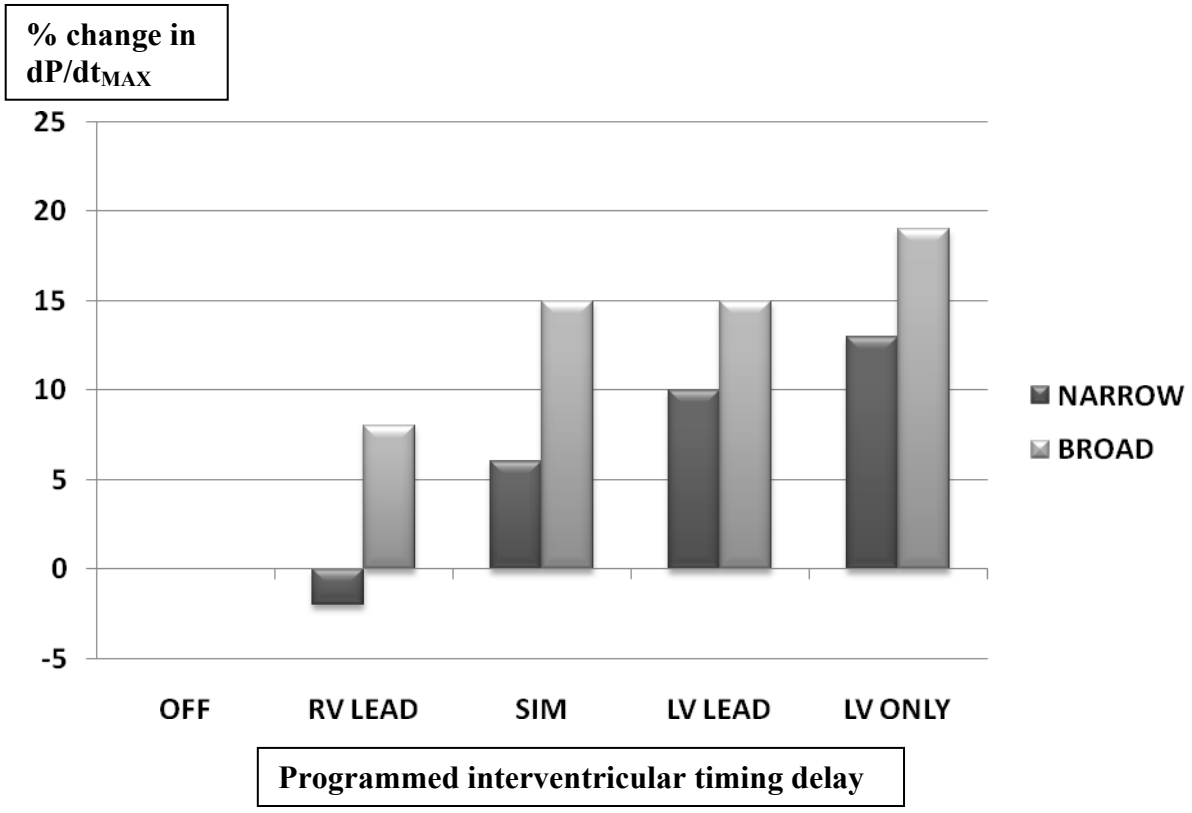
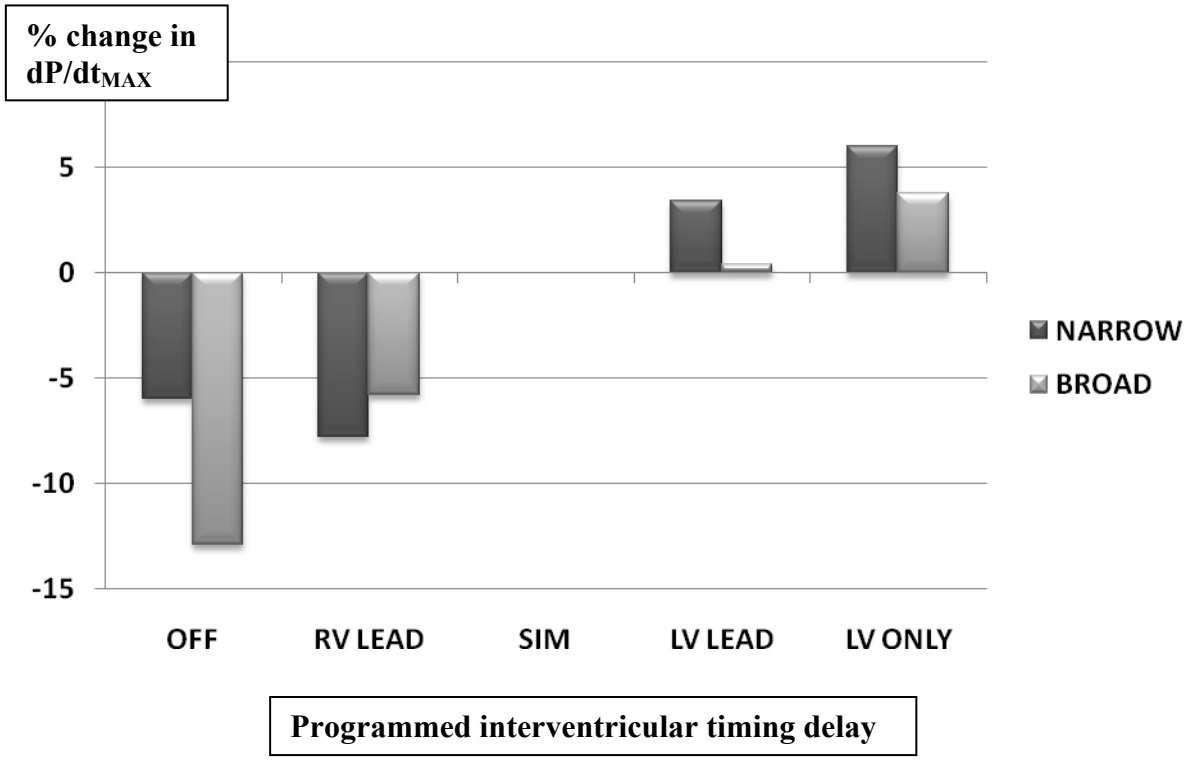


Figure 5.5C. Percentage change in dP/dt_{MAX} using BIVP as a comparator according to baseline QRS

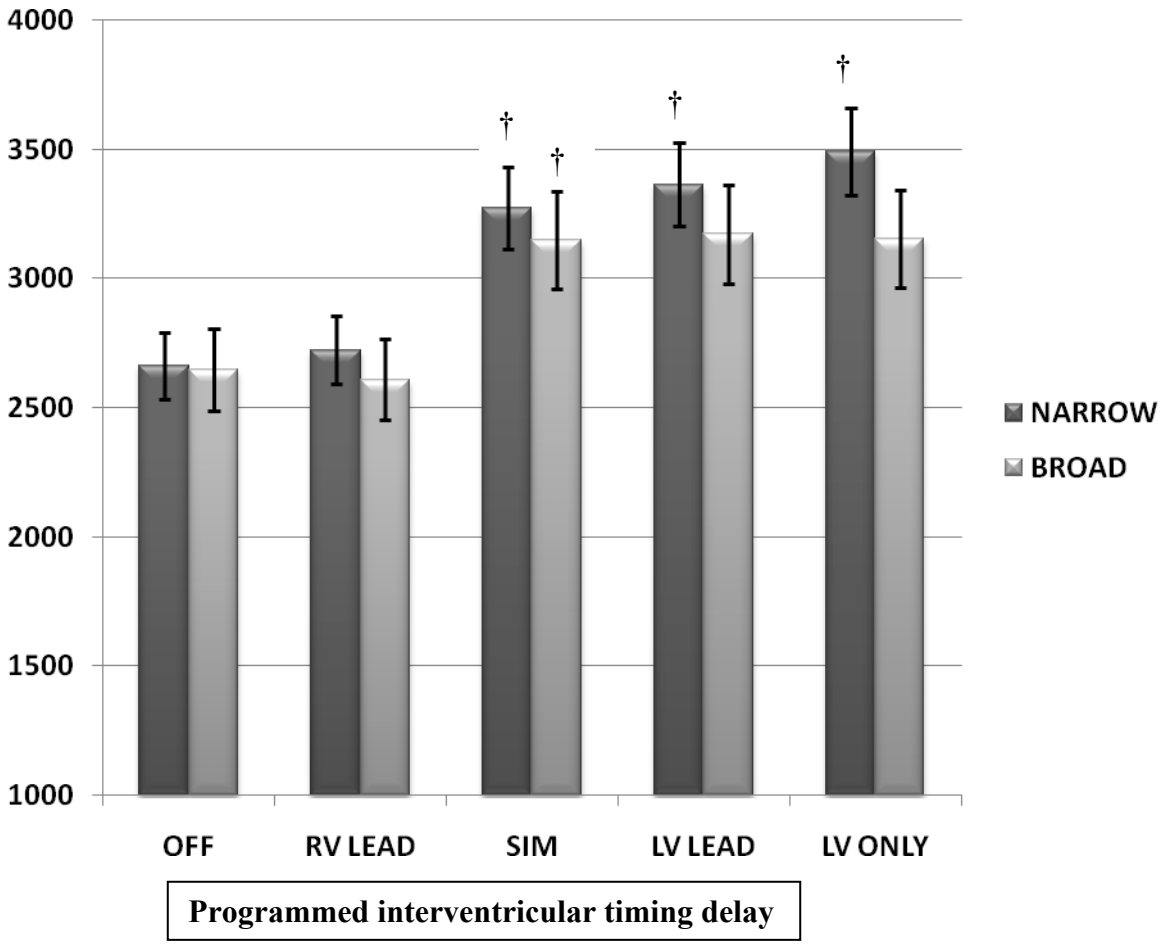


Effect on LVSW

LVSW decreased in response to pacing with a V-V delay of RV first by 80ms, but increased in response to all other programmed interventricular delays in both groups. The data for grouped V-V delays are shown below. There was a significantly greater increase in LVSW with those parameters where the LV was the first chamber paced ($p<0.01$) (Figure 5.6A). Percentage changes from baseline and simultaneous BIVP for all programmed V-V delays are shown in Figure 5.6B and 5.6C respectively.

Figure 5.6A. LVSW at various V-V delays according to baseline QRS duration

LVSW (ml*mmHg)



Error bars indicate ± 1 SEM; † indicates a significant change from OFF ($p<0.05$)

Figure 5.6B. Percentage change in LVSW from OFF according to baseline QRS

% change in LVSW

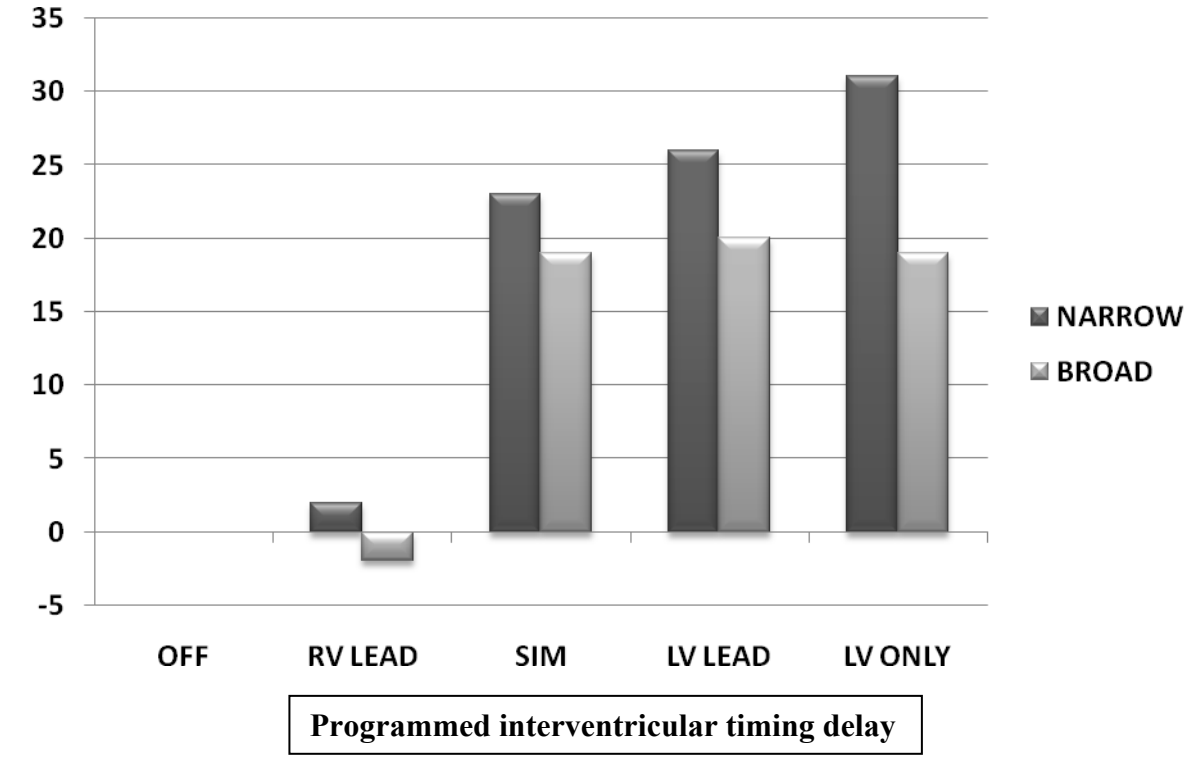
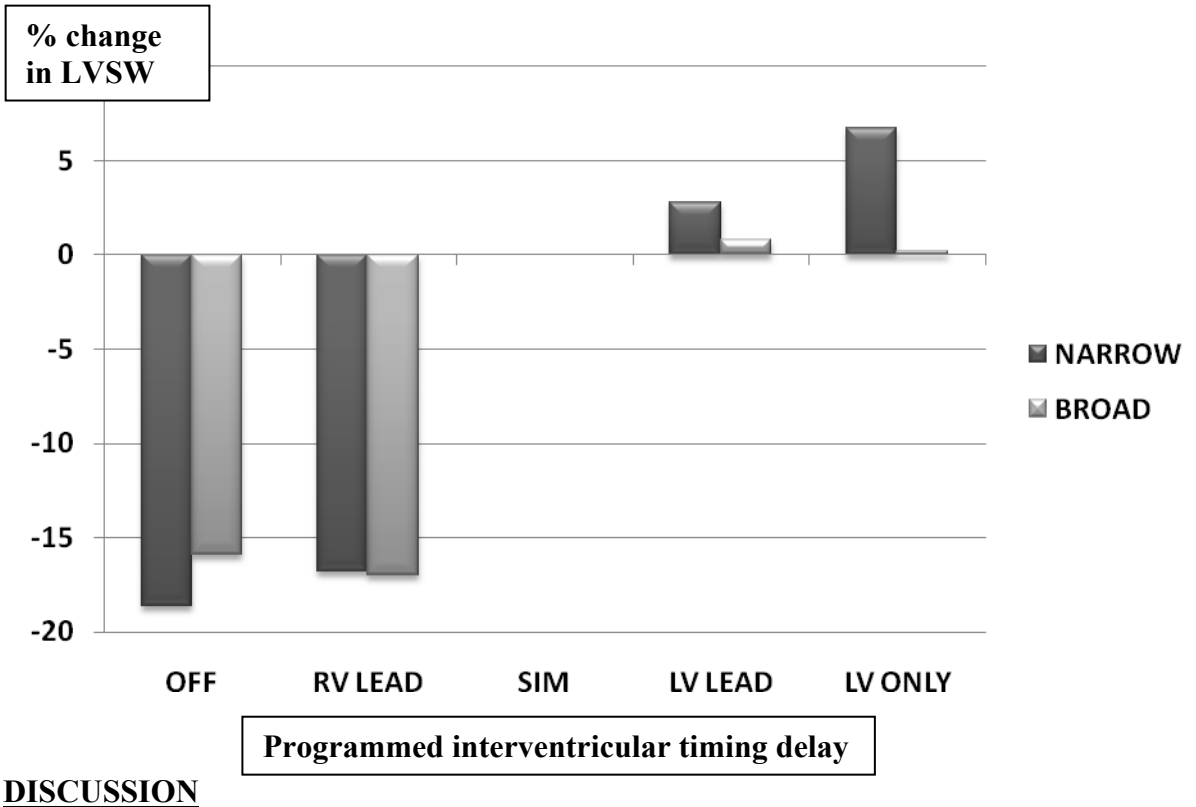


Figure 5.5C. **Percentage change in dP/dt_{MAX} using BIVP as a comparator according to baseline QRS**



DISCUSSION

In the present study we have demonstrated a significant increase in dP/dt_{MAX} in response to V-V delays in which the LV led by >20ms, and a significant increase in LVSW in response to V-V delays ranging from RV first by 12ms through to LVP. In addition, we have demonstrated the acute detrimental haemodynamic effect of right ventricular pacing in patients with heart failure and severe left ventricular impairment.

In patients with significant external constraint to left ventricular filling, there was a trend towards a greater increase in LVSW with those interventricular delays where the LV was the first chamber paced, whereas is patients without external constraint, in whom interventricular delays ranging from the RV leading by 12ms to the LV leading my 20ms appeared to be optimal.

Although numerous pivotal randomized controlled trials have demonstrated the efficacy of CRT in patients with medically refractory symptomatic heart failure, several issues remain regarding the indications for implant, optimal programming parameters, and the role of atrioventricular (A-V) and interventricular (V-V) optimization. Acute haemodynamic studies comparing sequential with simultaneous ventricular stimulation have demonstrated a significant increase in LV dP/dt_{MAX} when the LV was stimulated before the RV (104;105). An observational echocardiographic study utilizing tissue tracking to optimize interventricular timings has demonstrated a significant long-term improvement in left ventricular function when sequential rather than simultaneous stimulation was applied (106). In a study by Vidal *et al*, utilizing both echocardiographic and electrocardiographic parameters to optimize CRT programming in a patient group with LBBB, the authors demonstrated that LV leading RV activation by 30ms was the optimal V-V delay in the majority of patients (107). In addition, sequential biventricular stimulation has been shown to

decrease the severity of mitral regurgitation and improve LV synchronicity compared with the simultaneous pacing of both ventricles (66; 104).

