Studies on the Pathophysiological Mechanisms of Hypertrophic Cardiomyopathy

A PhD Thesis

Presented to the

University of Birmingham

by

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In Partial Fulfilment

of the Requirements for the Cardiovascular Medicine PhD Degree

In the

College of Medical & Dental Sciences, University of Birmingham

2017

Studies on the Pathophysiological Mechanisms of Hypertrophic Cardiomyopathy

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Abstract

Hypertrophic cardiomyopathy (HCM) is a common inherited heart muscle disease. Symptoms (exertional breathlessness, chest pains, palpitations, syncope) occur frequently. In at least half of these patients exertional breathlessness is usually a consequence of impaired left ventricular diastolic filling. For these patients therapies are frequently ineffective. Pulmonary hypertension frequently develops acutely on exercise in such patients (due to the acute rise in left ventricular end diastolic pressure). The associated increase in right ventricular volume might be expected to stretch the surrounding pericardium. In these circumstances left ventricular filling may be impeded by external constraint from the pericardium (pericardial constraint) and from the right ventricle via the interventricular septum (diastolic ventricular interaction).

We hypothesised that deleterious diastolic ventricular interaction may be present at rest in some patients with HCM and develop on exercise in others, and that biventricular pacing may be able to relieve diastolic ventricular interaction with consequential improvement in myocardial performance. We also hypothesized that given the nature of the myocardial substrate in HCM, that biventricular pacing may affect improved contractile function through amelioration of dyssynchrony both acutely and chronically.

To test these hypotheses, we conducted initially a set of acute studies. Using gated heart pool scanning, we measured myocardial performance indices at rest, on exercise, and following application of lower body negative pressure, with and without biventricular pacing. Using echocardiography, we measured parameters of dyssynchrony at rest, with and without biventricular pacing.

In addition, we hypothesised that chronic biventricular pacing (4 months) in patients with symptomatic, exercise-limited non-obstructive HCM, would improve exercise capacity (study primary end point) and improve quality of life (study secondary end point). To test these two hypotheses, we undertook a double blind, randomised, sham-controlled, cross over study of biventricular pacing in a group of 31 patients who met the inclusion and exclusion criteria.

We demonstrate that biventricular pacing significantly increases exercise capacity (measured as peak Oxygen consumption - by 1.17ml/kg/min $p=0.032$) and significantly improves quality of life ($p=0.001$).

We found that these HCM patients had only minor left ventricular systolic dyssynchrony at rest. We report that following acute biventricular pacing, some parameters of dyssynchrony improved, but that these improvements were not sustained with chronic biventricular pacing.

Using gated heart pool scanning, we found that none of the patients had a left ventricular ejection fraction less than 50% at rest and none developed significant left ventricular systolic dysfunction on exercise. Further, we report that biventricular pacing had no effect on resting or exercise left ventricular ejection fraction or on left ventricular end systolic elastance.

We found that following right ventricle volume unloading, (when supine, at rest) using lower body negative pressure, that left ventricular end diastolic volume decreased in the majority of patients, however in a small number of patients (4) it increased, and that biventricular pacing was able to reverse this increase in left ventricular end diastolic volume in 3 of these 4 patients. In approximately half of the patients left ventricular diastolic volume increased on exercise with 'sham' pacing, but in the remainder, it fell. The latter patients had a greater degree of exercise limitation and the increase in peak Oxygen consumption associated with chronic biventricular pacing was almost exclusively confined to this group. In the group of patients in whom left

ventricular end diastolic volume decreased with exercise, biventricular pacing augmented late diastolic filling during exercise and this resulted in an increase in left ventricular end diastolic volume on exercise - resulting in stroke volume augmentation via the Starling mechanism. These effects are consistent with relief of diastolic ventricular interaction as the mechanism.

Thus, for the first time, we show that severely symptomatic patients with non-obstructive hypertrophic cardiomyopathy may benefit, subjectively and objectively, from biventricular pacing. Furthermore, we present data that argues for the first time for the amelioration of diastolic ventricular interaction, rather than mechanical resynchronisation, as the predominant mechanism of benefit following biventricular pacing in this group of patients.

Declaration and Statements

Declaration

This work has not previously been accepted in substance for any degree and is not being concurrently submitted in candidature.

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Statement 1

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Acknowledgements

I would like to thank several people, without whom this research would not have been possible.

Professor Michael Frenneaux for having immeasurable patience and giving me the opportunity to undertake this project I also thank him for his help in generating the ideas for this research and for his vision, support and guidance throughout.

Professor Janice Marshall for providing support and understanding when most required, without whose help this thesis would not have been completed.

I would like to thank Dr Peter Nightingale, for his expert statistical advice, and patient explanation.

I would like to thank Dr Khalid Abozguia, Dr Abdul Rehman Maher, Dr Ganesh Nallur Shivu, and Dr Thanh Trung Phan for their support with exercise tests, nuclear studies and all-round, excellent companionship.

I would also like to thank the British Heart Foundation and Medtronic Inc. for generously funding this research.

Statement of contribution to research

Professor Frenneaux and I conceived and designed all the studies.

Execution

I performed all of the recruitment and organisation of the appointments at the centres involved in the study. I performed the metabolic exercise tests, echocardiogram, radionuclide ventriculography studies at the University of Birmingham. Metabolic exercise test data was analysed and reported by Rebekah Weaver. Measurements of ventricular septal radius of curvature were carried out by Dr Fergus McKiddie.

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Abbreviations

AoV	Aortic valve
AV	Atrioventricular
BiV	Biventricular
CHF	Chronic Heart Failure
DBP	Diastolic Blood Pressure
DT	Deceleration Time
DVI	Diastolic Ventricular Interaction
EDV	End Diastolic Volume
EF	Ejection Fraction
ESV	End Systolic Volume
Exe	Exercise
fps	Frames Per Second
Gp1	Group 1
Gp2	Group 2
HCM	Hypertrophic Cardiomyopathy
HF	Heart Failure
HR	Heart Rate
ITT	Intention To Treat
IVS.	Intraventricular Septum
LA	Left Atrium
LAV	Left Atrial Volume
LAVI	Left Atrial Volume Index
LBNP	Lower Body Negative Pressure
LV	Left Ventricle
LVEDP	Left Ventricular End Diastolic Pressure
LVEDV	Left Ventricular End Diastolic Volume
LVEDD	Left ventricular End Diastolic Dimension
LVESV	Left ventricular End Systolic Volume
LVESD	Left ventricular End Systolic Dimension
LVEF	Left ventricle Ejection Fraction
LVOT	Left ventricular Outflow Tract
MRI	Magnetic Resonance Imaging
MLHFQ	Minnesota Living with Heart Failure
NOHCM	Non-obstructive Hypertrophic Cardiomyopathy
NYHA	New York Heart Association
PA	Pulmonary Artery
PP	Per Protocol

PFR	Peak Filling Rate
QOL	Quality of Life
RER	Respiratory Exchange Ratio
rot	rotation
rot-r	rotation rate
RR	R-R interval
Rs	Normalised Ventricular Septal Radius of Curvature
RV	Right Ventricle
RVEDP	Right Ventricular End Diastolic Pressure
RVEDV	Right Ventricular End Diastolic Volume
SAM	Systolic Anterior Motion
SBP	Systolic Blood Pressure
SCD	Sudden Cardiac Death
SD	Standard Deviation
SEM	Standard Error Mean
STE	Speckle Tracking
SV	Stroke Volume
TAPSE	Tricuspid annular plane systole excursion
TDI	Tissue Doppler Imaging
TTPF	Time to Peak Filling
VO_{2max}	Peak Oxygen Consumption
vs.	Versus

Publications resulting from projects

Abstract: Oral presentation American Heart Association, New Orleans.
Circulation. 2008;118:S_869
Biventricular Pacemaker Therapy Corrects Dyssynchrony in Non-Obstructive Hypertrophic Cardiomyopathy.

Background.
Previous studies have reported dyssynchrony using Tissue Doppler in patients with hypertrophic cardiomyopathy (HCM). In this study, we assessed dyssynchrony using Speckle tracking echocardiography (STE) in patients with non-obstructive hypertrophic cardiomyopathy *vs.* a healthy control group and in a subgroup of highly symptomatic patients evaluated the acute effects of biventricular pacing on STE and Tissue Doppler (TDI) derived measures of dyssynchrony.
Methods.
We studied 48 healthy controls (age 48 ± 18yrs, 22 males, LVEF 63 ± 5%, QRS 86 ± 7ms) and 57 patients with HCM (age 54 ± 11yrs, 38 males, LVEF 61 ± 7%, QRS 110 ± 36ms). A subgroup of 15 symptomatic patients with HCM (Peak VO_2< 60% predicted) underwent biventricular pacing (age 53 ± 12yrs, 12 males, LVEF 61 ± 7%, QRS 110 ± 32ms). Echocardiography was performed with the pacemaker off (VVI30) and on (DDDR, AV delay 90ms, LV-RV delay 0-4ms). Using STE, the standard deviation (SD) in time to peak longitudinal strain (Tε-SD), the time to peak longitudinal systolic velocity (Ts) for each of 18 left ventricular segments and the SD of this timing (Ts-SD) was derived. Using TDI dyssynchrony was assessed from the SD of Ts for the basal six segments and the maximum difference in Ts between any two basal segments (Ts-peak[basal]).

Results.
Using STE, Tε-SD (54.99 ± 33.61ms *vs.* 24.55 ± 21.18ms p< 0.001), Ts-SD (71.06 ± 32.32ms *vs.* 46.17 ± 21.50ms p< 0.001) and Ts (155.74 ± 23.14ms *vs.* 123.71 ± 11.25ms p< 0.001) were greater in HCM than in controls. Using STE, we demonstrated that biventricular pacing significantly reduced Tε-SD and Ts-SD to values similar to those observed in controls (Ts-SD p=0.13). Using TDI we demonstrated that biventricular pacing significantly reduced Ts, Ts-SD, and Ts-peak[basal]. See Table. (All values expressed as mean ± SD)
Conclusion. Cardiac resynchronisation therapy significantly reduced dyssynchrony in symptomatic patients with non-obstructive HCM as demonstrated using STE and TDI.

		Off-Pace (mean ± SD)	**On-Pace** (mean ± SD)	**P**
STE	Tε-SD (ms)	51.94 ± 26.93	37.44 ± 17.88	0.02
	Ts-SD (ms)	67.93 ± 21.15	55.05 ± 19.84	0.02
	Ts (ms)	159.68 ± 23.49	133.83 ± 24.27	0.001
TDI	Ts (ms)	195 ± 22	169 ± 32	0.003
	Ts-SD (ms)	68 ± 42	36 ± 20	0.008
	Ts-peak[basal] (ms)	151 ± 94	85 ± 50	0.006

Chapter 1

Introduction

Hypertrophic cardiomyopathy (HCM), (Figure 1.1), is the myocardial phenotypic expression of single gene mutations affecting sarcomeric components[5] (Figure 1.3), in association with environmental factors. Macroscopically observed as an abnormal thickening of the myocardium, in variable distributions, (Figure 1.2), histologically myocyte disarray with increased interstitial fibrosis is described (Figure 1.4). The functional consequences are widely varied with some patients being asymptomatic, others having severe symptoms, and others dying suddenly with or without prior symptoms (Figure 1.5). In patients who have obstruction to the outflow of blood from the left ventricle (LV) and those that develop LV systolic dysfunction, successful treatment modalities exist. However approximately a third of patients have marked limitations of exercise tolerance and experience breathlessness, in the absence of obstruction to the outflow of blood[6], and a 'normal' LV ejection fraction. This subgroup of patients has at present few medical management options, mainly beta blockers and Verapamil (Figure 1.6), with heart transplantation remaining the final recourse should symptoms of refractory heart failure develop[7]. In this subgroup of patients diastolic dysfunction[8] is thought to account for the symptoms experienced. The mechanisms involved in producing the abnormalities of diastolic function have not been clearly elucidated. This has been compounded by limitations in current non-invasive techniques of assessing diastolic function[9].

In previous work, Frenneaux et al. and others have described mechanisms involved in the genesis of diastolic dysfunction in patients with chronic heart failure, in particular diastolic ventricular interaction[4] (DVI). Because pulmonary hypertension is associated with DVI and is present in a minority of HCM patients at rest, but a substantial proportion of patients on exercise there is reason to believe that diastolic ventricular interaction may be present in patient with HCM

at rest, and develop on exercise. Further, Frenneaux et al. have shown that using pacing techniques that this mechanism may be modified[10].

Against this background, the aims of the present study were to use gated ventriculography to assess myocardial performance at rest, on exercise, and following lower body negative pressure. These measurements were made with and without BiV pacing, focussing on the presence of DVI at rest and its development on exercise, and on the effects of BiV pacing. Given that HCM exhibits increased myocyte disarray and fibrosis, this may be suitable substrate to give rise to a dyssynchronously contracting and relaxing myocardium[11]. Dyssynchronous contraction has been well established in patients with systolic heart failure, with few studies in HCM patients[12 13]. A number of studies have demonstrated improvement in parameters of mechanical dyssynchrony following BiV pacing in patients with systolic heart failure[14]. However, as far as we know, the impact of BiV pacing on dyssynchrony in HCM has not been reported. Therefore, in the present study we assessed the effect of acute and chronic BiV pacing on echocardiographic measures of dyssynchrony in patients with HCM.

Chronic BiV pacing has been well established to improve exercise tolerance, (as measured using peak Oxygen consumption) in patients with systolic heart failure[15, 16]. In order to assess the impact of chronic BiV pacing on exercise tolerance in this group of patients, we carried out a double blind, randomised, cross over trial (Figure 1.15). The primary end point was peak Oxygen consumption (VO_2max), and the secondary endpoint being quality of life (Minnesota living with heart failure questionnaire). As far as we know The trial described in this thesis is the first one to assess the effect of chronic BiV pacing on peak Oxygen consumption in patients with symptomatic limited non-obstructive hypertrophic cardiomyopathy.

Given these general aims, the remainder of this Chapter provides a detailed overview of the clinical presentation of Hypertrophic Cardiomyopathy, its underlying pathophysiology and its current clinical management. This is followed by a discussion of how its pathophysiology may overlap with the more established entity of systolic heart failure focussing in particular on the origins and measures of dyssynchrony and diastolic ventricular interaction. Finally, the treatment modality of BiV pacing is discussed and the mechanisms by which it might have beneficial effects, so providing a foundation for the hypotheses tested in the present study.

Hypertrophic Cardiomyopathy Definition

Hypertrophic Cardiomyopathy (HCM) is defined as the presence of left ventricular wall hypertrophy (LVH), in any distribution, occurring in the absence of a disease process sufficient to explain the extent of hypertrophy seen[17]. It is inherited in an autosomal dominant fashion[18]. Clinically a wall thickness of greater than or equal to 15mm is required for the diagnosis except in known gene carriers or in those with affected first degree relative in whom a maximum wall thickness of greater than 12mm is sufficient [17]. Electrocardiographic changes and deterioration in diastolic function may precede the development of visible hypertrophy[19]. There are histologically characteristic features, though none are pathognomonic. Classically, there is extensive myocyte disarray[20], with disorientation of myocytes, which vary in size and shape. In the interstitial space the amount of collagen is increased seen as fibrotic scar tissue[21]. Even in what appears macroscopically normal myocardium the content of interstitial matrix is increased. Small vessels show wall thickening with reduction of lumen[22].

Sub classification

Patients with Hypertrophic Cardiomyopathy can be further sub classified dependent on the distribution of hypertrophy[23], and presence or absence of significant obstruction, usually affecting the outflow tract[6] (LVOT) (gradient > 30mmHg)[24] and less commonly the midcavity (Figure 1.1). Virtually any distribution of hypertrophy can be consistent with a diagnosis of HCM. The commonest distribution is hypertrophy affecting predominantly the septum (asymmetric septal hypertrophy) (ASH)[25]. Patients may however exhibit other patterns including concentric LVH and apical hypertrophy (Figure 1.2).

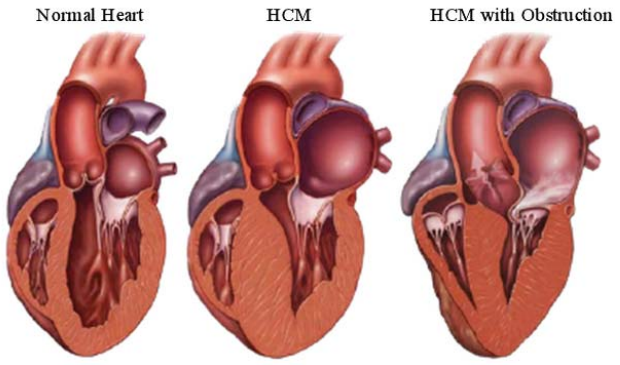

Figure 1.1 : The Hypertrophic Heart

Approximately a third of HCM patients may have significant LVOT obstruction at rest[24], a third develop a LVOT gradient on exercise, and a third have neither a resting nor an exercise induced obstruction[6]. Obstruction of the LV outflow tract may be labile, characterised by spontaneous variability on a day to day basis affected by various factors that alter LV contractility and loading. Mechanical obstruction to the outflow of blood from the LV is produced by systolic anterior displacement of either the anterior[26] or posterior leaflet, but sometimes by mid-cavity muscular apposition[27]. The presence of a LVOT gradient, whether at rest or on exertion, is important to

establish since it relates to the progressive development of heart failure symptoms[31] and cardiovascular mortality[28, 29]. Furthermore, symptoms of heart failure may be treated successfully by LV outflow tract obstruction reduction[30, 31].

Echocardiography is a relatively easy, non-invasive method of establishing the presence/absence of an out-flow tract gradient. The same technique applied immediately following exertion may demonstrate an LV outflow gradient previously not seen at rest [6].

Over time a subset of patients with HCM may progress to a 'burnt out stage' with thinning of the LV walls, dilation of the LV, and progressive systolic dysfunction[32]. Other patients may have profoundly 'restrictive' physiology, with other members of their family sometimes presenting as restrictive cardiomyopathy without significant left ventricular hypertrophy.

Natural History of Non-Obstructive Hypertrophic Cardiomyopathy

This subset of patients has been less intensively studied compared to obstructive HCM, so the natural history has been less clearly defined. Maron et al.[33] prospectively followed up 249 HCM patients with NYHA symptom class I-II, who had no LVOT obstruction at rest or on exercise, over a time course of 6 years. They report that the vast majority (≈ 90%) of patients remained asymptomatic, with an average ejection fraction of 60%. These patients had a low risk of progressive heart failure symptoms (1.6%/year) and a mortality rate comparable to the general population (0.5%/year) with infrequency of sudden cardiac death. However over 6 years, 10% of HCM patients developed progressive HF symptoms, with approximately 3% requiring heart transplantation, in contrast no patients with obstructive HCM required transplantation. Though HCM patients with obstruction have a fivefold greater risk of developing debilitating symptoms,

this group of patients has recourse to invasive obstruction relieving procedures, consequently the need for transplantation is avoided

Rowin et al.[34] reported that 1% of HCM patients (20 out of 2100), requiring transplantation for refractory HF symptoms had no LV outflow obstruction (rest or exercise) and had preserved LV systolic function. The mean age at the onset of heart failure symptoms was 35years and at time of listing for transplant 41years. Of interest mean pulmonary artery pressure was elevated at rest (31±11mmHg), with evidence of elevated LV end diastolic pressure at cardiac catheterisation, of note two patients at cardiac catheterisation had normal resting mean pulmonary artery pressure, but on exertion this increased to >30mmHg. HCM transplant candidates with reduced systolic function usually show diffuse (often transmural) LV myocardial scarring, in contrast this subgroup of 20 patients with advanced HF symptoms showed no or minimal myocardial fibrosis on histology or on MRI imaging, which would suggest perhaps a more distensible myocardium in this subset. It is of interest that almost half of these patients demonstrated a restrictive pattern of filling on echocardiography.

In summary, the vast majority of patients with NOHCM and preserved LV systolic function, have few symptoms and an excellent prognosis. Nevertheless, a small but not insignificant number develop debilitating heart failure symptoms at a relatively young age, for whom heart transplantation is currently the most effective form of therapy.

Figure 1.2 : Macroscopic Types of HCM[3]

Prevalence

Population studies have shown that HCM affects approximately 1 in 500 of the General population[35], making it the commonest inherited cardiac condition. This may represent an underestimate as it is based exclusively on phenotype positive disease, ignoring genotype positive, phenotype negative patients.

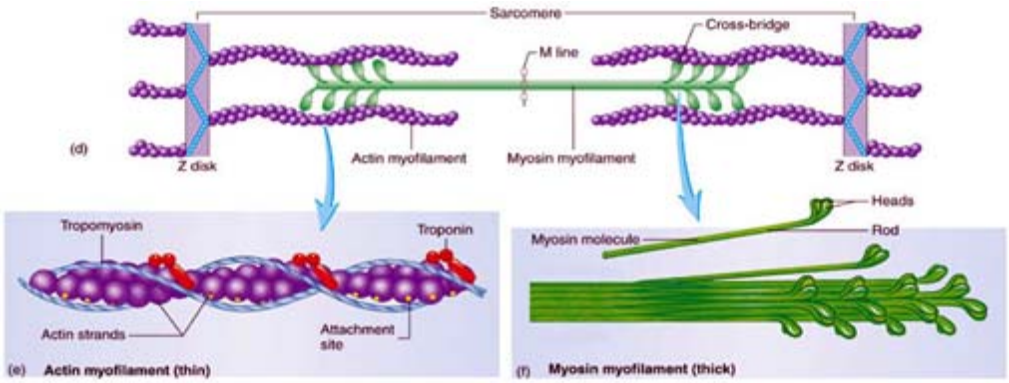

Figure 1.3 : The Sarcomere. Schematic demonstrating the components of the sarcomere. (http://people.fmarion.edu/)

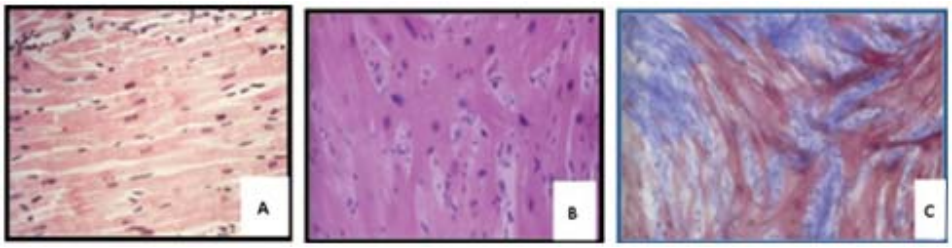

Figure 1.4 : Histology HCM. The normal histology (A) is perturbed in HCM, with marked enlargement and disarray of myocytes (B) with increased interstitial fibrosis (C)[36].

Genetics

Although sporadic cases occur, heritable HCM is a Mendelian autosomal dominant trait with variable penetrance. The vast majority of families in whom a disease-causing mutation is identified have a mutation of a gene encoding a sarcomere protein. Thus far, 434 mutations in any of 10 genes encoding sarcomeric proteins have been identified, most of which are missense mutations[1]. Three HCM causing genes have been found to account for over half patients genotyped[17]. Despite these advances all the genetic variations causing HCM have not been identified, with current genetic testing identifying a recognised disease causing mutation in approximately 50% of probands[37]. Phenotypic expression is myriad a genotype-phenotype

correlation rather poor and consistent with a interplay between modifier genes and environmental factors[38].

Clinical Presentation

Given the varied natural history of HCM (Figure 1.5), prognostication is difficult. Patients may experience few symptoms for long periods of time, with 25% of patients achieving a normal life span[39]. Patients frequently complain of breathlessness and exercise intolerance. In some the predominant cause is dynamic left ventricular outflow tract obstruction[40, 41] in a small proportion a progressive impairment of left ventricular systolic function is responsible. In at least 50% an abnormality of LV relaxation and diastolic filling is the predominant mechanism[42-44].

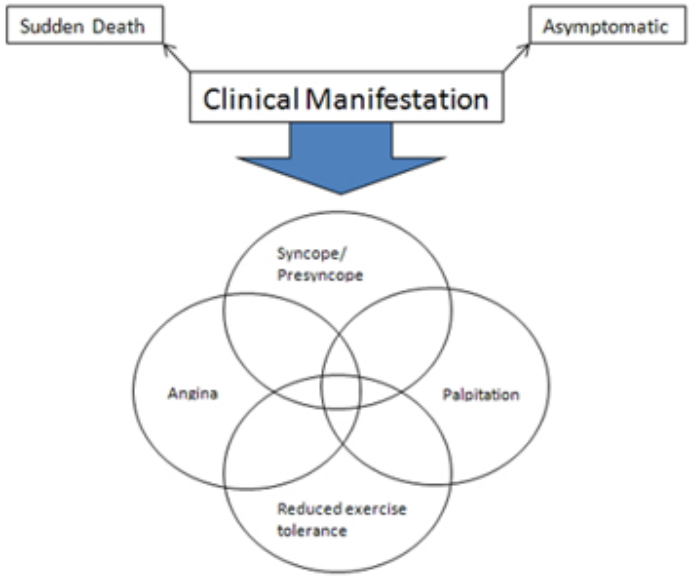

Figure 1.5 : HCM Clinical presentation

Sudden cardiac death (SCD) is the most feared complication of HCM, being the commonest cause of premature death in this condition. HCM is arguably the commonest cause of SCD in young adults although it may also occur in later life but with lower frequency[45]. Ventricular

arrhythmia has been reported as the most common cause of SCD events, using data collected from implanted cardioverter-defibrillator units[46]. It is thought that ventricular arrhythmias arise from electrically unstable myocardial substrate resulting in the sudden loss of cardiac output and death.

Patients may be risk stratified for SCD based on the presence or absence of several recognised risk factors for SCD. These include a history of unexplained syncope[47], or a family history of SCD[48], severe myocardial thickening (>30mm), significant LVOTO (>30mmHg), documented evidence of ventricular tachycardia (sustained or non-sustained) [49] and failure of the systolic blood pressure to rise by at least 25mmHg at peak exercise on stress testing[50, 51], particularly in those less than 40 years of age. Patients with the presence of two or more risk factors (annual SCD rate of 3% (95% CI 2-7%) were traditionally offered prophylactic Implantable Cardioverter Defibrillator Therapy (ICD). More recently a model for risk stratification has been developed by O'Mahoney et al.[52], has applied a more continuous weighting to risk factors for SCD, rather than a binary approach. This model has been validated as a risk prediction tool for SCD (http://doc2do.com/hcm/webHCM.html), allowing better identification of high risk patients, with avoidance of patient harm through unnecessary ICD implantation.

Exercise Intolerance in HCM: The Role of Diastolic Function

Patients with HCM are often symptomatic and complain of exercise intolerance [41, 53]. The underlying pathophysiology is multifactorial and complex. Diastolic dysfunction is one component that is traditionally cited as the cause for exercise intolerance in non-obstructive HCM[7].

Subjective effort intolerance is now widely evaluated objectively by exercise testing. Aerobic exercise, progressively increasing to the maximal tolerance is a common physiological stress that can elicit cardiovascular abnormalities not present at rest, while aiding in the

determination of the adequacy of cardiac function. As exercise is initiated there is an increase in Oxygen requirement from the body in general, but primarily from working muscle [54]. To supply these demands cardiac output is normally increased by a combination of stroke volume augmentation and increased heart rate. In health, given the skeletal muscles ability to utilize Oxygen far exceeding the capacity of the cardiovascular system to deliver Oxygen[55] [56], cardiac output becomes the limiting step in determining the bodies peak Oxygen consumption during exercise. Peak Oxygen consumption (VO_{2max}) can be measured during the performance of dynamic exercise involving a large part of total muscle mass. Cardiac output explains 70-85% of the variance in VO_{2max} with the remainder being determined by peripheral Oxygen extraction[57]. VO_{2max} is considered to be one of the best measures of cardiovascular fitness and exercise capacity[58].

In health, cardiac output can increase as much as 4-6 fold above basal levels during exercise [59]. Studies in patients with HCM have shown that the peak Oxygen consumption achieved is clearly related to peak cardiac output [42, 60]. Given that cardiac output is the product of heart rate and stroke volume, both of these variables will have an influence on VO_{2max}. This is clinically exemplified by the fact that almost 25% of HCM patients with chronotropic incompetence, have a reduced VO_{2max} and greater symptom burden[61, 62].

LV stroke volume (SV) (in the presence of competent valves) is the difference between end-diastolic (EDV), and end-systolic volumes (ESV) (SV = EDV - ESV). An increase in LV SV would mandate an increase in LV EDV and/or a reduction in LV ESV. Patients with HCM often have supranormal systolic function[63], at rest, suggesting a limited role for further reductions in ESV on exercise[42] to contribute to an increase in SV, even in health reductions in ESV on exercise are modest[64].

The volume of blood accommodated in the LV chamber during diastole is related to the functional characteristics of the LV myocardium and to filling pressures, the relative contributions of each being dynamic and interrelated throughout the course of the cardiac cycle.

On exertion, an increased HR reduces the duration of diastole[65], abbreviating the time available for LV filling, ≈0.55 seconds at 70 beats min^{-1} to ≈0.12 seconds at 195 beats min^{-1} [66]. To augment LVEDV, or even to maintain it[67], the rate of LV filling *has* to increase for a significant portion of the LV filling period [68, 69]. The acceleration of blood flow into the LV is determined by the pressure drop across the mitral valve (LA pressure -LV Pressure)[70], which in turn is determined largely by LV diastolic function and LA pressure at the time of mitral valve opening. In health, LV diastolic function is in the main a reflection of a composite of LV intrinsic stiffness and its ability to relax, with extra-myocardial elements (e.g. pericardium) having a limited influence. A rapidly relaxing ventricle (reduced tau[71]), with negligible pericardial constraint, allows for the development of an increased gradient across the MV ('suction') in diastole, without necessitating an excessive increase in LA pressure [68].

Any mechanism then, that adversely affects LV diastolic function, will have repercussions seen in LA pressures and upstream in the pulmonary vasculature, and in reduced cardiac output augmentation, manifest clinically as dyspnea and exercise intolerance.

Invasive and non-invasive techniques have been used to characterize indices of global and individual components of diastolic function, and which have then been related to exercise tolerance and symptom burden in patients with HCM.

Measuring the characteristics of individual components of myocardial mechanics during diastole, on exercise, would appear to be the most direct approach at evaluating myocardial diastolic function. This has proven difficult, perhaps not so surprising given the diastolic

myocardium experiences a laminated wave front of thinning (radially), lengthening (longitudinally and circumferentially) and un-twisting, atop a distending force, all completed in just over a tenth of a second! Nevertheless, investigators have attempted to define measures of diastolic mechanical function, in particular using echocardiography, specifically tissue doppler imaging and more recently speckle tracking.

Patients with HCM have been reported to have reduced early diastolic longitudinal velocities (e'), even prior to the development of symptoms and overt hypertrophy [72]. Early longitudinal diastolic velocity at the septal mitral annulus has been inversely related to tau (time constant of isovolumic relaxation)[73] perhaps a reflection perhaps of reduced relaxation, and elasticity. However, the reduction in e' has been inconsistently related to a reduction in exercise tolerance and symptoms [8, 74-76].