In our study, patients with significant external constraint to left ventricular filling at baseline showed a greater increase in LVSW when the LV was the first chamber paced, with an incremental increase the greater the programmed delay between LV and RV. This was in contrast to patients without external constraint, in whom more simultaneous interventricular delays ranging from the RV leading by 12ms to the LV leading my 20ms appeared to be optimal. This can be explained by the effect of LV pacing on the timing of events in the left and right ventricle respectively. We recently demonstrated that LV pacing ameliorated external constraint to LV filling by the right ventricle through the interventricular septum (diastolic ventricular interaction – DVI), and by the pericardium (pericardial constraint) (the combined impact of which we refer to as external constraint) (55). In addition, in a recent study we have shown that both BIVP and LV pacing significantly reduce external constraint in a heart failure population with a narrow QRS duration and no significant dyssynchrony on echocardiography (102). In a previous study in a more conventional patient group we exclusively studied LV pacing and reported a reduction in external constraint (55).

Relief of external constraint causes an acute increase in LV diastolic volume despite a similar LVEDP, thereby increasing stroke work by the Starling mechanism. With this technique, external constraint is quantified as the difference in LVEDP before and after removal of the pericardium while a constant LVEDV is maintained. This technique can only be used when the chest is open. However, in the present study we applied a modified approach by continuously measuring LV pressure and volume during occlusion of the IVC to acutely reduce RV volume and pressure (51). This acute reduction in RV volume removes external

constraint to LV filling from the RV and pericardium. The mechanism for the reduction in external constraint is probably related to the induction of a phase shift in the timing of LV filling relative to RV filling (more pronounced with LVP compared to BIVP), resulting in the timing of events being brought forward in time in the left ventricle. This effectively results in LV filling occurring at a time when RV pressure and volume are lower; hence RV diastolic pressure and pericardial pressure are likely to be lower at any given LV diastolic volume. It would appear from our current data that an incremental benefit can be achieved by increasing the degree of LV pre-activation beyond 20ms.

Whether these acute haemodynamic effects associated with interventricular optimization will translate into chronic symptomatic benefit remains to be determined. The RHYTHM II ICD trial, which utilized echocardiography to optimize the V-V interval in patients receiving a CRT-D device, demonstrated no additional benefit of interventricular timing optimization at 6 months compared with empiric programming parameters (108). Similarly, the DECREASE-HF trial showed comparable improvements in LV volumes and echocardiographic parameters with simultaneous biventricular and sequential pacing, with a trend towards a greater reduction in LV volumes with simultaneous pacing (109). However, the programmed V-V interval in this study was based on intrinsic conduction only. In contrast, the recent INSYNC III study demonstrated an increase in left ventricular stroke volume with sequential biventricular stimulation (with the optimal V-V interval determined by echocardiography in individual patients) (110).

Despite conflicting results, V-V optimization may prove beneficial in some patients who demonstrate no or a suboptimal response to CRT, and may partially compensate for suboptimal LV lead positions in difficult cases. It may also allow for correction of individual

heterogeneous ventricular activation patterns (including areas of slow conduction related to scar near the LV pacing site) (111). Although many would argue that the optimal V-V delay shows great variability and must be individualized, we have demonstrated optimal V-V delays in patient groups based on the presence or absence of external constraint.

STUDY LIMITATIONS

The calibration method of the conductance catheter was not based on assessment of absolute volume, but this would not affect results, which depend entirely on relative changes within each patient in response to the pacing mode.

Because of the invasive nature of the study, only a small sample of patients was studied in the short-term, hence these results may not predict the medium and long-term effects of CRT on cardiac function.

CONCLUSION

In the present study we have demonstrated a significant increase in both dP/dt_{MAX} and LVSW in response to V-V delays in which the LV led by >20ms, In patients with external constraint, there was a trend towards a greater increase in LVSW with those interventricular delays where the LV was the first chamber paced, compared with patients without external constraint, in whom near-simultaneous interventricular delays ranging from the RV leading by 12ms to the LV leading by 20ms appeared to be optimal. Although many would argue that the optimal V-V delay shows great variability and must be individualized, we have demonstrated optimal V-V delays in patient groups based on the presence or absence of external constraint.

CHAPTER 6

MECHANISMS BY WHICH CARDIAC RESYNCHRONISATION THERAPY IMPROVES CARDIAC PERFORMANCE IN HEART FAILURE

INTRODUCTION

Recent trials in selected patients with heart failure have shown that biventricular pacing in which the two ventricles are paced synchronously (or one ventricle slightly before the other), improves symptoms, and reduces number of hospitalisations and hospital bed days (18;20). Currently the therapy is reserved for patients with NYHA III and IV Class symptoms despite optimal medical therapy who have prolonged QRS durations (>120msec). The latter is based on the original rationale that biventricular pacing acts via an improvement in cardiac 'electrical synchrony', hence the frequently used term "resynchronization therapy". It is becoming increasingly evident that mechanical resynchronisation is an important contributor to the benefit but that this is dissociated to a considerable extent from electrical resynchronisation Inco-ordinate ventricular contraction is frequently present in CHF and contributes to impaired overall contractile function (38). We and others have shown that biventricular pacing, particularly with the LV pacing electrode pacing the LV free wall, reduces LV mechanical dyssynchrony (25;65;112). Mechanical dyssynchrony is not however limited to broad QRS patients (28) and we recently showed that biventricular pacing also reduced mechanical dyssynchrony in narrow QRS patients (25).

In addition, short AV delay pacing reduces pre-systolic mitral regurgitation (113). The presence and magnitude of the latter is related to left ventricular end diastolic pressure (LVEDP) and to prolongation of the A-V interval. Pacing leads to an increase in the effective diastolic filling period by a reduction in pre-systolic mitral regurgitation. However this is believed to make only a modest

contribution to the overall haemodynamic benefit of biventricular pacing in the majority of patients. Biventricular pacing may also reduce the magnitude of systolic 'functional' mitral regurgitation, by a reduction in ventricular sphericity, and/or by an increase in mitral valve 'closing pressure' leading to improved coaptation of the mitral valve leaflets (39;114).

Whilst the large chronic studies published to date have assessed biventricular pacing, left ventricular pacing has produced equivalent or superior acute haemodynamic and chronic symptomatic benefits compared with biventricular pacing (65;112). We and others have shown that although LV pacing typically prolongs QRS duration and increases 'electrical dyssynchrony', it nevertheless reduces mechanical dyssynchrony in both broad and narrow QRS heart failure (25;38). Recently we have demonstrated an additional potential mechanism by which both LV pacing (55) and biventricular pacing (55;102) improve haemodynamics in patients with heart failure via a reduction in external constraint to left ventricular filling.

Currently approximately 30% of patients with broad complex QRS complexes who undergo biventricular pacing derive no benefit. Conversely some patients with narrow QRS complexes (who do not fulfill current criteria) may benefit. A better understanding of the mechanisms of benefit of biventricular and left ventricular pacing may lead to improved patient selection and optimisation of pacing strategy in individual patients.

This study will assess the mechanisms by which biventricular and left ventricular pacing improves acute haemodynamic performance in patients with heart failure. It will assess the relative contributions of reduced diastolic ventricular interaction, reduced mitral regurgitation and enhanced contractility to the acute benefit of each pacing modality in CHF patients with both narrow and wide QRS complexes. The findings will inform better patient selection for this therapy and also optimisation of pacing strategy (biventricular vs. left ventricular) in individual patients.

METHODS

Patients. Thirty one patients with narrow QRS duration and 23 with broad QRS duration heart failure were recruited into the study. All patients had an LVEF≤35% and had NYHA class III or IV symptoms despite optimal tolerated medical therapy. In addition, all patients with a narrow QRS ≤ 120ms had no evidence of inter- or intraventricular dyssynchrony. Baseline patient characteristics for the two groups are shown in Table 6.1.

TABLE 6.1. Baseline patient characteristics

	Narrow QRS (n=31)	Broad QRS (n=23)
Age	62 ± 14 years	69 ± 10 years
Male	28/31 (90%)	19/23 (83%)
Ischaemic cardiomyopathy	17/31 (55%)	14/23 (61%)
NYHA Class III	29/31 (94%)	21/23 (91%)
NYHA Class IV	2/31 (6%)	2/23 (9%)
LVEF	26 ± 5%	24 ± 7%
Qp-Qa interval	15 ± 9ms	N/A
Septal-posterior wall delay	126 ± 54ms	N/A
Yu-dyssynchrony index	22 ± 7	N/A

Acute Haemodynamic Studies. Acute haemodynamic studies were performed in the cardiac catheterization laboratory at the time of CRT device implantation with patients in the non-sedated and supine state. Catheterisation of the left ventricle was performed by a standard over-the-wire technique. The dual-field conductance catheter (CA-71103-PL catheter, CD Leycom, The Netherlands) was then positioned in the apex of the ventricle. We applied a modified parallel conductance calibration via a right atrial injection (78) to avoid catheterisation of the right ventricle or pulmonary artery.

All data were acquired during an unforced end-expiratory breath hold. From each acquisition run, the derivatives of pressure and volume were calculated as the mean of the 10 to 15 consecutive beats free from atrial or ventricular ectopic activity. Pressure-volume analysis was also performed during an inferior vena caval (IVC) occlusion, which reduced central blood volume and RV pressure acutely, achieved with a 40-mm IVC occlusion balloon catheter (Meditec, Boston Scientific International). Data were acquired with a CFL-512 system (CD Leycom), which allows further offline analysis (CircLab, Leiden University, The Netherlands). The haemodynamic measurements were undertaken during no pacing (OFF), in biventricular (BIVP) and in left ventricular only pacing (LVP) modes with AV intervals set at 100msec, an interventions applied in a random order, each with a run-in (stabilization) period of 5 minutes.

The following parameters were derived from the pressure volume loops (PVL) at baseline (OFF), during inferior vena cava occlusion (IVCO), and in both BIVP and LVP pacing modes: dP/dt_{MAX} and dP/dt_{MIN}, absolute left ventricular stroke work (LVSW), cardiac output (CO) and left ventricular end-diastolic volume (LVEDV). A plot was constructed of beat-by-beat LV end-diastolic volume versus LVSW before and during IVC occlusion in all pacing modes (the Preload Recruitable Stroke Work Relation or PRSWR).

Assessment of the magnitude of acute haemodynamic benefit of LVP and BIVP which is due to a reduction of DVI versus improved LV contractile function

External constraint was quantified as described in Chapter 2. A plot was constructed of beat by beat left ventricular end-diastolic volume (LVEDV) versus left ventricular stroke work (LVSW) before and during inferior vena caval occlusion with pacing OFF, BIVP and LVP. The slope of this relation, the Preload Recruitable Stroke Work relation (PRSW) and is a load-independent measure of LV contractile function.

Fig 6.1 is such a plot from a patient in whom LVP increased LVSW almost exclusively via relief of external constraint, resulting in preload recruitment. The pacing OFF inferior vena caval occlusion (IVCO) run is shown in grey squares with the pre-IVCO occlusion point shown as the large grey square. The corresponding LVP parameters are shown in black squares. Note the slope of the LVEDV/LVSW (preload recruitable stroke work-PRSW) is unchanged by pacing. This implies that the increase in absolute LVSW is entirely due to a higher end-diastolic volume (due to relief of external constraint).

FIGURE 6.1. Improvement in LVSW due to preload recruitment/relief of external constraint

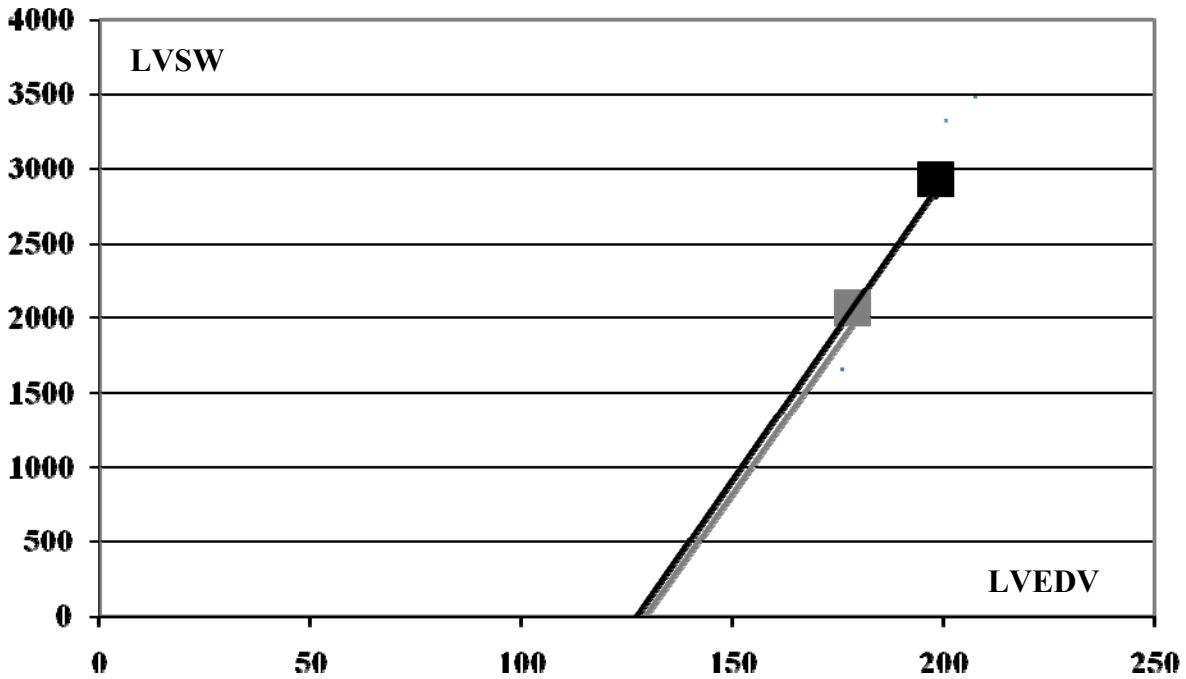
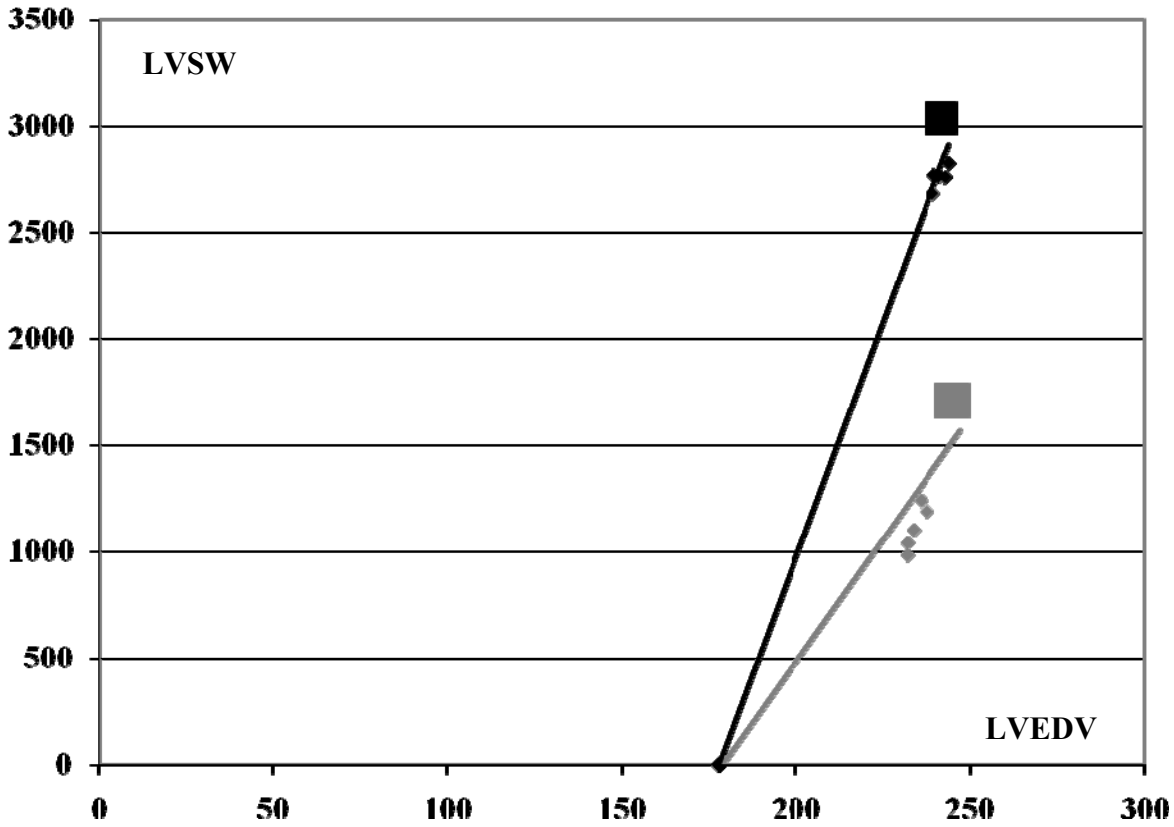


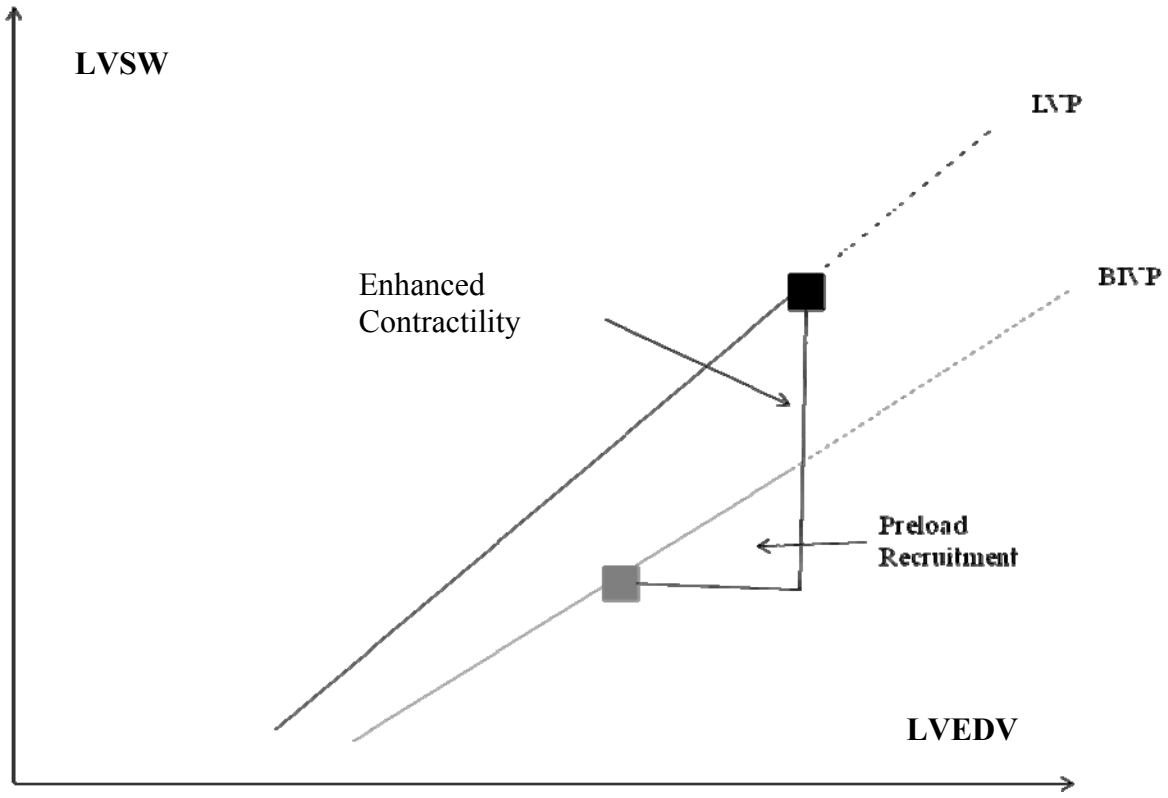
Fig 6.2 is a plot from a patient in whom LVP increased LVSW almost exclusively via enhanced contractility. The pacing OFF inferior vena caval occlusion (IVCO) run is shown in grey squares with the pre-IVCO occlusion point shown as the large grey square. The corresponding LVP parameters are shown in black squares. Note the slope of the LVEDV/LVSW (preload recruitable stroke work-PRSW) is steeper with LVP, without an acute change in LVEDV. This implies that the increase in absolute LVSW is entirely due to enhanced contractility.