Kato et al. [77] using TDI, reported a marked reduction in early diastolic longitudinal strain rate in patients with HCM, to less than half, compared to controls and patients with LVH secondary to hypertension. A strong correlation was reported by Mizukoshi et al. [78] between early diastolic longitudinal strain rate during exercise and peak Oxygen consumption (Figure 1.16). Of important note, no correlation was found at rest.

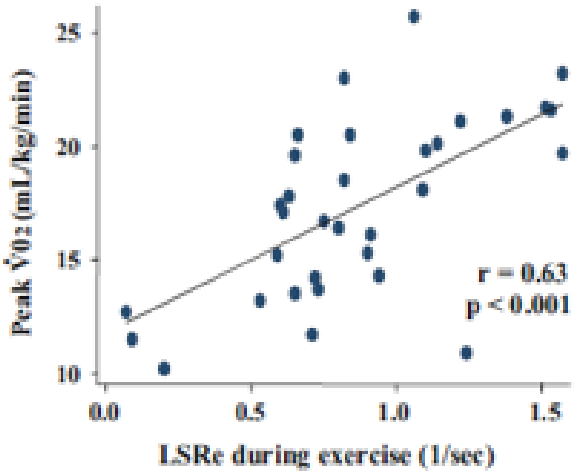

Figure 1.6 : Association between peak VO_{2max} versus early diastolic longitudinal strain rate (LSRe) during exercise. ($r = 0.63$, $p<0.001$) [78]

Untwist, a relatively load independent metric of diastolic function[79], increases during exercise in healthy individuals[80]. The peak rate of untwist has been shown to be temporally and sequentially related to the development of the peak intraventricular pressure gradient[80]. Of important clinical relevance Rovner et al.[81], observed a direct relationship between intraventricular pressure gradients("suction") to peak Oxygen consumption.

In patients with HCM untwist has been shown to be delayed [82] [83] when compared to healthy volunteers, and to correlate, though weakly, ($r=0.36$ $p=0.006$) with peak Oxygen consumptions[83]. The underlying cause of altered twist/untwist in HCM may relate to regional abnormalities of systolic and diastolic function. Knudtson et al. [84] demonstrating degradation in untwisting function following myocardial ischemia.

Given the intrinsic limits of the information obtained from examining individual components of myocardial function, investigators have assessed markers of global diastolic function.

Using radionuclide ventriculography Bonow et al.[85] demonstrated that the LV peak filling rate (PFR) in patients with HCM at rest was increased by Verapamil, and that this increase correlated, reversibly, with an improvement in exercise capacity. Though they observed a reduction in time to peak filling (TTPF) acutely following Verapamil (ΔTTPF 23ms $p<0.001$), this appears not sustained at longer term follow-up (ΔTTPF 5ms p=ns) however PFR remained increased. These findings suggest that improved diastolic function is related to an increase in exercise capacity. Frenneaux et al.[86] correlated exercise capacity in patients with HCM, measured using peak Oxygen consumption, with peak cardiac output, but observed no relation of peak exercise capacity with resting peak filling rate. Chikamori et al.[60] reported that patients with NOHCM with marked exercise limitation (VO_{2max} <70% predicted), had a reduced LV PFR, however they observed that the time to LV PFR (TTPF) did not discriminate between patient with and without marked exercise limitation. Though it needs pointing out that, studies by Chikamori et al. were carried out at rest.

Lele et al.[42] demonstrated that compared to healthy controls, resting LV PFR was modestly lower (p=ns) in patients with HCM, but on exercise this difference was significantly more pronounced (p=0.001). The authors observed a strong inverse relationship between TTPF and VO_{2max} in HCM patients. A prolonged TTPF was noted both at rest and on exercise in patients compared to healthy controls. On exercise, both healthy controls and HCM patients experienced a reduction in the TTPF, however in health this was more than 50% but just over 33% in patients. Furthermore, in patients there was a loss of the normal inverse relation between HR and TTPF[87], with some patients experiencing a paradoxical prolongation of TTPF on exercise.

These finding suggest that for the LV to fill effectively during diastole on exercise, the LV has not only to have a greater filling rate, but for a duration sufficient to increase LVEDV. Not only does

this not happen in HCM, with evidence suggesting baseline dysfunction, but diastolic function may deteriorate further on exercise.

Given the ease with which LV filling velocity may be measured non-invasively using echocardiography, at first sight it would appear to have the potential to be a readily available index of global diastolic function. Though LV filling velocities have been demonstrated to be reduced at rest, using standard doppler, in HCM patients compared to healthy volunteers[88], this was not related to exercise capacity[89]. The variance of LV filling velocity is dependent on LV loading conditions[70], making it an unreliable indicator of LV myocardial function during diastole.

Left atrial volume has been suggested as a marker of the chronicity and severity of global LV diastolic dysfunction[90]. An increased LA size reflects the cumulative effect of LV filling pressure over time. Nishimura et al.[91] demonstrated that increasing LA pressure positively correlated with doppler evidence of diastolic dysfunction, with Matsuda et al.[92] showing that as diastolic function deteriorates, LA volume increases. Kjaergaard et al.[93], using echocardiography to measure LA volumes in patients with HCM, observed an inverse correlation with peak Oxygen consumption. Though the correlation was weak ($r= -0.2$ $p=0.06$), on multivariate linear analysis LA volume was an independent predictor of exercise capacity in patients with HCM.

The cause of diastolic dysfunction in HCM is likely multifactorial. Passive left ventricular stiffness is probably increased by hypertrophy, myocyte disarray, and interstitial fibrosis, compounded by microvascular ischemia[94]. However, Abozguia et al. have shown that the abnormal LV relaxation response to exercise is related to impaired cardiac energetics. Both were corrected by the metabolic modulator Perhexiline, which resulted in an increase in peak Oxygen consumption[95].

In summary, measuring diastolic function, particularly on exercise, has proven difficult, with many indices of diastolic function influenced by loading conditions, making interpretation difficult. However, though limited, there is direct and indirect evidence that suggests that diastolic function is impaired in patients with HCM, with consequential adverse effect on exercise tolerance and symptom status.

Symptom Management

Pharmacotherapy

HCM with significant obstruction is commonly treated with Beta-blockers +/- Disopyramide[17] symptomatic non-obstructive HCM is often first managed with calcium channel blockers. Beta blockers lower the heart rate, prolonging diastole with increased passive ventricular filling[96, 97]. However, beta blockers also slow the rate of LV active relaxation which may offset the beneficial effects of a slower heart rate[98]. The negative inotropic properties of beta blockers may lessen myocardial Oxygen demand and decrease the outflow gradient particularly during exercise[99] and potentially mitigate against arrhythmia[100]. Disopyramide, a sodium channel blocker, has also been used in patients with severe refractory symptoms in obstructive HCM, the reduction in the obstruction being due to its negatively inotropic properties[101], and improved diastolic function being demonstrated[102]. However due to Disopyramides' anticholinergic properties, and concern regarding potentially enhanced conduction through the AV node, it is often combined with a small dose of beta blocker.

Calcium channel blockers can be a therapeutic option, usually when beta blocker therapy is contraindicated, with Verapamil being the first in its class to be used [63, 103]. It has been used for both obstructive and non-obstructive cardiomyopathy, particularly in those with chest pain[104] in

addition to exercise limitation. Its strongly negatively chronotropic and inotropic properties improving ventricular relaxation, and ventricular filling, which probably have a beneficial effect on the myocardial Oxygen supply-demand ratio[105, 106]. However, concern has been raised over deaths linked to Verapamil use in patients with severely obstructive HCM, who had severe symptoms (orthopnoea, paroxysmal nocturnal dyspnoea) with elevated pulmonary artery pressures.[107] Hence, some clinicians advocate the use of Disopyramide combined with beta blocker therapy in such patients[108].

The majority of patients with non-obstructive HCM do not develop symptoms of heart failure[33]. A small subset, 10%, may develop exertional dyspnoea (with persevered systolic function)[33]. In these patients management strategies, have been limited to beta blockers and calcium channel blockers, and diuretics for several decades [85, 109, 110]. Beta-blocking drugs are recommended first line in patients who can tolerate them[47], dose titration guided by heart rate, target heart rate of 60-65 beats per minute[110]. Verapamil[63] is the calcium channel blocker that is recommended in patients with side-effects or with contraindications to beta-blockers[110]. If symptoms of heart failure persist despite rate limiting drugs, then diuretic therapy may be added[109]. More recently Abozguia et al.[95] have demonstrated the effectiveness of the metabolic manipulator Perhexiline in improving exercise tolerance and symptom, in this group of patients. A small but significant proportion of patients with NOHCM develop symptoms of heart failure refractory to medical management despite normal systolic function. For this group of patients heart transplantation currently is the most effective form of therapy[34].

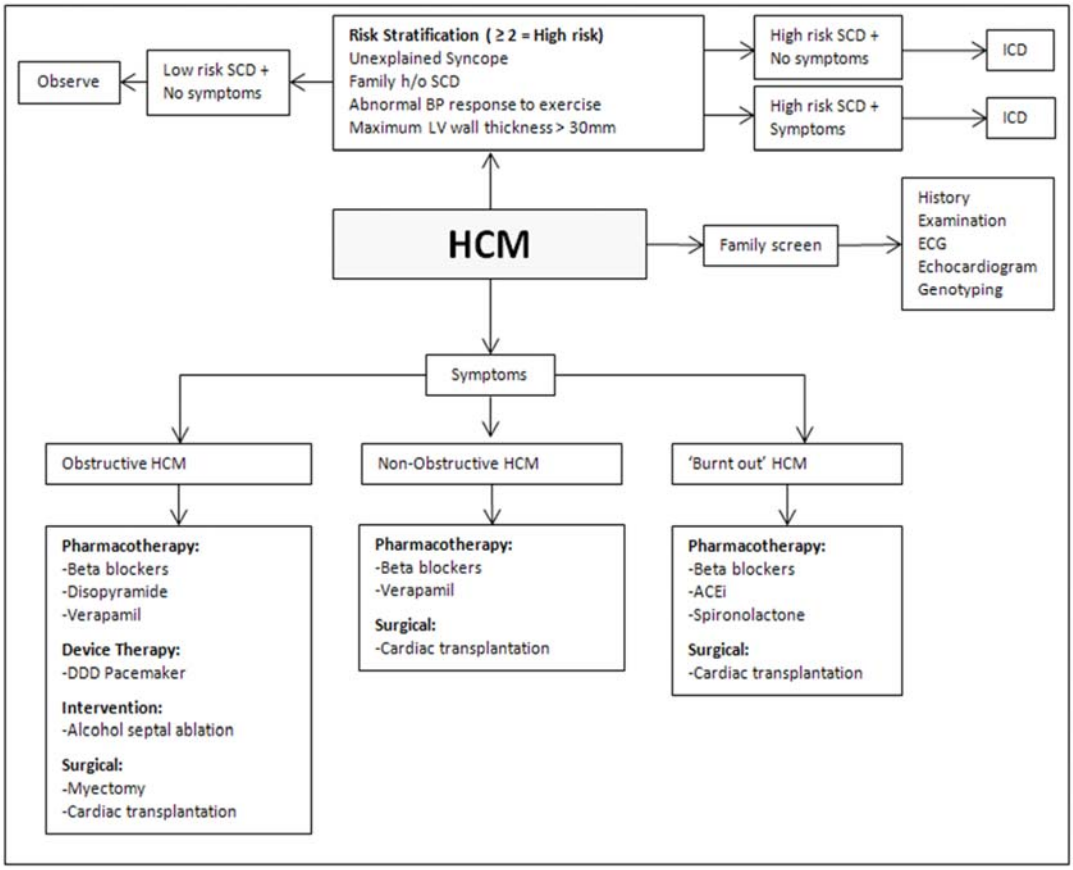

Figure 1.7 : A simplified flow chart detailing the management of HCM following diagnosis.

Device therapy

It was chance clinical observations in the 1960s and 1970s that suggested a role for ventricular pacing in patients with obstructive HCM. Investigators initially presented case reports, and small case series of ventricular pacing diminishing LVOT gradients in patients with obstructive HCM. [111-113]

In 1975 Johnson & Daily,[114] published a case report in which they described the co-incidental abolition of the LV outflow tract gradient in a 71 year old man with HCM requiring atrioventricular pacing for high grade AV block. Several observations they made are particularly

noteworthy and pertinent today. The authors report that elimination of the outflow tract gradient was only observed when atrial contraction preceded ventricular pacing (Figure 1.7), and when atrial contraction preceded a QRS complex there was associated increase in LV end diastolic dimension. Furthermore, the patient was haemodynamically intolerant of fixed rate ventricular pacing necessitating that he receives AV sequential pacing (A-V delay 175ms). These features suggest the importance of increasing LVEDV as mechanism of LVOT gradient reduction, and maintaining haemodynamic stability. Permanent pacing was delivered via right atrial and *left* ventricular epicardial (via sternotomy) electrodes. The authors state that the patient convalesced satisfactorily.

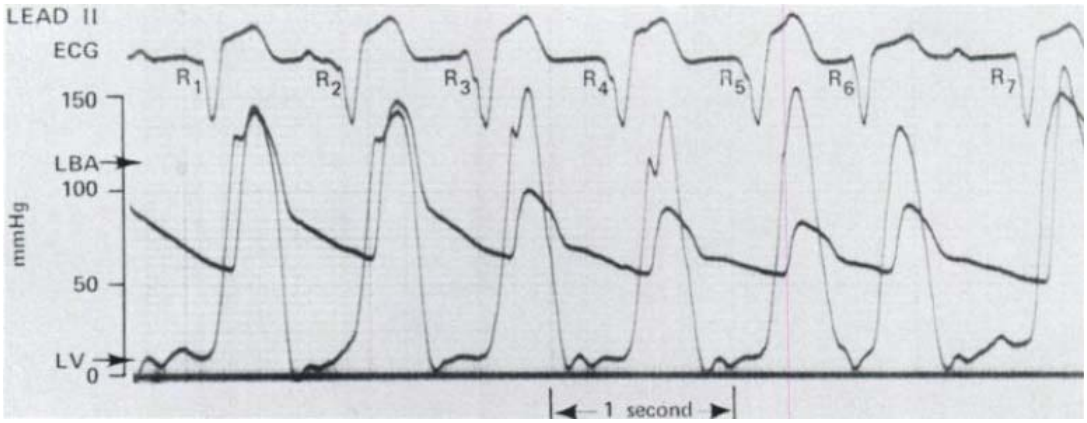

Figure 1.8 : Ventricular pacing HOCM. Left ventricular and left brachial artery pressures recorded during ventricular pacing. Beats preceded by a P wave (R1, R2, R7) have no systolic gradient. [114]

Ventricular pacing was used successfully by the original investigators to reduce LV outflow tract gradient, but compromised LV stroke volume and systolic pressures [111, 112]. A subsequent small case series, using atrioventricular sequential pacing, demonstrated successful reduction in LV outflow gradient and importantly the preservation of stroke volume [115]. The mechanism of improvement was not clear, the authors suggested that the altered sequence of ventricular activation

caused an enlargement of the LVOT (similar to the understanding we have today). The therapeutic potential of AV sequential pacing was highlighted in a case series by McDonald et al., who reported improvement in exercise tolerance in 9 out of 11 patients implanted.[116], though no mention is made on the impact of pacing on LVOT gradients in these patients.

These initial reports of amelioration of underlying pathophysiology, and symptomatic benefit of AV sequential pacing were encouraging. In 1992 Jeanrenaud et al. [117] published a small prospective non-randomised study which evaluated the acute and chronic (over 3years) effects of AV sequential pacing on the symptom status and haemodynamics of 13 patients with severely symptom limited obstructive HCM. The investigators reported an acute reduction in LVOT gradient of greater than 40% (with no loss of cardiac output), and over a period of 3 years symptomatic improvement. The paced AV interval reported as the key determinant for LVOT gradient reduction. This both needed to be long enough to allow optimum filling of the LV and short enough to preserve apical pre-excitation. The authors suggested that RV apical excitation altered the ventricular pattern of contraction such that septal contraction was attenuated, delaying the onset of the mitral leaflet-septal contact mechanism of gradient generation during systole [40].

Following the report by Jeanrenaud et al.[117] a number of investigators [118-122] reported non-randomised prospective cohort studies, suggestive of therapeutic benefit from AV sequential pacing with an associated reduction in LVOT gradients.

Fananapazir et al.[119] initially reported a non-randomised, non-blind, short term (3 months) study, examining the role of AV sequential pacing in 44 patients with obstructive HCM and severe symptoms (NYHA III-IV). Impressively, subjective symptomatic benefit was reported in all 44 patients, and a substantial improvement in peak Oxygen consumption of 2ml/kg/min ($p<0.005$). LVOT gradient was reduced, acutely, by almost 60% together with an increase in systemic arterial

pressures. Of further interest, when AV sequential pacing was discontinued following 3 months of pacing, the reduction in LVOT gradient persisted. The authors suggest this as evidence for remodelling.

Two years later the same group of investigators [120] conducted a chronic (over 2 years) non-randomised, non-blind, prospective study investigating the effect AV sequential pacing on 84 patients with symptom limited (mean NYHA class 3.2) obstructive HCM (mean gradient 96mmHg). Symptom reduction was again impressive, reported in almost 90% of patients, by the end of follow-up over a third of the original cohort required no pharmacotherapy. The authors reported a mean reduction in LVOT gradient of 60mmHg with complete elimination in 50% of patients. The severity of mitral valve SAM was reduced as was mitral regurgitation, with no reduction in cardiac output. Of particular clinical relevance was their observation of regression in LV wall thickness, consistent with earlier reports[123]. A statistically significant increase in LV end systolic dimension was reported (≈1.5mm, no change in LVEDD), though small, this would have a particular clinical significance if put in the context of a thinning LV wall. However, the authors point out that wall thinning was segmental, and there was no correlation with reduction in LVOT obstruction. This is reassuring, as the only other time when the wall thickness regresses in HCM is the end-stage phase, which preludes to transplantation. Of interest this reduction in wall thickness has not been reported following reduction in LVOT gradient following myectomy or septal ablation.

These initial pilot cohort studies made a powerful argument for the role of AV sequential pacing in symptomatic obstructive HCM. Nevertheless, it was noted that they were all non-randomised, non-blind, uncontrolled, prospective studies, with inherent shortcomings.

Investigators subsequently conducted randomized crossover trials focusing on symptom reduction, improvement in exercise tolerance and relief of outflow obstruction.

In 1997 Kappenberger et al.[121] reported the outcomes of a short-term, randomized, double blind, cross-over study. This group evaluated the effects of 3 months of AV sequential pacing in 83 patients (mean age 53years) with obstructive HCM, who were symptom limited (NYHA II-III), with objective evidence of reduced exercise tolerance ($VO_{2max} \leq 85\%$). All patients experienced 3 months of AV sequential RV pacing and 3 months of sham pacing, in random order. No washout period was defined. The authors reported that following AV sequential pacing, on average a 1 class improvement in NYHA grading of symptoms was seen, but with no change in exercise tolerance. A marked (50%) reduction in LVOT gradient was observed, reassuringly no change in ejection fraction was reported. Kappenberg et al.[121] reported that 20 patients experienced symptomatic benefit even during sham pacing, suggestive of a possible placebo effect. Of interest, they found no correlation between the acute reduction in LVOT gradient and reported reduction in symptoms, suggesting underlying mechanisms of symptom improvement following pacing, [124] [125] [126] other than LVOT gradient reduction.

Nishimura et al. [127] conducted a smaller (21 patients), short term, double-blind, randomized, cross-over study to evaluate the effect of AV sequential pacing in patients with obstructive (LVOT gradient>50mmHg) HCM who were severely symptomatic (NYHA III-IV) and exercise limited (meanVO_{2max} 19.4ml/kg/min. Patients experienced a 3-month duration of AV sequential pacing and sham pacing, in random order, with no washout period. Using temporary pacing studies at cardiac catheterisation, the AV interval (mean 70ms) to be programmed for chronic pacing was determined as the interval that allowed, at rest at least, the maximum reduction in LVOT gradient without compromising aortic pressure (as described by Jeanrenaud et al.[117]). The authors reported

that patient symptoms were significantly reduced following pacemaker implantation regardless of pacing mode (42% of patients reported symptom improvement during sham pacing), but no significant difference in symptom reports when comparing the periods of sham pacing and AV sequential pacing. Theses finding are strongly suggestive of a placebo component to the improvement in patient symptom experience. Similarly, neither exercise duration nor peak Oxygen consumption was significantly different between AV sequential pacing and sham pacing. LVOT gradient was reported as reduced, by 30%. Nonetheless the residual gradient was still substantial (55mmHg), meeting the criterion for surgical myectomy. Though baseline LVOT gradient was greater in those patients who experienced symptom improvement, there was no correlation between reduction in LVOT gradient (acute pacing) and symptom improvement. Analyses of those patients that experienced AV sequential pacing first, because of concerns regarding a possible carry-over effect, again revealed no improvement in of symptom, exercise tolerance or LVOT gradient reduction.

Maron et al.[128] Conducted a short-term (3month), randomized, cross-over study assessing the impact of AV sequential pacing in 48 patients with obstructive HCM. Patients were severely symptomatic NYHA III-IV (≈80% of patients), exercise limited (VO_{2max} 16.2±5ml/kg/min), and had a minimum peak resting LVOT gradient of ≥ 50mmHg. The AV delay (85±35ms) was determined during temporary pacing at cardiac catheterisation, similar to Jeanrenaud et al[117]. The authors report no difference in symptoms, or in exercise tolerance (treadmill exercise time and VO_{2max}) between AV sequential pacing and sham pacing. Although there was no washout period designed into the study, the results remain unchanged whether patients experienced AV sequential or sham pacing first. Of interest, patients reported a significant reduction in symptoms ($p<0.001$)

following pacemaker insertion compared to baseline, regardless of whether they were actively or sham paced, again suggestive of a placebo component to the benefit seen.

Maron et al.[128] report that AV sequential pacing was associated with an average reduction in the LVOT gradient of 40%, comparable to Kappenberger et al. [121](50%), but modest when compared to Fananazapir et al.[120] (60%), however over a third of patients experienced minimal to no change in LVOT gradient. Of particular note, no correlation was identified between a reduction in LVOT gradient, and exercise tolerance ($r = -0.08$) or change in symptoms ($r = 0.14$). A subgroup analysis suggested 6 patients experienced a non-placebo reduction in symptoms and improvement in exercise capacity following AV sequential pacing, of note all these patients were greater than 65years old.

The initial findings in support of the beneficial effects on symptoms and exercise tolerance for AV sequential pacing were generated for the most part by non-randomized, uncontrolled, cohort studies. These findings have not been borne out in subsequent randomized, cross-over, studies which have suggested a significant placebo component to the symptomatic benefit seen. Unrelated to changes in the underlying pathophysiology, except possibly in a subgroup of elderly patients.

Nevertheless, the magnitudes of reduction observed in resting LVOT gradient, following AV sequential pacing, has been statistically significant, with no placebo effect being reported. However, the clinical significance of this observation is questioned in light of no relationship between resting LVOT gradient reduction and symptom improvement.

At present sequential atrio-ventricular sequential pacing has been given a class IIb indication[129] in patients with obstructive HCM who otherwise have a contraindication to septal alcohol ablation or septal myectomy.

Percutaneous alcohol septal ablation

In patients with obstructive HCM with severe symptoms despite maximal medical therapy, an intracoronary injection of 1-4ml of alcohol may be given into a suitable septal perforator artery with the aim of producing a localised infarct in that area of myocardium with consequent reduction in septal thickness and resultant increase in LV outflow tract area[31, 130]. However, concerns have been raised about the long-term sequelae of an alcohol-induced myocardial infarction and associated scarring. In particular, the possibility of the resultant scar tissue to behave as a substrate for potentially lethal arrhythmia[131 132, 133].

Surgical myectomy

This is the gold standard method with which to reduce left ventricular outflow tract obstruction in severely symptomatic patients who prove resistant to pharmacotherapy[134, 135]. This procedure is associated with a substantial immediate and permanent reduction in the obstruction to outflow reported in the vast majority of patients[136]. As a consequence, excellent long-term symptomatic outcomes have been reported[137]. In contrast to alcohol septal ablation surgical myectomy has not been shown to cause intra-myocardial scarring[138]. The risks associated with surgery considered to be very low and in some of the most experienced centres mortality rates approach zero[139].This is usually the final recourse in patients with obstructive HCM with drug refractory symptoms.

Dyssynchrony

Dyssynchrony in Hypertrophic Cardiomyopathy

Several studies have reported that HCM is characterised by dyssynchronous contraction and relaxation[11, 140-143] which is presumably due to the patchy nature of both myocyte disarray and fibrosis, and possibly due to ischemia. Maron et al. found no correlation between the severity of myocardial thickening and extent of myofiber disarray on histological examination[144] suggesting that even myocardium that looks macroscopically normal may exhibit abnormal contractile patterns.

In the early 1990s Betocchi et al. using biplane ventriculography was able to assess regional systolic and diastolic asynchrony in 22 patients with hypertrophic cardiomyopathy[11] of whom 12 had significant LVOT obstruction. This method was used to create 12 sectors of the LV from which were derived time-volume curves. Systolic and diastolic dyssynchrony indices were derived from the standard deviation of the time taken for each sector from end-diastole to end-systole or from the time to peak filling rate for each sector. This method is similar to the more contemporaneous method of deriving the Yu index for quantifying ventricular synchrony (SD of time to peak systolic velocity for 12 segments of the LV). Betocchi et al.[11] found systolic dyssynchrony in 50% of patients, but diastolic dyssynchrony in only 23% (5 patients). This is more prevalent than that reported in heart failure with a preserved ejection fraction (35-40%)[145], but not quite as common as that seen in systolic heart failure with broad QRS (60-90%)[146]. Rather unfortunately, Betocchi et al. do not comment on ECG QRS durations in their cohort of patients.

Bonow et al.[147] reported on diastolic dyssynchrony using radionuclide ventriculography in HCM patients. Compared to healthy volunteers they found a greater regional variation in time to peak filling. Furthermore, they found that Verapamil was able to smooth out this temporal variation

in diastolic function within the left ventricle (i.e. reducing diastolic dyssynchrony), with an attendant reduction in time to peak filling (TTPF), suggesting a mechanism for improvement in global diastolic function.

Using contemporary Tissue Doppler Imaging (TDI) techniques both intra- and interventricular dyssynchrony has been reported in patients with HCM despite normal QRS duration on surface ECG[148]. Perhaps unsurprisingly, a direct positive correlation between systolic dyssynchrony and wall thickness (r=0.69) was reported but, counterintuitively a positive correlation with LVOT gradient(r=0.51) was observed (In contrast to diastolic dyssynchrony which was found to be inversely related to LVOT obstruction[11]). Clinically important, the presence of systolic dyssynchrony was found to be predictive of ventricular arrhythmia and sudden cardiac death [148, 149].

Echocardiographic Speckle tracking image analysis (STE) has suggested that the dyssynchrony seen in HCM may be more than just a function of hypertrophy alone[12], consistent with the histological findings described by Maron et al.[144]. Using STE Nagakura et al. assessed 20 patients with non-obstructive HCM with narrow complex QRS[12]. Using an 18 segment model of the LV and they derived a global dyssynchrony index from the SD of time to peak strain for all 18 segments. This is similar to the Yu index, but theoretically at least appears more robust as it overcomes the shortcomings of tissue Doppler-derived longitudinal velocities and also includes the apex. They demonstrated that, as perhaps anticipated, patients with HCM had a greater degree of systolic dyssynchrony compared to controls but more interestingly that patients with hypertensive hypertrophy had no significant difference in dyssynchrony compared to age-matched healthy controls.

Using Magnetic Resonance Imaging (MRI), Schwammenthal et al.[150] demonstrated that there were marked differences in contraction time between hypertrophied and non-hypertrophied segments of myocardium in patients with obstructive HCM, with hypertrophied segments ending contraction early in systole.

In summary, mechanical dyssynchrony has been identified in HCM by a number of investigators, with multiple modalities despite a narrow QRS duration of the surface electrocardiograph. This has been linked to global diastolic dysfunction, LV outflow tract obstruction and ventricular arrhythmia, and importantly that its amelioration with Verapamil was linked to improved global diastolic function.

Dyssynchrony in Narrow QRS Heart Failure

A QRS duration <120ms on the surface ECG suggests electrical synchrony, and intuitively might imply mechanical synchrony. This is of particular relevance to the current study, because the HCM patients we studied had a mean QRS duration of 98.82±4.05ms. However significant mechanical dyssynchrony has been shown to be present in patients with systolic heart failure despite a narrow QRS (<120ms) complex on the surface ECG by a number of investigators[151-154]. Ghio et al.[152], examined 61 patients with systolic heart failure with a narrow QRS (<120ms) using TDI. They reported that intra-ventricular dyssynchrony was present in 29.5% of these patients despite a narrow QRS complex, and its presence an independent predictor of morbidity and all-cause mortality. The investigators observed a correlation between the extent of systolic mechanical dyssynchrony and duration of the surface QRS complex, though this was weak(r=0.27).

Yu et al.[153] studied 71 systolic heart failure (EF<50%) patients with narrow QRS (<120ms), using TDI (Ts-SD) to assess for both systolic and diastolic dyssynchrony. They

observed a greater prevalence of systolic dyssynchrony, (Ts-SD +2 SD of normal controls) in 43% of patients, compared to Ghio et al. (29.5%), and diastolic dyssynchrony (T_e-SD +2 SD of normal controls) in 43% of these patients.

Shin et al.[155] assessed 381 (340 with QRS<120ms) patients with significant LV systolic dysfunction following myocardial infarction. Using STE, this group measured the dispersion of time to peak velocity and strain as indices of dyssynchrony. They report that the pattern of ventricular contraction (dyssynchronous contraction) was a predictor of death or heart failure independent of overall ventricular function and of regional wall motion abnormalities. Of particular note, only 7% of the patients with the greatest degree of dyssynchrony studied by Shin et al. had a prolonged QRS interval, emphasising the poor sensitivity of the surface ECG in detecting clinically significant cardiac dysfunction.

The poor correlation of mechanical dyssynchrony with QRS duration may perhaps be due to the insensitivity of a surface electrocardiogram to represent electrical delay in all areas of the myocardium. Notwithstanding this, in the presence of an intact His Purkinje network (narrow QRS) conceptualizing the origin of mechanical dyssynchrony is difficult. In myocardium, isolated from failing human hearts, alteration in calcium handing with disturbances in excitation contraction coupling have been demonstrated. These changes may partly explain the observation of mechanical dyssynchrony despite 'normal' electrical conduction as measured by a surface ECG[156, 157]. It may be that there is no significant impairment of electrical conduction, and so a narrow QRS complex, but despite this there is significant mechanical delay due to changes such as interstitial fibrosis, hypertrophy[158, 159], or due to changes at the subcellular level[160]. Similarly, it is conceivable that the Purkinje network could be affected predominantly in its terminal portions, at the Purkinje myocyte

junction in limited areas of myocardium, so as to significantly alter mechanical activation sequence, without having a significant effect on the surface ECG recordings.

Echocardiographic measures of dyssynchrony

Three broad groups of mechanical dyssynchrony have been described i) Intraventricular dyssynchrony ii) Interventricular dyssynchrony and iii) Atrioventricular dyssynchrony.

i) Intraventricular Dyssynchrony

Tissue Doppler Imaging

Tissue Doppler imaging (TDI) can be used to measure regional longitudinal velocities of the myocardium. Regional velocities can be related to a common fixed point in time, usually the onset of electrical activity (surface ECG derived QRS complex). This technique has been used extensively to derive indices to quantify clinically significant mechanical dyssynchrony[14, 161-172]. The advantage of color coded TDI and post processing, is that it allows simultaneous measurement of velocities in multiple segments of the same cardiac cycle, which diminishes variation in measurement due to differences in heart rate, respiration and loading conditions. The disadvantage is that it is angle of insonation dependent and unable to distinguish active from passive translational or tethering generated myocardial velocity.

Using color coded-TDI initially, simple models looking at the differences in time to peak velocity in two basal segments, the basal-septal and basal-lateral wall were developed[163]. A more comprehensive model of the LV was developed by Yu et al.[173]. This group measured time to peak, longitudinal systolic velocity in twelve segments of the LV, obtained from the apical window 4 chamber, 3 chamber and 2 chamber views, basal and mid segments. A global dyssynchrony index was derived from the standard deviation of these 12 time intervals (Ts-SD Yu Index). A Yu index

of more than 31.4ms was shown to be predictive of reverse remodelling after CRT[173]. The Yu index correlated better with reverse remodelling than any of the other TDI-derived indexes. Recognising this, The American Society of Echocardiography suggests measuring opposing wall delay, using either apical 4-chamber or apical Long-axis views (cut off 65ms) or deriving the Yu index as measures of dyssynchrony using color coded TDI[174].

Speckle Tracking

This is an angle of insonation independent, non-doppler technique (thereby overcoming the limitation of TDI), which utilizes information from 2D grey scale B-mode images to assess regional myocardial mechanics. This method tracks the displacement of unique speckle footprints through successive digitally stored 2d B-mode images[175, 176]. The distance between the speckles is measured as a function of time, from which parameters of myocardial velocity and deformation including strain, strain rate and rotational velocity can be derived[177 178]. Radial, circumferential and longitudinal strain can be easily measured in all segments and be temporally related to the QRS complex. Good quality 2d B-mode images are required for adequate tracking of the speckles, however despite good quality images, tracking may be limited by out of plane motion, and lateral resolution in the far field and image drop out.

A number of indices of dyssynchrony have been derived using STE[178-180]. One of the more promising (ability to predict response to BiV pacing) has used STE to measure the time to peak radial strain for each of six myocardial segments at the mid left ventricular level, using the short axis view at the papillary level. A time interval of greater than 130ms between the first and last segment reaching peak systolic radial strain was found to be predictive of improvement in systolic function following Biventricular pacing[178-180]. The American Society of Echocardiography

suggests using STE to quantify LV radial dyssynchrony, with a cut-off of ≥ 130ms being suggested as indicative of clinically significant dyssynchrony[174].

ii) Interventricular dyssynchrony

Interventricular mechanical dyssynchrony can be defined as the delay in time between the onset of blood being ejected from the right and left ventricles. This can be measured using pulsed blood flow doppler traces obtained from the right and left ventricular outflow tracts, using the onset of the QRS complex as a common temporal reference point. The difference between these intervals (Qp-Qs) is taken as a measure of interventricular dyssynchrony[152, 181, 182]. A delay of > 44ms was found to be an independent predictor of response to CRT therapy[181].

The technique of TDI has been applied to quantify interventricular dyssynchrony[181 14, 167, 183]. The time delay between the basal RV wall and basal lateral LV wall attaining peak systolic velocities has been used as a measure of interventricular dyssynchrony (Ts LV-RV).

iii) Atrioventricular dyssynchrony

A LV filling time of < 40% of the cardiac cycle (R-R interval) is suggestive of atrioventricular dyssynchrony[184]. Ventricular filling time can be obtained using echocardiography, from the transmitral blood flow Doppler trace. Filling time may be reduced because of intraventricular dyssynchrony with a resultant increase in isovolumic time periods during the cardiac cycle (R-R interval). A reduction in effective filling time may be seen in patients with a prolonged PR interval which results in sufficient decay in the atrioventricular filling gradient to allow consequential backflow of blood into the atrium during diastole (pre-systolic mitral regurgitation), this phenomenon may be further exacerbated in the presence of elevated end

diastolic pressures. Reducing the PR interval by RV pacing to any value below physiological has been shown to reduce pre-systolic mitral regurgitation, and thus, prolong effective filling time[185].

Hypertrophic Cardiomyopathy: Twisting, Untwisting and Strain

The contraction of obliquely-oriented, helically-arranged left ventricular myocardial fibers, from a right hand helix in the subendocardium, through to a left-hand helix in the subepicardium, results in a 'wringing' motion responsible for left ventricular twist seen during systole[186]. During the cardiac cycle, when viewed from the apex, counterclockwise twist develops during the systolic period, whereas the clockwise recoil of untwisting occurs during diastole, largely during the period of isovolumic relaxation[187 188]. This 'twist', plays an important role in left ventricular ejection and in the storage of elastic potential energy at the end of the systolic period. Studies have shown that some of this elastic energy may be stored during systole in a giant spring-like molecule found in the sarcomere, Titin (3-3.7MDa). The abrupt release of this elastic energy contributes to restoring forces[189, 190], manifesting as the rapid untwisting of the LV seen during the diastolic isovolumic relaxation period, with a resultant suction effect[191] enhancing left ventricular filling[192, 193]. Both twist and untwist of the left ventricle has been reported as being altered in HCM. Twist has been reported as increased[80, 194 147] and diastolic untwist as delayed[83, 195, 196]. The significant contribution of ventricular untwisting to diastolic function has been demonstrated[197, 198]. Speckle tracking (STE) has been shown to be a feasible non-invasive method with which to measure these parameters[177, 199]. Furthermore, the measurement of untwisting may present an index of diastolic dysfunction that is largely load independent[79, 200].

Myocardial strain (Figure 1.7) is a dimensionless measure of tissue deformation. In health, during systole, the left ventricular myocardium shortens longitudinally and circumferentially, measured

strain being negative in value, but thickens radially, producing positive strain. Strain rate represents the local velocity of this deformation. Using STE, Serri et al. have shown that in patients with non-obstructive HCM, the longitudinal, circumferential and radial strain were all reduced, when compared to healthy volunteers[201]. The demonstration of a reduction in longitudinal strain has been repeated by other groups[202, 203], though data on circumferential strain has been variable[80, 204]. Clinically very pertinent, these deformation parameters may be abnormal even prior to the development of overt hypertrophy[17, 205]

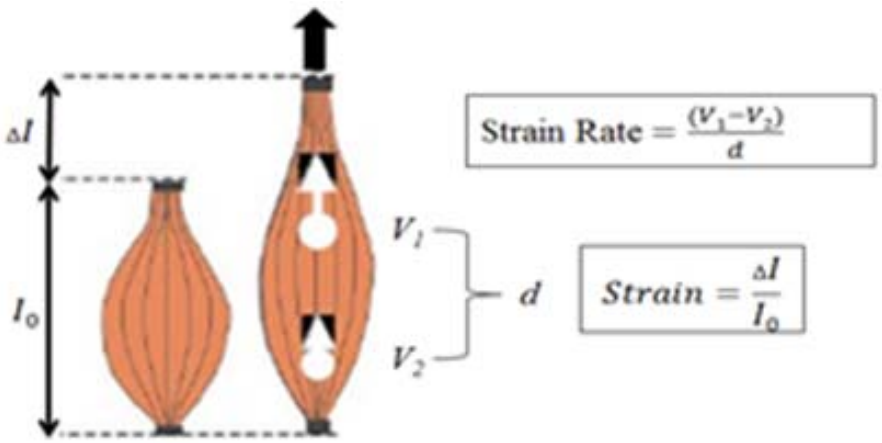

Figure 1.9 : Strain. A dimensionless measure of the extent of tissue deformation.

Diastolic Ventricular Interaction (DVI)

In health the right ventricle is wrapped around the left ventricle and both are contained within a predominantly, closely-apposed fibrous sac, the pericardium, which exhibits a J shaped stress-strain relation[206] (Figure 1.8).

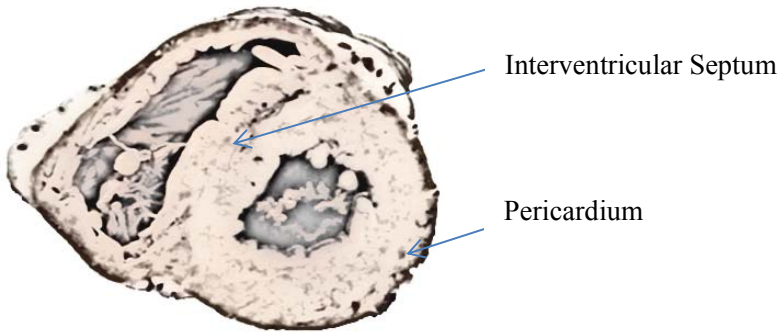

Figure 1.10 : Short axis section through the ventricular mass. Showing how the right ventricle wraps itself around the left ventricle, sharing a common septum, enclosed by pericardium.

The ventricles close proximity to one another allows changes in pressure or volume of either chamber to influence the functional characteristics of the other[207, 208]. This interaction between the ventricles occurs directly across the shared interventricular septum and via shared myocardial fibres in the outer muscle layers. This interaction is potentiated by both ventricles sharing an acutely non-distensible volume (created by the pericardium). Furthermore, the pericardium couples stresses from one part of the heart to the other. In effect, any change in the volume, or pressures within one ventricular cavity, has the ability to influence the pressure/volumes of the other, given the largely non-compressible nature of myocardial tissue. This ability for ventricles that are in a series relationship, to directly interact, offers a form of feed-forward control[209] between the ventricles, which may be passive during rest in health, and become dynamic during exercise; and in sickness become pathological. Direct interaction between the ventricles during systole, has been

termed systolic ventricular interaction, and that during diastole, diastolic ventricular interaction (DVI).

Almost half a century ago Laks et al.[210] demonstrated in an elegant study using explanted, isolated canine hearts with pericardium removed, how the compliance of each ventricle was dependent upon the state of filling of the contralateral chamber, clearly demonstrating the concept of direct ventricular interaction (Figure 1.10).

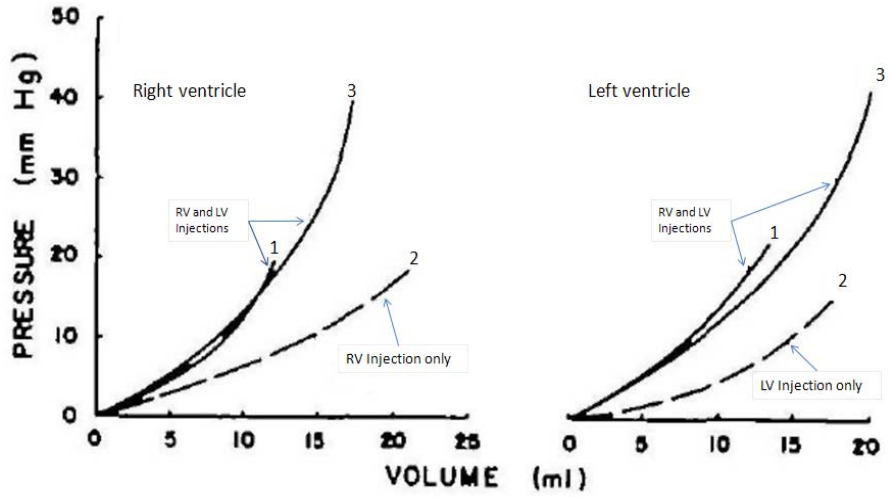

Figure 1.11 : Pressure volume relationship of the right and left ventricle explanted canine heart. Curve 1 refers to pressure volume curve produced after simultaneous biventricular continuous injection of fluid, followed in time by curve 2, injection of fluid into right ventricle alone and then by curve 3, simultaneous biventricular injection. Right hand panel represents the left ventricle[2].

In their work, they emphasised that the ventricles were able to accommodate more fluid when filled in isolation, then when filled simultaneously. This ability for the ventricle to increase its volume is of crucial importance, if the ventricle is to utilise Starling law of the heart, which states that the more the left ventricle fills with blood, the more volume it ejects[211].

The Right Ventricle

In a beating, perfused, isovolumic, rabbit heart Santamore et al.[212] demonstrated the presence of ventricular interaction by showing that the diastolic pressure volume relationship of either ventricle could be changed by altering the volume of the other ventricle. Evidence for the right ventricle (RV) affecting the contractile properties of the left ventricle (LV), was demonstrated by Moulopoulos et al.[213] using canine hearts. During experimental pressure-loading of the right ventricle, LV function was reduced[213] and LV rate of contraction (dp/dt) decreased. This relationship was found at higher RV filling pressures, and may have been a reflection of reduced LVEDV with leftward shift along the Starling curve. However, by using isolated beating canine hearts Bemis et al.[214] found that alteration of RV filling pressures over the entire range, was able to affect alterations in LV geometry, (a leftward shifting of the interventricular septum). Of note, in the study by Bemis et al., the pericardium was retained intact whereas in the study of Moulopoulos et al. it was not. This would suggest a very significant role for the pericardium in modulating the interaction between RV and LV. In contrast to these findings, Maughan et al.[215] have reported, in the pericardium-free, isolated canine heart that the right ventricle had little influence on LV diastolic pressures.

Kass et al.[216] have shown (Figure 1.10) in humans at rest, including patients with left ventricular hypertrophy (n=5), that acutely reducing pressure in the right ventricle, using inferior vena cava occlusion, resulted in a sudden decrease in left ventricular diastolic pressures with minimal change in filling volumes (represented as downward displacement of the LV end diastolic pressure volume curve of the left ventricle), before any reduction in cardiac output was seen. They reported that as much as 40% of the resting left ventricular diastolic pressure was due to factors

that are extrinsic to the left heart, the right heart and the pericardium being the two major sources for generation of external forces on left ventricular diastolic pressure.

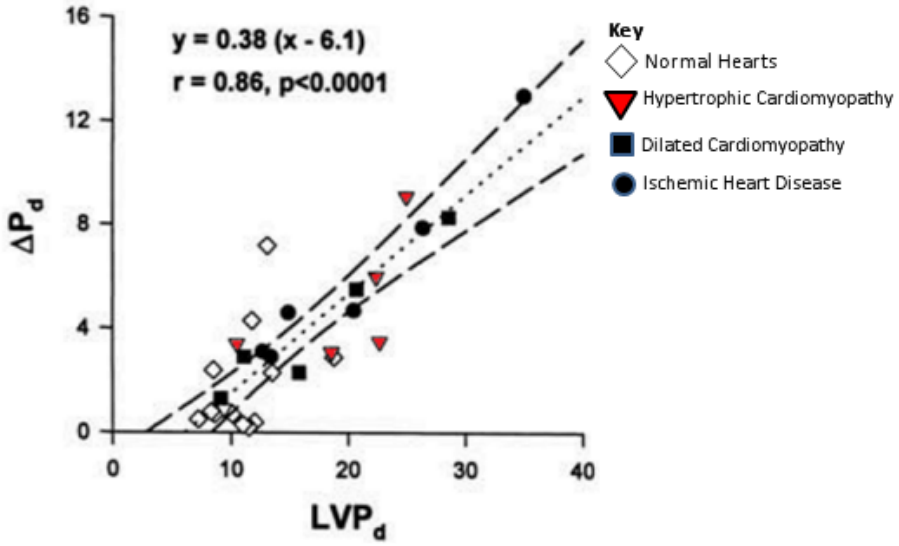

Figure 1.12 : Relation between initial resting left ventricular diastolic pressure (LVP_d) and the component of this pressure that is due to external forces (ΔP_d). Four groups of patients are shown. The data fell along a single relation that was well fit by linear regression. The slope of (0.38) indicating that 38% of the resting LVEDP was due to forces external to the left ventricle[1]

The Pericardium

The importance of the pericardium in enhancing direct diastolic ventricular interaction comes as no major surprise given that it provides, at least acutely, a non-distensible volume enclosing both ventricles. Since the turn of the 20th century it had been suggested that the pericardium plays a protective role, in shielding the heart from over-distending itself[217]. The fibrous nature, mostly collagen bundles, of the pericardium make it a suitable candidate for this role. The physiological effect of this construct is demonstrated by the J-shaped relationship of its pressure volume curve[206]. That the pericardium does enhance diastolic ventricular interaction has now been demonstrated by a number of investigators[218-220]. Initially, using in vivo canine hearts, Glantz et

al.[218] demonstrated that a correlation existed between left and right ventricular diastolic pressures, but that this correlation was tighter with the pericardium intact, and increasingly so at higher diastolic pressures on the steep part of the pericardial pressure volume curve, where the predominant contributor to end diastolic pressure generation becomes the pericardium. In effect, with increasing ventricular volumes, there is a gradual move away from them behaving as two individual chambers, towards them behaving as one chamber (created by the pericardium).

This work was followed by Janicki and Weber[220], who, by using isolated canine hearts, studied DVI with and without the pericardium. The presence of DVI was suggested by the increase in diastolic pressures in either ventricle, following an increase in volume of the other. This relationship was much more marked with the pericardium intact. Furthermore, in health, Kroeker et al.[209] showed that the pericardium may modulate beat-beat diastolic ventricular interaction. By using canine hearts, they demonstrated acute changes in the output of the two ventricles in opposite directions when filling of the ventricles was changed by acute atrial volume loading and unloading. This compensatory, homeostatic, mechanism was absent at low ventricular pressures (<5mmHg) and absent with the pericardium opened.

The role of the pericardium in health, in limiting maximum exercise capacity was suggested by Robinson et al.[221], following a study in healthy human males. They looked at central venous filling pressures, SV and cardiac output, both at rest and during maximal exercise, before and after acute volume loading. In the upright resting state, a small increase in central venous filling pressure, following volume loading, was associated with marked increases in SV and cardiac output. However, during exercise, volume loading produced a more marked increase in central venous filling pressures, but with little increase in stroke volume and a failure to increase LV end diastolic volume (LVEDV) which they proposed reflected pericardial constraint. Later work by

Higginbotham et al.[222] demonstrated that at higher exercise workloads, it is HR that drives the increase in cardiac output, with no further increase in LVEDV, despite increasing LV filling pressures. Pericardial constraint, as suggested by Robinson et al. would again explain this observation.

The role of the pericardium in relation to exercise capacity was assessed directly by Stray-Gunderson et al.[223] in a canine model. This group looked at exercise performance (peak Oxygen consumption) before and after removal of the pericardium in untrained dogs. They reported that following pericardiectomy, dogs developed greater increases in stroke volume and cardiac output on exercise (maximal heart rates unchanged) and in peak Oxygen consumption. These findings would suggest that the pericardium plays an important role in limiting exercise capacity. Unfortunately, this study did not measure LV volumes, so was unable to comment whether it was in increase in LVEDV, or a reduction in LV end systolic volume that gave rise to the increase in SV seen following pericardiectomy. However as discussed earlier, investigators have[224] suggested improved LV compliance following removal of the pericardium, making it more likely that it was an increase in LVEDV that led to the increase in SV seen following removal of the pericardium.

More recent work by Fujimoto et al.[225], suggests the presence of diastolic ventricular interaction and pericardial constraint to be a mechanism that is present even at rest. They studied 50 healthy volunteers, applying supine lower body negative pressure (LBNP) to transiently volume unload the right ventricle, and then immediately following relief of LBNP, measured beat-beat changes in SV and LV transmural filling pressure (Pulmonary Capillary Wedge Pressure (PCWP) - Right Atrial Pressure (RAP)). They demonstrated that during the first 7 beats immediately following relief of LBNP, the increase in RAP was greater than the increase in PCWP, resulting in an acute decrease in LV transmural filling pressures, and an associated fall in SV, whilst HR and

pulse pressure remained constant. This suggests that pericardial constraint is apparent even at low cardiac filling pressures, and is significant enough to cause a reduction in SV. However, a pericardium that is compliant, such as is present in the young may prevent this phenomenon, and conversely, a stiff pericardium may exacerbate it. Of interest the pericardium in health demonstrates organised wavy bundles of collagen, which straighten when stretched[226]. Unfortunately, a literature review did not reveal the histological nature of the pericardium in patients with hypertrophic cardiomyopathy, the muscle of which demonstrates fibre disarray and fibrosis. A pericardium which demonstrates similar loss of architectural organisation may lend itself to DVI.

Diastolic Ventricular Interaction in the Clinical Context

Otto Frank described the relation between the diastolic stretch of the left ventricle (preload) and the force of contraction[227]. In cardiological practice, changes in left ventricular preload are usually assessed by measuring changes in direct, or indirect left ventricular end diastolic pressure (LVEDP), as described originally by Starling[228], based on the assumption that changes in LVEDP correlate with changes in left ventricular diastolic stretch. In health, the latter assumption is correct, but in certain pathophysiological states it is erroneous.

In health, the effective left ventricular (LV) distending pressure is close to the measured LVEDP because pericardial and right ventricular pressures at end diastole are both close to zero and there is therefore minimal external constraint to LV filling. However, the pericardium exhibits an exponential stress-strain relation[229-232] in experimental, and pathological situations e.g. pulmonary embolism (Figure 1.11) where there is an acute RV pressure and volume overload, such that as it becomes stretched, the surrounding pericardial pressure increases. Right ventricular

end-diastolic pressure is usually almost identical to pericardial pressure because the relatively thin walled RV does not maintain a significant transmural gradient [233]. In this setting, LV filling is impeded by the pericardium (pericardial or external, constraint) and from the RV, across the shared inter-ventricular septum (diastolic ventricular interaction – DVI). The effective distending pressure in these circumstances is *not* the LVEDP, but the LVEDP *minus* the additional external constraint from the pericardium and right ventricle. This phenomenon is highlighted by Glantz et al.[218] who reported that acute right ventricular distension by pulmonary artery constriction, though elevating both ventricular diastolic pressures, was associated with a reduction in LV size suggesting a reduction in LV distending pressures; by contrast, a reduction in LV size following acute RV distension was not seen with the pericardium open (i.e. a loss of pericardial constraint).

Similarly, a small MRI study conducted by Holverda et al.[234] looking at the effects of submaximal exercise in patients with idiopathic pulmonary hypertension, reported a small decrease in LVEDV and an increase in RVEDV (with total end diastolic volumes, RV and LV, remaining the same during rest and exercise) with failure to augment SV on exercise. They hypothesised that in the presence of a closed volume created by the pericardium, increased RV pressures may have directly impaired LV filling by enhancing ventricular interaction and shifting the septum to the left.

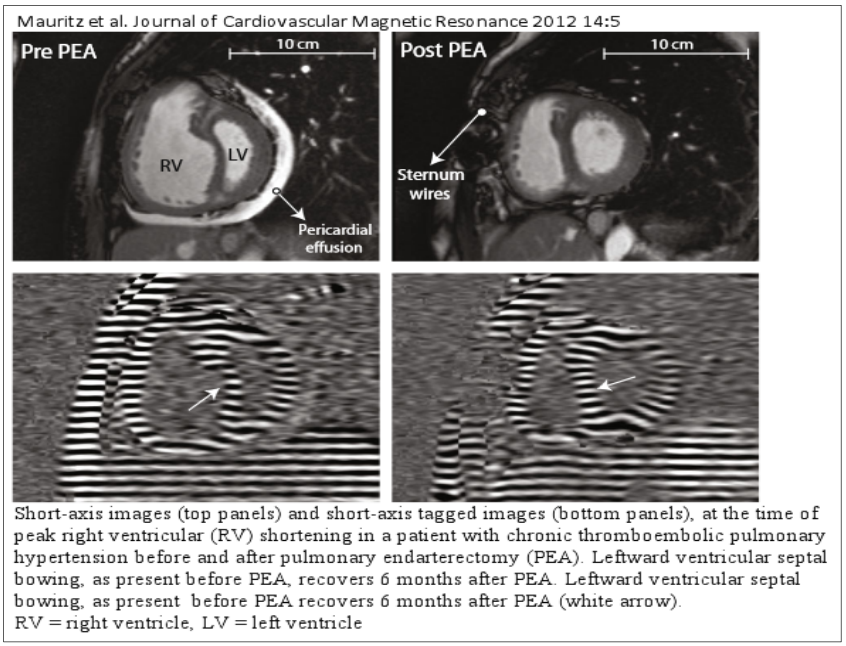

Figure 1.13 : DVI following pulmonary embolism, and relief following embolectomy[235]. Note the enlarged RV compressing the LV and leftward bowing of the ventricular septum pre-pulmonary embolectomy.

Diastolic Ventricular Interaction in Chronic Heart Failure

Chronic heart failure (CHF) is a disorder often associated with elevated RV pressure and RV volume overload. Frenneaux et al. have shown that there is significant DVI in approximately 40-50% of patients with CHF[4, 216]. In such patients, blood volume unloading achieved by applying lower body negative pressure, resulted in a 'paradoxical' increase in LV end-diastolic volume (Figure 1.12 and Figure 1.13), despite a fall in measured LV 'filling pressures'. Further, in a canine model of heart failure, they showed that as LVEDP was lowered by IVC occlusion, the pressure in the pericardium and RV fell to an even greater extent, so that the effective LV distending pressure increased. Changes in LV diastolic volume and stroke work were completely predictable on the basis of changes in the LV transmural pressure gradient (i.e. the effective distending pressure). In

patients with CHF, the presence of this abnormal LV volume response was strongly predicted by a restrictive trans-mitral Doppler profile, providing a simple non-invasive marker of DVI[236].

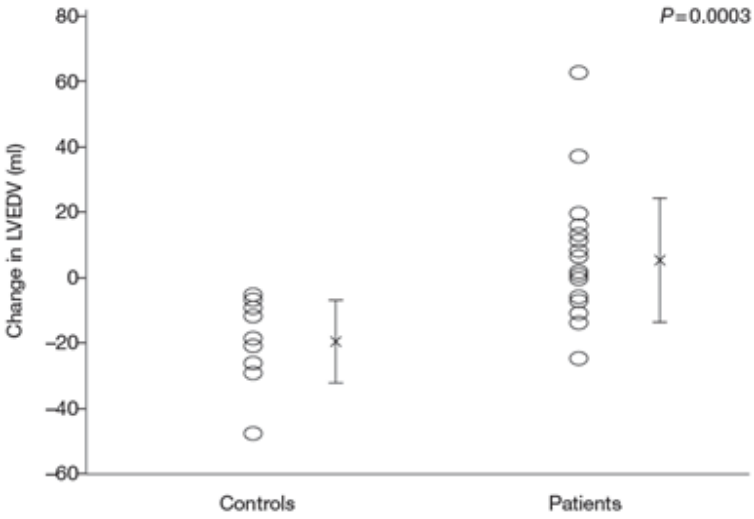

Figure 1.14 : Change in LVEDV during LBNP, in controls and patients with chronic heart failure[4]. Vertical bars indicate mean (SD)

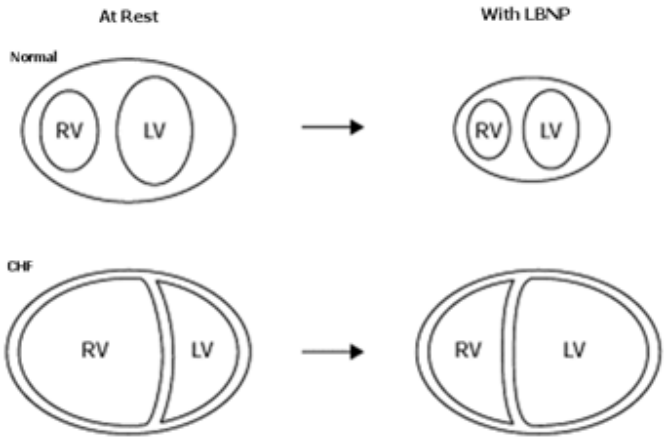

Figure 1.15 : Ventricular volume changes with LBNP[4]

Diastolic Ventricular Interaction in Hypertrophic Cardiomyopathy

Frenneaux et al. have previously shown that patients with HCM have a markedly impaired ability to utilise the Starling mechanism to increase stroke volume during exercise i.e. LVEDV fails to increase despite a substantial increase in pulmonary capillary wedge pressure [10, 42]. Intrinsic abnormalities of myocardial compliance, and of active relaxation due to myocyte hypertrophy, fibrosis and ischaemia[237] are likely to contribute to this phenomenon. However diastolic ventricular interaction (DVI) might provide an additional or alternative explanation for the inability to utilise the Starling mechanism during exercise.

Ong et al.[238], using echocardiography, identified pulmonary hypertension in over a third (138 patients out of 373) of patients with NOHCM with an EF >50%. The presence of pulmonary hypertension in this subgroup was related to an increase in mortality, not seen in patients with obstructive HCM. Losse et al.[239] have shown that over a quarter of patients with NOHCM, failed to increase SV on exercise, which was associated with a pathological increases in pulmonary artery pressures (Figure 1.15). The largest increment in pulmonary pressures noted to occur at the lower workloads. Though a pathological increase in pulmonary artery pressure was correlated to symptom severity, a number of patients exhibited pathological rises in PA pressure, but denied symptoms (NYHA I), perhaps suggesting adjustment to exercise limitation.

In patients who experience pathological increases in right ventricular pressure on exercise, DVI may become physiologically relevant. This concept has been supported by animal studies. Belenkie et al.[240] induced acute pulmonary hypertension (result of pulmonary artery constriction) in a closed pericardium canine model. Pulmonary artery constriction, as might be anticipated, reduced stroke volume (by 50%), right ventricular diameter increased with an associated reduction in LV area. Of note, opening of the pericardium, during pulmonary artery constriction, resulted in

an increase LV area, a left ward shift of the ventricular septum, and increase in stroke volume. These investigators demonstrated that though a series interaction accounts for much of the reduction in cardiac output during acute pulmonary hypertension, pericardial constraint and leftward septal shift were also important.

Acute pulmonary embolism increases pulmonary vascular resistance, as a consequence the mean pulmonary artery pressure can double[241], under extremis it may even exceed systemic arterial pressure. An increased right ventricular afterload, may lead to right ventricular dilation and displacement of the ventricular septum to the left. Belenkie et al.[242] volume loaded closed chest dogs, pericardium intact, before and after pulmonary embolization with autologous clot. Prior to embolization, volume loading increased the left to right transeptal pressure, and importantly increased LV transmural pressure gradients, and stroke work. Following embolization of the pulmonary artery, volume loading failed to increase the trans-septal gradient, the ventricular septum shifted to the left at the end of diastole with an associated reduction in stroke work. Transmural LV diastolic pressure failed to increase despite an increase in LVEDP. Pericardiectomy corrected this 'paradoxical' response[243].

Some patients with HCM have raised LVEDP and right ventricular end diastolic pressure (RVEDP) at rest. During exercise, the increase in both LVEDP and RVEDP is often very marked in these patients[42, 244]. Based on observations in patients with CHF[4], DVI might be anticipated to be present at rest in some patients but to develop in many, during exercise. If this is so, then the effective distending pressure in the LV might not increase in spite of an increase in measured LVEDP during exercise, resulting in an impaired stroke volume response during exercise[245-247]. There are, however, two theoretical reasons why patients with HCM might not have significant DVI despite markedly elevated LVEDP and RVEDP. First, the abnormally thickened

interventricular septum may limit interaction between the ventricles. Secondly, right ventricular hypertrophy is present in a minority of patients with hypertrophic cardiomyopathy[248] and this may permit the generation of a significant right ventricular trans-mural pressure gradient, i.e. pericardial pressure may not be elevated despite a markedly raised RVEDP.