FIGURE 6.2. Improvement in LVSW due to enhanced contractility



Using such plots we assessed the contribution of preload recruitment (i.e. relief of external constraint) versus enhanced contractility to the increase in LV stroke work for both LVP and BIVP. The contribution of each was then calculated as shown in figure 6.3.

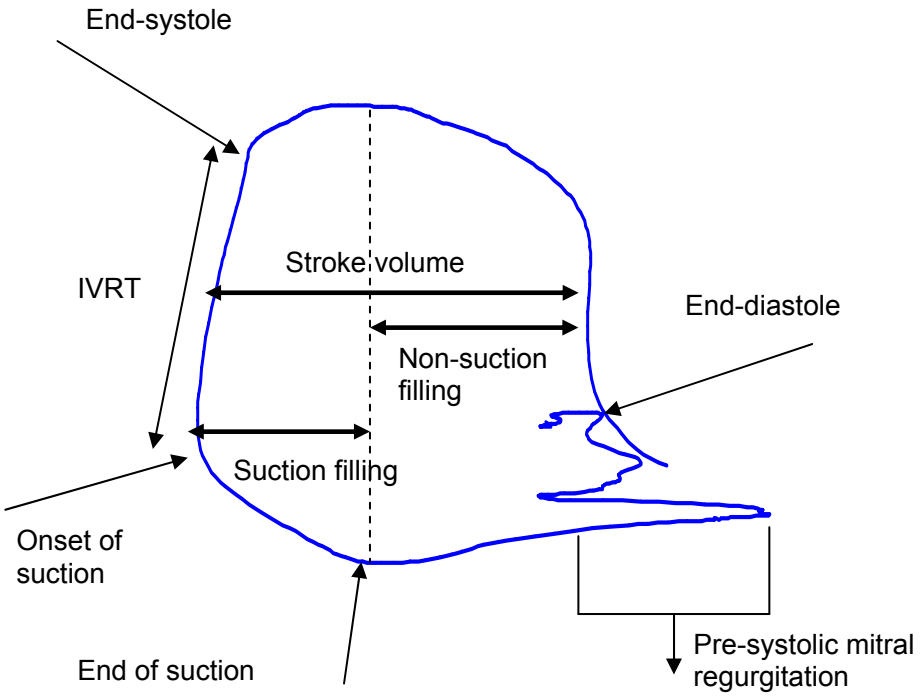
FIGURE 6.3. Improvement in LVSW due to enhanced contractility



Assessment of the pre-systolic mitral regurgitation

Pre-systolic mitral regurgitation was assessed from the pressure-volume loop as the difference between the maximum left ventricular volume and the volume at end-diastole just prior to the onset of isovolaemic contraction, as shown in Figure 6.4.

Figure 6.4. Assessment of pre-systolic mitral regurgitation (PSMR)



Statistical Analysis. All data are expressed as the mean value ± SD. The Mann-Whitney rank-sum test was used to compare independent samples between the two groups. A one-way ANOVA was used to assess the effect of vena caval occlusion and pacing if the data was normally distributed based on a Kolmogorov-Smirnov test. For data that was not normally distributed, a Kruskal-Wallis test was used. Statistical significance was assumed at $p < 0.05$.

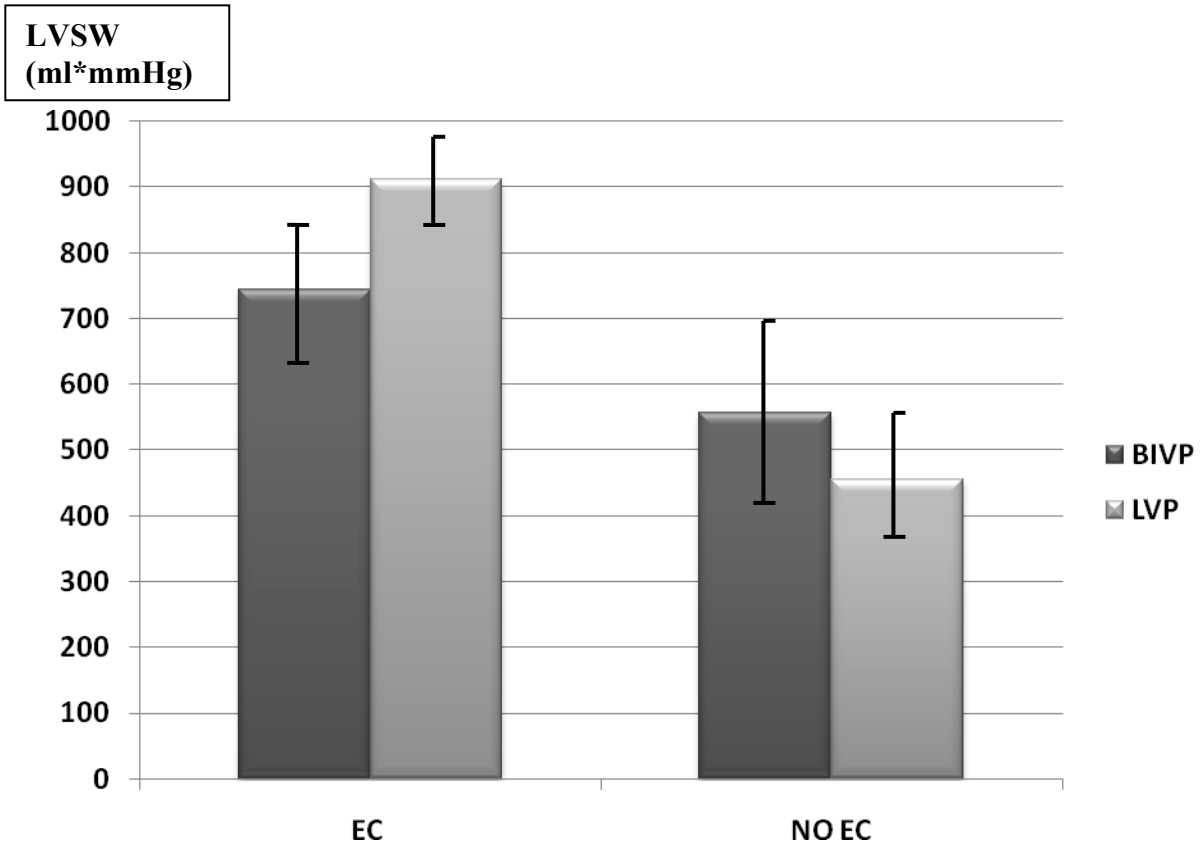
RESULTS

Contribution to increased LVSW

Heart Failure Group (Narrow and Broad QRS Groups)

For the heart failure group as a whole, both BIVP and LVP resulted in a greater increase in LVSW in those patients with external constraint (n=29) compared with those without (n=25). LVP resulted in a significantly greater increase in LVSW inthose with external constraint than those without. Results are shown in Figure 6.5.

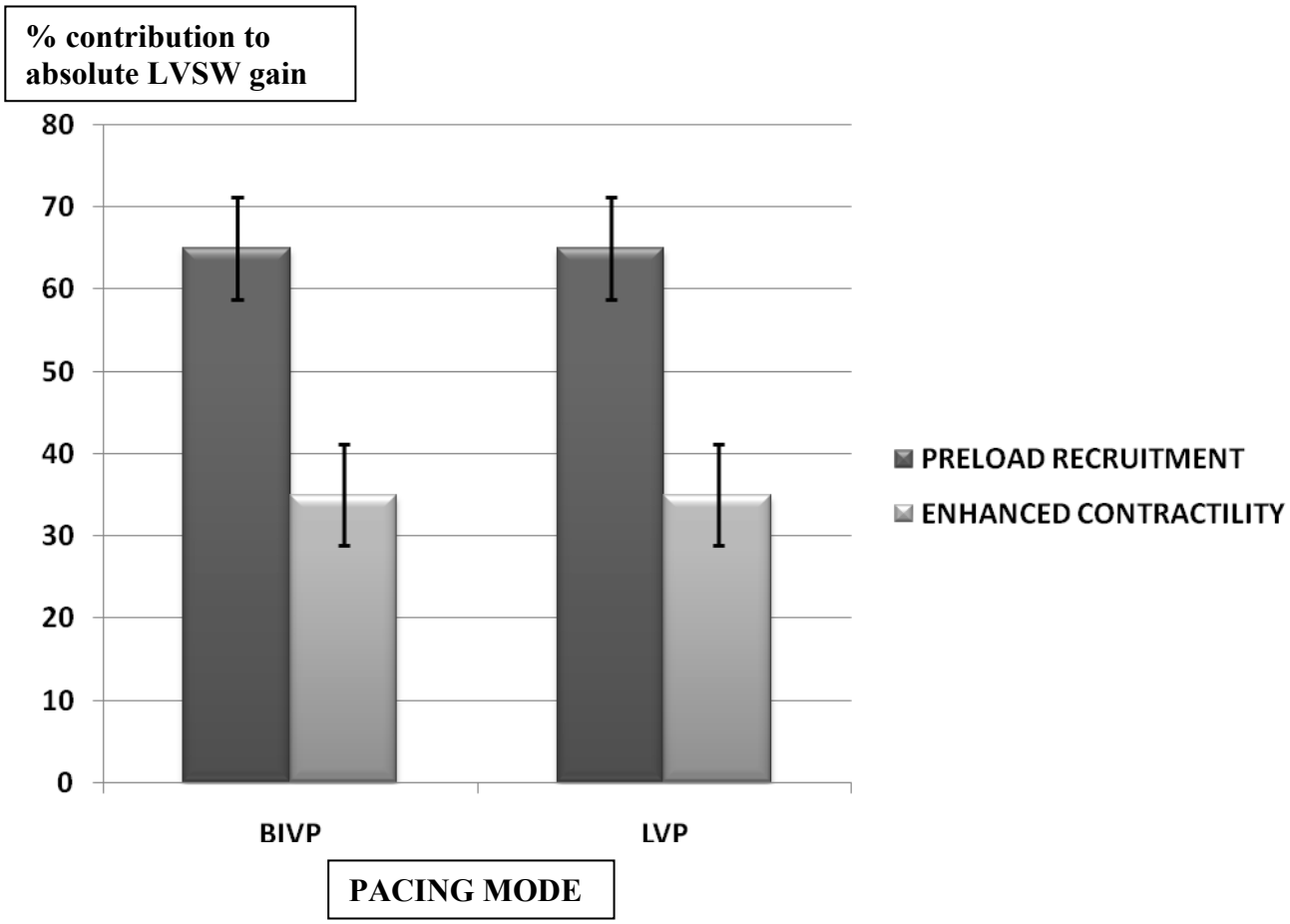
Figure 6.5. Absolute increase in LVSW in patients with (EC) and without (NO EC) external constraint for the heart failure group as a whole



Error bars indicate ± 1 SEM

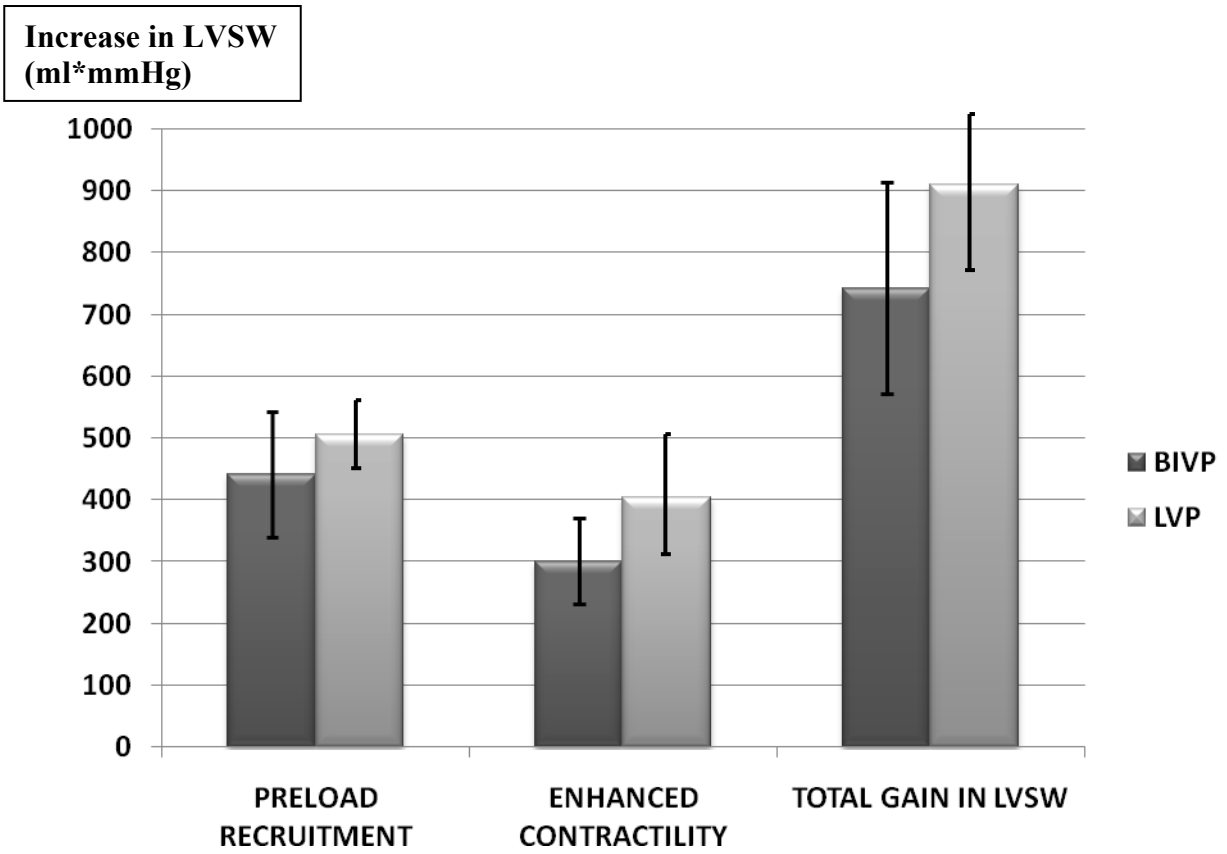
For the heart failure group with external constraint as a whole (n=29), preload recruitment resulted in a significantly greater contribution to the increase in absolute LVSW compared with enhanced LV contractility (65% versus 35% respectively; $p < 0.01$). The percentage contributions were identical for both BIVP and LVP, although LVP resulted in a greater absolute gain in LVSW compared with BIVP (911 versus 743ml*mmHg respectively) without reaching statistical significance. Results are shown in Figure 6.6 and 6.7.