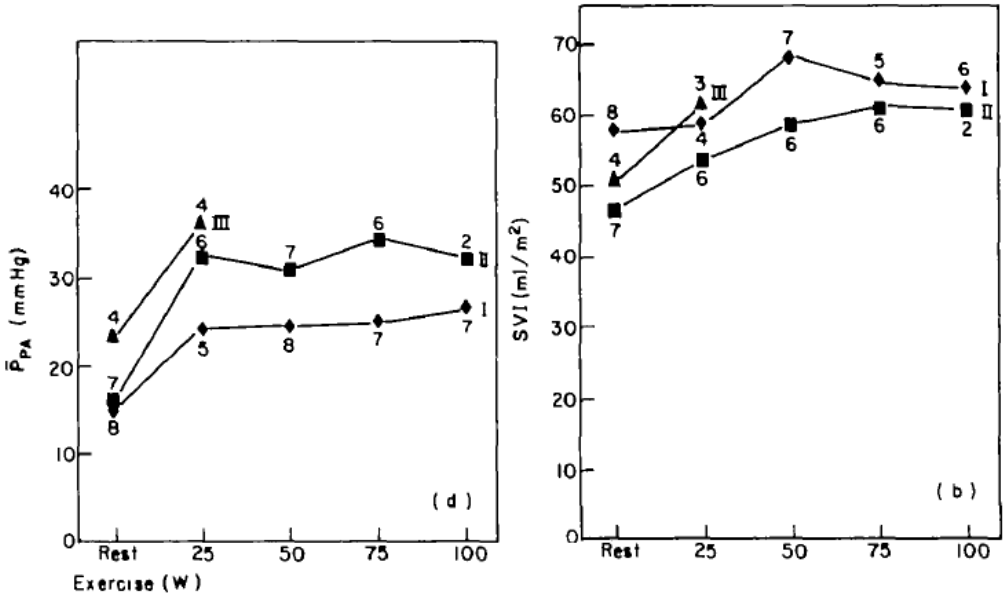

Figure 1.16 : Mean changes in stroke volume index (SVI) and mean pulmonary artery pressure (P_{PA}), during exercise in 19 patients with non-obstructive hypertrophic cardiomyopathy classified according to New York Heart Association criteria for clinical severity. The mean values are designated with the respective number of patients in each group. Adapted from Losse et al.[239]

Biventricular Pacing

The idea that electrically stimulating the myocardium may be of clinical benefit occurred when it was noticed that patients with systolic heart failure often had prolonged PR and QRS intervals on surface ECG (25-50%), and that patients with more severe heart failure have a greater prevalence of broad QRS and often an ECG pattern consistent with left bundle branch block (15-27%)[249]. Atrioventricular dyssynchrony secondary to a prolonged PR interval was reported in up to a third of patients with heart failure[250]. The acute hemodynamic benefit of cardiac pacing was then demonstrated using simple right ventricular (RV) pacing with a short AV delay, in an attempt to reduce pre-systolic mitral regurgitation[185, 251] secondary to atrioventricular dyssynchrony. Despite this technique substantially reducing pre-systolic regurgitation, it did not translate into long term improvement[252, 253], probably because the benefit of improved AV synchrony was countered by increased mechanical dyssynchrony caused by the RV pacing[254].

Observations in the late 1980s showed that left bundle branch block had a deleterious impact on left ventricular contractile function [255] with an associated increase in mortality[256]. The attempted amelioration of this pattern of electrical and consequential intraventricular mechanical dyssynchrony followed. A series of studies then demonstrated that simultaneous pacing of the left and right ventricle improved cardiac function in patients with heart failure and electrical conduction delay[257-259]. Initially, placement of the LV lead required a thoracotomy, understandably making patient-acceptability limited. However once transvenous pacing of the LV was possible, there followed a slew of randomised controlled trials which demonstrated symptomatic benefit[184, 260-263] and objective improvements in exercise capacity demonstrated by improvements in peak Oxygen consumption of 10-15%[15]. These smaller trials were followed by large landmark trials that demonstrated that BiV pacing therapy improves cardiac structure and function, reduces morbidity,

hospitalization and importantly is associated with a 10% reduction in risk of death in addition to the benefit gained from standard therapy[264, 265]. Of note, the CIBIS-II trial was stopped prematurely following a 5.5% reduction in mortality in HF patients treated with Bisoprolol. The magnitude of the benefit from BiV pacing was as great and in addition to, the established pharmacological therapies. As a result, biventricular pacemakers are now a Class 1 indication, with level of evidence A, therapy for heart failure in the European Society of Cardiology Guidelines.

A subset of patients with HCM develop LV systolic dysfunction, with wall thinning and LV dilation[266]. In this group of patient, the presence heart failure symptoms, reduction in systolic function and ECG evidence of LBBB, case reports [267] and one prospective, non-randomised, non-blinded cohort study [268] suggested that BiV pacing may improve symptoms and induce reverse remodelling of the LV in this subset of HCM patients, consistent with the findings of larger, randomised controlled trials in patients with systolic heart failure.[262, 264]

In patients with HCM with heart failure symptoms in the presence of normal systolic function, there are case reports, and small case series which suggest symptomatic and hemodynamic improvement following BiV [269 270] and LV pacing [271 272].

Yufu et al. [272] report the case of a 55-year-old female with symptom limited obstructive HCM (resting LVOT gradient 198mmHg) refractory to pharmacotherapy. Echocardiogram showed asymmetric septal hypertrophy, with systolic anterior motion of the anterior mitral valve leaflet, and mild mitral regurgitation. During cardiac catheterisation studies, temporary AV sequential pacing of the RV resulted in no reduction in LVOT gradient. The patient then underwent AV sequential pacing of the LV, via an epicardial lead. This resulted in a dramatic reduction in the LVOT gradient from 198mmHg to 10mmHg. The authors report that a month later, the patient was asymptomatic, with a reduction of mitral regurgitation and a LVOT gradient of 10mmHg.

Unfortunately, no comment is made on the LVEDD. The authors postulate that the mechanisms underlying the improvement seen following LV pacing but not RV pacing, involve modification of ventricular excitation contraction coupling sequences, that alter LV wall movement, and consequently reduce systolic anterior motion of the mitral valve leaflet. An alternate mechanism of improvement has been suggested by Kass et al.[273] This group of investigators have suggested that pacing increases LV end-systolic volume, which would open up the LVOT, with a consequent decrease in LV outflow tract velocities and with an attendant reduction in the Venturi phenomenon.

Rinaldi et al. [274] examined the role of BiV pacing, in a series of 8 symptomatic HCM patients with preserved LV systolic function, with a mean QRS interval of 132ms, as a 'cardiac resynchronisation' therapy. Of the 8 patients, 5 patients had obstructive HCM, 2 patients having already undergone alcohol septal ablation, and 1 having had a myectomy. The authors reported 3 patients experiencing symptomatic benefit following 4 weeks of BiV pacing with an attendant 68% reduction in LVOT gradients. However, over 5 years, 2 of these 3 patients developed progressive LV failure, of which one died 43 months following implantation. The third patient developed atrial arrhythmia and pacemaker infection, requiring explantation. The authors did not report any measure of mechanical dyssynchrony. This small case series suggests short term benefit from BiV pacing. But over the longer term at best no benefit, and at worst a deleterious effect on LV function. At present no guidelines [108] [129] advocate the use of BiV pacing in patients with HCM, obstructive or non-obstructive, with normal systolic function.

The mechanisms involved in producing benefit from BiV pacing in patients with systolic heart failure have not been completely elucidated. At present, approximately 70% of patients selected, who meet all the current implantation criteria I) symptoms of heart failure refractory to optimal medical therapy, II) objective evidence of systolic heart failure ejection fraction <35%,

III) surface electrocardiographic QRS duration >120ms, derive benefit. Extensive work has been done over the last decade to try to elucidate the mechanisms involved in producing this benefit, with the goal of improving patient selection. This has been hampered because the benefits of the response to BiV therapy have no universal definition. Benefit defined in terms of reverse ventricular remodelling (a benchmark metric of 'response') has been shown to be tenuously associated with symptom benefit, if at all [275, 276]. Because of difficulties in elucidating both the mechanisms at work and the patients response, refinement to the guidelines for BiV therapy have been limited, and broadly stand today as they did 15 years ago[277].

Postulated mechanisms involved in producing benefit from BiV pacing therapy:

I Restoration of electrical synchrony

It might be intuitive to think that if a broad QRS is harmful, then its correction would result in benefit. This is incorrect. It has been shown that correction of the QRS interval does not correlate with haemodynamic benefit or mechanical resynchronisation[278]. Furthermore, LV pacing, which produces a wider QRS complex than BV pacing, was demonstrated by Kass et al. to result in acute hemodynamic improvement[259] and by Gasparini et al. [239] and others, to confer as much clinical benefit as BiV pacing in patients with refractory heart failure[279, 280]. Thus, it appears that electrical resynchronisation, as determined by surface ECG, is not mandatory for benefit.

II Restoration of mechanical synchrony

That biventricular pacing can ameliorate dyssynchrony was shown in man decades before clinical application[281] . Mechanical dyssynchrony has been demonstrated in patients with systolic heart failure by using MRI[282], echocardiography, radionuclide techniques and invasively, with conductance catheters[283], but the vast majority of work has been done using echocardiographic techniques. Delays in timing of contraction between the right and left ventricle (interventricular dyssynchrony) and intersegmental temporal variation in contraction within the left ventricle (intraventricular dyssynchrony) have been demonstrated in patients with heart failure. Patients with the widest QRS complexes often demonstrate the greatest degrees of mechanical dyssynchrony, however a normal QRS does not always confer mechanical synchrony and conversely, patients with LBBB may have relatively normal mechanical synchrony[153]. A large number of studies have suggested that the identification of mechanical dyssynchrony is a more sensitive and specific indication for BiV pacing therapy than the duration of the QRS complex and

particularly, that the correction of mechanical dyssynchrony is a prerequisite for benefit to be realized[284]. Further, highlighting the importance of the role of mechanical dyssynchrony, investigators have shown that heart failure patients with evidence of mechanical dyssynchrony gain benefit from BiV pacing despite a narrow surface QRS complex (electrical synchrony) [285] [286], demonstrating LV reverse remodelling, improved systolic function and overall functional improvements. However, initial enthusiasm for BiV therapy in patients with systolic heart failure and a narrow QRS duration has recently been tempered by multicentre, randomized, controlled studies which have failed to demonstrate a benefit in mortality [287]. Of concern one study was brought to a premature halt due to safety concerns; of note this study had no dyssynchrony inclusion criteria[288]. The difficulties in reliably measuring mechanical dyssynchrony has recently been brought into focus by the results of the PROSPECT trial, highlighting particularly the shortcomings in the echocardiographic techniques [289].

III Reverse remodelling and the amelioration of mitral regurgitation

Reverse remodelling has been shown to occur with Angiotensin converting enzyme inhibitors, Angiotensin receptor blockers, and beta receptor blockers. Furthermore, the improvement in ventricular geometry is positively correlated with reduction in morbidity and mortality. Biventricular pacing has been shown to promote sustained reverse remodelling with reductions in LV end-systolic, end diastolic volumes and improvement in ejection fraction[15, 290-293]. Discontinuation of pacing resulting in reversal of improvement[294]. A number of studies have shown that BiV pacing may ameliorate the degree of mitral regurgitation[295, 296]. Multiple mechanisms may be at play. In the original studies, reduction in atrioventricular(AV) conduction delay reduced presystolic mitral regurgitation with acute hemodynamic improvement[185].

Biventricular pacing not only shortens AV delay, but restores intraventricular mechanical synchrony, resulting in a more rapid increase in transmitral pressure gradients with the effective pushing together of the mitral leaflets and thus further reducing pre-systolic regurgitation[295].

BiV pacing-induced changes in ventricular geometry, with reductions in LVEDD and LVESD[297], are likely to reduce the mitral regurgitation that is associated with a failure of coaptation seen in the dilated failing ventricle.

IV Augmented diastolic filling

The effective diastolic filling period can be prolonged by a reduction in pre-systolic mitral regurgitation, by using short AV delay pacing[185]. This has been clearly demonstrated at rest, but whether this benefit is sustained during exercise is unknown. Restoring systolic synchrony may shorten systole and increase the diastolic filling period. A synchronously relaxing ventricle might be expected to improve the rate of relaxation and so reduce the time wasted in 'isovolumic' phase of the cardiac cycle allowing more time for filling and ejection. Despite these theoretical considerations, the effect of BiV pacing on parameters of LV relaxation (tau or passive left ventricular compliance), have been mixed [259, 298].

Frenneaux et al. have previously shown that a substantial proportion of the acute hemodynamic benefits seen with LV and BiV pacing may be a result of a reduction in the external constraint to left ventricular filling. In patients with CHF, almost 50% had impediment of left ventricular filling by a) external constraint from the right ventricle, via the shared interventricular septum (direct diastolic ventricular interaction) and b) from the stretched pericardium (pericardial constraint)[4]. Left ventricular pacing temporally shifts left ventricular contraction to be earlier then right ventricular contraction: consequently, LV filling occurs before RV filling. Given that the

pericardial volume is relatively fixed, a smaller RV volume would allow greater LV filling both via reductions in direct DVI, and reductions in pericardial constraint. Subsequently, an increase in LVEDV and by the Frank-Starling mechanism, a greater left ventricular stroke work would have to be matched with increased RV stroke work. Following LV pacing, Frenneaux et al. showed that despite measured LVEDP remaining unchanged (a finding consistent with Kass et al.[259]) the effective LV filling pressure increased and suggested this may result from of a reduction in external constraint to LV filling, with a consequent significant increase in LV filling[10]. Furthermore, QRS duration was not predictive of response to LV pacing. Bleasdale et al.[10] showed that acute hemodynamic improvement with LV pacing was predictable in the presence of elevated left ventricular filling pressures. Perhaps not surprising given that external constraint to left ventricular filling is related linearly to left ventricular end diastolic pressures.

V Transcriptome

Initial work demonstrated that in patients and in animal models of dyssynchronous heart failure there were regional variations in myocardial protein expression[299 300]. Subsequent studies have found marked regional variation in gene expression, corroborating the variation in protein expression[301]. More importantly, work done in canine heart, demonstrated that BiV pacing can reverse these variations in gene expression[301].

VI Mitochondrial subproteome

From canine dyssynchronous heart failure models treated with BiV pacing, mitochondria were isolated and analysed [302]. This work demonstrated up regulation of enzymes involved in key pathways such as pyruvate carboxylation and branched amino acid oxidation. In this way, BiV

pacing seems to behave as a metabolic therapy, altering energy metabolism in the mitochondria. This may be another mechanism by which BiV pacing is able to improve work performance.

VII Beta adrenoceptor regulation

Biventricular pacing has been shown in canine heart models to enhance myocyte beta-adrenergic responsiveness. Some of this enhancement is due to upregulation of beta1-adrenoreceptor abundance, increased adenylate cyclase activity, and reduction of inhibitory G-protein activity[303].

Future direction

The management of drug-refractory symptoms in patients with non-obstructive hypertrophic cardiomyopathy remains challenging, with few options outside of a cardiac transplant. Obstruction to outflow, in patients with drug refractory symptoms, can be ameliorated with invasive strategies including septal myectomy or percutaneously with alcohol septal ablation.

Many of the pathophysiological abnormalities that contribute to symptoms in non-obstructive HCM are common to patients with chronic heart failure secondary to systolic left ventricular impairment. A number of recently published studies have shown that Biventricular pacing can improve exercise capacity, quality of life, and substantially reduce hospitalization and mortality in patients with drug-refractory NYHA Class III/IV CHF. The mechanism of improvement has been thought to be predominantly related to a reduction in intra-ventricular contractile dyssynchrony. However, the studies of Frenneaux et al. have shown that at least some of the acute haemodynamic benefit of Biventricular pacing in CHF is due to a reduction in the external constraint to LV filling by the pericardium and right ventricle, a phenomenon known as diastolic ventricular interaction.

In view of the findings discussed above, the objective of this PhD was to examine the role of Biventricular pacing in patients with non-obstructive Hypertrophic Cardiomyopathy (HCM) with drug refractory symptoms. The study had an acute and chronic component. The acute component examined the role of diastolic ventricular interaction, impaired diastolic filling and dyssynchrony at rest and on graded exercise, in patients with drug refractory symptoms of exercise intolerance, and the acute impact of Biventricular pacing on these parameters. The chronic component of the study consisted of a double-blind, cross-over, sham-controlled trial, which examined the impact of Biventricular pacing on echocardiographic parameters of cardiac function, symptoms and exercise capacity (VO_2 max) over a period of 4 months.

Study Objectives

First Objective

I) To assess the impact of acute Biventricular pacing on myocardial dyssynchrony in patients with non-obstructive Hypertrophic Cardiomyopathy (HCM).

Hypothesis: Biventricular pacing will improve parameters of dyssynchrony.

Second Objective

II) To measure, diastolic myocardial function at rest and on exercise in patients with non-obstructive HCM and the effects of acute Biventricular pacing on diastolic myocardial function at rest and exercise in patients with non-obstructive HCM.

Hypothesis: We hypothesised that diastolic ventricular interaction may be present at rest in some patients with HCM and may develop during exercise. We hypothesised that Biventricular pacing would acutely improve myocardial filling parameters at rest/on exercise in patients with HCM

Third Objective

III) To investigate the impact of right ventricular unloading on left ventricular diastolic filling by using lower body negative pressure in patients with non-obstructive HCM, with and without Biventricular pacing.

Hypothesis: We hypothesised that in patients with HCM, right ventricular unloading would improve diastolic filling via relief of diastolic ventricular interaction, and that Biventricular pacing may relieve diastolic ventricular interaction.

Fourth Objective

IV) To assess the effects of chronic Biventricular pacing on dyssynchrony, ventricular strain, twist and untwist parameters in patients with non-obstructive HCM.

Hypothesis: We hypothesised that chronic Biventricular pacing would improve dyssynchrony, twist and untwist rates in patients with HCM

Fifth Objective

V) Primary end point: To assess impact of Biventricular pacing on peak Oxygen consumption (VO_2 max). To assess the impact of Biventricular pacing on symptomatic status using the Minnesota Living with Heart Failure Questionnaire; the secondary outcome measure of the chronic component of this study.

Hypothesis: We hypothesised that Biventricular pacing would reduce myocardial dyssynchrony, improve diastolic function, and thereby improve exercise capacity (Primary end point) and improve symptomatic status (Secondary end point) in patients with drug refractory symptomatic HCM

Chapter 2

General Methods

i) Study design

We used the University of California, Los Angeles (UCLA) power calculator to determine that a sample size of 23 patients would have a power of 90% to detect an increase in VO_{2max} of at least 3ml/kg/min (primary end point) with a standard deviation of 3ml/kg/min, and an alpha equal to 0.05. In our experience, technical problems in the placement of pacemaker and in invasive studies would precludes analysis in approximately 25-30% of patients, hence at the outset of the study we aimed to recruit approximately 30 patients.

The crossover methodology has been suggested to be the gold standard for evaluation of therapeutic effectivness[304]. Each patient is able to act as their own control, this allows reduction in bias associated with variances in known and unknown confounders. This method allows between and within group analysis[305]. A further major advantage of crossover methodology is statistical efficiency[306], compared to non-crossover designs, fewer patients are required. Crossover trials are particularly suited to chronic conditions, with effect of intervention that is of short duration and reversible. Methodological difficulties include allocation concealment, patient drop out, and issues related to potential carryover effects[307] (sequence order effect). Allocation concealment refers to the technique used to implement the randomisation sequence[308]. Ideally the person allocating treatment should not be involved with the trial e.g. a pharmacist or technician.

Even a well conducted crossover trial, is prone to weakness. when the patient drops out after the first intervention period, and declines subsequent treatment, within-subject comparison is then not possible. This is of particular clinical relevance should the patient have dropped out because of adverse effects related to treatment.

A carry-over effect suggests that the observed difference between treatments has been influenced by the order in which the treatment was received; hence the estimated overall treatment

effect will be affected (usually resulting in the treatment effect being under estimated, leading to a bias towards the null). Argument has been put forwards against consistent testing for carryover effects of interventions across periods as carry-over effects are rare and statistical manipulation after the fact cannot address the impact of a carry-over effect. A common sense approach to crossover trials is suggested, where no carry-over is assumed and thus, not tested for [309]. Instead it is recommended that the washout period be sufficient to prevent carry-over effects.

The complete study was performed on a total of 29 patients from 31 enrolled into the study (Figure 2.1). Two patients discontinued at the crossover phase of the chronic component of the study these two patients were excluded from all analysis. One of these patients became extremely symptomatic when crossed over to the sham pacing arm of the study, and declined further participation. The second patient developed intractable diaphragmatic twitching and was unable to continue. Therefore 29 patients took part in both the acute haemodynamic study and completed both arms of the chronic cross over study. Data are presented for the 29 patients that completed the study. There were no deaths or major adverse events during the study period. The study was approved by the South Birmingham Research Ethics Committee and conformed to the principles outlined in the Declaration of Helsinki. All participants provided written informed consent.

Patients were recruited nationally. Biventricular pacemaker implant took place at the Queen Elizabeth, University Hospital Birmingham (n=9) and at the Heart Hospital, London (n=22). Following implantation, devices remained in sham pacing mode (VVI30), eliminating any active Biventricular (BiV) pacing. Patients were seen 2 weeks following implantation of BiV pacemaker, when they underwent the acute component of the study. The acute component of the study took place over a period of one day. Following completion of this patients were then randomized into a double-blind cross over trial (4 months in each limb) to assess the effects of chronic BiV pacing

vs. sham pacing (VVI30). In order to assign participants to either BiV pacing first or Sham pacing, a random allocation sequence was generated using the block randomization method [310], with 8 blocks of size 4. A cardiac pacing physiologist, not part of the research team, programmed the device according to the allocation, at entry into the trial and at cross-over.

The primary end point was peak Oxygen consumption (VO_{2max}) achieved during treadmill ergometer testing. The secondary end point was of symptom status, assessed using Minnesota living with heart failure questionnaire. At the end of each 4-month period patients also underwent transthoracic echocardiographic studies as outlined below. All patient who completed the study, experienced 4 months of BiV pacing, and 4 months of sham pacing. A period of 4 months was selected to eliminate any carry over effect[161]. Patients and investigators were blind to the mode of pacing.

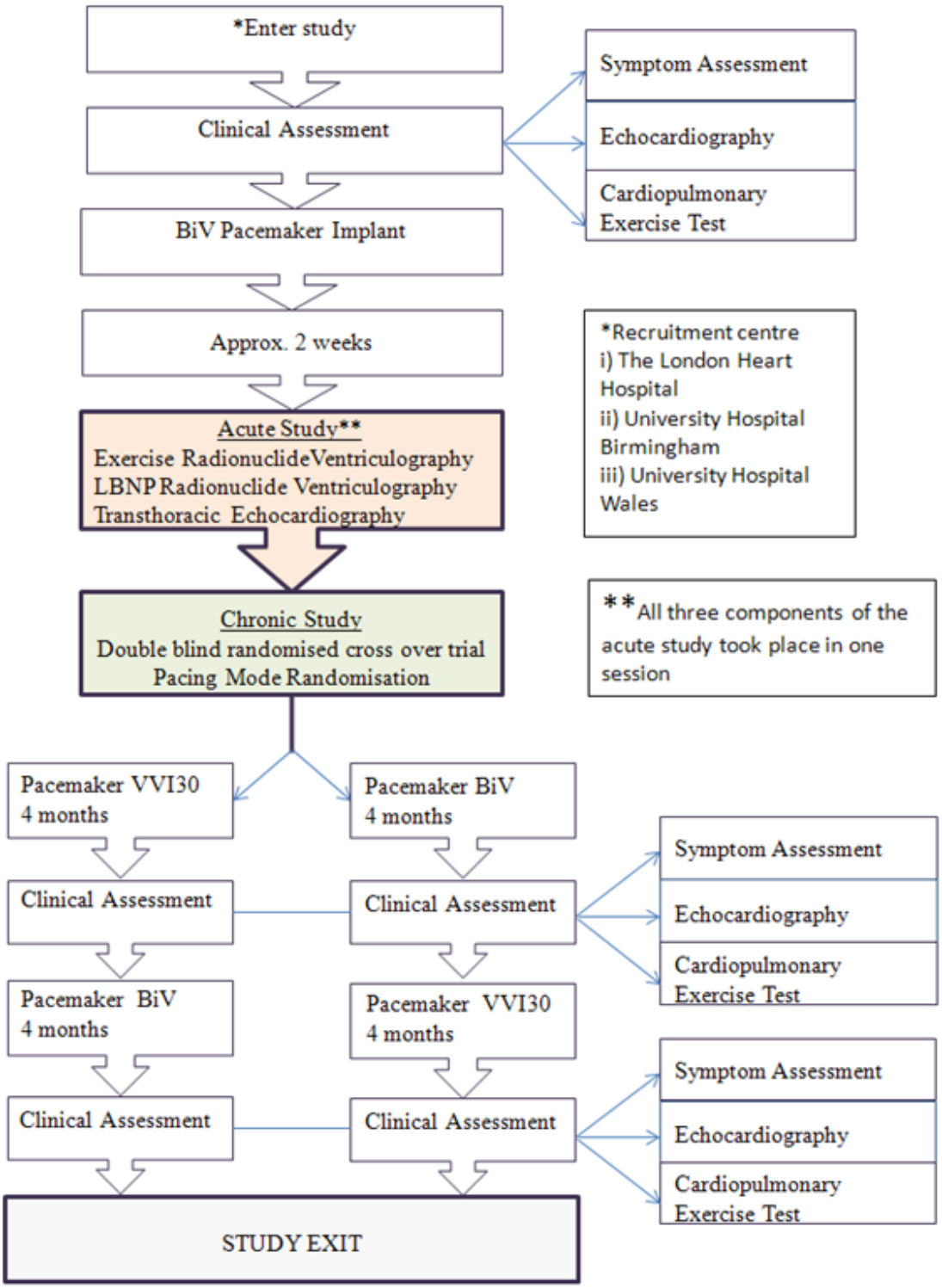

Figure 2.1 : Study Flow Chart

ii) Patient selection

Patients were consecutively recruited from cardiomyopathy clinics at the Heart Hospital, University College London Hospitals, London and Queen Elizabeth Hospital, Birmingham, UK between 2006 and 2008.

Inclusion criteria:

i) Fulfilled conventional echocardiographic criteria for the diagnosis of HCM

(LV wall thickness greater than 1.5 cm in the absence of another cause for hypertrophy)[311]

ii) Absence of LVOT obstruction at rest or on provocation (peak gradient < 30mmHg).

iii) Age 18 to 80 years.

iv) Exertional symptoms (NYHA ≥ 2b)

v) Normal sinus rhythm.

vi) Peak VO_2 < 75% of predicted for age and gender.

Exclusion criteria:

i) Presence of epicardial coronary artery disease.

ii) Conventional indications for pacing

iii) Women of childbearing potential

iii) Biventricular pacemaker implant

Patients who fulfilled the entry criteria underwent implantation of a biventricular pacing device, with the right ventricular electrode placed at the apex of the right ventricle, and the left ventricular electrode via the coronary sinus in a lateral position, using a standard technique (Figure 2.2). 13 Guidant, 10 Medtronic and 6 St Jude devices were implanted

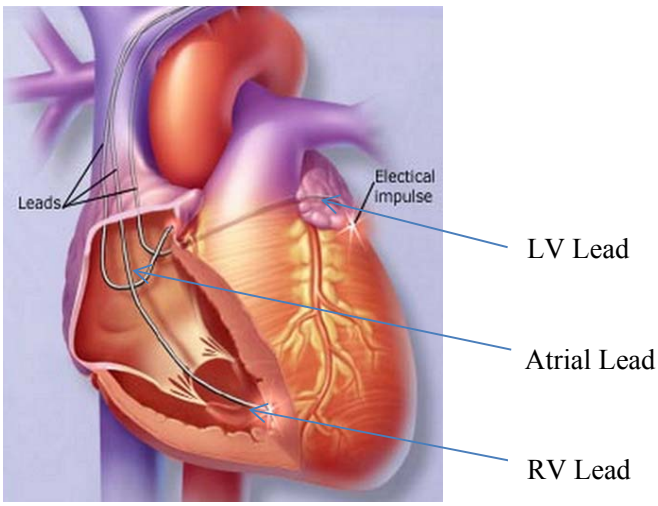

Figure 2.2 : Biventricular pacemaker

iv) Biventricular pacemaker programming

At implant the pacemaker was programmed for sham pacing (VVI30). During the acute and chronic components of the study the pacemaker was programmed to one of two modes either (i) Active Biventricular pacing (BiV) or (ii) Sham pacing mode(VVI30), in effect no pacing. On the day of the acute component of the study, the pacemaker had its lead stability, integrity, pacing thresholds and sensitivities measured to ensure consistent ventricular pacing when active. For active pacing the pacemaker was programmed to BiV pacing mode. When in BiV pacing mode an atrioventricular delay (A-V delay) was set to 90ms together with LV and RV pacing lead outputs and vectors set to ensure consistent capture of the ventricles whilst avoiding Phrenic nerve stimulation. When active BiV pacing, the delay between the LV and RV pacing (V-V delay) was set to the minimum possible 0-4ms. For the chronic component of the study identical pacemaker settings were used for active BiV and for sham pacing (VVI30) as were used in acute component, with a complete pacemaker check at crossover.

v) Exercise gated radionuclide ventriculography

Within two weeks of pacemaker implantation patients completed a protocol of graded semi-supine exercise gated radionuclide ventriculography with and without BiV pacing (Figure 2.3).

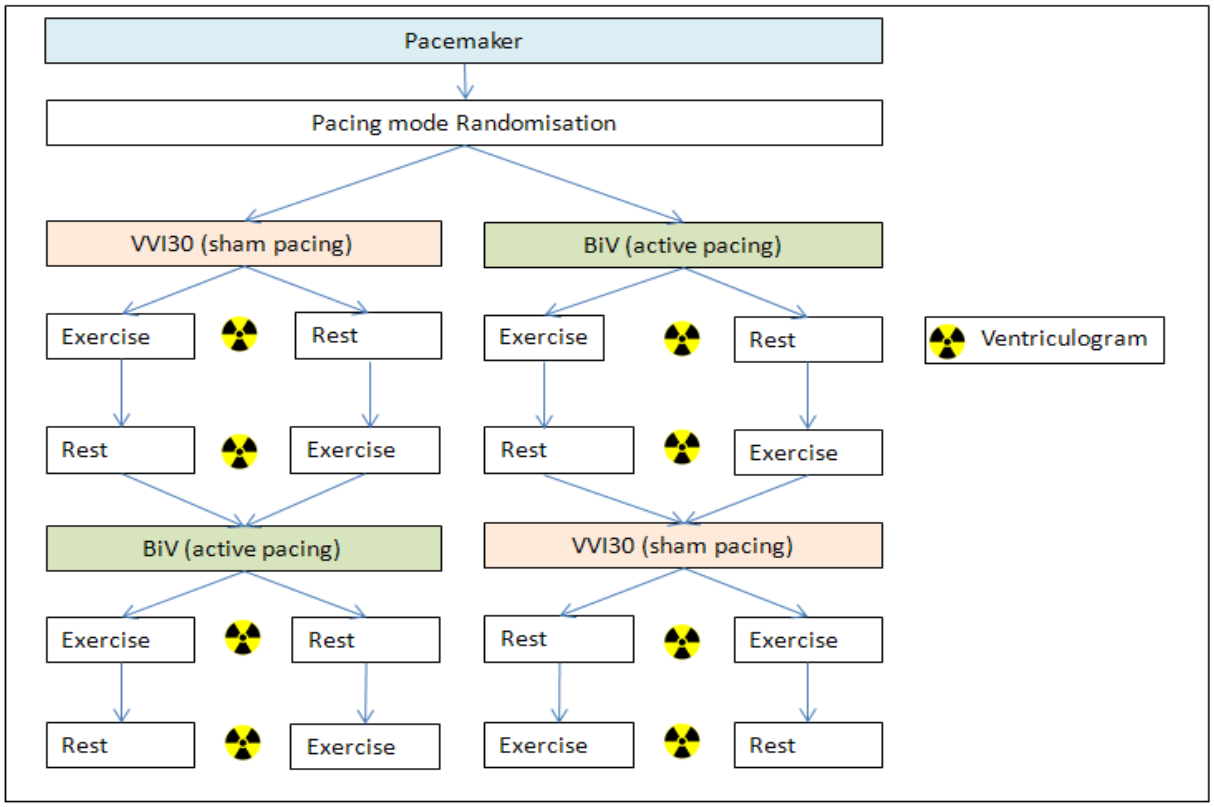

Figure 2.3 : Flow chart Acute Study: Exercise Radionuclide Ventriculography. This protocol was completed, within one session, as part of the Acute study component.

Patients undertook two levels of semi-supine workloads i) Rest or at ii) 50% of heart rate reserve (based on a prior maximum exercise test, see Inclusion criteria - peak metabolic exercise test) in random order. These were undertaken in BiV and sham pacing modes, in random order. The patient's brachial blood pressure was manually measured during the final minute of scintigram acquisition. A set of four, gated ventriculograms were acquired per patient.

Red blood cells were labelled by means of a modified in-vivo technique[312]: in brief, 10 minutes after intravenous injection of stannous pyrophosphate (0.02 mg/kg), 5 mL blood were drawn into a heparinised syringe and agitated for 20 minutes with 750MBq of Technetium-99m-pertechnetate before reinjection.

Left ventricular end systolic, and end diastolic volumes, ejection fraction and rates of diastolic filling were assessed by equilibrium R-wave gated blood pool scintigraphy. We used a small field of view gamma camera fitted with a parallel hole, general purpose, low energy collimator (camera Olivetti Modulo-M-200ESL) which was linked to a dedicated microprocessor. Studies were carried out at rest and during graded semi-erect exercise (achieving 50% of heart rate reserve) on a cycle ergometer (Lode B.V medical technology, Groningen, Netherlands)[313] as previously described by our group[42] with and without active BiV pacing. With the patient on the cycle ergometer, the detector was adjusted for the left anterior oblique view with the best ventricular separation and 10 to 15 degrees of caudal tilt. Each RR interval was divided into 32 equal frames throughout with a 20% tolerance window was set about the patient's heart rate. A constant number of frames per RR interval ensured consistent temporal resolution during diastole at all heart rates.

Data from each beat were acquired into a memory buffer in a 64x64 "word" matrix and if accepted were reformatted with two-thirds forward, one-third backward gating. 3 minutes of data was acquired during rest and on exercise following a 60 second period for stabilization of heart rate (RR interval). In order to be able to make the volumes derived from each scintigram comparable, the physiological (during exercise mobilisation of red cells from the spleen results in a reduction in radioactive counts per ml of blood[4]) and physical decay was corrected for, by taking a 5ml sample of blood into a preweighed tube at the beginning of each acquisition. The composite

cycle derived from each stage was spatially and temporally filtered. Left ventricular counts in each frame were determined by a semi-automated edge-detection algorithm. Data were analysed using Link Medical MAPS software, Sun Microsystems (Figure 2.4).

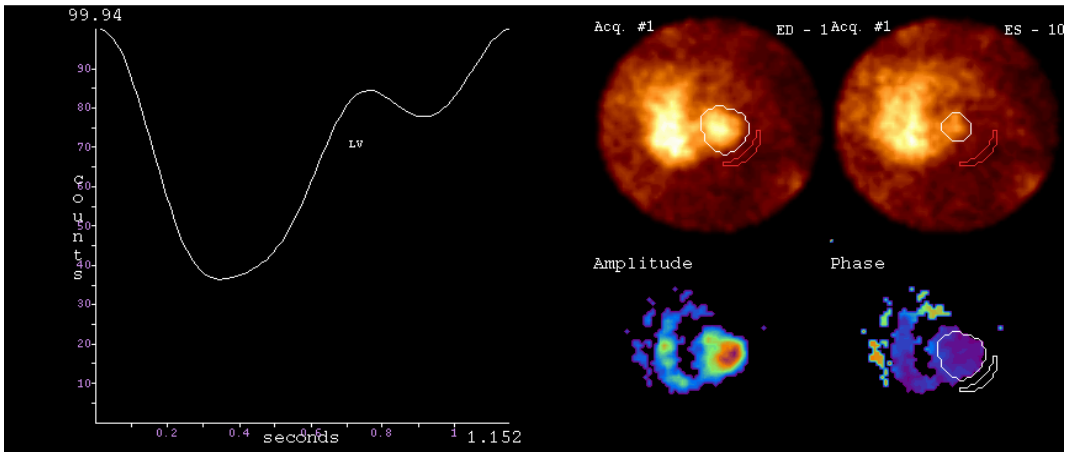

Figure 2.4 : Time activity curve/Ventriculogram

The following volumes were measured, LV end-diastolic volume, LV end-systolic volume, and stroke volume. LV end-systolic elastance index was calculated from ESP/end-systolic volume ratio [314]. Changes in volume are expressed as a percentage of baseline. From the LV time activity curve filling fractions were derived by splitting the diastolic filling phase of the LV time activity curve (minimum volume to maximum volume) into 3 equal tertiles. The proportion of filling occurring during each tercile of diastole expressed as a percentage of total filling (Figure 2.5).

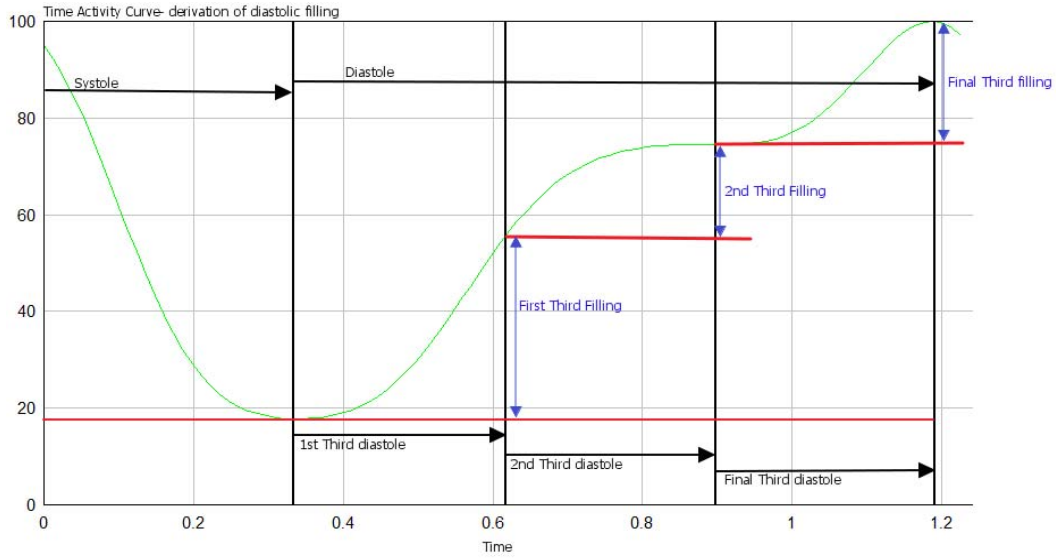

Figure 2.5 : Time activity curve derivation of filling thirds

vi) Lower body negative pressure with gated radionuclide ventriculography

Changes in ventricular volume were assessed before (LBNP0) and following the application of lower body negative pressure (LBNP30)[4, 315] whilst measuring LV function using gated radionuclide ventriculography as described above. The patient lay supine in a specially constructed Perspex lower-body negative pressure tank, encased from below the iliac crests in an airtight seal. Lower body negative pressure of 30mmHg (LBNP30) was applied in order to volume off load the right ventricle. A scintigram was acquired in the left anterior oblique view, prior to and following the application of Lower-body negative pressure of 30mmHg for six minutes; during the final 4 minutes of which the scintigram was acquired. The patient's brachial blood pressure was manually measured during the final minute of scintigram acquisition. Gated ventriculograms were acquired during sham pacing and in BiV pacing mode (Figure 2.6). Each pacemaker mode was given a five-minute run in period before image acquisition. A 5ml sample of blood was taken, into a previously

weighed tube, at the beginning of each image acquisition in order to correct for physical and physiological decay, so as to make volumes measured comparable. A set of four, gated ventriculograms were acquired per patient. This protocol was completed the same day as the exercise gated radionuclide ventriculography studies.

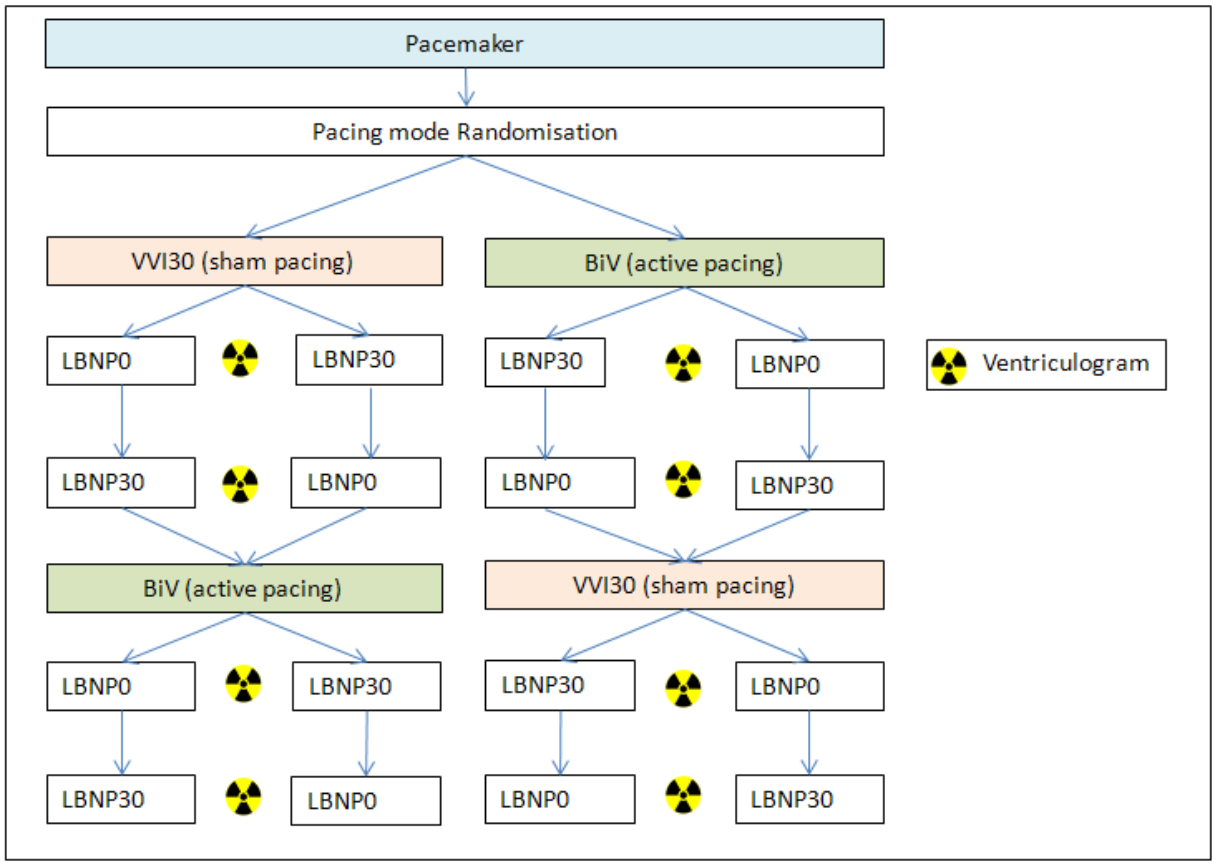

Figure 2.6 : Flow chart Acute Study: LBNP Radionuclide Ventriculography. Ventriculograms were acquired when lower body negative pressure applied was 0mmHg (LBNP0), then repeated with a lower body negative pressure of 30mmHg (LBNP30). This was done following sham (VVI30) and active pacing (BiV).

vii) Normalised ventricular septal radius of curvature (Rs)

This measurement is based on methodology described by Dong et al.[316]. From the gated radionuclide ventriculography end diastolic frame (Figure 2.7), the ventricular septum was traced. The septal radius of curvature (R) was measured over the middle 60% of the ventricular septum. This was then normalised for LV area as follows. The end diastolic LV region was measured, from which a radius (r) is calculated based on the assumption of the LV profile being a circle. The normalised radius of curvature (Rs) is then calculated by calculated by dividing R by r. The flatter the septum, the greater the normalised radius of curvature (Rs).

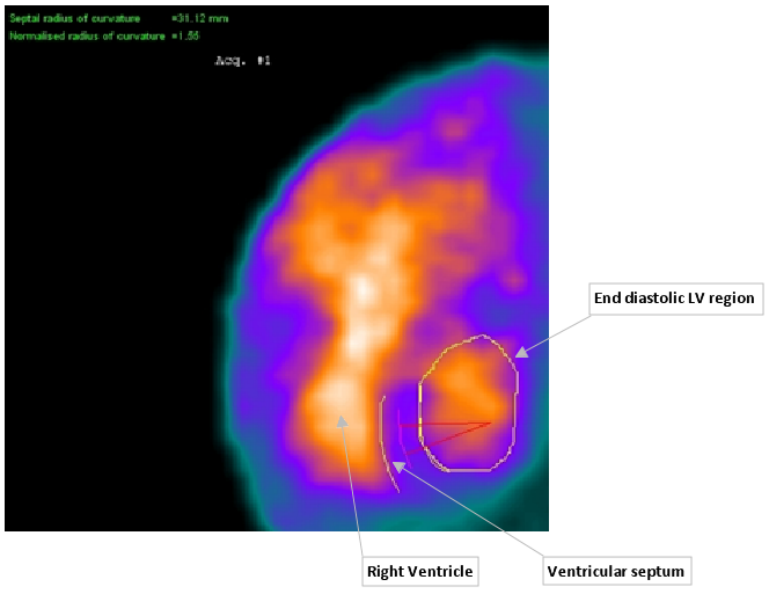

Figure 2.7 : Gated radionuclide ventriculography end diastolic frame.
Using this image ventricular septal radius of curvature measurements (R) were made.

viii) Transthoracic Echocardiography

These studies were carried out during the Acute study component, then following 4 months of active BiV pacing and again following 4 months of sham pacing (VVI30).

a) Two-Dimensional Echocardiography

Standard Echocardiography, including tissue doppler studies were performed with patients in the left lateral decubitus position (Vivid 7, GE Vingmed Ultrasound, Horten, Norway). Images were acquired using a 2.5MHz transducer. From the parasternal window, short axis views were acquired from 3 levels (basal, papillary muscle and apical levels (distal LV cavity where papillary muscle is not visible) [177]) and a standard long-axis view was recorded. From the apical window standard two-chamber, four-chamber, and long axis views were acquisitioned. Blood flow velocity profiles were assessed using standard doppler. Two-dimensional gray scale images were acquired at a minimum 60 frames per second (fps). Pulsed wave tissue doppler images were acquired at a minimum of 150fps, with sector width and depth being adjusted to obtain the highest frame rate. 2D gray scale and color coded tissue doppler images were saved as 3 consecutive cycles, triggered to the QRS complex in a digital format for analysis post-acquisition. Mitral annulus velocities (pulse wave tissue doppler imaging [PW-TDI]) were recorded from basal anterolateral and basal inferoseptal segment in apical 4-chamber view. Left atrial volumes were calculated using the area length method from apical 2 and 4 chamber views as has been previously described [317] calculated LA volumes were indexed to body surface area to derive LA volume index (LAVI). LV mass was calculated by the area length method and then indexed to body surface area to determine the LV mass index as previously described [318]. The greatest thickness measured in the LV wall at any short axis parasternal view was considered to represent maximal wall thickness in HCM patients [319].

LV volumes were calculated using Simpsons biplane method, using the apical four and two- chamber planes, and LV ejection fraction was derived from LV volumes in diastole and systole using a modified Simpson's formula [317]. Stroke volume was calculated from the product of time velocity integral and cross sectional area of the left ventricular outflow tract. Cross sectional area of the LVOT was measured from the parasternal long axis view, immediately beneath aortic annulus, midsystole, inner edge to inner edge. Cardiac output[320] was derived from stroke volume and heart rate. LV Myocardial performance index was calculated as the sum of isovolumic contraction and relaxation time divided by LV ejection time[321]. All measurements were taken from 3 consecutive beats and an average derived. Transmitral blood flow was assessed by placing a pulse wave doppler sample volume at the mitral valve tips, 3 cardiac cycles were recorded.

b) Speckle Tracking

Speckle tracking (STE) is a direction independent, non-doppler method which utilizes information from 2d gray scale images to assess myocardial mechanics. This method temporally tracks the displacement of unique speckle footprints through successive digitally stored two-dimensional B-mode images[175]. The distance between the speckles is measured as a function of time, from which parameters of myocardial velocity and deformation including strain, strain rate and rotational velocity can be derived[177 178].

To allow high quality STE analysis, high definition standard B-mode images, at a minimum frame rate of 60fps were acquired. Images were acquired from the apical 2-, 4-, and long axis views, as well as the parasternal short axis views at the basal level (identified with the mitral valve), the mid-level (identified with papillary muscles) and apex (below the papilla), obtaining images which by eye had the most circular geometry in order to try and avoid oblique views[178]. Speckle

tracking analysis was carried out using Echopac software (version 4.2.0). From an end-systolic single frame, a region of interest was traced on the endocardial cavity interface by a point and-click approach. Then an automated tracking algorithm followed the endocardium from this single frame throughout the cardiac cycle. Further refinement of the region of interest was performed to ensure that all of the myocardial regions of interest were included in STE analysis. Adequacy of two-dimensional image tracking was verified in real time. A tracking score of ≥ 2.5 was accepted. This method has been validated with MRI, the current gold standard methodology for non-invasive assessment of myocardial deformation[322], to be accurate in providing measures of myocardial strain[176, 323]. Left ventricular peak, longitudinal, radial and circumferential strain and strain rate in each view were calculated with the use of the entire length of the LV myocardium.

c) Echocardiographic Assessment of Intraventricular Synchronicity

Colour coded Tissue Doppler Images (TDI), (with sector width, depth, gain settings, pulse repetition frequency, and color saturation optimization to acquire a minimum frame rate of 90 frames per second (fps)) were obtained from the apical four, two and long axis views. At least three consecutive beats were stored and post image acquisition analysis was done using a customized software package (Echo Pac version 4.2.0 for PC, GE Vingmed Ultrasound). To assess left ventricular systolic intraventricular synchronicity myocardial pulse tissue doppler velocity profile signals were reconstituted from each of 12 segments of the left ventricle, using a six basal and six mid-segmental model derived from apical 4, 3 and 2 chamber images. With use of the onset of QRS complex as the reference point, the time to peak myocardial systolic velocity (S wave) and peak early diastolic velocity (E wave) were measured for each of the 12 segments. From these time interval the following indices of dyssynchrony were derived i) The standard deviation of the time

to onset of peak longitudinal systolic velocity for twelve segments[173] (Yu Index) (LTs-SD) and likewise for early diastolic velocity (LTe-SD) [151] , ii) Basal septal to lateral delay in time to peak velocity (LTs(S-L)) [163] and iii) Maximum difference of time to peak systolic velocity for the basal six segments left ventricle[289](LTs-peak[basal]), iv) Maximum delay between peak systolic velocities among the four walls (4c and 3c views) at the basal level[14]. The left ventricular pre-ejection time (>140ms) was measured as marker of global left ventricular synchrony (QRS onset to start of Doppler flow in the aortic outflow tract)[184].

Indices of dyssynchrony, as derived using color-coded tissue doppler measures of velocity, were similarly, derived from Speckle tracking data. From Speckle tracking derived longitudinal and radial *strain*, the following indices of dyssynchrony were derived[174] i) Standard deviation of time to peak longitudinal systolic strain 12 segment model of LV(LTε-SD) ii) Radial dyssynchrony was measured from the short axis mid-left ventricular (papillary) view. The short axis view was divided into 6 standard segments. Standard deviation of time to peak systolic radial strain for these six segments[178]was derived as an index of radial dyssynchrony (SD_{t6s}) and time delay between the peak strain in the anteroseptal and inferolateral segments and time difference between the earliest and latest segments (AS-P delay)[179] were used as measures of dyssynchrony[324].

d) Echocardiographic Assessment of Interventricular Synchronicity

Colour coded tissue doppler imaging was used to assess Interventricular dyssynchrony. The delay in time to peak systolic velocity between basal free wall of the right ventricle and the basal LV lateral segments[161] was measured (Ts LV-RV). To further assess inter-ventricular dyssynchrony pulse wave doppler images of aortic and pulmonary flow velocities were used. Interventricular mechanical delay was calculated as the difference between the ECG derived Q

wave and the onset of the LV outflow (Aortic pre-ejection time) and the onset of RV outflow (Pulmonary pre-ejection time) (Qp-Qs)[184].

e) Echocardiographic Assessment of Atrioventricular Synchrony

Atrioventricular synchrony was assessed by measuring the proportion of the RR interval occupied by left ventricular filling. LV filling duration was measured as the time from the onset of the E wave to the end of the A wave on transmitral pulsed wave doppler. A LV filling time of less than 40% percent of R-R interval, was suggestive of atrioventricular dyssynchrony[184, 325, 326].

f) Echocardiographic Assessment of Diastolic Function

This was assessed indirectly by looking at blood flow patterns through the heart, with standard doppler and directly by assessing myocardial tissue velocities with pulsed wave tissue doppler, and by combinations of the two.

A trans-Mitral blood flow velocity profile was acquired by placing a pulsed waved doppler sampling volume at the mitral valve leaflet tips in the apical 4 chamber view. This profile has an early component, the E wave, and a late filling component the A wave. The ratio of these (E/A), and the deceleration time(DT) of the early filling wave (E) were measured[327]. To assess early diastolic filling, the isovolumic relaxation time (IVRT) was measured. This was acquired by placing a pulsed wave doppler sample volume between the aortic and mitral valve, in the apical 4 chamber view[328]. Myocardial tissue velocities were measured, as a direct measure of LV relaxation, using pulsed wave tissue doppler imaging. Pulsed wave tissue velocities are measured during image acquisition from the Mitral valve annulus, lateral and septal sites. These have characteristic profiles, consisting of a systolic velocity (s'), early diastolic velocity (e') and a late

diastolic velocity (a'). The ratio E/e' was derived from blood flow and tissue velocity profiles to provide a more preload independent estimate of LV filling pressures[329].

f) Echocardiographic Assessment of Myocardial Rotation

Rotation of the LV base and apex was measured using STE analysis. Speckle tracking analysis was applied to 2d gray scale images acquired from the basal and apical short axis views, to derive basal and apical LV global rotation (rot) and LV rotational rates (rot-r) respectively (Figure 2.8).

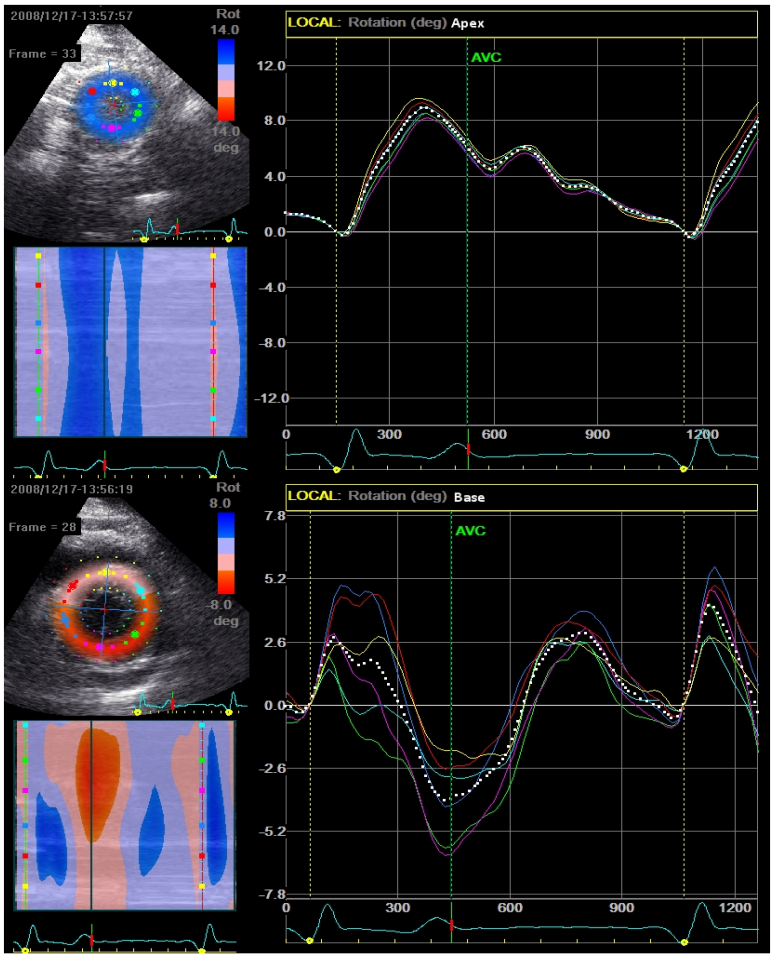

Figure 2.8 : STE derived rotation. This is an example of STE measured myocardial rotation(degrees) of the Apex (top image) and Base (lower image). Aortic Valve Closure (AVC).

These data were first exported to a spreadsheet program (Excel 2010, Microsoft Corp, Seattle, Washington) and then exported to DPlot Graph Software (2001-2008 by HydeSoft Computing, Inc) to allow calculation of LV twisting and untwisting rates[177]. To adjust for variance in heart rate that may occur between basal and apical image acquisition and so allow isochronous comparison of basal and apical rot/rot-r the R-R interval was converted to 100%. Left ventricular twist (twist rate) was calculated as the isochronous net difference between apical and basal rotation (rotation rate) (Figure 2.9).

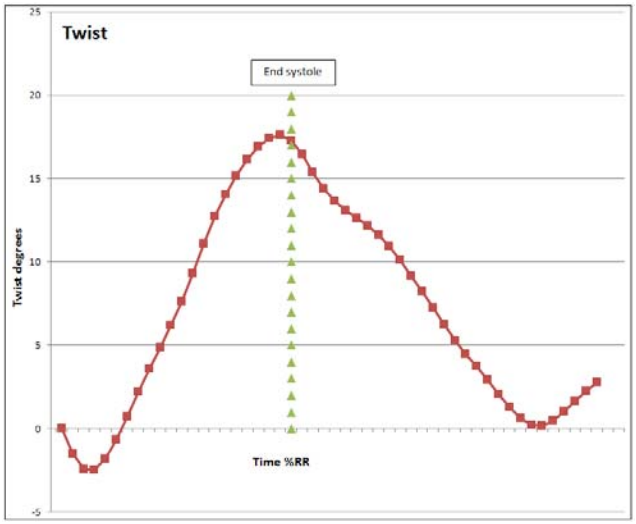

Figure 2.9 : Twist. Each point (red box) represents an isochronal difference between apical and basal rotation, thus giving a twist value.

ix) Symptom status assessment

An assessment of symptoms was made at baseline (0 months), at cross over (4 months) and at completion of study (8 months), patients scoring their symptoms by completing the Minnesota Living with Heart Failure questionnaire (Figure 2.10).

MINNESOTA LIVING WITH HEART FAILURE® QUESTIONNAIRE

The following questions ask how much your heart failure (heart condition) affected your life during the past month (4 weeks). After each question, circle the 0, 1, 2, 3, 4 or 5 to show how much your life was affected. If a question does not apply to you, circle the 0 after that question.

Did your heart failure prevent you from living as you wanted during the past month (4 weeks) by -	**No**			**Very Little**					**Very Much**
1. causing swelling in your ankles or legs?	0	1	2	3	4	5
2. making you sit or lie down to rest during the day?	0	1	2	3	4	5
3. making your walking about or climbing stairs difficult?	0	1	2	3	4	5
4. making your working around the house or yard difficult?	0	1	2	3	4	5
5. making your going places away from home difficult?	0	1	2	3	4	5
6. making your sleeping well at night difficult?	0	1	2	3	4	5
7. making your relating to or doing things with your friends or family difficult?	0	1	2	3	4	5
8. making your working to earn a living difficult?	0	1	2	3	4	5
9. making your recreational pastimes, sports or hobbies difficult?	0	1	2	3	4	5
10. making your sexual activities difficult?	0	1	2	3	4	5
11. making you eat less of the foods you like?	0	1	2	3	4	5
12. making you short of breath?	0	1	2	3	4	5
13. making you tired, fatigued, or low on energy?	0	1	2	3	4	5
14. making you stay in a hospital?	0	1	2	3	4	5
15. costing you money for medical care?	0	1	2	3	4	5
16. giving you side effects from treatments?	0	1	2	3	4	5
17. making you feel you are a burden to your family or friends?	0	1	2	3	4	5
18. making you feel a loss of self-control in your life?	0	1	2	3	4	5
19. making you worry?	0	1	2	3	4	5
20. making it difficult for you to concentrate or remember things?	0	1	2	3	4	5
21. making you feel depressed?	0	1	2	3	4	5

Figure 2.10 : Minnesota Living with Heart Failure Questionnaire

x) Cardiopulmonary exercise testing

Patients underwent an erect treadmill test, symptom limited, using a standard ramp protocol with simultaneous respiratory gas analysis[330, 331](Schiller CS-200 Ergo-Spiro exercise machine). This test was carried out as part of the inclusion/exclusion criteria screening, then at the cross over point of the chronic study (4 months), then at study exit (8 months) (Figure 2.1). All patients underwent spirometric studies prior to each exercise test. During the treadmill test samplings of expired gases was performed continuously, and data expressed as 30s means. Minute ventilation, Oxygen consumption, Carbon Dioxide production and the respiratory exchange ratio (RER) were measured. Peak Oxygen consumption, expressed in ml/kg/min (Peak VO_2), was defined as the greatest VO_2 attained by the patient during the exercise test. Cardiac monitoring by ECG was continuous throughout the exercise test. Blood pressure at the brachial artery was measured manually using a cuff sphygmomanometer every minute throughout the test. Active encouragement was given to patients to continue exercising till exhaustion, achieving a minimum RER of at least 1.

xi) Statistical analysis

Randomised and controlled trial outcome data may be examined by conducting an intention to treat (ITT) or Per-protocol (PP) analysis. The ITT approach, includes all randomized patients in the groups to which they were assigned, regardless of their adherence to entry criteria, of the treatment they actually received, and regardless of subsequent withdrawal from treatment or deviation from protocol[332]. In brief a 'once randomized, always analysed' approach to trial data analysis. ITT reflects real-life clinical scenario more closely, as it acknowledges variable compliance, and protocol non-adherence. An ITT analysis maintains the balance generated from

the original randomisation. ITT analysis preserves sample size and hence statistical power[333]. It minimizes type I error and allows for greater generalizability of subsequent trial outcomes[334]. However, if a patient who actually receives no treatment is included in the analysis as a subject who received treatment, in particular for mechanistic studies, then the information it provides about effect of treatment on the mechanism under scrutiny will be limited, if not incorrect. Furthermore, ITT analysis is prone to under-estimate of treatment effect because of dilution due to non-compliance. Interpreting the outcomes of an ITT analysis may become difficult if a large number of patients break with protocol, and cross over to the opposite limb of the study[335]. ITT analysis may then fail to reject the Null hypothesis (Type II error).