<u>Figure 6.6.</u> Relative percentage contributions of preload recruitment and enhanced contractility for the heart failure group as a whole



Error bars indicate ± 1 SEM

Figure 6.7. Absolute increase in LVSW due to preload recruitment and enhanced contractility for the heart failure group as a whole

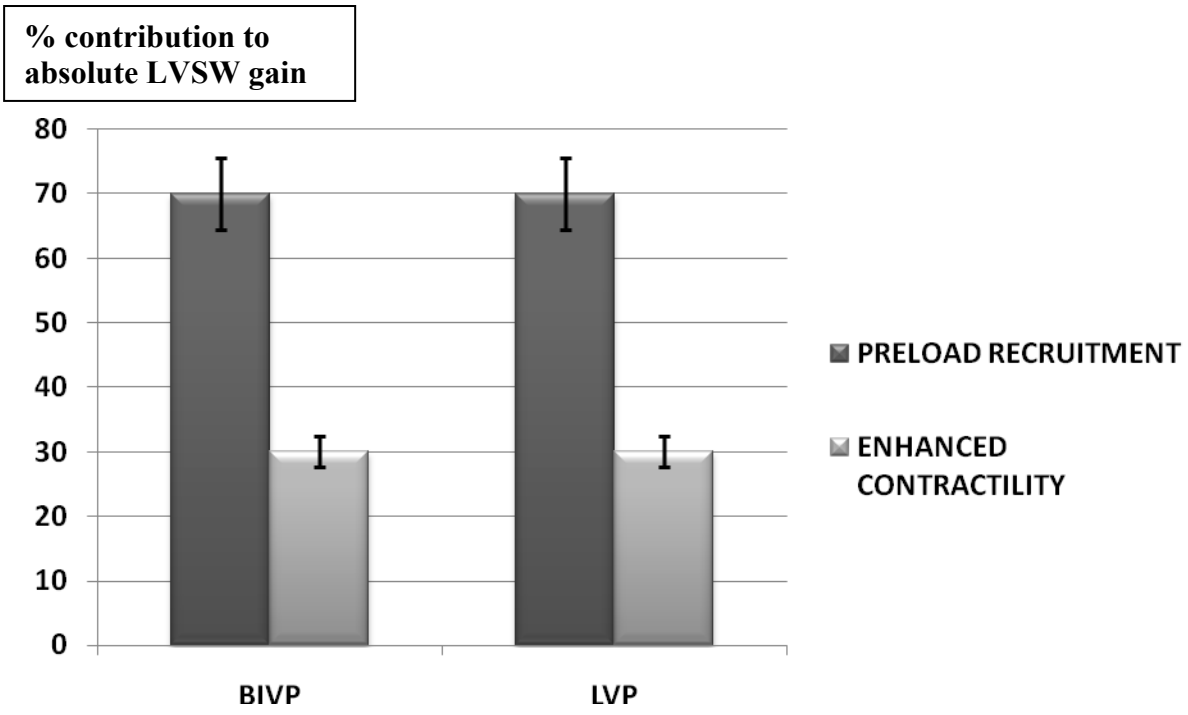


Error bars indicate ± 1 SEM

Narrow QRS Group

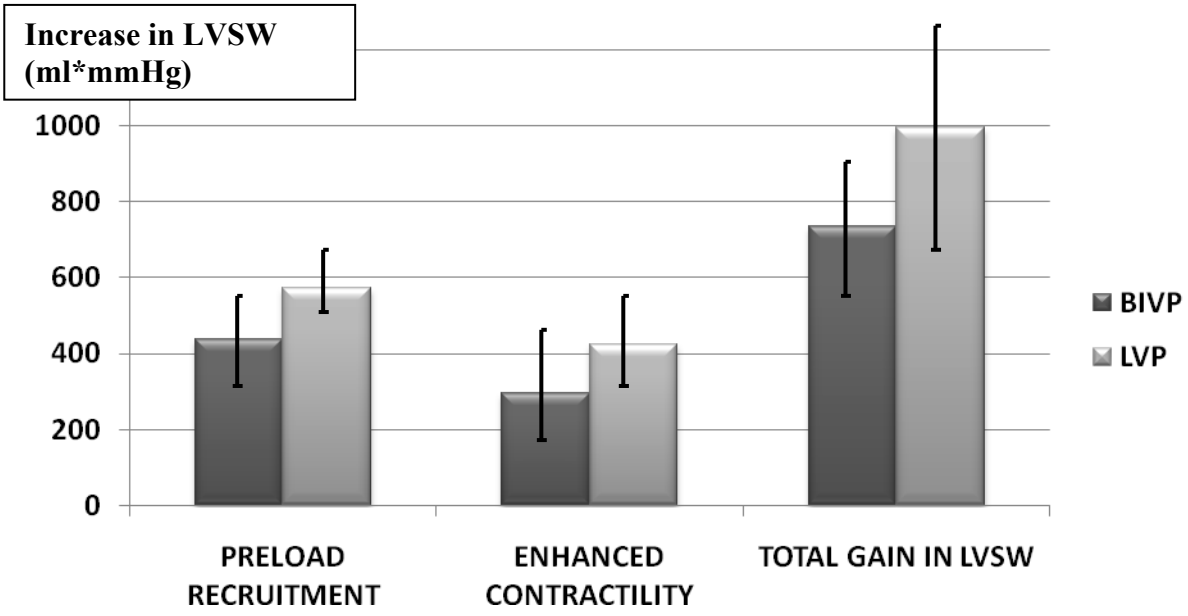
For the narrow QRS group with external constraint (n=16), preload recruitment resulted in a significantly greater contribution to the increase in absolute LVSW compared with enhanced LV contractility (70% versus 30% respectively; $p < 0.01$). The percentage contributions were again identical for both BIVP and LVP, although LVP resulted in a greater absolute in LVSW compared with BIVP (995 versus 736ml*mmHg respectively) without reaching statistical significance. Results are shown in Figure 6.8 and 6.9.

Figure 6.8. **Relative percentage contributions of preload recruitment and enhanced contractility for the narrow QRS group with external constraint**



Error bars indicate ± 1 SEM

Figure 6.9. **Absolute increase in LVSW due to preload recruitment and enhanced contractility for the narrow QRS group with external constraint**

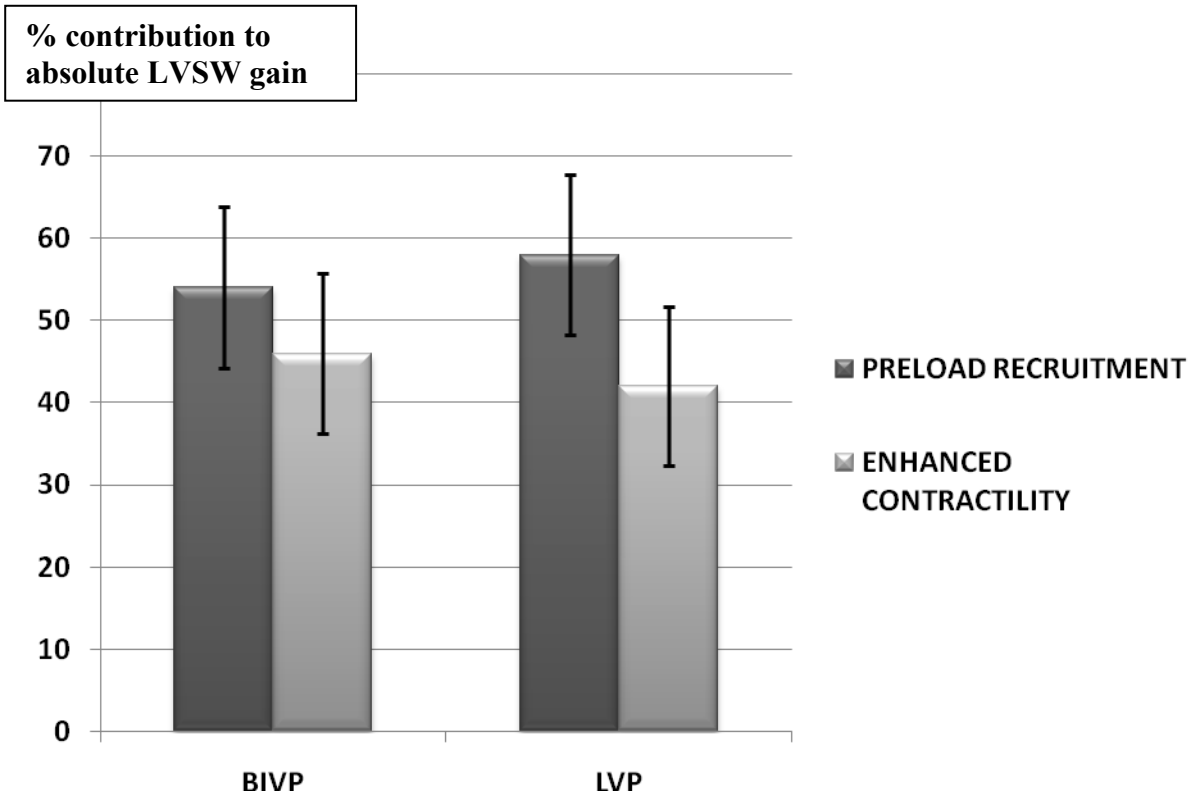


Error bars indicate ± 1 SEM

Broad QRS Group

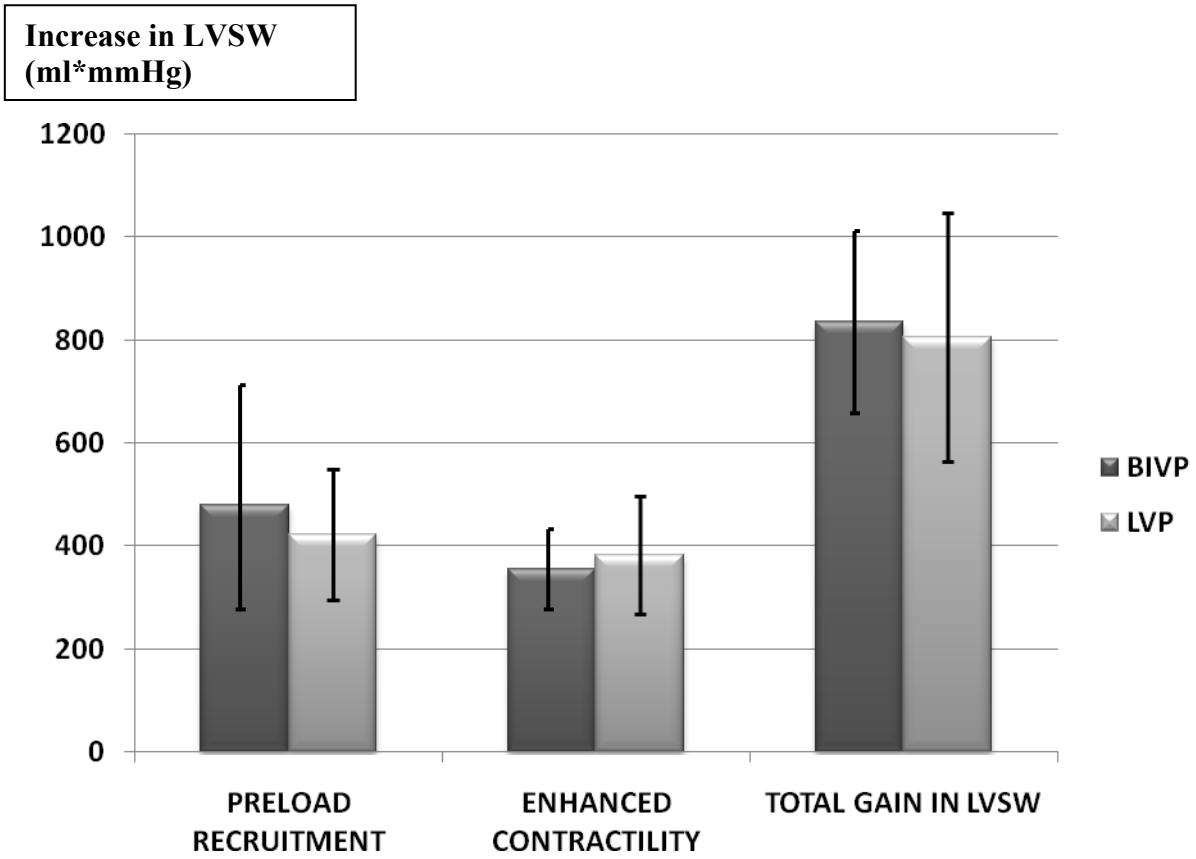
For the broad QRS group with external constraint (n=14), preload recruitment resulted in a similar contribution to the increase in absolute LVSW as enhanced LV contractility (54% versus 46% respectively for BIVP and 58% versus 42% for LVP; p = NS). The absolute gain in LVSW was similar for both LVP and BIVP (806 versus 837ml*mmHg respectively). Results are shown in Figure 6.10 and 6.11.

Figure 6.10. Relative percentage contributions of preload recruitment and enhanced contractility for the broad QRS group with external constraint



Error bars indicate ± 1 SEM

Figure 6.11. Absolute increase in LVSW due to preload recruitment and enhanced contractility for the broad QRS group with external constraint



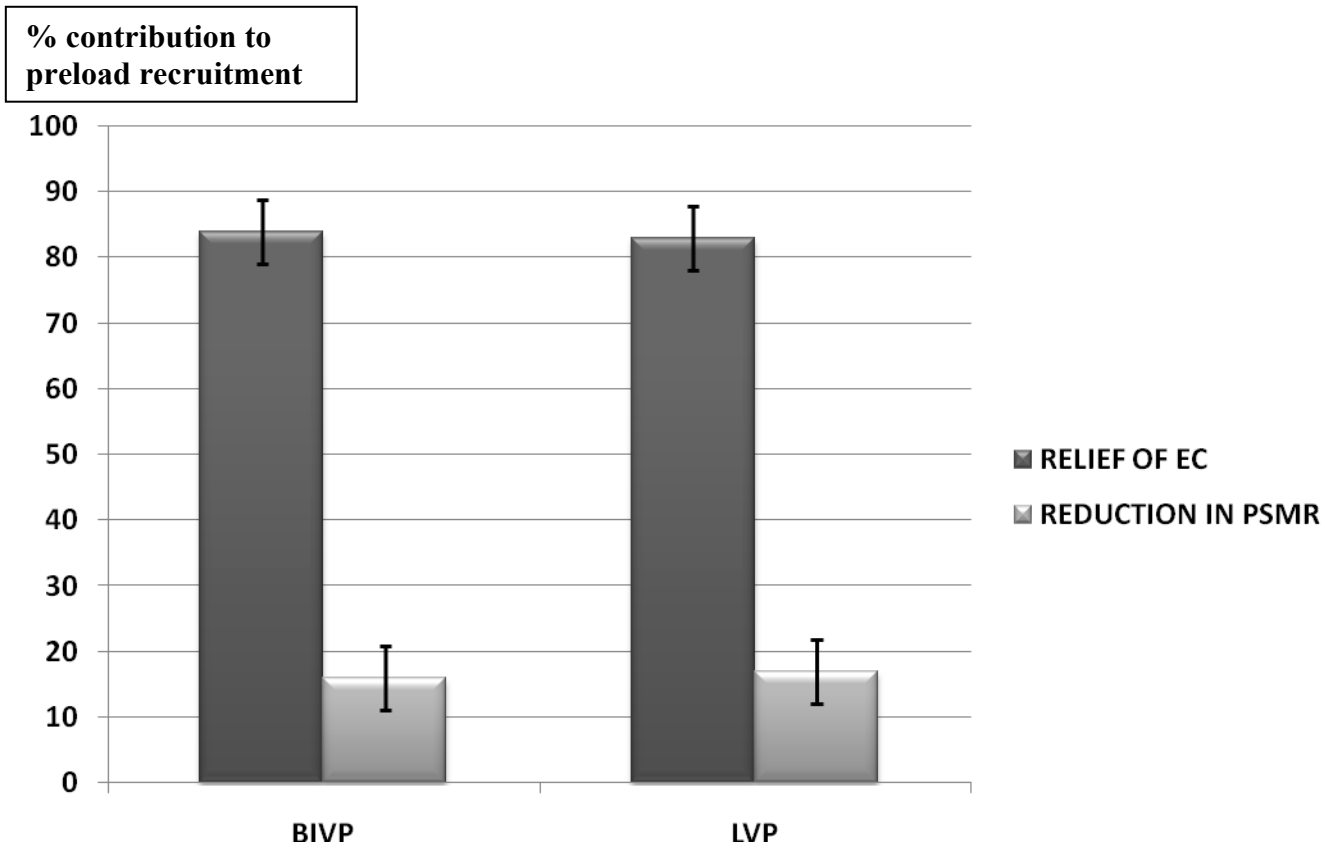
Error bars indicate ± 1 SEM

Components of preload recruitment

Heart Failure Group

For the heart failure group with external constraint as a whole (n=29), relief of external constraint resulted in a significantly greater contribution to the increase in LVEDV compared with a reduction in pre-systolic mitral regurgitation (84% versus 16% with BIVP and 83% versus 17% with LVP; $p < 0.01$). Results are shown in Figure 6.12.