A Per Protocol (PP) analysis of data, could be defined as the examination of the subset of the ITT population who completed the study without any protocol violation[336]. Also, known as an "on-treatment" analysis, as those "off-treatment" are excluded. The PP analysis answers the question as to whether the treatment works among those that comply, allowing retention of clarity when investigating underlying mechanisms of disease, in so doing a PP approach is a more sensitive approach then ITT analysis in determining the biological effect of the new treatment modality. It should, perhaps, be the preferred analysis for purely mechanistic studies[337].

However, when considering treatment effect of a new therapy excluding patients who do not comply makes PP analysis more likely to reject the Null hypothesis (Type I error), and the result less generalisable when considering the real world practical value of the new therapy.

Data were analyzed using SPSS version. 17.0 for Window and Microsoft Office Excel 2010, and expressed as mean ± standard error (sem). Comparisons of variables were determined by Student's t-test (2-tail) if variables were normally distributed and the Mann-Whitney U-test if the

data were non-normally distributed. Categorical variables were compared with the Pearson chi-square test. A difference of $p < 0.05$ was taken to indicate statistical significance.

During the chronic component of the study, comparison of the measured variables between BiV pacing, and sham pacing was performed using repeated measures analysis of variance. Statistical significance was set at $p< 0.05$.

The Acute Study

Chapter 3) *The effects of acute biventricular (BiV) pacing on left ventricular dyssynchrony in patients with Hypertrophic Cardiomyopathy (HCM) at rest.*

Chapter 4) *The effects of acute BiV pacing on myocardial function during exercise in HCM.*

Chapter 5) *The impact of right ventricular volume unloading, using Lower Body Negative Pressure (LBNP), on Left ventricular diastolic function in patients with HCM, with and without Biventricular pacing.*

Chapter 3

The Acute Study

The effects of acute Biventricular pacing on left ventricular dyssynchrony, in patients with Hypertrophic Cardiomyopathy at rest.

Introduction

As discussed in the General Introduction (section Dyssynchrony in Hypertrophic Cardiomyopathy) several investigators have reported dyssynchronous contraction and relaxation in patients with HCM[11, 140-143], which is probably related to the loss of normal architecture of the underling substrate with myocyte disarray, fibrosis and microvascular ischemia (Figure 1.4). A number of techniques have been used to demonstrate this discoordinate functioning of the Hypertrophic cardiomyopathic myocardium. The current gold standard in myocardial imaging, MRI, has also been used to demonstrate and quantify the presence of myocardial dyssynchrony in patients with HCM. Importantly Bonow et al.[147] demonstrated that amelioration of diastolic dyssynchrony using Verapamil was associated with improved global diastolic function. This study, though over 25 years old, is still cited today for the current use of Verapamil in patients with HCM.

Using contemporaneous ultrasound echocardiography techniques, (as discussed in the General introduction section Measuring dyssynchrony using echocardiography) a number of investigators have demonstrated that despite a normal QRS interval (an electrical synchrony surrogate) in patients with HCM, there is evidence for the presence of mechanical dyssynchrony. Dyssynchrony has been demonstrated to be present both intra- and interventricular, and to be directly correlated with wall thickness.

Biventricular pacing (as discussed in Chapter 1 Biventricular Pacing) has been shown to be life prolonging in patients with systolic heart failure. Of the several postulated mechanisms involved in producing benefit from BiV pacing, one that has been suggested is the attenuation in dyssynchronous myocardial contraction. Numerous studies have demonstrated exactly this using contemporary ultrasound imaging techniques. The correction of intraventricular dyssynchrony

using BiV pacing has been correlated with parameters of improved global cardiac function [161], reduction in symptom status, and improved exercise tolerance[163].

However, to date no studies have addressed the possible effects of BiV pacing on dyssynchrony in patients with symptomatic non-obstructive hypertrophic cardiomyopathy. Thus, the aim of this study was to answer this specific question. We hypothesized that BiV pacing would acutely improve echocardiographic parameters of dyssynchrony in patients with HCM.

Methods

29 HCM patients (20 males mean age 55years), were selected according to the inclusion and exclusion criteria described in Chapter 2 (section ii). Two sets of Echocardiographic studies were carried out on these patients at rest, during sham pacing and then after 1 hour of BiV pacing, as described in Chapter 2 (section iii). 4 measures of myocardial systolic synchrony and 1 measure of diastolic synchrony, and 2 measures of interventricular synchrony were assessed using conventional doppler, tissue doppler and STE echocardiographic techniques as described in Chapter 2 (section viii).

Statistical analysis

In brief data were analysed using SPSS v17.0 and Microsoft Excel. Comparisons of variables were determined by the Students paired t test. A difference of $p<0.05$ was taken to indicate statistical significance (see Chapter 2 section xi for details). Using SPSS retrospective observed power calculations were carried out for results with $p > 0.05$.

Results

The clinical and cardiopulmonary characteristics of the study population are shown in Table 3.1. 29 patients were able to tolerate active Biventricular (BiV) pacing. Patients had a lower

exercise capacity as compared to healthy controls[338], with significant symptoms. Baseline QRS interval was not prolonged.

Over half the patients were on rate limiting medications (beta blockers and/or calcium channel blockers). These were continued throughout the study period.

LV ejection fraction on echocardiography was unchanged following acute BiV pacing, with no change observed in LV filling time, E/A ratio or in E/E' (Table 3.2).

Speckle Tracking

Speckle tracking derived measures of systolic intraventricular dyssynchrony are show in Table 3.3. SDt_{6S} and AS-P delay both demonstrated a tendency towards reduction, though statistical significance was not achieved.

Tissue Doppler Imaging

Both indices of systolic intraventricular dyssynchrony measured using TDI were reduced following BiV pacing. The Yu index of systolic dyssynchrony was significantly reduced (p=0.005) following application of acute BiV pacing,(Table 3.3, Figure 3.1). Similarly, the basal systolic intraventricular dyssynchrony as measured using TDI, was reduced (p=0.05). Diastolic intraventricular dyssynchrony measured using TDI did not show any significant change following acute BiV pacing (p=0.941), (Table 3.3).

Parameters of interventricular dyssynchrony as measured using TDI did not show any significant change following acute biventricular pacing (p= 0.81) similarly, interventricular dyssynchrony measured using conventional pulse wave doppler, did not demonstrate any significant change following BiV pacing (p= 0.36), (Table 3.3).

Table 3.1 Baseline characteristics of study population

Age (Years)	55±2.11
Heart Rate (bpm) – Baseline Resting	67.82±2.7
Systolic BP (mmHg)- Baseline Resting	129.48±3.47
Diastolic BP (mmHg)- Baseline Resting	77.07±1.69
$VO_{2\ max}$ ml/kg/min (% predicted)	17.89±0.76 (45.93±3.20)
Peak Heart rate achieved bpm	119±4.44
Exercise duration(Sec) -Baseline	422±25
Minnesota QOL score- Baseline	49.07±4.08
ECG QRS (ms)- Baseline Resting	98.82±4.05
Drug therapy	**n**
Beta-blocker	15
Ca^{2+} Channel Blocker	15
Diuretic	6
ACE inhibitor	7
Warfarin	3
Echocardiography	
Mean Wall Thickness (MWT) (mm)	18.65±0.88
Left Atrial Volume Index ml/m2 - Baseline	35.42±1.87
LV EF, %	61.68±1.22
Mitral E velocity, m/s	0.73±0.04
Mitral A velocity, m/s	0.71±0.04
Mitral E/A ratio	1.16±0.10
TDI S velocity, cm/s	0.05±0.003
TDI E' velocity m/s	0.05±0.003
TDI A' velocity cm/s	0.04±0.006
E/E'	15.67±1.87

LV EF Left Ventricle Ejection Fraction; TDI Tissue Doppler Imaging
Values are mean ± sem (standard error mean)

Table 3.2 Effect of Acute Biventricular (BiV) pacing on echocardiographic variables.

At Rest Whole Group n=29	**VVI30**	**Acute BiV**	***p***
LVEF, %	62.54±1.28	65.30±1.43	0.13
LAV Index (ml/m^2)	35.07±1.73	30.08±2.12	0.11
RV Tei Index	0.39±0.07	0.32±0.05	0.86
Isovolumic Relaxation Time (ms)	118.44±4.31	120.18±5.84	0.71
Isovolumic Contraction Time (ms)	11.65±23.22	11.17±28.16	0.75
LV Tei index	0.43±0.07	0.35±0.08	0.25
AoV Peak Gradient (mmHg)	11.83±2.53	7.69±0.96	0.05
Cardiac index l/min/m^2	3.57±0.27	3.46±0.19	0.25
LV Filling time (s)	0.52±0.02	0.53±0.02	0.55
Mitral E velocity (m/s)	0.71±0.03	0.71±0.04	0.92
Mitral A velocity (m/s)	0.68±0.04	0.68±0.04	0.87
E/A ratio	1.16±0.09	1.13±0.08	0.70
Mitral DT (ms)	235.25±9.81	262.75±15.45	0.16
E/E'_{antlat}	15.01±1.66	12.42±1.10	0.06
Total Isovolumic time s (60s)	12.58±1.59	13.50±2.22	0.74
Total LV ejection time s (60s)	17.80±0.75	17.05±0.89	0.55
Total LV filling time s (60s)	29.61±1.48	29.44±1.87	0.94
Effective LV Filling Time(FT) (FT/RR)	0.49±0.02	0.49±0.03	0.94
TAPSE (mm)	14.27±1.74	14.48±1.78	0.75

Values are mean ± sem. p values are for BiV *vs*. VVI30.

Table 3.3 Effects of Acute BiV pacing on dyssynchrony at rest n=29. mean ± sem

	Acute Pacing Mode		
Intraventricular dyssynchrony n=29	**VVI30**	**BiV**	***p***
[178]SDt_{6s} (s) (ste)	0.058±0.007	0.039±0.01	0.14
[178]AS-P delay by RS (s) (ste)	0.11±0.01	0.053±0.018	0.078
[173]Yu index by TDI (s)	0.07±0.009	0.038±0.007	0.005
[14]Basal systolic dyssynchrony TDI (s)	0.10±0.01	0.084±0.017	0.053
[151]Diastolic dyssynchrony Te-SD TDI (s)	0.049±0.006	0.051±0.034	0.941
Interventricular dyssynchrony n=29			
Qa-Qp (ms)	14.27±3.24	15.90±3.35	0.36
Ts LV-RV TDI (s)	0.08±0.01	0.09±0.02	0.81

ste: speckle tracking
SDt_{6s}: Standard Deviation time to peak systolic radial strain for six segments papillary level
AS-P delay by RS: Anteroseptal – Posterior wall delay in time to peak Radial Strain.
Te-SD: Standard deviation 12 segments to peak early diastolic velocity (e).
Basal systolic dyssynchrony TDI: Maximum delay between peak systolic longitudinal velocities basal level four walls.
Qa-Qp: Pre-ejection interval difference aortic and pulmonary flow.
Ts LV-RV: Time interval (Ts) to peak longitudinal systolic velocity basal wall lateral left ventricle (LV) and basal free wall right ventricle (RV).
Values are mean ± sem. p values are for BiV *vs.* VV130.

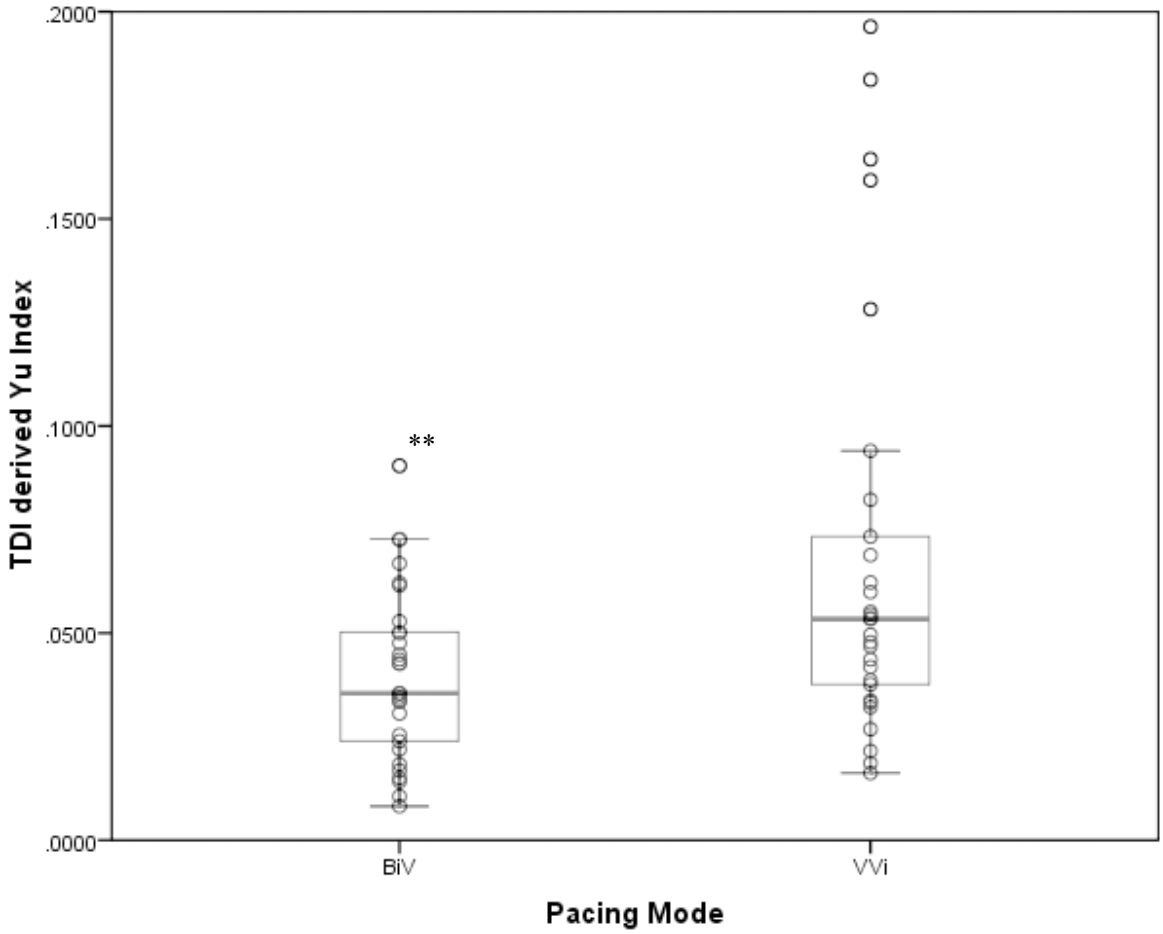

Figure 3.1 : Box-whisker plot showing data collected in 29 patients. TDI derived Yu index during sham pacing (VVI) and following Acute active pacing (BiV). Open circles show individual patients, bold line is median. **p = 0.005; BiV *vs*. VVi.

Discussion

Hypertrophic cardiomyopathy potentially harbors the correct substrate to produce clinically significant dyssynchronous myocardial contraction, with patchy myocyte disarray and fibrosis[339, 340]. Even with an intact rapid conduction network, the myocardium may still demonstrate mechanical dyssynchrony due to fibrosis, differential wall stresses, microvascular ischemia, and myocyte mal-alignment, all seen in hypertrophic cardiomyopathy[340, 341]. The duration of the QRS complex is often used as a surrogate marker for dyssynchronous myocardial contraction, however the relationship between the width of the QRS complex and response to BiV pacing is poor[342]. This may in part be explained by up to a third of patients with prolonged QRS not demonstrating mechanical dyssynchrony[343, 344]. Conversely mechanical dyssynchrony is not infrequently reported in heart failure patients with a narrow width QRS complex[345]. In patients with heart failure the presence of dyssynchrony is detrimental to both morbidity and mortaliy[346]

Acutely, biventricular pacing has been shown to be able to restore coordinate contraction in patients with systolic heart failure, with an immediate positive impact (in a heartbeat) on ventricular performance[259] and chronically on mortality and morbidity[264] with most benefit seen in patients with basal dyssynchrony[347, 348]. Rogers et al.[268] report that BiV pacing in patients with end-stage non-obstructive HCM (mean EF 41±14%), and left bundle branch block, improves symptoms and induces reverse remodeling of the left ventricle. However, comment on the impact of BiV pacing on measures of dyssynchrony is not made. As discussed earlier, Rinaldi et al.[274] reported a case series of 8 patients with obstructive HCM and preserved systolic function, experiencing varied clinical outcomes following BiV pacemaker implantation, with no comment made regarding dyssynchrony parameters. A literature review did not reveal any previously published work

examining the impact of BiV pacing on indices of dyssynchrony in patients with non-obstructive HCM with preserved systolic function.

In the present study, we investigated the acute effects of BiV pacing, at rest, on several measures of dyssynchrony, in patients with non-obstructive exercise limited HCM. Despite a narrow QRS complex, at baseline, the order of magnitude of dyssynchrony when measured using STE and tissue doppler, was similar to that described in patients with systolic heart failure[173, 178]. We observed that following acute BiV pacing there was a tendency for a reduction in LV intraventricular systolic dyssynchrony, similar to that reported in patients with systolic heart failure. However, we found that it was only the TDI-derived measures that reached statistical significance. A tendency towards a reduction in intraventricular dyssynchrony was seen using STE techniques, however statistical significance was not achieved. Though the sample size was small, a retrospective analysis of observed power was calculated at 80%, which would suggest lack of a true biological effect.

These are conflicting results. Tissue doppler imaging derived measures of dyssynchrony utilise data from the longitudinal motion (note, not contraction) of the myocardium data. However due to the orientation of epicardial and subendocardial fibers, myocardial contraction in principally radial[349]. Helm et al.[350] have demonstrated that in the failing heart, longitudinal derived indices are poorly sensitive to mechanical dyssynchrony. In contrast to TDI, speckle tracking derived measure of myocardial dyssynchrony are based on radial contraction. Suffoletto et al.[179] and others[178] have shown using STE, radial strain derived indices to be powerful predictors of response to BiV pacing in patients with systolic heart failure. Furthermore Chung et al.[289] showed that TDI derived measures of dyssynchrony suffer moderate to high intra- and inter-observer variability, as compared to STE derived measures of radial dyssynchrony[351]. STE derived strain overcomes some

of the inherent short comings of TDI, as discussed earlier, and may provide a more accurate measure of myocardial mechanics.

We found that measures of interventricular dyssynchrony were essentially unchanged by BiV pacing, perhaps unsurprising given that pre-pacing values were similar to post-pacing values reported in the literature[352]. The measure of diastolic dyssynchrony was unaffected following BiV pacing, similar results have been reported in systolic heart failure studies[284, 353]. If systolic contraction was more synchronous following BiV pacing one might anticipate that diastolic relaxation would as consequence be more synchronous, however given that only approximately a third of systolic heart failure patients have both systolic and diastolic dssycnhrony[354], suggests mechanisms more than just mechanical dyssynchrony at play.

In this study, all measures were carried out using 2-dimensional echocardiography at rest, with the patient supine. However, it is when erect and on exertion that most patients experience symptoms. This is a serious limitation of the current work, as it may be during exercise related myocardial stress when clinically significant myocardial mechanical dyssynchrony is prevalent. Furthermore, echocardiography was carried out 1 hour following initiation of BiV pacing. It is possible that this is not a duration long enough to have an impact significant enough on myocardium in HCM to be detected by speckle tracking.

Future studies performed using 3D speckle tracking echocardiography[355], on exercise, maybe able to provide a more comprehensive assessment of LV mechanics, overcoming some of the shortcomings of two-dimensional imaging at rest, and thus be able to make a more accurate assessment of the impact of BiV pacing on myocardial mechanics.

The question of whether the improvements seen acutely in systolic TDI measures of dyssynchrony are sustained chronically, and perhaps more importantly whether this translates into a clinically significant response will be addressed in the chronic component of this study.

Chapter 4

The Acute Study

The effects of acute Biventricular pacing on myocardial function during exercise in Hypertrophic Cardiomyopathy.

Introduction

Patients with HCM often complain of exertional breathlessness. In those patients who do not have obstruction to outflow at rest or on exercise[6] and who have normal systolic function, the symptoms of breathlessness and reduced exercise tolerance are attributed to diastolic dysfunction[8, 40, 356, 357], as discussed in Chapter 1. The suggested mechanisms contributing towards impaired diastolic function include altered ventricular relaxation, filling and compliance, producing symptoms of heart failure. As discussed earlier in Chapter 1, it has been shown in patients with systolic heart failure, with volume overload, and pulmonary hypertension, that restricted filling of the LV by pericardium and right ventricle may too have a part to play[4] in generating diastolic dysfunction. In patients with non-obstructive HCM, the established management options are largely limited to diastole prolonging pharmacotherapy[108], though Frenneaux et al. have recently demonstrated the benefit of metabolic energy modulation using Perhexiline[95]

A number of studies have now shown that BiV pacing can improve exercise capacity, improve the quality of life, and reduce mortality in patients with NYHA III/IV systolic heart failure with broad QRS complex. The mechanism of improvement has been thought to relate primarily to an amelioration of ventricular contractile dyssynchrony, giving rise to the commonly used term cardiac resynchronisation therapy. However reliable measures of dyssynchrony that may be used to predict response to BiV pacing have been frustratingly difficult to find, with almost innumerable indices described[163, 165, 167, 171, 173, 179, 181, 184, 358-361], this predicament is highlighted by current guidelines advocating no parameter of mechanical dyssynchrony when considering BiV pacing therapy[362, 363].

However our group has shown that at least some of the acute hemodynamic benefit seen by LV and BiV pacing in systolic heart failure is due to a reduction in the external constraint to LV

filling by the pericardium (pericardial constraint) and by the right ventricle through the interventricular septum, a phenomenon known as diastolic ventricular interaction (DVI) [10], as discussed in Chapter 1. We proposed that this benefit may be due to an alteration in the relative timing of LV *vs.* RV filling**.**

As discussed in the introduction there is reason to postulate that DVI may occur commonly in patients with Hypertrophic Cardiomyopathy who are very symptomatic. On exercise pulmonary artery pressure commonly rises markedly in patients with HCM[239](Figure 1.15), with the most marked increase seen at the lower exercise levels. This increase in PA pressure might be expected to cause enlargement of the RV on exercise, with leftward ventricular septal shift, and pericardial stretch, resulting in pericardial constraint and DVI. Animal studies [240, 242, 243], with increased pulmonary artery pressures, either via embolization or pulmonary artery constriction, support the concept of consequential deleterious diastolic ventricular interaction and loss of stroke work. Of important note in the animal studies, pericardiectomy contributed to an improvement in diastolic ventricular interaction. Then Biventricular pacing might be expected to affect a reduction in external constraint to LV filling by altering the relative timing of LV and RV filling, restoring the ability to utilize the Starling mechanism on exercise.

The goal of the present study was to look at ventricular function of HCM patients at rest and on exercise, with and without biventricular pacing specifically looking of LV end diastolic volumes, stroke volumes and ventricular filling patterns. We hypothesised that DVI may be present in some patients at rest, develop further on exercise, and may be relieved by BiV pacing.

Methods

This study was performed on the 29 HCM patients (20 males mean age 55years), selected according to the inclusion and exclusion criteria described in Chapter 2 section ii.

In brief changes in ventricular volume, and patterns of filling were measured, using gated radionuclide ventriculography, at rest and during semi-supine bike exercise (at 50% heart rate reserve) (as described in detail in Chapter 2 section v), with and without BiV pacing (as described in Chapter 2 section iv).

10 patients had images of paired studies of sufficient quality to allow normalised ventricular septal radius of curvature (Rs) measurements (as described in detail in Chapter 2 section vii). The ventricular septal radius of curvature was measured (normalised for LV area), at rest and during exercise with and without BiV pacing.

Statistical analysis

Data were analyzed using SPSS version. 17.0 for Windows and Microsoft Office Excel 2010, and expressed as mean ± standard error (sem), described in detail in Chapter 2 section xi.

Results

The clinical and cardiopulmonary characteristics of the patient cohort are shown in Table 3.1 (see Chapter 3). 29 patients were able to tolerate active Biventricular pacing. Patients had a significantly reduced exercise capacity, with significant symptoms. Baseline QRS interval was not prolonged. Over half the patients were on rate limiting medications (beta blockers and/or calcium channel blockers).

i) LVEDV response to exercise (Table 4.1 and Figures 4.1 and 4.2)

In the group, as a whole (n=29), during sham pacing, there was a failure of LVEDV to increase with exercise (-1.79±4.92% p=0.53) (Table 4.1). Patients were divided into two groups based on LVEDV response to exercise during sham pacing. Those in whom LVEDV fell during semi-supine exercise, suggestive of more marked diastolic dysfunction, (Group 1) (n=15) than those in whom LVEDV increased during semi-supine exercise (Group2) (n=14).

For the whole group (n=29) the change in LVEDV during exercise did not significantly differ between BiV pacing and sham pacing (p=0.18), (Figure 4.1). However, in Group 1 patients, there was a significant difference in LVEDV response to exercise between BiV *vs.* sham pacing with a modest increase in mean LVEDV with BiV pacing (p=0.004) (Figure 4.2). For differences between sham *vs.* BiV pacing see Table 4.1.

ii) Stroke volume (Table 4.1, Figures 4.3 and 4.4)

Stroke volume fell on exercise in Group 1 patients (-21.04±5.31%) during sham pacing, but increased during BiV pacing (5.80±7.66% p=0.008). In contrast, stroke volume increased during exercise in Group 2 patients (24.46±5.02%) with sham pacing and the response was similar during BiV pacing (p= 0.28), (Figure 4.4).

iii) Heart Rate (Table 4.3)

During sham pacing in the whole group, heart rate increased significantly in patients on exercise and in both Groups 1 and 2. Peak exercise heart rates were comparable in Groups 1 and 2 (p= 0.49). During sham pacing resting heart rate, though lower in Group 1(58±2.09) compared to Group two (63±2.61), was not significantly different (p=0.23), and may be a reflection of greater beta blocker and calcium channel blocker use in Group 1. Blood pressure increased appropriately

in patients in both Groups with no significant difference between the Groups 1 and 2 of peak pressure achieved (p=0.54).

iv) Left Ventricular contractile function at rest and during exercise (Tables 4.1and 4.3)

In the whole group, LV end systolic (es) elastance, a measure of LV contractile function, was similar at rest (p=0.80) and on exercise (p=0.41) during BiV *vs.* sham pacing. This was so in both Group 1 and Group 2 patients (Table 4.3). During sham pacing on exercise in Group 1 patients, LV end systolic elastance was statistically greater than in Group 2 (p=0.01) but this difference was largely driven by a single individual without whom p=0.07.

Similarly, LV ejection fraction did not significantly differ between BiV pacing and sham pacing at rest or on exercise (Table 4.3). However BiV pacing was associated with a significant shortening of the duration of systole at rest (p=0.03), and on exercise (p=0.002) *vs.* sham pacing, in the whole group (Table 4.3). In the two subgroups this tendency for a reduction in duration of systole with BiV pacing was maintained, but was most marked in Group 1 on exercise (p=0.02) (Table 4.3).

v) Diastolic Filling (Table 4.4, Figures 4.5-4.10)

In the whole group the percentage of total filling occurring in the first third of diastole was reduced both at rest and on exercise (p< 0.005) during BiV pacing *vs.* sham pacing (Figure 4.7). This effect was significant for Group 1 (p=0.02 rest, p=0.002 exercise), and for Group 2 (p= 0.01 rest p= 0.04 exercise) (Figure 4.9). The percentage of filling occurring in the final two thirds of diastole was accordingly increased in the whole group at rest (p< 0.005), (Figure 4.5), and during exercise (p< 0.005) (Figure 4.8), with significant increases in both Group 1 and Group 2 at rest, (Figure 4.6) and on exercise, (Figure 4.10). The diastolic filling period was substantially increased

on exercise in Group 1 patients, less so in Group 2 patients during BiV *vs.* sham paced mode, (Tables 4.3, and 4.5).

vi) Normalised ventricular septal radius of curvature (Rs) (Table 4.2)

In 10 patients, the radionuclide ventriculograms were of sufficient quality during both studies (BiV and sham pacing) to allow ventricular septal radius of curvature measurements, (5 from Group 1 and 5 from Group 2). Unpaced, during exercise there was a trend for an increase in Rs (p=0.08), this was more marked in Group 1 (1.75±1.09) patients as compared to Group 2 (1.09±0.03) patients. During BiV pacing, on exercise, the increase in Rs was less marked when compared to sham pacing (BiV Rs Exe 2.27±0.27 *vs.* VVI30 Rs Exe 3.64±0.81 p=0.16). The attenuation in the increase in Rs on exercise, during BiV pacing, was more marked in Group 1 patients (Δ Rs (BiV Exe - VVI Exe) -1.96±0.98) compared to Group 2 patients (Δ Rs (BiV Exe - VVI Exe) -0.79±0.36). However, all of these differences were non-significant.

	Exercise *vs.* Rest	Whole Group n=29	Group 1 n=15	Group 2 n=14	Gp1 *vs.* Gp2
Pacing Mode					
VVI30	**Δ LVEDV %**	-1.79±4.92	-22.32±4.29	20.2±3.86	p < 0.005
	ΔSV %	0.929±5.6	-21.04±5.31	24.46±5.02	p < 0.005
	Δ end systolic Elastance %	16.09±13.60	27.23±26.44	4.17±4.57	p=0.41
BiV	**Δ LVEDV %**	8.09±5.31	3.40±7.00	13.13±8.09	p=0.347
	ΔSV %	9.20±5.94	5.80±7.66	12.84±9.39	p=0.55
	Δ end systolic Elastance %	4.89±6.81	6.12±12.45	3.57±5.25	p=0.85
BiV *vs.* VVI30					
	Δ LVEDV	p=0.18	p=0.004	p=0.43	
	ΔSV	p=0.31	p=0.008	p=0.28	
	Δ end systolic Elastance	p=0.442	p=0.443	p=0.932	

Table 4.1 Semi-supine exercise data during, sham pacing (VVI30) and active pacing (BiV). delta Left Ventricular End Diastolic Volume (ΔLVEDV %), delta Stroke Volume (ΔSV %). Active pacing (BiV), Sham pacing (VVI30). Group 1 and Group 2 as defined in Chapter 4. All values expressed as mean±sem.

		Normalised ventricular septal radius of curvature (Rs)			
		n=10	**Gp1 n=5**	**Gp2 n=5**	***p* (Gp1*vs.* Gp2)**
VVI30	Rest	2.21±0.15	2.45±0.15	1.98±0.14	0.16
	Exe	3.64±0.81	4.20±1.71	3.08±0.16	0.54
p (Rs VVI Rest *vs.* Rs VVI Exe)		0.08	0.32	0.43	
BiV	Rest	2.07±0.19	2.03±0.24	2.12±0.15	0.86
	Exe	2.27±0.27	2.24±0.32	2.29±0.23	0.93
p (Rs BiV Rest *vs.* Rs BiV Exe)		0.45	0.36	0.73	
p (Rs VVI Exe *vs.* Rs BiV Exe)		0.16	0.53	0.11	
Δ **Rs** (BiV Exe -VVI Exe)		-1.37±0.72	-1.96±0.98	-0.79±0.36	0.45
Δ **Rs** (VVI Exe - VVI Rest)		+1.42±0.73	+1.75±1.09	+1.09±0.03	0.68
Δ **Rs** (BiV Exe - BiV Rest)		+0.19±0.25	+0.21±0.14	+0.17±0.34	0.94
p (ΔRs VVI30 *vs.* Δ Rs BiV)		0.14	0.36	0.15	

Table 4.2 Effect of semi-supine exercise and Biventricular (BiV) pacing on normalised ventricular septum radius of curvature (Rs) measurements. Sham pacing (VVI), Active pacing (BiV), Semi-supine exercise (Exe). Group1 (Gp1) and Group2 (Gp2) as defined in Chapter 4. mean ± sem.

		VVI30	BiV	*p*
Whole Group n=29				
	HR (Heart Rate) bpm	60.91±1.6	65.33±2.18	0.09
	SBP (Systolic Blood Pressure)	133.17±3.	131±3.57	0.75
	EF (Ejection Fraction) %	72.37±2.25	73.78±7.73	0.62
Rest	LV end systole elastance	57.48±11.43	53.44±11.43	0.80
	Duration systole (s)	0.38±0.02	0.33±0.02	0.03
	Duration of diastole(s)	0.61±0.03	0.58±0.03	0.35
	HR	89.02± 3.03	90.21±3.21	0.78
	SBP	161.66±3.5	154.66±3.76	0.18
	EF %	73.74±2.37	74.16±2.13	0.90
Exercise	LV end systole elastance	73.58±13.07	58.33±13.07	0.41
	Duration of systole (s)	0.32±0.01	0.27±0.01	0.002
	Duration of diastole(s)	0.35±0.03	0.42±0.02	0.002
Group 1 n=15				
	HR (Heart Rate) bpm	58.97±2.09	63.63±2.65	0.18
	SBP mmHg	135.73±5.43	134.93±5.05	0.91
	EF (Ejection Fraction) %	71.03±3.37	71.73±2.46	0.87
Rest	LV end systole elastance	67.21±20.79	60.83±20.79	0.83
	Duration systole (s)	0.38±0.03	0.34±0.02	0.14
	Duration of diastole(s)	0.61±0.05	0.56±0.06	0.19
	HR	86.97±4.6	87.12±4.58	0.98
	SBP	163.73±5.04	156.6±5.27	0.34
	EF %	71.17±3.11	73.02±2.70	0.66
Exercise	LV end systole elastance	94.43±23.76	66.96±23.76	0.42
	Duration of systole (s)	0.33±0.01	0.27±0.01	0.02
	Duration of diastole(s)	0.34±0.02	0.44±0.03	0.002
Group 2 n=15				
	HR (Heart Rate) bpm	62.99±2.61	67.28±3.59	0.29
	SBP mmHg	130.42 ±4.24	128±5.03	0.72
	EF (Ejection Fraction) %	73.79±3.04	75.97±2.37	0.58
Rest	LV end systole elastance	47.05±8.39	45.51±8.39	0.89
	Duration systole (s)	0.37±0.02	0.32±0.02	0.13
	Duration of diastole(s)	0.57±0.05	0.59±0.04	0.81
	HR	91.21±3.96	93.65±4.49	0.69
	SBP	159.43±4.95	152.57±5.52	0.36
	EF %	76.493.57	75.38±3.41	0.85
Exercise	LV end systole elastance	51.23±8.24	49.08±8.24	0.85
	Duration of systole (s)	0.32±0.01	0.26±0.02	0.05
	Duration of diastole(s)	0.35±0.04	0.38±0.04	0.47

Table 4.3 Semi-supine exercise data following sham pacing (VVI30) and active pacing (BiV). SBP mmHg. Patients are divided into Group1 and Group2 as defined in Chapter 4. Values are shown as mean ±SEM. p values are for BiV *vs.* VV130.

		VVI30		BiV		BiV *vs.* VVI30	
		1st Third filling %	**Final 2/3 filling %**	**1st Third filling %**	**Final 2/3 filling %**	**1st Third filling**	**Final 2/3 filling**
Whole Group Rest n=29		48.32±3.04	51.67±3.04	32.53±2.93	67.46±2.93	p<0.005	p<0.005
Gp2 Rest n=14		49.01±4.35	50.98±4.35	33.79±3.47	66.20±3.47	p=0.01	p=0.01
Gp1 Rest n=15		47.62±4.42	52.37±4.42	31.18±4.92	68.81±4.92	p=0.02	p=0.02
Whole Group Exercise n=29		36.26±2.71	63.70±2.69	22.03±2.18	77.96±2.18	p<0.005	p<0.005
Gp2 Exercise n=14		34.27±3.73	65.65±3.72	23.61±3.04	76.38±3.04	p=0.04	p=0.04
Gp1 Exercise n=15		38.40±3.99	61.88±4.32	20.44±3.18	79.55±3.18	p=0.002	p=0.003
Gp1 *vs.* Gp2	**Rest**	p=0.82	p=0.82	p=0.66	p=0.66		
	Exercise	p=0.46	p=0.46	p=0.47	p=0.47		

Table 4.4 Effect of sham pacing (VVI30) and active pacing (BiV), on Diastolic filling thirds during semi-supine exercise, whole group n=29, and by Groups (Gp) as defined in Chapter 4. Values are shown as mean ±SEM

	Pacing Mode		
	VVI30	**BiV**	**BiV *vs.* VVI30**
Duration diastole rest (s)			
Whole Group (s) n=29	0.61±0.03	0.58±0.03	p=0.35
Group2 (s) n=14	0.57±0.05	0.59±0.04	p=0.81
Group1 (s) n=15	0.61±0.05	0.56±0.06	p=0.19
Group1 *vs.* Group2	p=0.91	p=0.47	
Duration diastole exercise (s)			
Whole Group n=29	0.35±0.03	0.42±0.02	p=0.002
Group2 (s) n=14	0.35±0.04	0.38±0.04	p=0.47
Group1 (s) n=15	0.34±0.02	0.44±0.03	p=0.002
Group1 *vs.* Group2	p=0.81	p=0.38	

Table 4.5 Effect on the duration of diastole in seconds(s) at rest and on semi-supine exercise, during sham pacing (VVI30) and during active pacing (BiV). Group 1 and Group 2 as defined in Chapter 4. Values are shown as mean ±SEM.

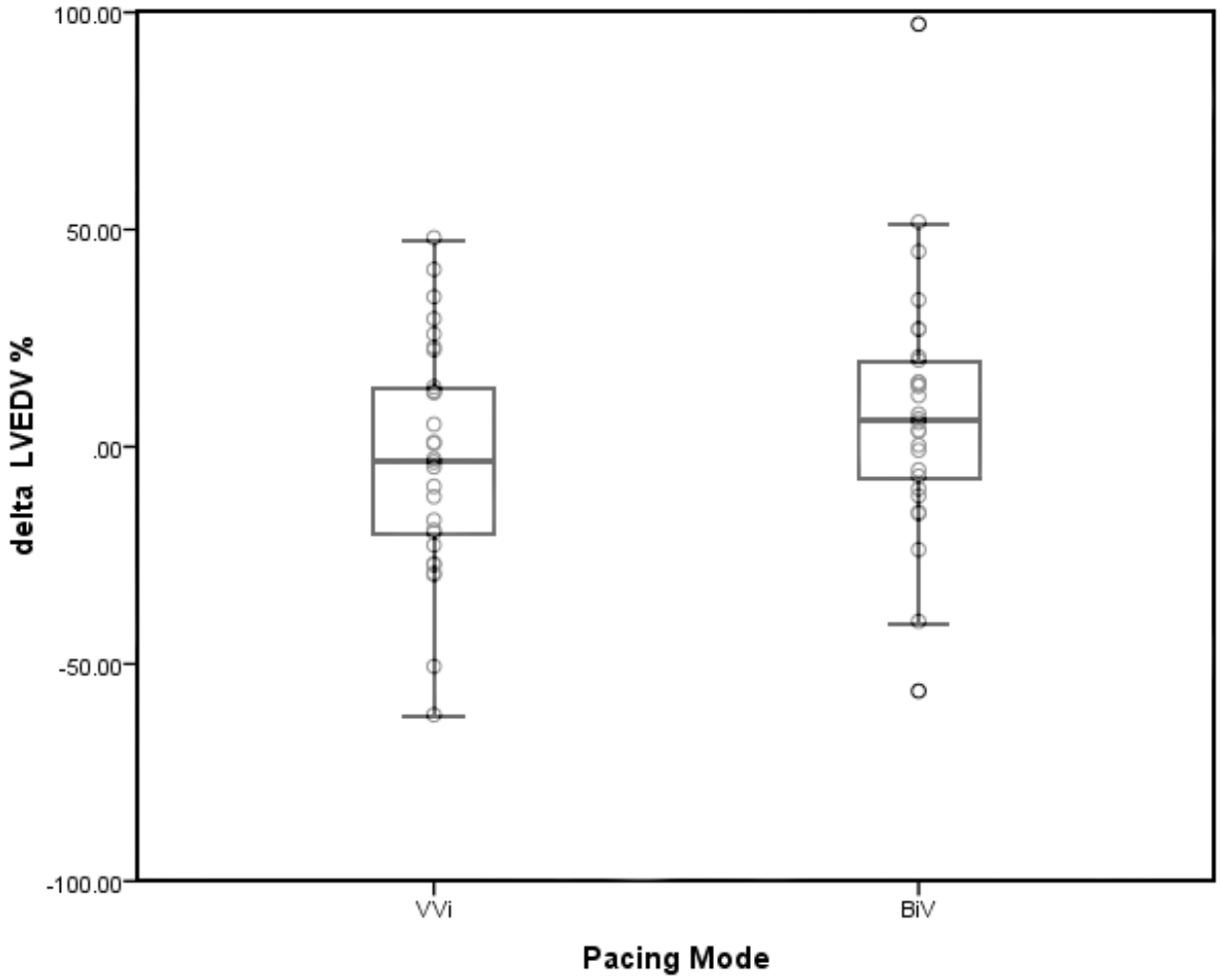

Figure 4.1 : Box-whisker plot showing delta LVEDV on exercise, during sham pacing (VVI) and following acute active pacing (BiV), n =29. Open circles show individual patients, bold line is median. There was no significant difference between VVi and BiV.

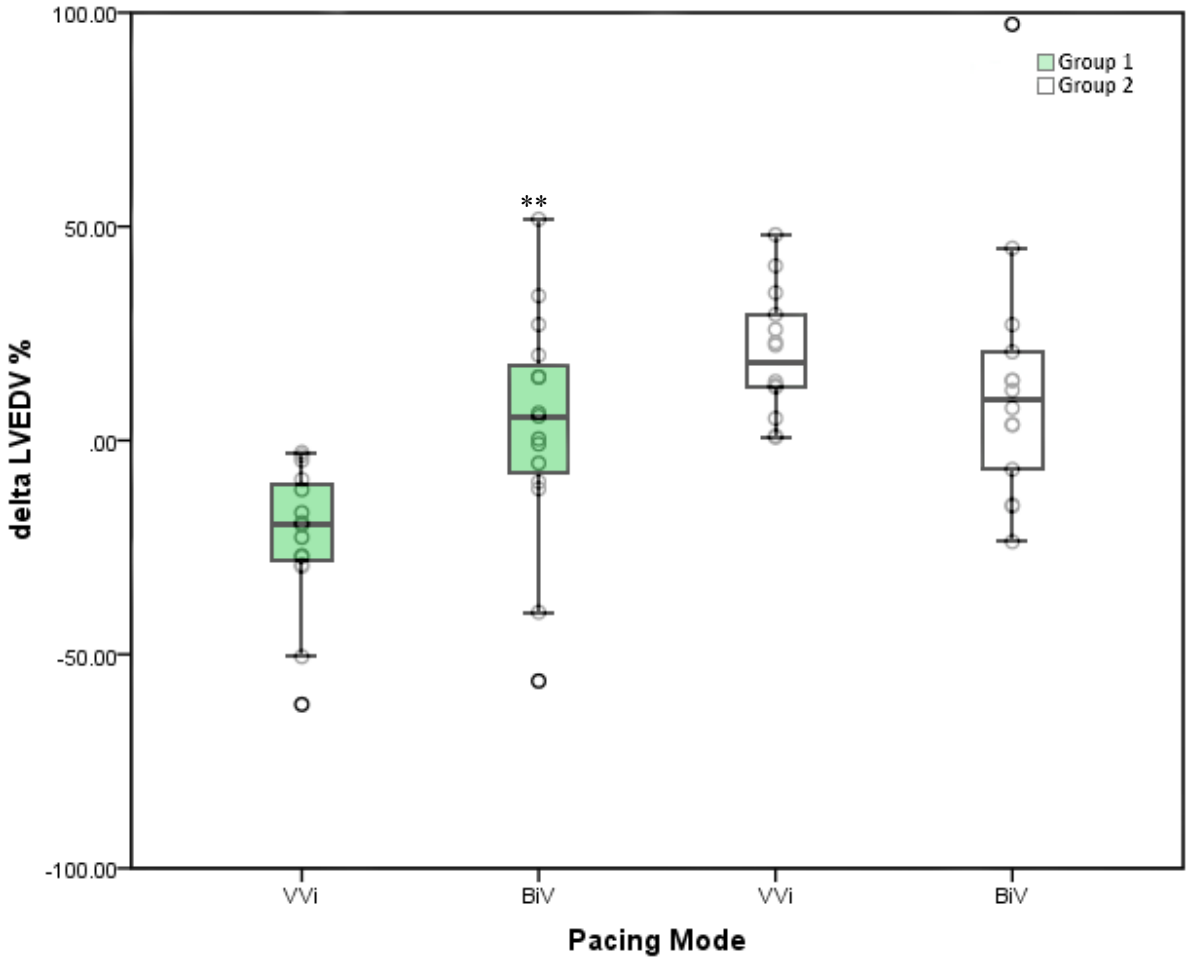

Figure 4.2 : This box-whisker plot shows delta LVEDV on exercise, during sham pacing (VVI) and following acute active pacing (BiV). Patients have been separated into two groups. Patients who during sham pacing demonstrate a reduction in LVEDV on exercise were collated into Group1 and those who do not are in Group 2. Group1 n=15, Group2 n=14. Open circles represent individual patients; bold line is median. **p=0.004; BiV *vs.* VVi in Group 1, p=0.43 for BiV *vs.* VVi in Group 2.

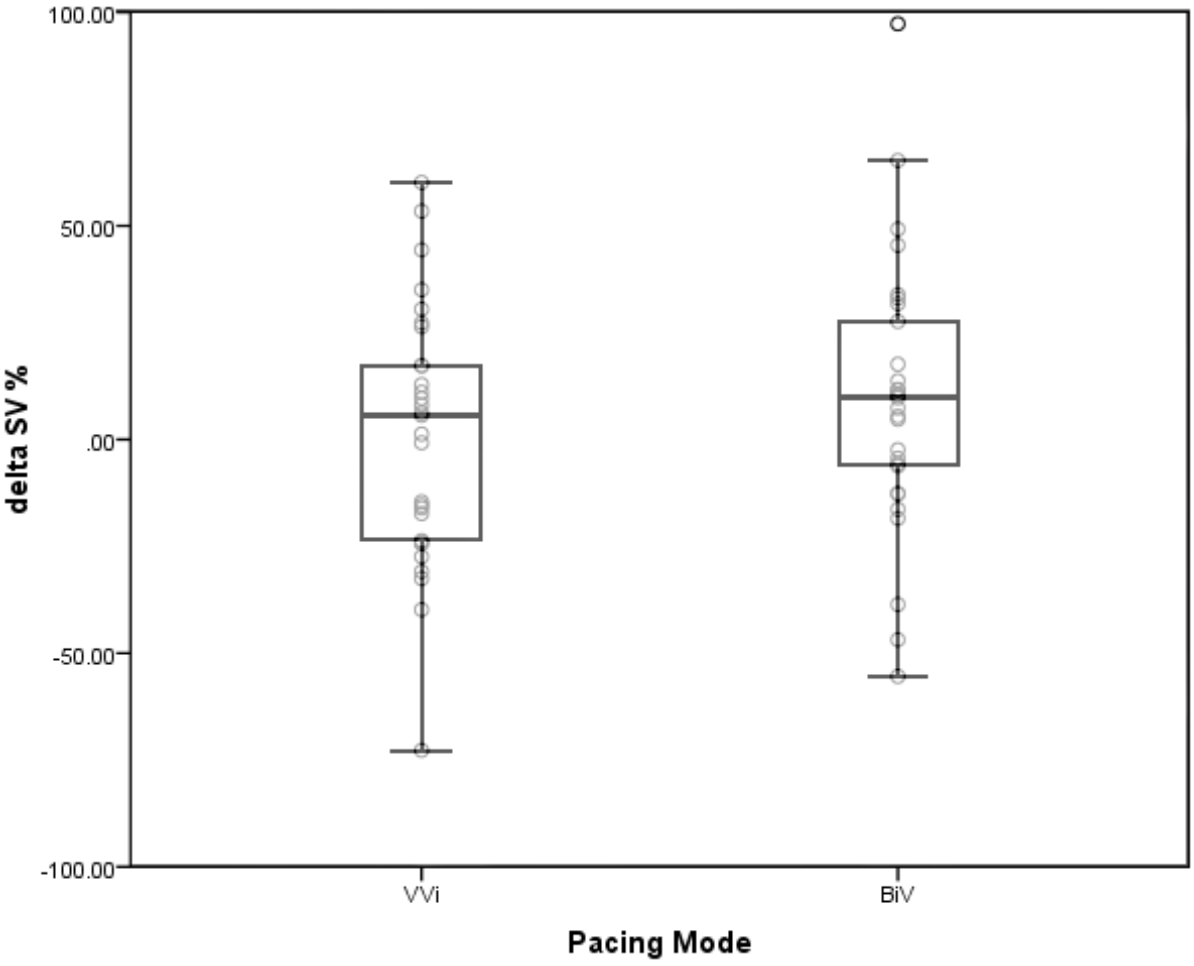

Figure 4.3 : Box-whisker plot showing delta stroke volume(SV) on exercise, during sham pacing (VVi) and following acute active pacing (BiV) n=29. Open circles represent individual patients, bold line is median. p=ns: BiV *vs.* VVi.

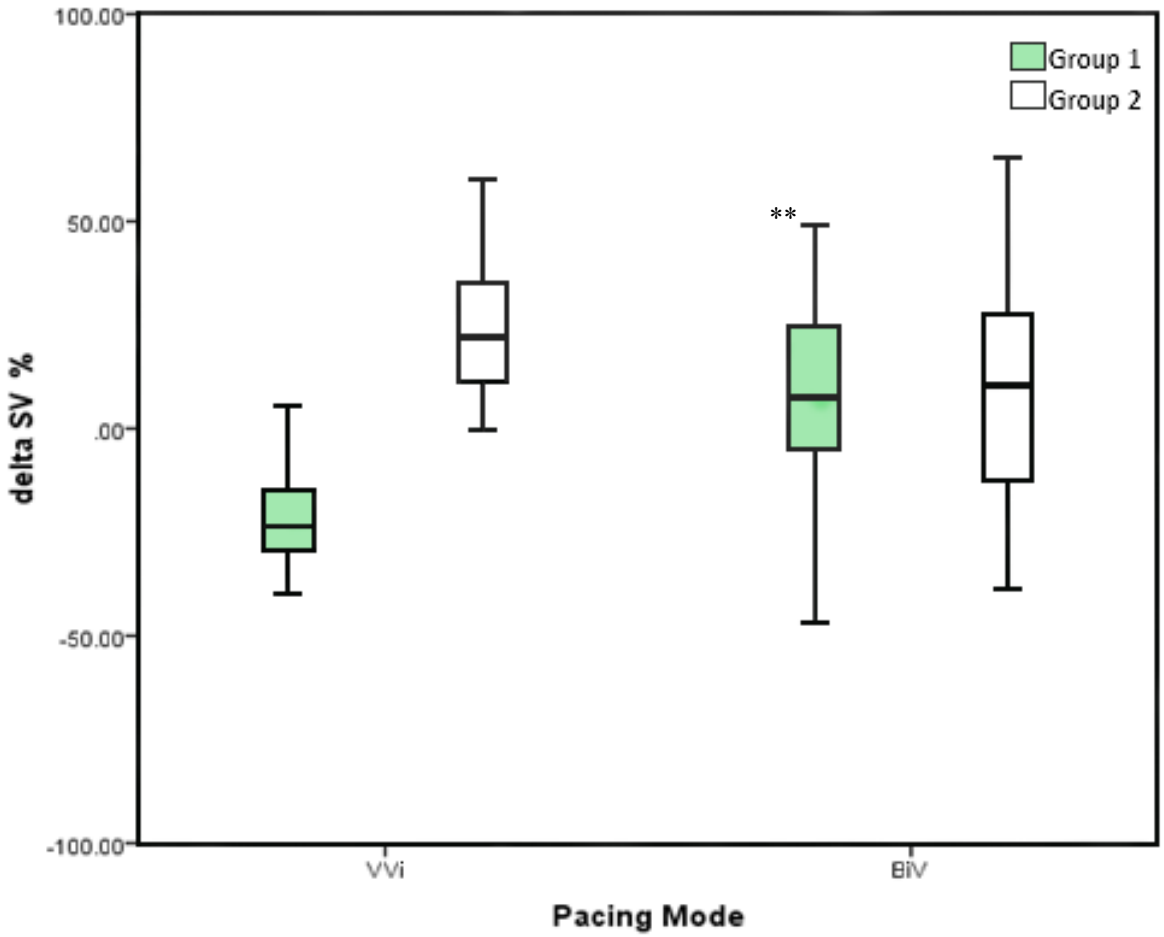

Figure 4.4 : Box-whisker plot showing delta SV on exercise, during sham pacing (VVI) and following acute active pacing (BiV), by group. Group1 n=15, Group2 n=14. Open circles represent individual patients, bold line is median. **p=0.008: BiV *vs.* VVi in Group 1; p=0.28: BiV *vs.* VVi in Group 2.

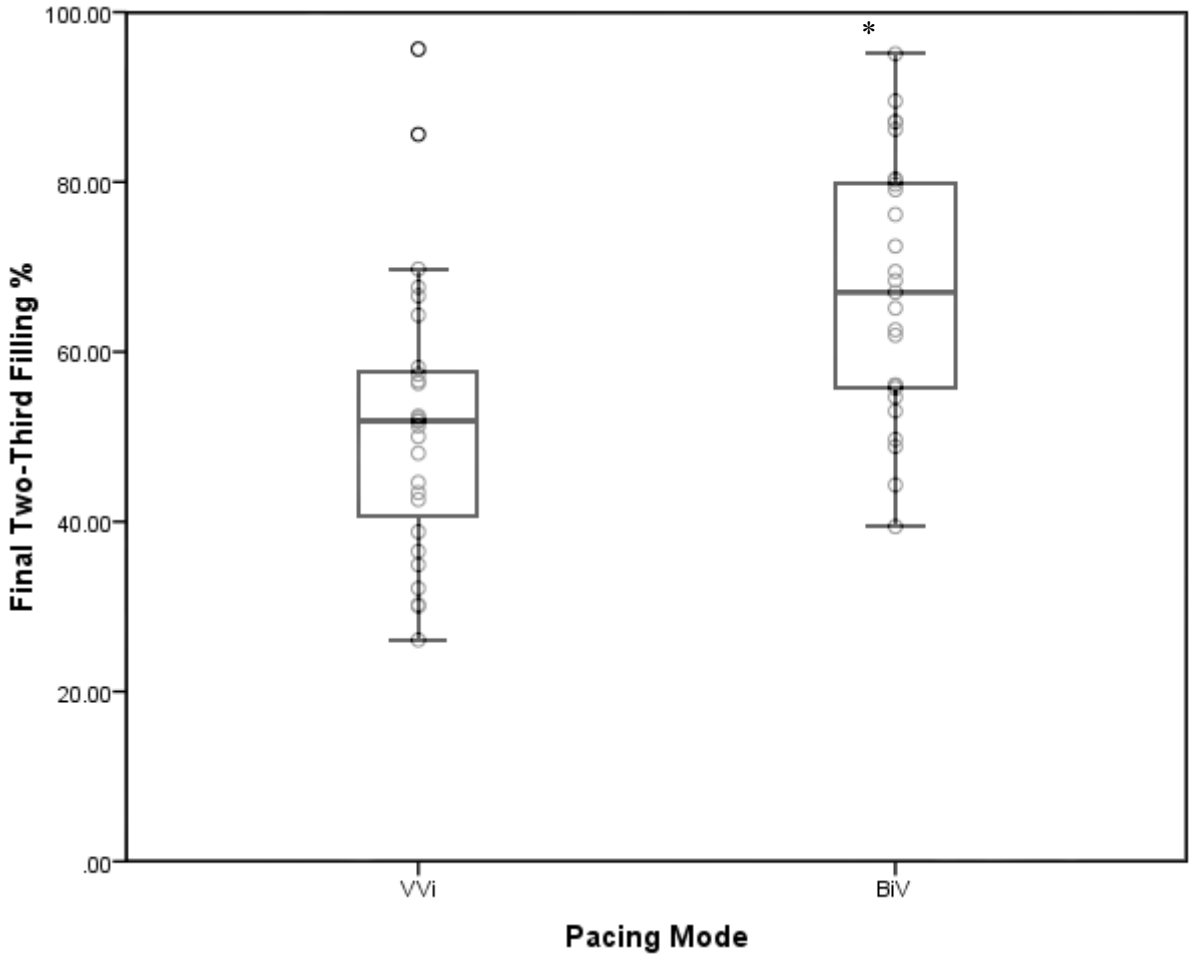

Figure 4.5 : Box-whisker plot showing percentage of total diastolic filling occurring in the final two-thirds of diastole at rest, during sham pacing (VVi) and following active (BiV) pacing (n=29). Open circles represent individual patients; bold line is median. *p<0.05: BiV *vs.* VVi.

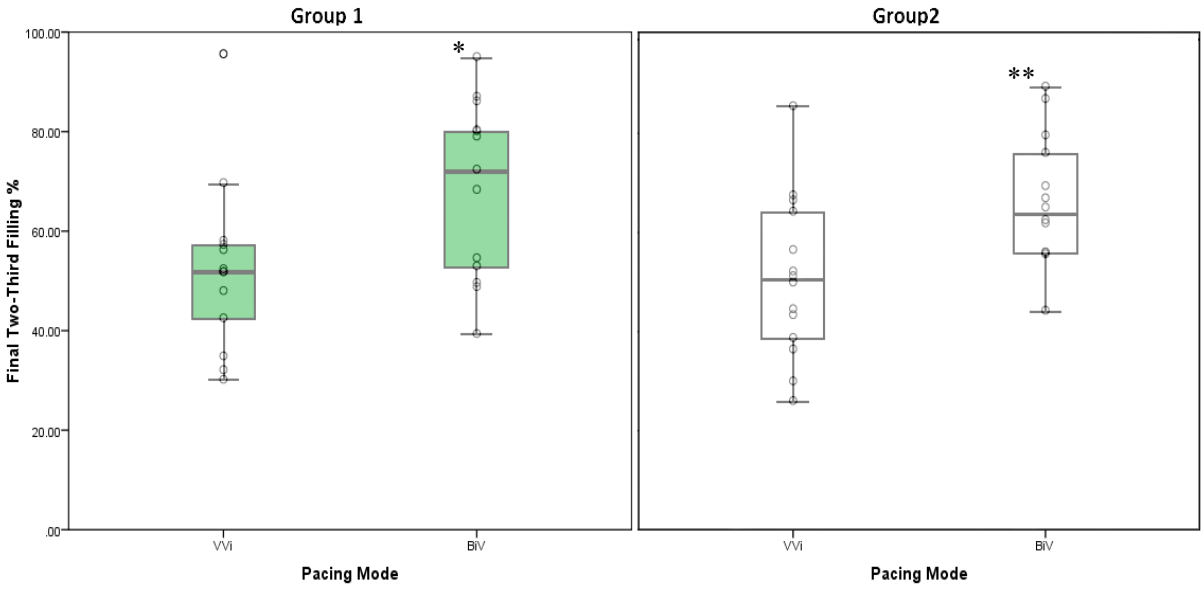

Figure 4.6 : Box-whisker plot showing percentage of total diastolic filling occurring in the final two-thirds of diastole at rest, during sham pacing(VVi) and following active(BiV) pacing by Group (n=29). Open circles represent individual patients; bold line is median. Group 1 (n=15) *p= 0.02: BiV *vs.* VVi, Group 2 (n=14) **p=0.01: BiV *vs.* VVi.