Figure 6.12. Relative percentage contributions of relief of external constraint (EC) and reduction in pre-systolic mitral regurgitation (PSMR) for the heart failure group as a whole with external constraint

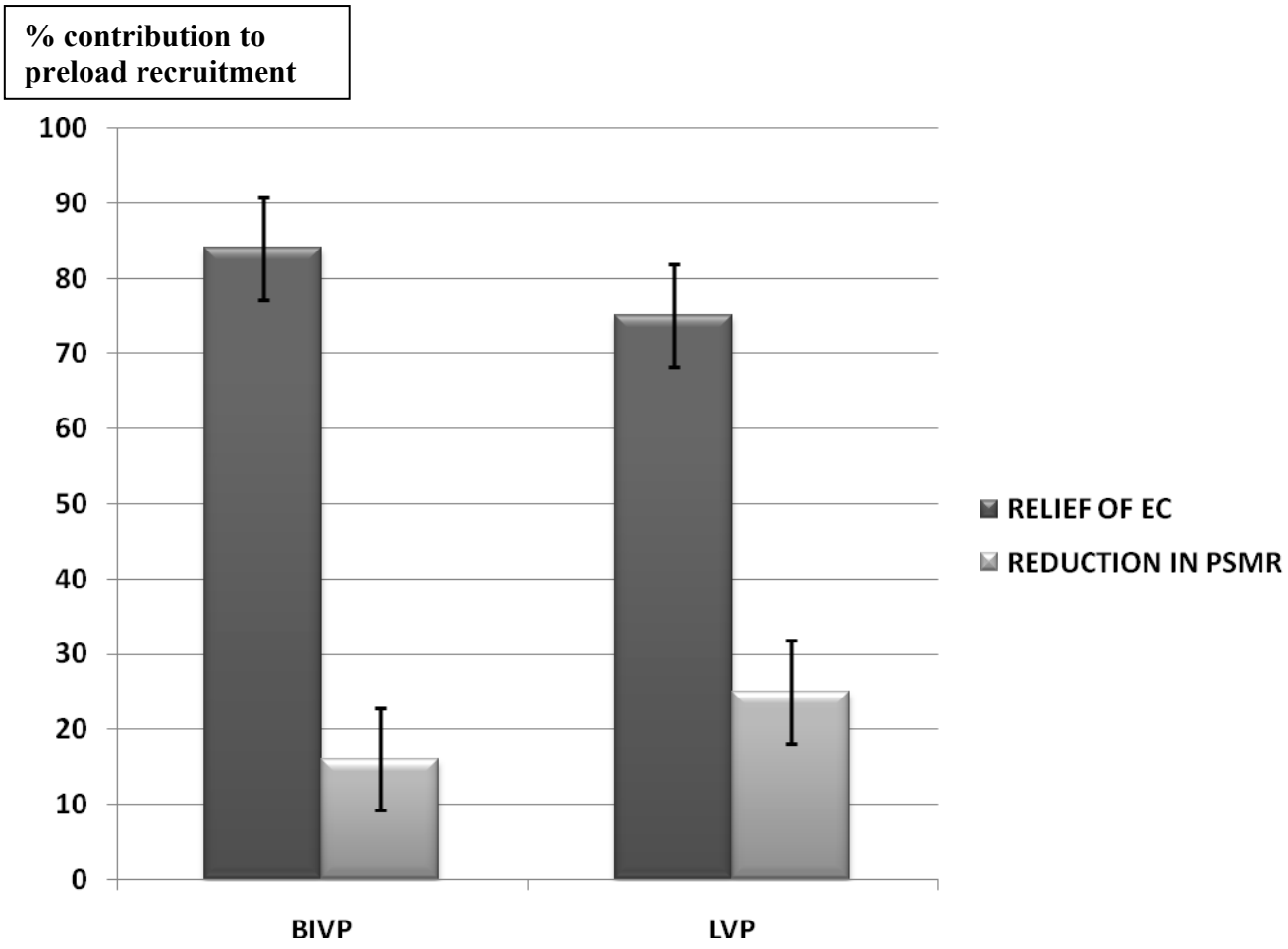


Error bars indicate ± 1 SEM

Narrow QRS Group

For the narrow QRS group with external constraint (n=16), relief of external constraint resulted in a significantly greater contribution to the increase in LVEDV compared with a reduction in pre-systolic mitral regurgitation (84% versus 16% with BIVP and 75% versus 25% with LVP; $p < 0.01$). Results are shown in Figure 6.13.

Figure 6.13. Relative percentage contributions of relief of external constraint and reduction in pre-systolic mitral regurgitation for the narrow QRS group

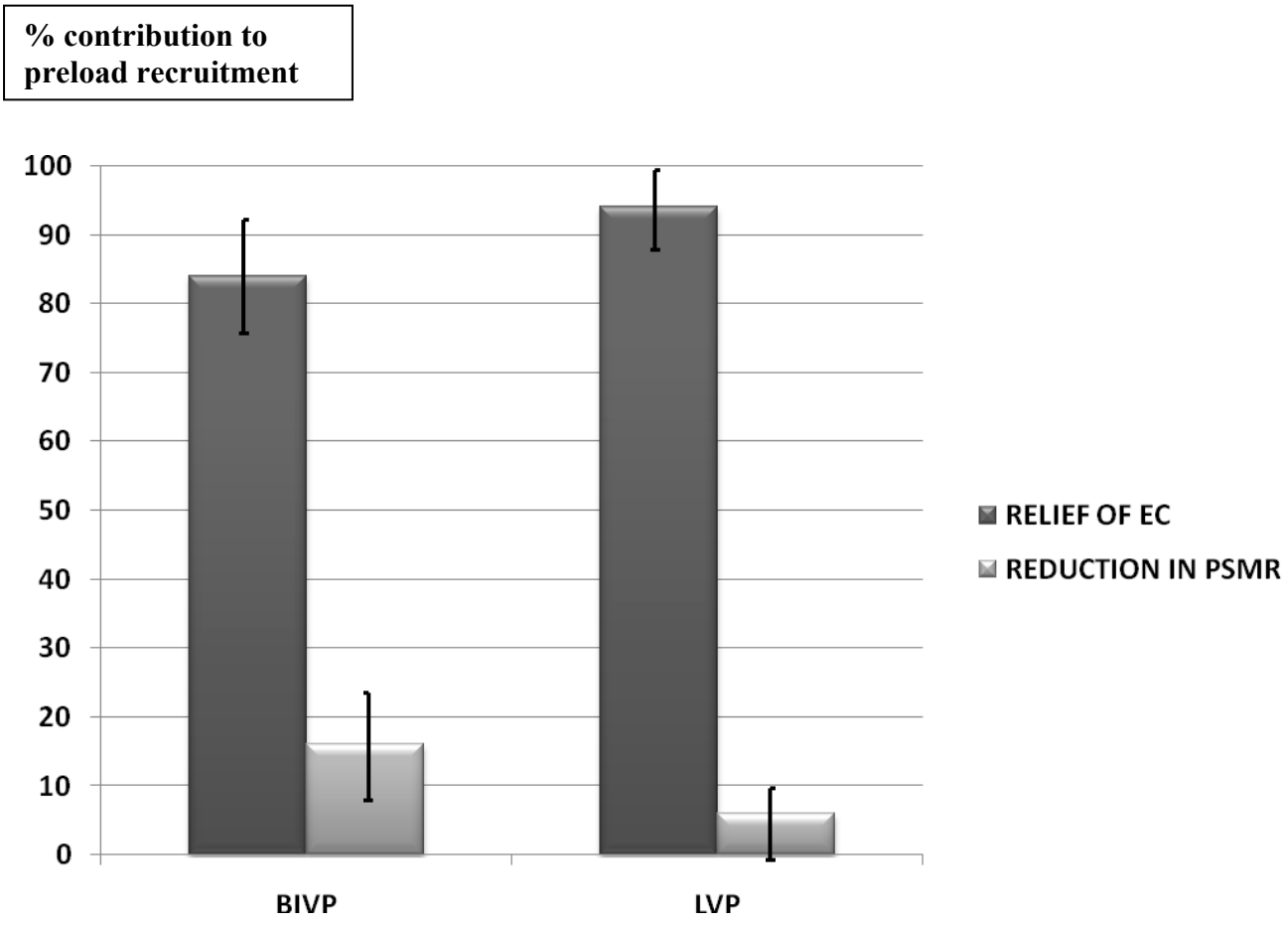


Error bars indicate ± 1 SEM

Broad QRS Group

For the broad QRS group with external constraint (n=14), relief of external constraint resulted in a significantly greater contribution to the increase in LVEDV compared with a reduction in pre-systolic mitral regurgitation (84% versus 16% with BIVP and 94% versus 6% with LVP; $p < 0.01$). Results are shown in Figure 6.14.

Figure 6.14. Relative percentage contributions of relief of external constraint and reduction in pre-systolic mitral regurgitation for the broad QRS group



Error bars indicate ± 1 SEM

DISCUSSION

In the present study we have demonstrated that in a group of heart failure patients with evidence of external constraint at rest, the acute haemodynamic benefits of both BIVP and LVP are principally due to preload recruitment (accounting for two-thirds of the absolute gain in left ventricular stroke work). For the group as a whole, there was a greater absolute increase in LVSW in those patients with external constraint compared to those without. This suggests that patients with external constraint may derive a greater haemodynamic benefit from pacing due to the significant increase in stroke work that is associated with relief of external constraint and preload recruitment, in addition to the increase in stroke work derived from enhanced contractility due to a reduction in dyssynchrony.

As expected, in the patients with a narrow QRS duration and no evidence of significant inter- or intra-ventricular dyssynchrony on baseline echocardiography, the predominant mechanism responsible for the increase in LVSW in response to LVP was preload recruitment (accounting for 70% of the absolute increase). LVP has previously been shown to be effective in reducing external constraint to left ventricular filling in heart failure patients undergoing CRT (55;102), and in those patients with a narrow QRS duration (102). The mechanism for the reduction in external constraint is related to the induction of a phase shift in the timing of LV filling relative to RV filling resulting in the timing of events being brought forward in time in the left ventricle, as previously demonstrated in a canine pacing model (54). Surprisingly, the contribution of preload recruitment to the overall gain in LVSW was similar in response to BIVP, despite the absence of electrical or mechanical dyssynchrony in this group of patients. This may be related to the presence of occult mechanical dyssynchrony in this group of patients, but could still be explained by the induction of a less pronounced phase-shift in the timing of left and right ventricular events.

Although the relative contributions of preload recruitment and enhanced contractility were similar for both pacing modes, the overall increase in total LVSW in the narrow QRS group was greater with LVP than BIVP. This was as a result of a combination of LVSW gain due to both preload recruitment and enhanced contractility.

In those patients with a broad QRS duration, as manifest by a left bundle branch block on surface electrocardiography, the contribution of preload recruitment and enhanced contractility were relatively similar, with no significant difference between BIVP and LVP. This group of patients had a traditional indication for cardiac resynchronisation therapy based on current clinical guidelines, and all had evidence of electrical dyssynchrony at baseline (QRS duration > 120ms). This group of patients would be expected to derive a benefit not only from the relief of external constraint, but also a significant increase in left ventricular contractility via a reduction in left ventricular dyssynchrony. In keeping with our current data, the contribution of enhanced contractility would be expected to be greater in a patients group with a broad QRS duration compared with those with a narrow QRS. The overall increase in total LVSW was similar in response to both BIVP and LVP, suggesting that in patients in whom relief of dyssynchrony is as important as relief of external constraint, there may be no significant additional benefit from LVP, compared with a narrow QRS patient group in whom resynchronisation plays less of a role and relief of external constraint a greater one.

The increase in left ventricular end-diastolic volume with pacing resulted due to both a relief of external constraint and a reduction in pre-systolic mitral regurgitation. Relief of external constraint played a significantly greater role in preload recruitment, accounting for over 80% of the volume gain. The subsequent increase in LVEDV results in a greater LVSW due to recruitment of contractility via the Frank-Starling mechanism.

Prolongation of the atrio-ventricular (AV) conduction time leading to AV dyssynchrony is common in patients with heart failure (22). Prolongation of the AV interval generates pre-systolic mitral regurgitation by generating a diastolic ventricular-atrial pressure gradient. This is because the end of atrial contraction occurs much earlier than the onset of the rise in intraventricular pressure. Because of the altered geometry within a dilated left ventricle, appropriate mitral or tricuspid closure is probably not complete until the start of ventricular contraction. This results in a lower left ventricular preload, higher pulmonary capillary wedge pressure, and a decreased cardiac output. The reduction in pre-systolic mitral regurgitation in these patients occurred as a result of short A-V delay pacing at an interval of 100ms, in keeping with previous data from Brecker *et al* (4) showing that pacing with short AV intervals can reduce or abolish diastolic mitral regurgitation.

STUDY LIMITATIONS

Patients with a narrow QRS duration were assessed for the presence or absence of inter- and intraventricular dyssynchrony using tissue Doppler imaging (TDI). Recent evidence suggests that conventional measures of dyssynchrony have high inter-observer variability and may also underestimate the magnitude of dyssynchrony because they ignore radial dyssynchrony. However, the limitation of this form of dyssynchrony analysis is that it is based on echocardiographic Doppler parameters which are largely derived from longitudinal motion data; hence the presence of radial dyssynchrony was not specifically excluded in this group of patients.

In addition, patients with a broad QRS duration were not formally assessed for the presence or absence of mechanical dyssynchrony on echocardiography.

The calibration method of the conductance catheter was not based on assessment of absolute volume, but this would have little effect on the results which depend entirely on relative changes within in each patient in response to the pacing mode. The catheter was calibrated during steady-state at the beginning of the study. Vena caval occlusion, which results in a fall in RV volume, could result in a decrease in parallel conductance which may result in a modest underestimation of LV volume. To estimate the effect of IVC occlusion we assessed parallel conductance at baseline and repeated the measurement during a caval occlusion in 3 patients. Results show that the decrease in parallel conductance was less than 5% in each patient, which would translate into an apparent (i.e. artificial) decrease of 10ml in absolute volume at most.

These studies were performed supine and at rest. The magnitude of ventricular interaction is variable; it is likely to decrease on adopting the upright posture as the RV volume decreases, and it is likely to increase on exercise, secondary to intestinal venoconstriction (100). Indeed, ventricular interaction may be an important mechanism contributing to stroke volume limitation and exercise intolerance in CHF (101). The present studies did not examine the effect of LV pacing on ventricular interaction during exercise.

CONCLUSIONS

In heart failure patients with evidence of external constraint at rest, the acute haemodynamic benefits of both BIVP and LVP are principally due to the relief of external constraint and preload recruitment. However, in those patients with evidence of electrical dyssynchrony and a broad QRS duration, a significant haemodynamic benefit is derived from an enhancement in left ventricular contractility, presumably as a result of a reduction in left ventricular dyssynchrony. Patients with external constraint may derive a greater haemodynamic benefit from pacing due to the significant increase in stroke work that is associated with relief of external constraint and preload recruitment, in addition to the increase in stroke work derived from enhanced contractility due to a reduction in dyssynchrony.

CHAPTER 7

SUCTION FILLING OF THE LEFT VENTRICLE IN HEART FAILURE AND THE EFFECT OF CARDIAC RESYNCHRONISATION THERAPY

INTRODUCTION

A restrictive filling pattern on transmitral inflow, characterised by a steep acceleration and deceleration slope of the E wave, is a common feature in patients with advanced heart failure, and is known to be an indicator of clinical severity of heart failure. Patients with restrictive filling patters are more symptomatic (115-117), have a reduced exercise capacity (118) and have an increased risk of death or the need for cardiac transplantation (115;119-122). Our previous work has shown that diastolic ventricular interaction (DVI) is common in such patients with advanced heart failure, and the presence of a restrictive filling pattern had a high sensitivity and specificity for detecting DVI (123). In heart failure the increased filling pressures distend the ventricles to such an extent that filling of the left ventricle is impeded by the right ventricle and surrounding pericardium. The presence of DVI would explain the rapid deceleration of the transmitral E wave. At the onset of diastole, left ventricular volume is low and external constraint is minimal, but in late diastole LV filling is impeded by the pericardium and right ventricle.

The term ‘suction filling’ has been defined by Katz as the phenomenon whereby the left ventricle relaxes faster than it can fill (86), resulting in a fall in pressure as the left ventricle enlarges. Suction filling is therefore the period of filling which occurs during the period of

pressure decline to minimum pressure after the mitral valve has opened. We hypothesised that an increase in suction filling is responsible for the rapid upstroke of the E wave on transmitral inflow in patients with advanced heart failure.

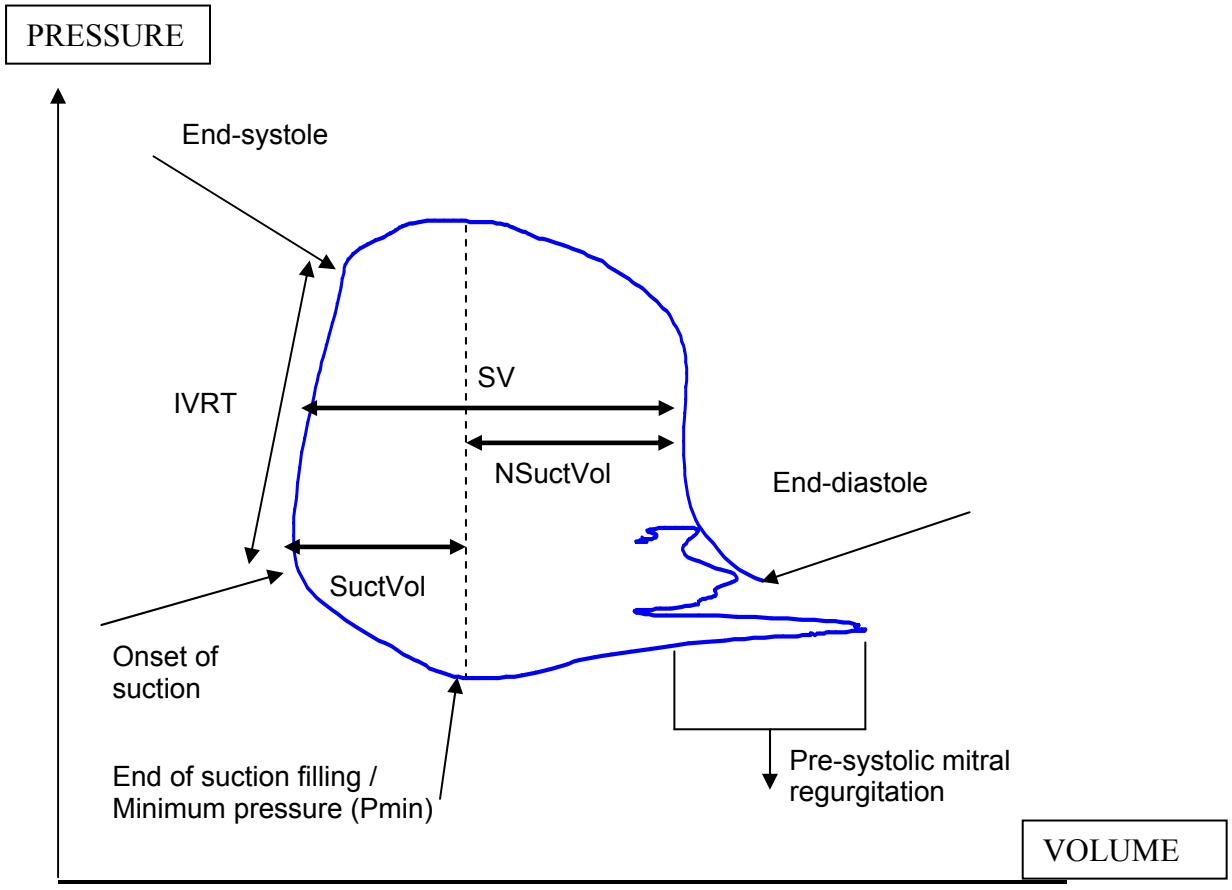
METHODS

Patients. Fifty three patients with chronic heart failure undergoing implantation of a biventricular pacemaker were studied who met the following inclusion criteria: NYHA Class III/IV symptoms despite maximally tolerated optimal medical therapy; left ventricular ejection fraction ≤ 35%; sinus rhythm. Ten patients with structurally normal hearts on echocardiography who were undergoing electrophysiology studies for radiofrequency ablation for symptomatic supraventricular arrhythmias acted as a control group for parameters of suction filling.

Acute Haemodynamic Studies. Acute haemodynamic studies were performed in the cardiac catheterisation laboratory at the time of pacemaker implantation with patients in the non-sedated and supine state as described in the Methodology in Chapter 2.
The following parameters were derived from the pressure volume loops (PVL) at baseline and during inferior vena cava occlusion: dP/dt_{MAX}, dP/dt_{MIN}, left ventricular end-diastolic pressure (LVEDP), pressure at minimum volume (P@Vmin), isovolaemic relaxation time (IVRT), Tau, volume of suction filling (SuctVol), volume of non-suction filling (NSuctVol), and stroke volume (SV). The volume of suction filling (SuctVol) was defined as the volume at minimum pressure (V@Pmin) minus the minimum volume (Vmin), the volume of non-suction filling as the SV minus SuctVol, and the percentage of suction filling was defined as the volume of suction filling divided by the stroke volume (% suction = SuctVol/SV). The

isovolaemic relaxation time was defined as the time from end-systole to the time of onset of filling (time at which volume increase occurs). The time to minimum pressure (T-Pmin) was defined as the time from end-systole to the time at which minimum pressure was reached (see Figure 7.1). In addition, the presence or absence of DVI was assessed according to the response to inferior vena cava occlusion as described in Chapter 2.

FIGURE 7.1. Representative pressure-volume loop from a patient with chronic heart failure



IVRT: isovolaemic relaxation time
SuctVol: suction volume
SV: stroke volume
NSuctVol: non-suction volume

Echocardiography. Eleven of the heart failure patients underwent echocardiography to compare time intervals related to left ventricular filling with those obtained from the acute haemodynamic studies. All studies were performed on a Vivid 7 scanner (GE Ultrasound Systems, Horten, Norway) with a 2.5MHz transducer for pulsed wave Doppler recordings. These recordings were obtained with the patients lying in a supine position at rest at identical heart rates to those during the pressure volume loop studies. Transmitral flow was recorded in the standard apical four-chamber view with the sample volume positioned between the tips of the mitral leaflets. The isovolaemic relaxation time (IVRT) was derived by subtracting the time interval from Peak R-Wave of the ECG to mitral valve opening (onset of E wave) from the time interval from Peak R-wave to aortic valve closure. This method incorporating the use of the ECG complex eliminates the possibility of measurement error caused by valve artifact when measuring small time durations using continuous or pulsed wave Doppler imaging. The time interval from the Peak R-Wave of the ECG to the peak of the E wave on transmitral flow (T-Peak E) was also measured. The IVRT and T-Peak E time intervals derived from echocardiography was compared with the IVRT and T-Pmin derived from the pressure volume loops.

Statistical Analysis. All data are expressed as the mean value ± SD. The Mann-Whitney rank-sum test was used to compare independent samples between the two groups. A repeated measure ANOVA was used to assess the effect of vena cava occlusion and pacing if the data was normally distributed based on a Kolmogorov-Smirnov test. For data that were not normally distributed, a Kruskal-Wallis test was used. Bland Altman plots were used to compare time intervals measured on echocardiography and pressure volume loops. Statistical significance was assumed at $p < 0.05$.

RESULTS

PVL vs. echocardiographic parameters

There was excellent agreement between echocardiographic Doppler indices and pressure-volume loop assessments for all parameters. The correlation coefficient between the two techniques was r=0.91 for IVRT (Figure 7.2) and r=0.86 for T-Pmin/T-Peak E (Figure 7.3).

FIGURE 7.2A. Bland-Altman plot of echocardiography vs. PVL for IVRT

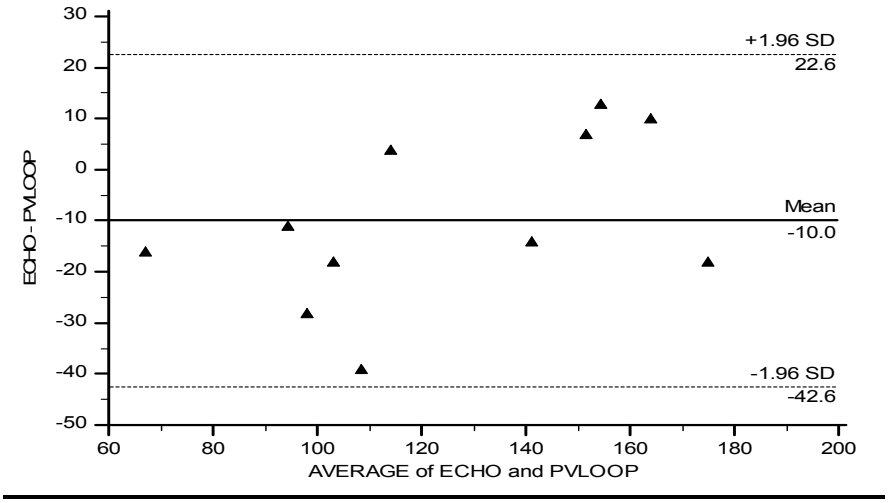


FIGURE 7.2B. Scatter diagram of echocardiography vs. PVL for IVRT

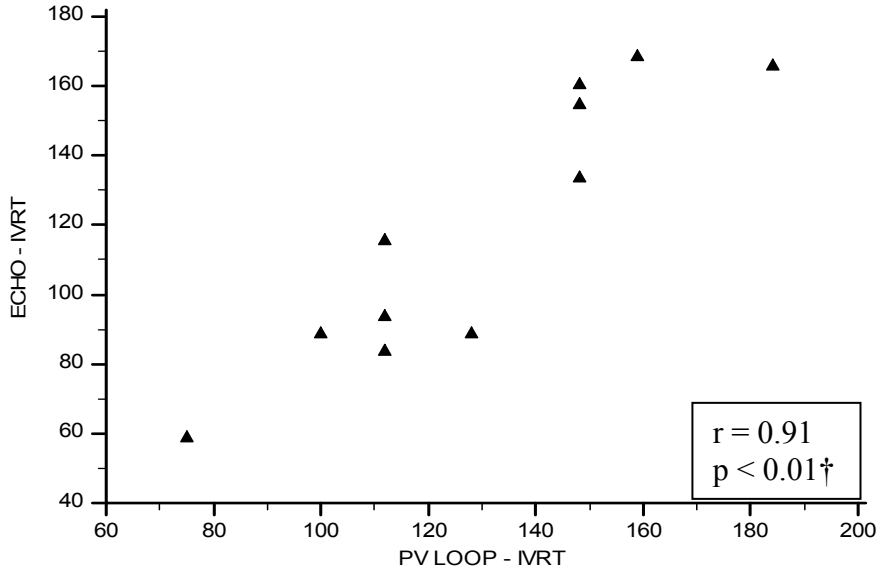


FIGURE 7.3A. Bland-Altman plot of echocardiography (T-Peak E) vs. PVL (T-Pmin)

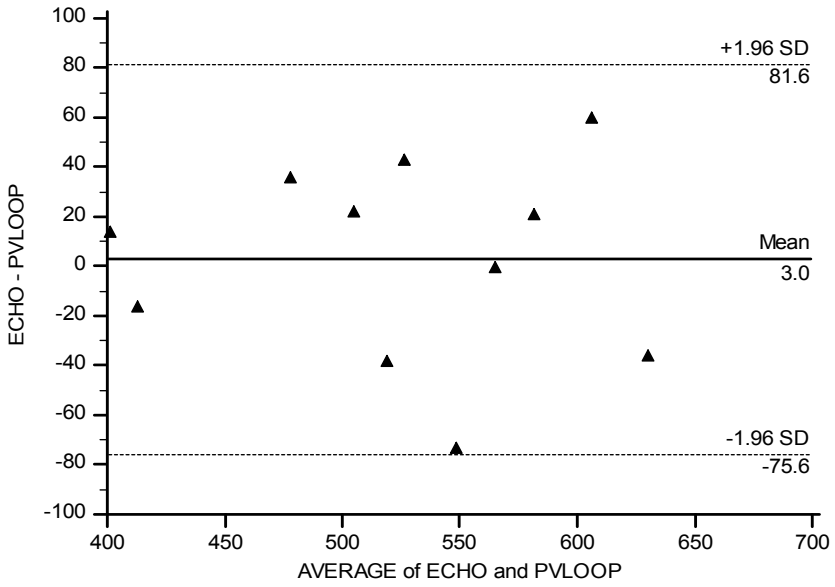
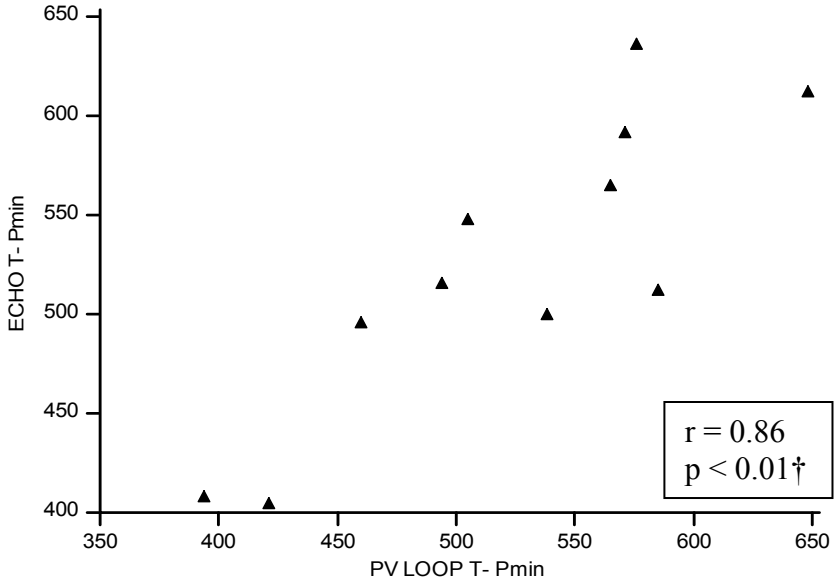


FIGURE 7.3B. Scatter diagram of echocardiography (T-Peak E) vs. PVL (T-Pmin)



Baseline suction filling parameters from PVL

Baseline suction filling parameters for both the heart failure and control groups are shown in Table 7.1. The percentage of suction filling was significantly higher in the patients with heart failure compared with controls (41 ± 23 vs. 17 ± 12%; $p<0.01$), despite a reduced dP/dt_{MIN} (-855 ± 311 vs. -1760 ± 367mmHg/s; $p<0.01$) and a prolonged Tau (82 ± 17.2 vs. 51.3 ± 14; $p<0.01$). LVEDP was significantly higher in patients compared to controls (18.5 ± 7.6 vs. 8.5 ± 2.9mmHg; $p<0.01$). IVRT was shorter in the heart failure group (126 ± 27 vs. 146 ± 22ms; $p=0.03$). Baseline suction filling parameters in those patients with and without external constraint (EC) at baseline are shown in Table 7.2.

TABLE 7.1. Baseline suction filling parameters for heart failure and control groups

	CONTROLS (n=10)	HEART FAILURE (n=53)	p value
LVEDP (mmHg)	8.5 ± 2.9	18.5 ± 7.6	p < 0.01†
P@ Vmin (mmHg)	10.3 ± 5.9	24 ± 12.1	p < 0.01†
IVRT (ms)	146 ± 22	126 ± 27	p = 0.03†
Tau	51.3 ± 14	82 ± 17.2	p < 0.01†
DP/DT_{MIN}	-1760 ± 367	-834 ± 311	p < 0.01†
DP/DT_{MAX}	1391 ± 294	786 ± 204	p < 0.01†
Suction volume (ml)	4 ± 4	13 ± 9	p < 0.01†
Non-suction volume (ml)	21 ± 12	20 ± 15	p = 0.57
% Suction filling	17 ± 12	41 ± 23	p < 0.01†

TABLE 7.2. Baseline suction filling parameters for heart failure patients with and without external constraint (EC)

	EC (n=30)	NO EC (n=23)	p value
LVEDP (mmHg)	21 ± 5	15 ± 9	p < 0.01†
P@ Vmin (mmHg)	28 ± 10	19 ± 14	p < 0.01†
IVRT (ms)	120 ± 24	136 ± 29	p = 0.05†
Tau	86 ± 16	76 ± 17	p < 0.01†
DP/DT_{MIN}	-753 ± 209	-983 ± 373	p < 0.01†
Suction volume (ml)	14 ± 9	12 ± 9	p = 0.39
Non-suction volume (ml)	18 ± 11	22 ± 18	p = 0.79
% Suction filling	44 ± 21	37 ± 25	p = 0.21

There was significant correlation between IVRT and % suction filling (correlation coefficient=0.50; $p < 0.01$), between LVEDP and % suction filling (correlation coefficient=0.48; $p < 0.01$), and between P@Vmin and % suction filling (correlation coefficient=0.60; $p < 0.01$). These results are shown in Figures 7.4A, 7.4B, and 7.4C respectively.

FIGURE 7.4A. Scatter diagram of IVRT and % suction filling

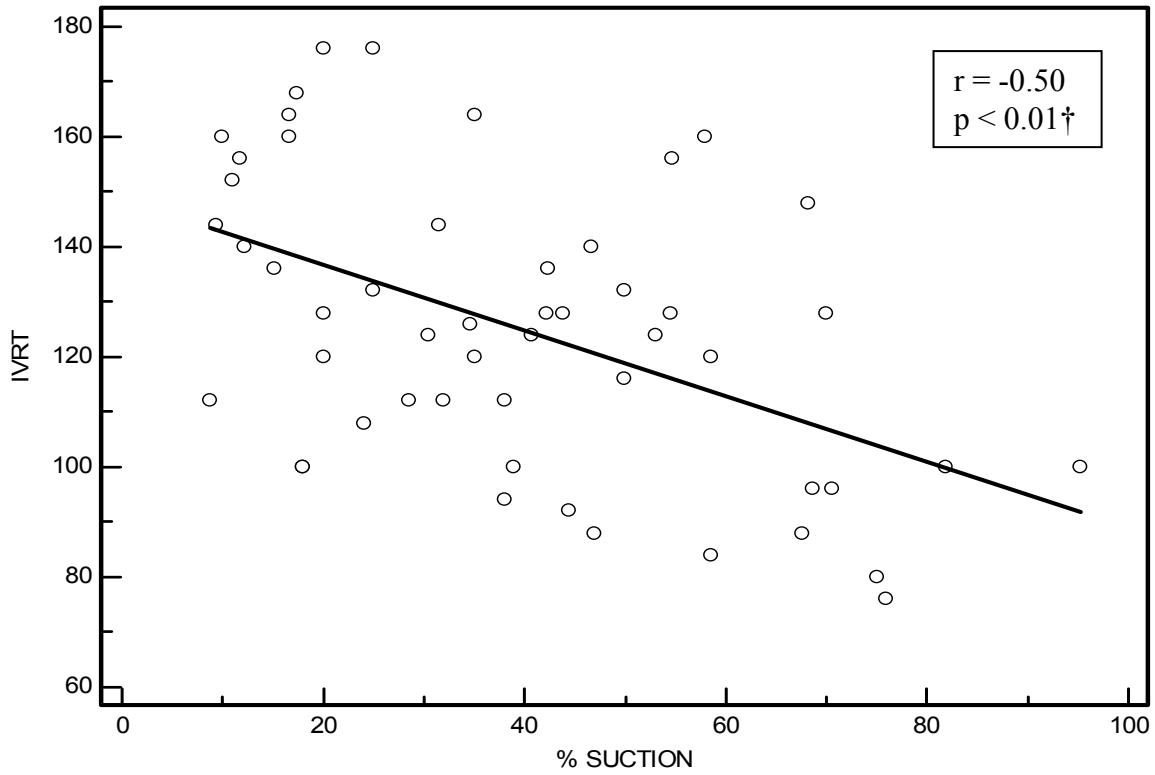


FIGURE 7.4B. Scatter diagram of LVEDP and % suction filling

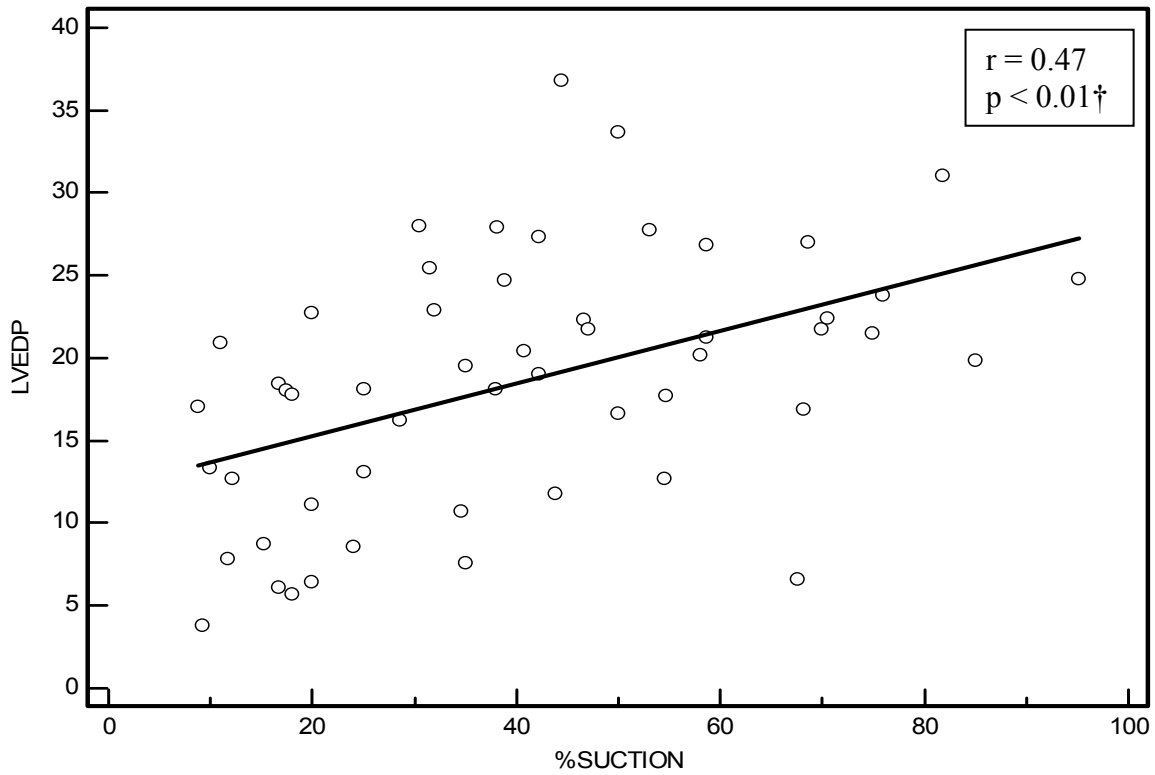
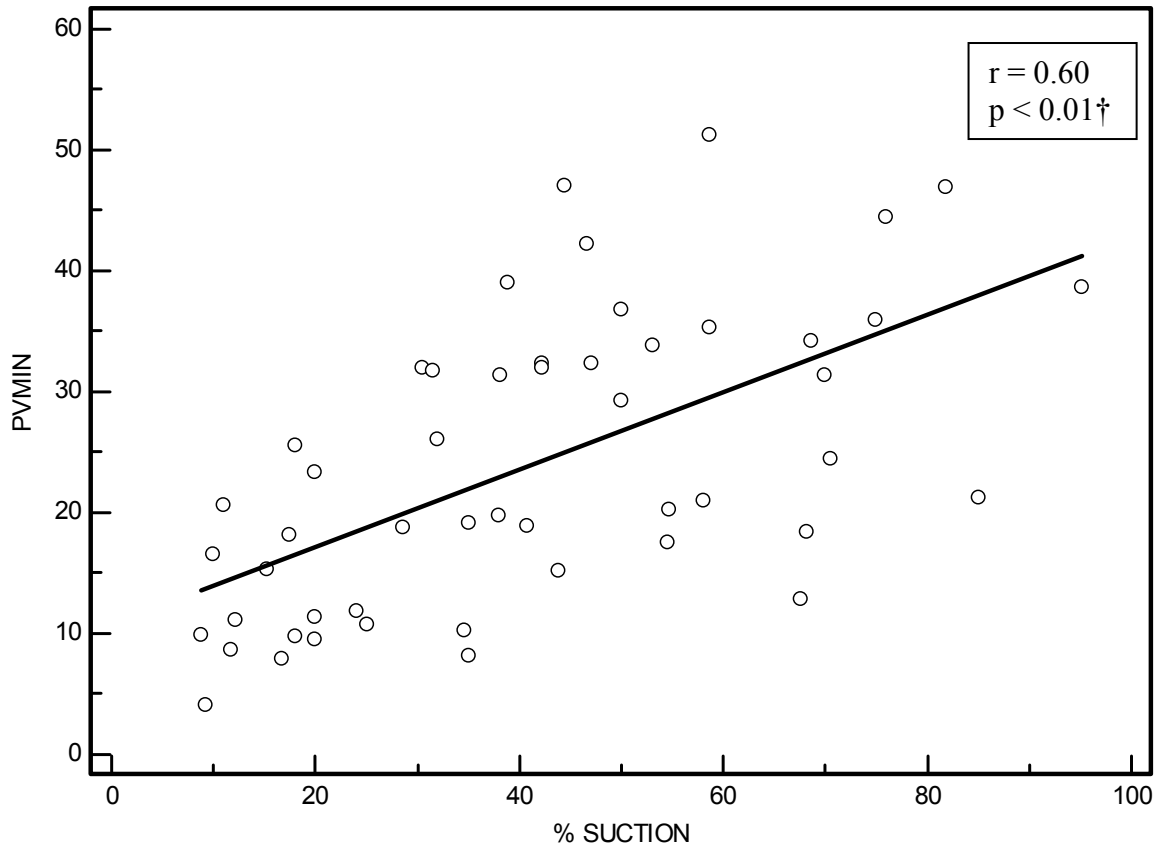


FIGURE 7.4C. Scatter diagram of P@Vmin and % suction filling



Changes in suction filling parameters in response to inferior vena cava occlusion (IVCO)

Results are shown in Table 7.3. IVCO in the heart failure group resulted in a 41% decrease in suction filling (41 ± 23 to 24 ± 17%; $p<0.01$), a 19% decrease in LVEDP (18.5 ± 7.6 to 14.9 ± 5.6mmHg; $p<0.01$), and a 33% increase in IVRT (126 ± 27 to 167 ± 37ms; $p=0.05$).

TABLE 7.3. Suction filling parameters for heart failure group in response to IVCO

	BASELINE	IVCO	p value
LVEDP (mmHg)	18.5 ± 7.6	14.9 ± 5.6	p < 0.01†
P@ Vmin (mmHg)	24 ± 12.1	16.8 ± 7.6	p < 0.01†
IVRT (ms)	126 ± 27	167 ± 37	p < 0.05†
Tau	82 ± 17.2	85.2 ± 17.5	p = 0.35
DP/DT_{MIN}	-855 ± 311	-801 ± 207	p = 0.70
Suction volume (ml)	13 ± 9	7 ± 7	p < 0.01†
Non-suction volume (ml)	20 ± 15	22 ± 14	p = 0.26
% Suction filling	41 ± 23	24 ± 17	p < 0.01†

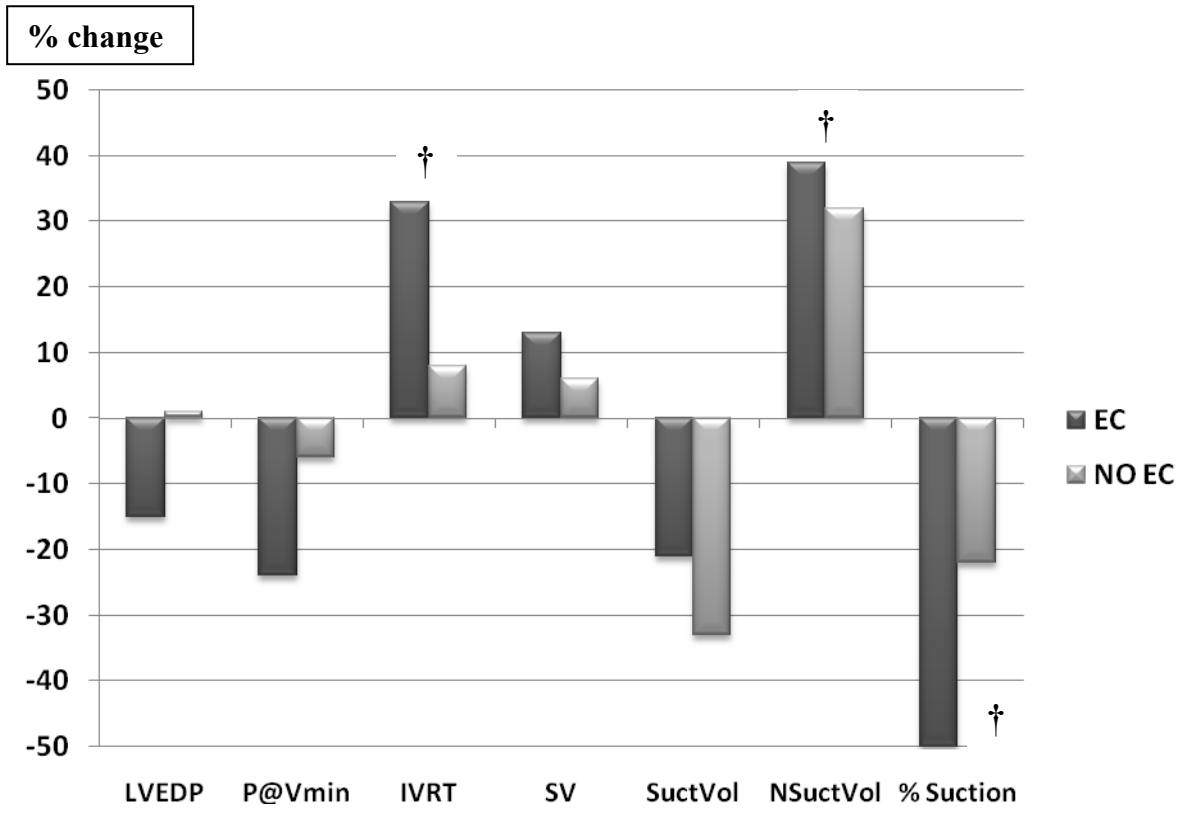
Changes in suction filling parameters in response to biventricular pacing (BIVP)

Results are shown in Table 7.4. Biventricular pacing in the heart failure group resulted in a 37% decrease in suction filling (41 ± 23 to 26 ± 14%; p<0.01) and a 22% increase in IVRT (126 ± 27 to 154 ± 28ms; p<0.01). In patients with EC at baseline there was a greater reduction in suction filling, LVEDP and P@Vmin, as well as a greater increase in IVRT, as shown in Figure 7.4.

TABLE 7.4. Suction filling parameters for heart failure group in response to BIVP

	BASELINE	BIVP	p value
LVEDP (mmHg)	18.5 ± 7.6	15.7 ± 6.5	p = 0.04†
P@ Vmin (mmHg)	24 ± 12.1	19.9 ± 7.9	p = 0.04†
IVRT (ms)	126 ± 27	154 ± 28	p < 0.01†
Tau	82 ± 17.2	83.2 ± 15.4	p = 0.69
DP/DT_{MIN}	-855 ± 311	-840 ± 296	p = 0.80
DP/DT_{MAX}	786 ± 204	893 ± 219	p = 0.01†
Suction volume (ml)	13 ± 9	10 ± 8	p = 0.09
Non-suction volume (ml)	20 ± 15	27 ± 14	p = 0.02†
% Suction filling	41 ± 23	26 ± 14	p < 0.01†

FIGURE 7.4. Percentage change in suction filling parameters in response to BIVP for heart failure patients with (EC) and without external constraint (NO EC)



† Indicates significant difference between EC and NO EC group ($p < 0.05$)

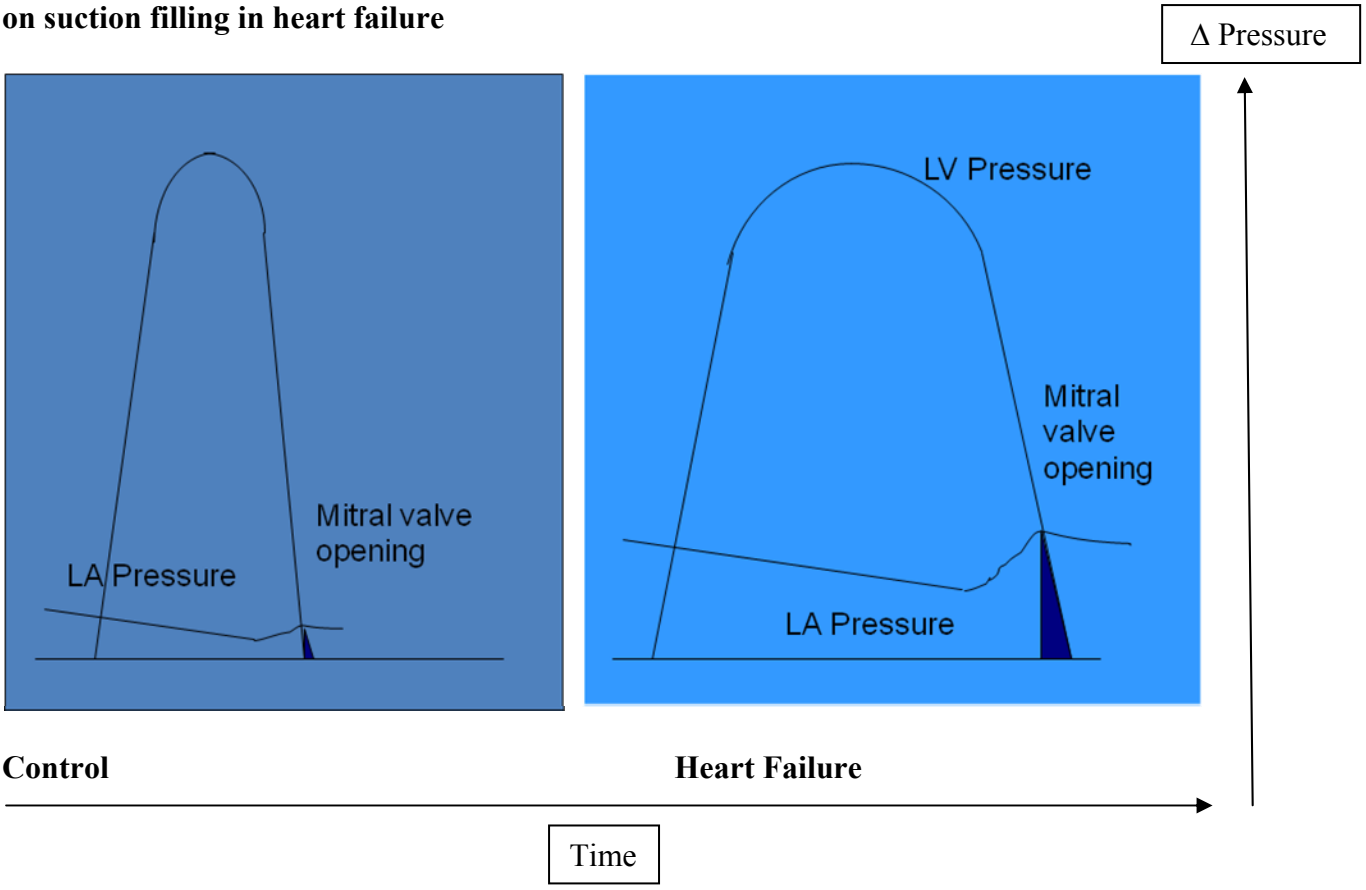
DISCUSSION

In the present study we have demonstrated a significant increase in the percentage of suction filling (the percentage of total filling occurring during the period in which the left ventricular pressure is falling) in patients with advanced heart failure compared with patients with a structurally and functionally normal heart.

At baseline we found an excellent correlation between timing intervals on echocardiography and pressure-volume loop analysis, confirming that filling of the left ventricle was occurring during a period of ongoing left ventricular relaxation and pressure decline. Despite a marked slowing of active relaxation of the left ventricle in the heart failure group at baseline, as evidenced by a reduction in dp/dt_{MIN} and a prolonged Tau, the percentage of suction filling was markedly increased.

This increase in suction filling was associated with a higher LVEDP, a shorter IVRT, and an onset of left ventricular filling and volume increase at a higher pressure (P@Vmin). A significant correlation was demonstrated at baseline between these three variables and the percentage suction filling, with the strongest association being between P@Vmin and % suction filling. Despite the slower rate of active relaxation of the left ventricle, the shorter IVRT is associated with an earlier opening of the mitral valve at a higher pressure. Filling therefore occurs during a period of ongoing pressure decline as ventricular relaxation is prolonged, as demonstrated in the schematic in Figure 7.5.

FIGURE 7.5. Effects of slowing of the rate of active LV relaxation and increase LVEDP on suction filling in heart failure



This is consistent with data from Wang *et al*, who have utilised wave intensity analysis in a canine animal model to assess left ventricular diastolic suction(124). They demonstrated that the relaxing left ventricle generates an expansion wave that first decelerates the stroke volume moving through the aorta, then rapidly declines in magnitude during isovolaemic relaxation, and finally accelerates blood in the mitral inflow tract. The total energy of that expansion wave and the energy remaining after mitral valve opening were shown to be inversely related to the rate of decline of LV pressure (i.e. Tau), but also inversely related to the completeness of left ventricular emptying or LVESV (left ventricular end-systolic volume). This suggests that although total energy expenditure may be reduced in heart failure a greater proportion of that energy expenditure occurs when the mitral valve is open and filling is occurring due to a prolongation of active relaxation. They too demonstrated an association between the size of the diastolic suction wave and the size of the E wave of early

transmitral filling, suggesting that the left ventricular diastolic suction wave is more important than the passive decompression of the left atrium in determining the size of the E wave.

However, Yotti *et al* have shown conflicting results utilising a non-invasive echocardiographic method of assessment of diastolic suction in patients with a dilated cardiomyopathy(125). Using colour M-mode Doppler they measured intraventricular diastolic pressure differences (DIVPD) from the apex to base, and demonstrated a significant reduction in total DIPVD in patients with DCM compared with healthy controls. Two types of DIVPD exist, and together contribute to the total DIVPD. Inertial DIVPD, as a result of inertial acceleration of blood, is responsible for generating a favourable suction force (pressure drop from base to apex) to accommodate the filling volume received from the left atrium. In contrast, the convective DIPVD results in deceleration of blood flow (pressure rise from base to apex) in opposition to flow. However, despite the overall decrease in total DIVPD in the DCM group as a whole, it is interesting to note that the patients group who had evidence of a restrictive mitral inflow pattern had an increase in inertial component and a reduction in the convective component of the total DIVPD in comparison to the patients without evidence of a restrictive filling pattern on baseline echocardiography. This suggests that patients with a restrictive filling physiology may indeed generate a greater diastolic suction wave than those with non-restrictive filling.

Preload reduction accomplished by inferior vena cava occlusion resulted in a significant reduction in the percentage of suction filling in the heart failure patients, accompanied by a significant reduction in LVEDP and P@Vmin, and a significant increase in IVRT (a consequence of delayed mitral valve opening due to a reduction in left atrial pressure as a

result of preload reduction). This was demonstrated despite no significant change in parameters of active LV relaxation (Tau and dp/dt_{MIN}).

In the present study biventricular pacing (BIVP) has been shown to have a significant effect on the percentage of left ventricular diastolic suction filling. As previously demonstrated by Turner *et al* (25), BIVP resulted in a significant reduction in both LVEDP and in P@Vmin, associated with a significant lengthening of the IVRT, indicating that mitral valve opening was occurring later. As previously demonstrated by ourselves (102), BIVP resulted in a significant improvement in dp/dt_{MAX}, but had no acute effect on the rate of active LV relaxation (as evidenced by an unchanged dp/dt_{MIN} and Tau). The significant reduction seen in the percentage of suction filling is a due to both a reduction in the volume of suction filling (as a result of delayed mitral valve opening and a longer IVRT) and a significant increase in the non-suction filling volume as a result of an increased stroke volume. This increase in stroke volume occurs as a result in increased contractility (significant increase in dp/dt_{MAX}) and an improvement in absolute left ventricular stroke work and preload recruitable stroke work (in part due to a relief of external constraint) in response to BIVP, as previously demonstrated by ourselves(102).

STUDY LIMITATIONS

The calibration method of the conductance catheter was not based on assessment of absolute volume, but this would not affect results, which depend entirely on relative changes within each patient in response to the pacing mode.

Assessment of left ventricular diastolic suction was based entirely on the volume of filling occurring during the period of left ventricular pressure decline, but did not involve the assessment of pressure gradients from the left ventricular base to apex.

CONCLUSIONS

In the present study we have demonstrated a significant increase in the percentage of suction filling (the percentage of total filling occurring during the period in which the left ventricular pressure is falling) in patients with advanced heart failure compared with patients with a structurally and functionally normal heart. Biventricular pacing (BIVP) has been shown to have a significant effect on the percentage of left ventricular diastolic suction filling. BIVP resulted in a significant reduction in both LVEDP and in P@Vmin, associated with a significant lengthening of the IVRT, indicating that mitral valve opening was occurring later. The significant reduction seen in the percentage of suction filling is due to both a reduction in the volume of suction filling and an increase in the non-suction filling volume as a result of an increased stroke volume.

CHAPTER 8

DISCUSSION, CONCLUSIONS, AND FUTURE STUDIES

The introductory chapters of this thesis outline the development of the role of cardiac pacing in patients with heart failure and describe the initial studies that guided the rationale for cardiac resynchronisation therapy, and subsequent patient selection. To date several randomised controlled studies have shown CRT to be effective in improving quality of life and exercise capacity, in addition to resulting in left ventricular reverse modeling. Most importantly, CRT has been shown to result in a reduction in morbidity and mortality. The mechanism by which CRT improves cardiac performance has always been thought to be primarily due to electrical and mechanical resynchronisation, with a reduction in mitral regurgitation occurring as a result of papillary muscle resynchronisation acutely and left ventricular reverse remodelling chronically. Recently, an additional mechanism for benefit has been demonstrated, in the form of relief of diastolic ventricular interaction and external constraint to left ventricular filling.

However, despite the wealth of data showing a benefit for CRT in refractory heart failure, several questions still remain regarding optimal patient selection and the exact mechanisms by which CRT improves cardiac function. These questions have been driven by the fact that up to 30% of patients who meet current clinical criteria for implantation of CRT fail to demonstrate a subjective or objective improvement in cardiac status.

The demonstration of a weak correlation between electrical (electrocardiographic) dyssynchrony, as evidenced by the duration of the QRS complex on surface ECG, and mechanical dyssynchrony has resulted in significant interest in the use of CRT in patients with a narrow QRS duration, with early small studies suggesting a benefit.

In addition, the question of optimal pacing mode and programming of particular atrio-ventricular and inter-ventricular timing intervals has led to studies assessing the effects of simultaneous biventricular pacing and left ventricular pacing only.

The principal objectives of the work presented in this thesis were to investigate whether cardiac resynchronisation therapy in patients with a narrow QRS duration would result in similar acute haemodynamic benefits to those seen in patients with a broad QRS duration. In addition, the mechanisms by which pacing improves cardiac performance were assessed in patients with both narrow and broad QRS duration, with a particular interest in defining the optimal pacing mode in patients with and without evidence of external constraint. These findings will aim to better inform patient selection and allow optimisation of pacing strategy in individual patients.

SUMMARY OF RESULTS

1. Cardiac resynchronisation therapy results in significant acute haemodynamic benefits in patients with heart failure, a narrow QRS duration, and no evidence of mechanical dyssynchrony on echocardiography. These acute haemodynamic benefits are comparable to those demonstrated in patients with a broad QRS duration in both the present study and from previously published data. These findings indicate that the benefit from cardiac resynchronisation therapy is not only related to resynchronisation, but that additional mechanisms are responsible for the benefit derived from pacing.

2. External constraint to left ventricular filling was present in 50% of patients regardless of baseline QRS duration. Both biventricular and left ventricular pacing were effective at significantly reducing the magnitude of external constraint in conjunction with an increase in left ventricular end-diastolic volume, allowing for preload recruitment and an increase in left ventricular stroke work via utilization of the Starling mechanism.

3. In patients with heart failure and severe left ventricular dysfunction, right ventricular pacing resulted in acute haemodynamic deterioration. The optimal interventricular timing delay can be predicted based on the presence or absence of external constraint at baseline. In those patients with external constraint, interventricular delays with the left ventricle being the first chamber paced resulted in a trend towards greater increase in left ventricular stroke work, whereas in patients without external constraint near-

simultaneous interventricular timing intervals appeared beneficial. These results indicate that patients with external constraint benefit from a greater phase shift in the timing of left ventricular events relative to right ventricular events, allowing the left ventricle to fill at a time when the right ventricular volume and pressure are lower.

4. The acute haemodynamic benefits of both biventricular and left ventricular pacing are principally due to a reduction in external constraint and preload recruitment, accounting for two-thirds of the absolute gain in left ventricular stroke work with pacing. Patients with external constraint demonstrated a greater haemodynamic benefit from pacing than those without due to preload recruitment in addition to the gain in stroke work from enhanced contractility.

5. In patients with a narrow QRS duration, preload recruitment accounted for 70% of the benefit from pacing, whereas in patients with a broad QRS duration, the contributions from preload recruitment and enhanced contractility were equivalent. This suggests that in patients without evidence of mechanical or electrical dyssynchrony, the benefit derived from resynchronisation may still be significant.

6. In patients with heart failure there is a significant increase in the percentage of suction filling, defined as filling occurring after mitral valve opening during a period of ongoing pressure decline to a minimum value. This increase in the percentage of suction filling correlated significantly with a higher LVEDP, a shorter isovolaemic relaxation time, and a higher pressure at the onset of left ventricular filling (P@Vmin). This suggests that although active relaxation in heart failure is prolonged,

a greater proportion of the total energy expenditure involved in LV relaxation occurs when the mitral valve is open at a time when left ventricular pressure is declining.

DISCUSSION

Although a significant number of patients with medically-refractory heart failure have benefitted from cardiac resynchronisation therapy, there remains a significant non-responder rate. Based on the initial rationale that pacing therapy improved cardiac function via a reduction in inter- and intra-ventricular dyssynchrony, current guidelines require the presence of electrical dyssynchrony (with or without mechanical dyssynchrony) in order to qualify for device therapy. However, it is accepted that electrical dyssynchrony (as evidenced by a prolonged QRS duration) is not synonymous with mechanical dyssynchrony, and in fact significant dyssynchrony may be demonstrated on echocardiography in patients with a narrow QRS duration. In addition, recent studies such as PROSPECT have cast doubt on the current echocardiographic methods used to assess the presence of dyssynchrony. The high rate of non-response to CRT suggests that a better understanding of the mechanism by which CRT improves cardiac function is required in order to best target those patients likely to derive a benefit from device therapy.

The current body of work highlights the limitations in the current guidelines, demonstrating an equivalent haemodynamic benefit from CRT in those patients with neither electrical nor mechanical dyssynchrony, a group currently excluded from receiving device therapy in the United Kingdom. Several small, randomised studies have demonstrated a beneficial effect from CRT in patients with a narrow QRS and evidence of mechanical dyssynchrony on

echocardiography, but this is the first study to demonstrate comparable haemodynamic benefits to those seen in heart failure patients with dyssynchrony. Whether this will translate into long-term symptomatic improvements with a reduction in morbidity and mortality has yet to be determined, but highlights the need for large, randomised controlled trials in this patient group.

Although the traditional view has been that CRT exerts its beneficial effect via a reduction in both inter- and intra-ventricular dyssynchrony, these data suggests that preload recruitment via the relief of external constraint is a significant mechanism resulting in improvements in left ventricular stroke work. In fact, in patients with evidence of external constraint at rest (accounting for half of the patients), the predominant mechanism resulting in improvement in cardiac function was the relief of external constraint, allowing preload recruitment and an increase in left ventricular stroke work via recruitment of the Starling mechanism. This effect was more pronounced in patients without evidence of mechanical or electrical dyssynchrony, but even in the patients with dyssynchrony this mechanism accounted for 50% of the improvement demonstrated in left ventricular stroke work. In addition, the fact that patients with external constraint demonstrated a greater haemodynamic benefit from CRT suggests that an assessment for the evidence of diastolic ventricular interaction on echocardiography may help to predict which patients are more likely to respond to pacing.

At present, the current practice amongst many physicians is to program the CRT at implant to default manufacturer settings (most commonly providing simultaneous biventricular stimulation with a short atrio-ventricular delay), with a view to an attempt at optimisation of atrioventricular and interventricular timings only in non-responders. Although a significant numbers of patients will respond favourably to these default settings, there is an argument for

predicting the optimal pacing strategy from the pre-implant echocardiography and haemodynamic indices at implant.

Patients with a restrictive filling pattern and a high LVEDP are very likely to have external constraint to left ventricular filling, and based on our current data would derive a greater haemodynamic benefit from a pacing strategy in which the left ventricle is activated significantly earlier than the right (or even left ventricular only pacing). In patients without external constraint and a low LVEDP it would appear reasonable to program simultaneous biventricular stimulation initially, with a view to reprogramming to left ventricular pre-excitation in non-responders.

Patients with external constraint derive a greater haemodynamic benefit from pacing, with the stroke work gain from preload recruitment accounting for around two-thirds of the benefit achieved with both biventricular and left ventricular pacing. In the present study we used an invasive measure of the presence or absence of external constraint, namely inferior vena caval occlusion and left heart catheterisation. However, this method of assessment is not feasible in all heart failure patients. Similarly, assessing the change in left ventricular end-diastolic volume in response to the application of lower body negative pressure to assess for external constraint remains a research tool and not widely clinically available.

Echocardiography provides the simplest and easily accessible method for assessing the volume and pressure of the right ventricle, right atrial pressure (an excellent surrogate for pericardial pressure), septal position, septal motion, and the transmitral filling pattern. As previously described, the presence of a restrictive transmitral filling pattern has both a high sensitivity and specificity for detecting diastolic ventricular interaction and external constraint (123).

In addition, the position of the interventricular septum at end-diastole provides valuable information relating to the trans-septal pressure gradient (LVEDP minus RVEDP). The normal interventricular septum is convex when viewed from the left ventricle, with the shape remaining the same in systole and diastole because the pressure in the left ventricle remains higher than in the right. The impact of right ventricular volume or pressure overload can lead to a reversal of the end-diastolic trans-septal pressure gradient, resulting in the septum becoming flattened or even concave at end-diastole (often in association with paradoxical septal motion as the septum moves rightward during systole as a result of restoration of the normal positive trans-septal pressure gradient). This is often seen as a delay in septal to posterior wall contraction on M-mode echocardiography of > 130ms. The echocardiographic assessment of ventricular interdependence could easily be incorporated into current protocols, in addition to non-invasive assessment of LVEDP using the E/E' ratio (transmitral E wave velocity / tissue Doppler E velocity derived at the mitral valve annulus), in order to identify patients more likely to derive a significant benefit from pacing.

Although initial work is necessary to better predict those patients most likely to respond to pacing, this study gives significant insight into the mechanisms of benefit derived from pacing, as well as clues to the optimal pacing strategy in individual patients. However, several questions arise which can be answered with future studies, as described below.

FUTURE STUDIES

(1) Assessment of the magnitude of external constraint on exercise

Although only 50% of patients with congestive heart failure have evidence of external constraint at rest, it is likely that it develops in most patients during exercise (and contributes significantly to the exercise limitation demonstrated in this group of patients). External constraint may help to explain why exercise tolerance is limited in patients with heart failure, since it prevents utilisation of the Starling mechanism to increase cardiac output as previously discussed).

Although it is not feasible to assess the magnitude of external constraint on exercise via pressure-volume loop analysis, it is possible to assess for the presence or absence of external constraint non-invasively using radionuclide ventriculography. In patients with heart failure, both LVEDP and RVEDP become elevated on exercise. If external constraint is present on exercise, the increase in RVEDP and RVEDV will result in significant diastolic ventricular interaction and external constraint to the left ventricular filling. In addition, a rise in pericardial pressure (as a result on the J-shaped stress-strain relationship of the pericardium) will occur, resulting in significant pericardial constraint. The combined effects will effectively restrain left ventricular filling, resulting in a decrease in LVEDV and subsequent reduction in left ventricular stroke volume. The change in RVEDV, LVEDV, and left ventricular stroke volume can be assessed using radionuclide ventriculography performed at rest and subsequently on exercise using supine cycle ergometry.

(2) *Assessment of the safety and efficacy of long-term resynchronisation therapy utilising a left ventricular pacing strategy*

Although left ventricular pacing has been shown to produce equivalent if not superior acute haemodynamic benefits compared with biventricular pacing, there is understandably still some hesitation from clinicians regarding the use of cardiac stimulation from a left ventricular electrode only. Left ventricular pacing electrodes are known to have a higher rate of displacement in part due to the extreme variability of the venous anatomy of the coronary sinus and in part due to the lack of a reliable active fixation method for these leads. There is some concern that a left ventricular based pacing strategy may lead to lead to issues with consistent capture and pacing.

In order to assess the safety of long-term left ventricular pacing it will be necessary to perform a randomised controlled crossover trial of left ventricular versus biventricular pacing to assess the safety of such a pacing strategy and to compare the percentage of pacing achieved with both pacing modes. The effect of pacing mode on quality of life, exercise capacity, left ventricular reverse remodelling, and symptomatic status will also be assessed.

(3) *Assessment of the feasibility and efficacy of a mode-switch algorithm in cardiac resynchronisation devices to left ventricular pacing*

As previously described, although only half of all heart failure patients have evidence of external constraint and diastolic ventricular interaction at rest, it is likely that many more will develop it with exercise. It is also likely that patients will develop significant external constraint from both the right ventricle and the lungs during acute decompensations of heart failure associated clinically with fluid retention.

As we have demonstrated in the current work, patients with external constraint derive a greater haemodynamic benefit from cardiac resynchronisation therapy than those without, with a trend towards a greater benefit from left ventricular pacing. The ideal pacemaker would incorporate a mode-switch algorithm allowing a switch from biventricular to left ventricular pacing triggered either by exercise, or by changes in thoracic impedance, allowing a left ventricular-based pacing strategy to be used in situation where significant external constraint is likely to develop.

CONCLUSIONS

This thesis provides new evidence for the acute haemodynamic benefit of cardiac resynchronisation therapy in patients with medically-refractory heart failure and a narrow QRS duration. Indeed these improvements in haemodynamic variables are comparable to those demonstrated in patients with a broad QRS duration, and suggests that current criteria for implantation of these devices may exclude a group of patients who may be expected to experience significant clinical benefit from pacing. In addition, it emphasizes the role of relief of external constraint in contributing to the increase in left ventricular stroke work, suggesting that this group of patients may be expected to benefit the most.

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APPENDIX

PUBLICATIONS ARISING FROM THIS WORK

ABTRACTS

(1) **Williams L**, Ellery S, Bleasdale R, Stegemann B, Patel K, Leyva F, Paul V, Steendijk P, and Frenneaux M. Acute haemodynamics effects of CRT in heart failure, a narrow QRS duration and no dyssynchrony. **Assoc Phys GB 2009.**

(2) **Williams L**, Ellery S, Patel K, Leyva F, Bleasdale R, Steendijk P, Paul V, and Frenneaux M. Acute Haemodynamic Effects of CRT in Heart Failure with a Narrow QRS Duration. **American College of Cardiology Scientific Sessions March 2008**.

(3) **Williams L**, Ellery S, Bleasdale R, Patel K, Leyva F, Paul V, Steendijk P, and Frenneaux M. Increased Suction Filling in Heart Failure: A Pressure Volume Loop and Echocardiographic Study. **American Heart Association Scientific Sessions November 2007.**

(4) Ellery S, **Williams L**, Bleasdale R, Stegemann B, Patel K, Leyva F, Paul V, Steendijk P, and Frenneaux M. CRT normalises Suction Filling in Heart Failure Patients. **American College of Cardiology Scientific Sessions March 2007.**

(5) **Williams L**, Ellery S, Stegemann B, Patel K, Leyva F, Paul V, and Frenneaux M. Left Ventricular Reverse Remodelling after CRT in Heart Failure with a Narrow QRS Duration. **American College of Cardiology Scientific Session March 2007.**

ORIGINAL RESEARCH PUBLICATIONS

(1) **Williams L**, Ellery S, Patel K, Leyva F, Bleasdale R, Phan T, Stegemann B, Paul V, Steendijk P, and Frenneaux M. Short-term hemodynamic effects of Cardiac Resynchronization Therapy in patients with heart failure, a narrow QRS duration, and no dysynchrony. *Circulation* 2009;120(17):1687-1694.

REVIEW ARTICLES

(1) **Williams L,** Frenneaux M. Diastolic Ventricular Interaction: Physiology to Clinical Practice. *Nature CMCP* 2006 3:368-76.

(2) Ellery S, **Williams L**, Frenneaux M. The Role of Cardiac Resynchronisation and Implantable Cardioverter-Defibrillators in Heart Failure. *Postgrad Med J* 2006;82:16-23.

(3) **Williams L**, Ellery S, and Frenneaux M. The Role of Cardiac Resynchronisation Therapy in Heart Failure. *Minerva Cardioangiol.* 2005;53(4):249-263.