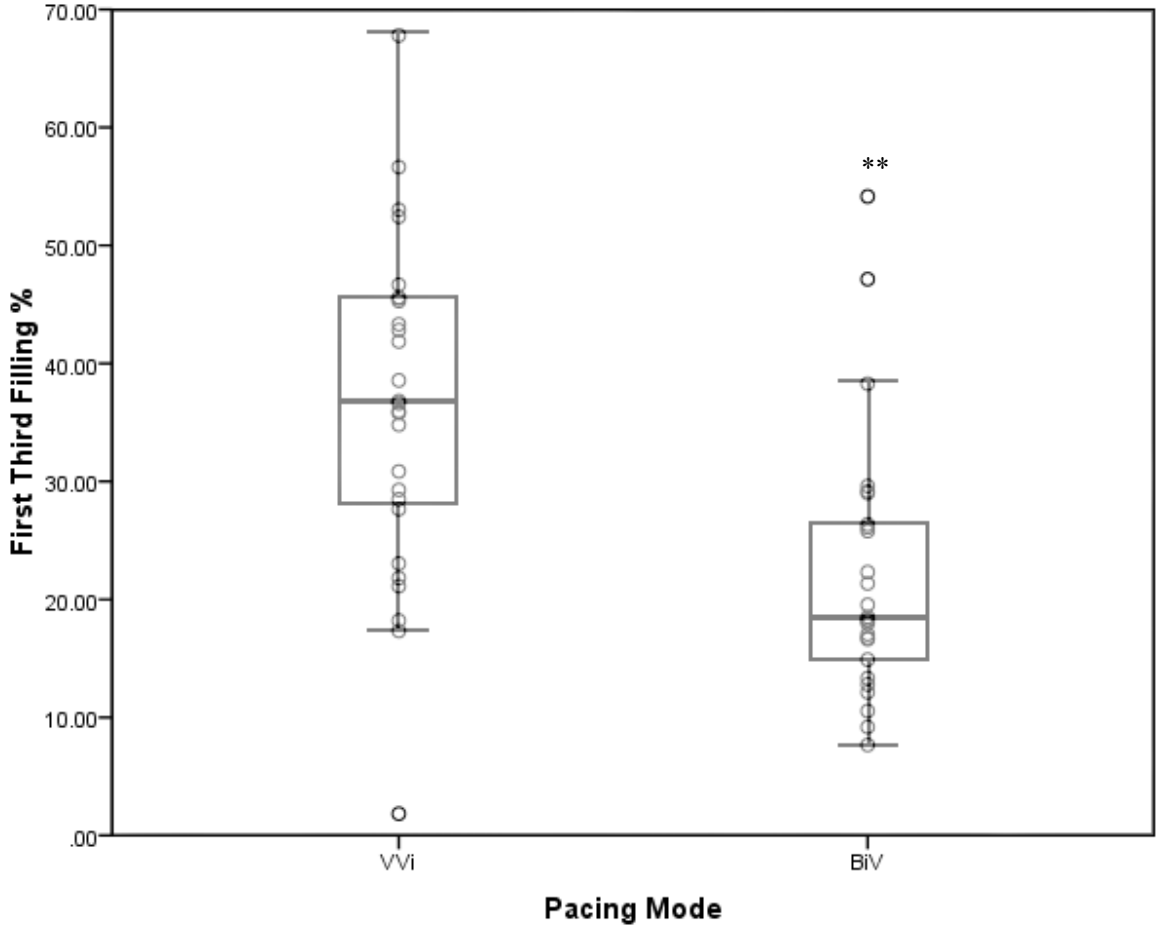

Figure 4.7 : Box-whisker plot showing percentage of total diastolic filling occurring in the first third of diastole on exercise, during sham pacing(VVi) and following active(BiV) pacing (n=29). Open circles represent individual patients; bold line is median. **p<0.005: BiV *vs.* VVi.

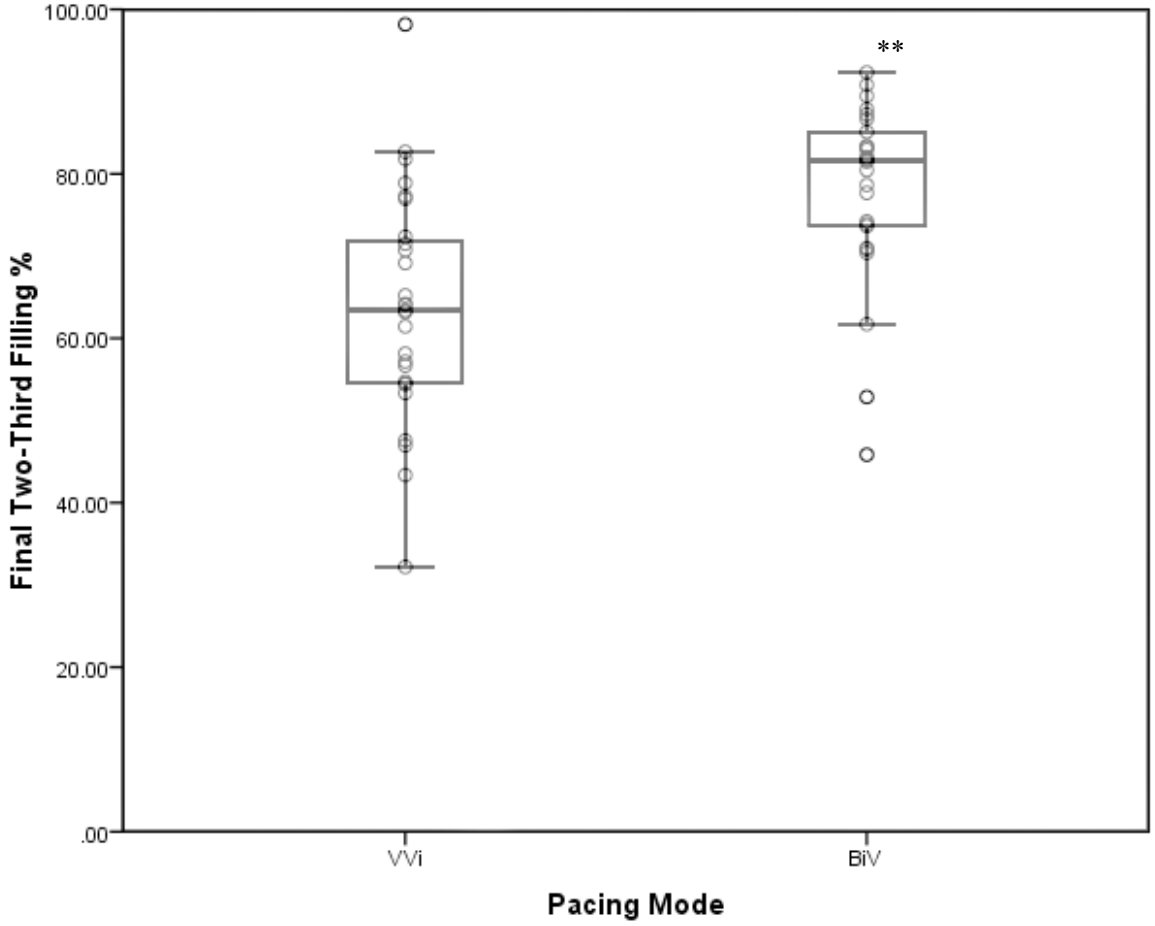

Figure 4.8 : Box-whisker plot showing percentage of total diastolic filling occurring in the final two-thirds of diastole during exercise, during sham pacing (VVi) and following active (BiV) pacing (n=29) Open circles represent individual patients, bold line is median. **p<0.005: BiV *vs.* VVi.

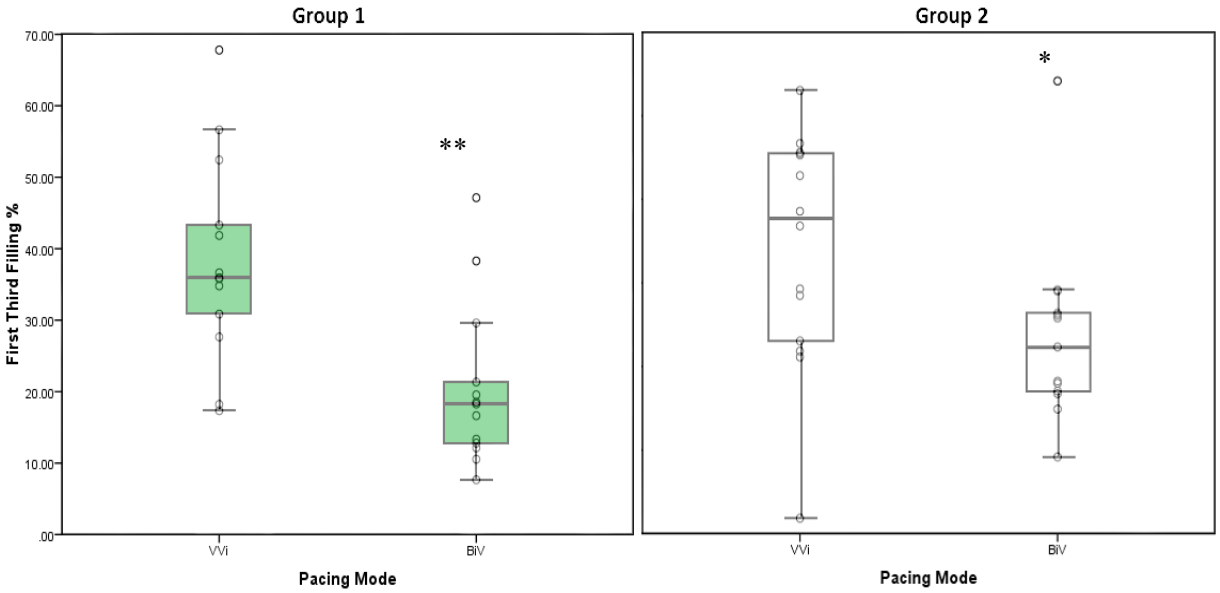

Figure 4.9 : This box-whisker plot shows percentage of total diastolic filling occurring in the first third of diastole during exercise, during sham pacing (VVi) and following active (BiV) pacing by Group. Group1 n=15, Group2 n=14. Open circles represent individual patients; bold line is median. **p=0.002: BiV *vs.* VVi for Group 1; *p=0.04: BiV *vs.* VVi for Group 2.

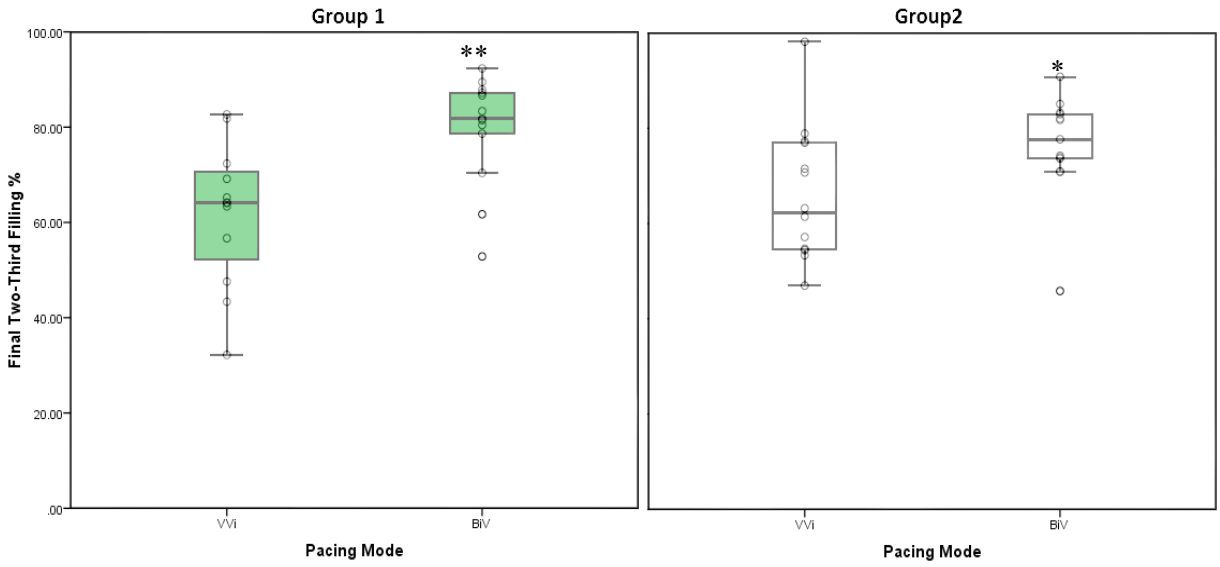

Figure 4.10 : This box-whisker plot shows percentage of total diastolic filling occurring in the final two-thirds of diastole during exercise, during sham pacing (VVi) and following active (BiV) pacing by Group. Group1 n=15 Group2 n=14 Open circles represent patients; bold line is median. **p=0.003: BiV *vs.* VVi for Group 1, *p=0.04: BiV *vs.* VVi for Group2.

Discussion

The purpose of the present study was to investigate the systolic and diastolic behaviour of the heart in patients with HCM on exercise, with and without BiV pacing. Focusing in particular on LV end diastolic volumes, ventricular filling patterns, stroke volume, ejection fraction, end systolic elastance and ventricular septal curvature at end diastole.

On exercise, we observed two contrasting changes in the LVEDV. In 14 patients (Group2), we noted an, as might be expected, increase in LVEDV on exercise, however in over half (n=15) (Group 1) of patients we observed an inappropriate reduction in LVEDV. A failure to increase, and more so a reduction in LVEDV on exercise reveals within the cohort of exercise limited HCM patients a subset with marked diastolic dysfunction. Furthermore, the subset of patients that experienced a fall in LVEDV on exercise had more severe exercise limitation at baseline. We focused on this group, examining the mechanisms underlying the diastolic dysfunction seen on exercise, and the effect of BiV pacing.

The results showed that BiV pacing resulted in a greater increase in LV stroke volume on exercise, an effect that was almost exclusively observed in Group 1 patients, i.e. those patients with the most marked diastolic dysfunction. The effect did not appear to be explained by an increase in LV contractility (as assessed by LV end systolic elastance and LV ejection fraction). Instead the effect appeared to be mediated by LV preload recruitment. In health, LV end diastolic volume increases during exercise, and thereby the Starling mechanism contributes to the increase in stroke volume[364]. This increase in LV end diastolic volume is usually a consequence of both an increase in the rate of LV active relaxation during exercise[280, 365] and the shifting of blood from the venous compartment to the central compartment due the effects of the muscle pump and to active vasoconstriction in the intestinal and splenic venous capacitance beds[366]. It has been shown that

the rate of LV active relaxation paradoxically slows during exercise in many patients with HCM on exercise, and that amelioration of the marked cardiac energetic impairment with the metabolic modulator Perhexiline reverses this abnormality[95]. In approximately 50% of the patients in this study, during sham pacing, there was an abnormal fall in LV end diastolic volume during exercise, and an associated fall in stroke volume (Group1) and unchanged ejection fraction. This abnormal fall in LVEDV, seriously attenuates the ability to increase cardiac output on exercise in our otherwise chronotropically competent cohort of patients. Given that the augmentation of cardiac output during exercise is the predominant determinant of peak exercise capacity[42], it is not unexpected that this pattern was associated with more severe exercise limitation and with worse symptoms than in those patients in whom LVEDV increased on exercise (Group2).

Biventricular pacing substantially corrected these abnormal responses in Group 1 patients (indeed overall there was a modest mean increase in LVEDV during exercise during biventricular pacing) with no significant effect observed on the increase in LVEDV during exercise seen in Group 2 patients. This was associated with a significant increase in LV stroke volume during exercise by biventricular pacing in Group 1 but not in Group 2 patients.

How might Biventricular pacing have effected this change in ventricular filling? Possibilities might include an increase in the rate of LV active relaxation on exercise or a reduction in intrinsic left ventricular stiffness, an increase in diastolic filling time or a reduction in external constraint to left ventricular filling. Diastolic dyssynchrony has been reported in HCM[11, 367] and a reduction in the degree of diastolic dyssynchrony by biventricular pacing (especially on exercise) might translate into more rapid LV active relaxation and reduced LV stiffness. However at least at rest we observed no significant effect of biventricular pacing on measures of diastolic dyssynchrony (see Chapter 3). Furthermore, we observed that biventricular pacing was associated

with a reduction in first third filling fraction at rest and on exercise and a marked increase in filling during mid and late diastole. External constraint to left ventricular filling by the pericardium[368] (pericardial constraint) and by the right ventricle through the interventricular septum (diastolic ventricular interaction, DVI) may be an explanation. DVI has been observed in experimental models associated with acute RV volume and/or pressure overload[216 214]. We have shown that these phenomena are seen in an experimental model of chronic heart failure[367] and in those patients with chronic heart failure who have elevated left ventricular end diastolic pressures (typically >15mmHg)[4]. We have previously shown that in patients with severe CHF both biventricular and left ventricular pacing reduced this external constraint to left ventricular filling and thereby recruited LV preload, presumably by shifting the timing of LV *vs.* RV filling[10]. It is possible that this is again the common mechanism at play, and being seen in this patient cohort. DVI is typically associated with a restrictive LV filling pattern[236] in which rapid early filling then ceases with the onset of external constraint. Consistent with the alleviation of DVI would be our observation of biventricular pacing reducing the rate of early filling but markedly increasing the filling in the latter part of diastole during exercise, with prolonged duration of diastole (potentially contributed to by a reduction in pre-systolic mitral regurgitation, although we have no assessment of this), and consequent improvement in the ability to utilize the starling mechanism, to increase stroke volume.

As a result of its anatomical site, the position, and curvature of the ventricular septum is a reflection of the interaction it mediates between the right and left ventricle[369]. In the healthy beating heart the septum is shaped concave to the left, its position determined by the transeptal pressure gradient it is exposed to, with Kingma et al.[370] observing an excellent correlation between end diastolic septal position and trans-septal gradient ($r=0.98$ $p<0.001$). Dong et al.[316] have further described that the left shift of the ventricular septum, during RV pressure loading, was associated

with an increase in Rs, even after correcting for LV cross sectional area, indicating a true relationship between ventricular septal position and Rs. Using the Mueller maneuver in man to volume load the RV, Guzman et al.[345] and others[371] have demonstrated ventricular septal flattening, with an increase in Rs in diastole, associated with a leftward shift, that persists during systole.

Though our numbers are small (n=10) we see, on exercise, a strong trend for an increase in normalised interventricular septal radius of curvature on exercise (p=0.08), indicating septal flattening, with this effect being more marked in Group 1 *vs.* Group 2 patients, suggestive of increased RV pressures causing a left shift of the septum. Importantly we found that BiV pacing tended to ameliorate this septal flattening during exercise, restoring septal curvature. These data though requiring confirmation with larger numbers provide support to the concept that DVI may be the mechanism at play in the failure to utilize the Starling mechanism on exercise in HCM Furthermore, these findings indicate that correction of this phenomenon may underlie at least some of the observed effects of BiV pacing. Of interest, when Kingma et al. induced LBBB (pacing from the RV outflow tract), they reported a resultant end diastolic transeptal pressure gradient reversal (RV pressure > LV pressure) due to earlier pressure development in the RV, perhaps due to a temporal phase shift in ventricular filling (RV filling before LV), we suggest the converse is occurring with BiV pacing (LV filling before RV).

In Group 2 patients, an appropriate increase in LVEDV on exercise, would be suggestive of, appropriate RV and LV filling and the absence of significant diastolic ventricular interaction. Hence temporally shifting LV filling prior to RV filling, with BiV pacing is unlikely to add further volume to an already appropriately filled, unrestricted LV. This is consistent with our observations of BiV pacing having a negligible effect on LVEDV or SV on exercise in Group 2 patients (Figure 4.2, Figure 4.4).

In summary, we have shown that over half of patients with symptom limited HCM demonstrate very severe diastolic dysfunction on exercise, with deleterious effects on stroke volume, but with preserved chronotropy and contractility. Furthermore, we have shown that BiV pacing may be able to improve LV diastolic function, and we suggest that this is through the amelioration of diastolic ventricular interaction, with consequent improved utilization of the starling curve. However, the question of whether this improvement in myocardial function translates into improved exercise tolerance and symptomatic benefit is not yet answered and is addressed in the chronic component of this study.

Chapter 5

The Acute Study

The impact of right ventricular volume unloading, using lower body negative pressure, on Left ventricular diastolic function in patients with Hypertrophic Cardiomyopathy, with and without Biventricular pacing.

Introduction

In the normal healthy heart the effective left ventricular (LV) distending pressure is close to the measured LV end diastolic pressure (LVEDP) because pericardial and right ventricular pressures at end diastole are both close to zero, there is therefore minimal external constraint to LV filling. As discussed in Chapter 1, Right ventricular (RV) end-diastolic pressure is usually almost identical to pericardial pressure (because the relatively thin walled RV does not usually maintain a significant transmural gradient). However, the pericardium exhibits a J shaped stress-strain relation[229-232]and in experimental models associated with acute RV pressure and volume overload, as the thin walled RV becomes stretched, pericardial pressure increases. In this setting of acute RV pressure and volume overload, LV filling is impeded by external constraint to filling from the pericardium (pericardial constraint) and from the RV, across the shared inter-ventricular septum[242] (diastolic ventricular interaction – DVI). The effective distending pressure in these circumstances is no longer the measured LVEDP, but the measured LVEDP *minus* the external constraint from the pericardium and right ventricle, giving result to the 'effective' LVEDP.

As discussed in the Chapter 1, the right ventricle is often volume and pressure overloaded in patients with chronic heart failure (CHF). It has previously been shown by our group that there is significant DVI in approximately 40-50% of patients with CHF[4, 216]. In such patients blood volume unloading (by applying lower body negative pressure) results in a 'paradoxical' increase in LV end-diastolic volume, (Figure 1.14, Figure 1.15), despite a fall in measured LV 'filling pressures'. In a canine model of heart failure Frenneaux et al. have shown that as LVEDP was lowered by inferior vena cava occlusion, the pressure in the pericardium and RV fell to an even greater extent, so the effective LV distending pressure increased. Changes in LV diastolic volume and stroke work were completely predictable on the basis of changes in the LV transmural pressure

gradient (i.e. the effective distending pressure). In patients with CHF the presence of this abnormal LV volume response was strongly predicted by a restrictive trans-mitral doppler profile [236]. Bleasdale et al.[10] have reported that LV pacing is able to improve diastolic function in patients with CHF, and that much of this benefit is via a reduction in external constraint to LV filling[372].

Thus, in the present study we looked for evidence of constraint to LV filling by the RV, as suggested by a 'paradoxical' increase in LVEDV following application of RV volume offloading (LBNP), in patients with HCM. Furthermore, we looked at the impact of acute Biventricular pacing on diastolic function, in particular looking for correction of 'paradoxical' increases in LVEDV.

We hypothesised that in some patients, at rest, with HCM, RV volume unloading (using LBNP) would improve diastolic filling via the relief of DVI, which we would observe as a 'paradoxical' increase in LVEDV. We further hypothesised that BiV pacing, by analogy to LV pacing in CHF, may then relieve the external constraint to LV filling in patients with non-obstructive HCM, which we would then see as an appropriate decrease in LVEDV following LBNP (i.e. correction of the 'paradoxical' response).

Methods

29 HCM patients (20 males mean age 55years), were selected according to the inclusion and exclusion criteria described in Chapter 2 (section ii). Baseline patient characteristics are given in Table 3.1 (Chapter 3). In brief, a set of 4 gated radionuclide ventriculography studies were acquired per patient, (Figure 2.6). Gated radionuclide ventriculography studies were carried out during sham pacing (VVI30) following the application of Lower Body Negative Pressure (LBNP) 0mmHg and 30mmHg and then the same repeated during BiV pacing (as described in Chapter 2 section iv).

Statistical analysis

In brief data were analysed using SPSS v17.0 and Microsoft Excel. Comparisons of variables were determined by the Students paired t test. A difference of $p<0.05$ was taken to indicate statistical significance (see Chapter 2 section xi for details)

Results

The clinical characteristics and cardiopulmonary exercise test characteristics of the patient cohort are shown in Table 3.1. Patients had a significantly reduced exercise capacity, with significant symptoms. Baseline QRS interval was not prolonged. Over half the patients were on rate limiting medications (beta blockers and/or calcium channel blockers). All 29 patients were able to tolerate the application of lower body negative pressure.

Effect of LBNP on LVEDV during sham pacing and BiV paced modes

In the whole group, during sham pacing, following the application of LBNP there was a significant reduction in LVEDV (-16.59±3.80% $p<0.001$), (Table 5.1 and Figure 5.1), with an associated reduction in SV (-18.31±3.78%). Following BiV pacing, the reduction in LVEDV (-21.08±3.42%) and SV (-21.65±4.06%) were more marked (Table 5.1 and Figure 5.2). Four patients experienced a paradoxical increase in LVEDV (19.81±4.23%) following the application of LBNP in sham pacing mode. This response was reversed following BiV pacing, resulting in a reduction in LVEDV (-23.89±10.12%) on application of LBNP in three of these patients. Unpaced patients from Group 1 (as defined in Chapter 4) also experienced a reduction in LVEDV following LBNP (-12.11± 6.35), but notably less so than Group 2 (as defined in Chapter 4) (-21.42± 3.80). This reduction in LVEDV, in Group 1 patients, became markedly more pronounced following BiV pacing (-20.97±6.19), (Table 5.1 and Figure 5.3).

	VVI30		BiV		BiV vs. VVI30	BiV vs. VVI30
LBNP30 – LBNP0	**Δ LVEDV**	**ΔSV**	**Δ LVEDV**	**ΔSV**	**Δ LVEDV**	**ΔSV**
Whole Group n=29	-16.59±3.80% (p<0.001)	-18.31±3.78% (p<0.001)	-21.08±3.42% (p=0.003)	-21.65±4.06% (p=0.025)	p=0.39	p=0.36
Group2 n=14	-21.42± 3.80 (p<0.001)	-21.35±4.26 (p<0.001)	- 23.01±3.32 (p<0.001)	-23.51± 3.61 (p=0.004)	p=0.74	p=0.68
Group1 n=15	-12.11± 6.35 (p<0.001)	-15.5±6.18 (p<0.001)	-20.97±6.19 (p<0.001)	-21.81± 7.37 (p=0.43)	p=0.31	p=0.51
Group1 vs. Group2	p=0.224	p=0.465	p=0.86	p=0.996		

Table 5.1 Effect of LBNP 30mmHg on LVEDV and SV following sham pacing (VVI30) and active (BiV) pacing. Group 1 and Group 2 as defined in Chapter 4.
Values are mean±sem.

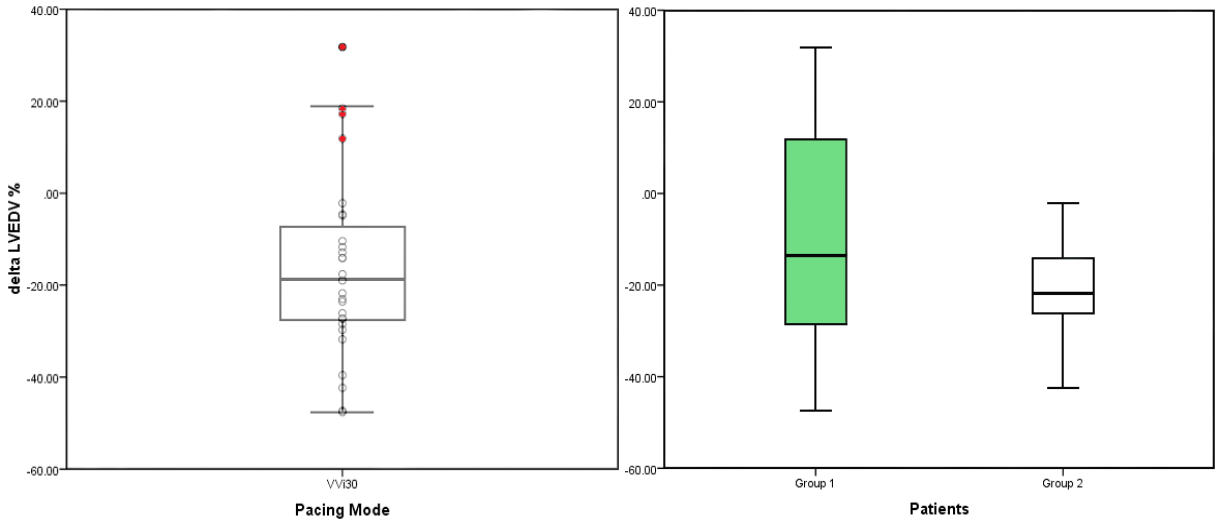

Figure 5.1 : This is a box whisker plot showing delta LVEDV following application of Lower Body Negative Pressure (LBNP) 30mmHg, with Sham (VVI30) pacing, as a whole group n=29 (figure on left) and by Group (figure on the right). Group1 n=15 Group2 n=14. The majority of patients show a reduction in LVEDV following application of LBNP 30mmHg, except 4 (red solid circles), and this reduction in LVEDV following LBNP30mmHg is more consistent in Group 2 patients. Groups1 and 2 as defined in Chapter 4. Open circles are patients, bold line is median.

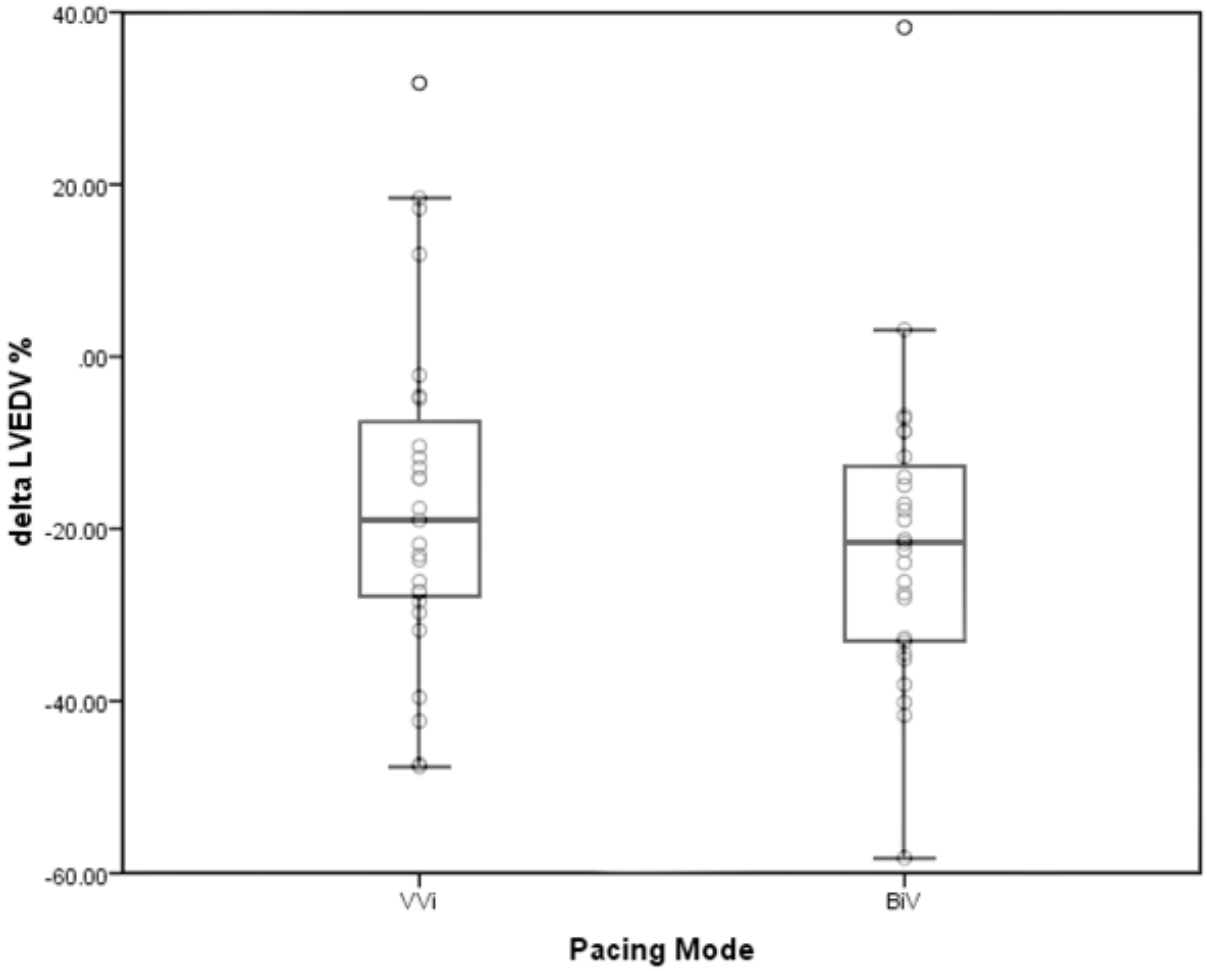

Figure 5.2 : This is a box whisker plot showing delta LVEDV following application of Lower Body Negative Pressure (LBNP) 30mmHg for the whole group, n=29. during sham pacing (VVi) and following active pacing (BiV).

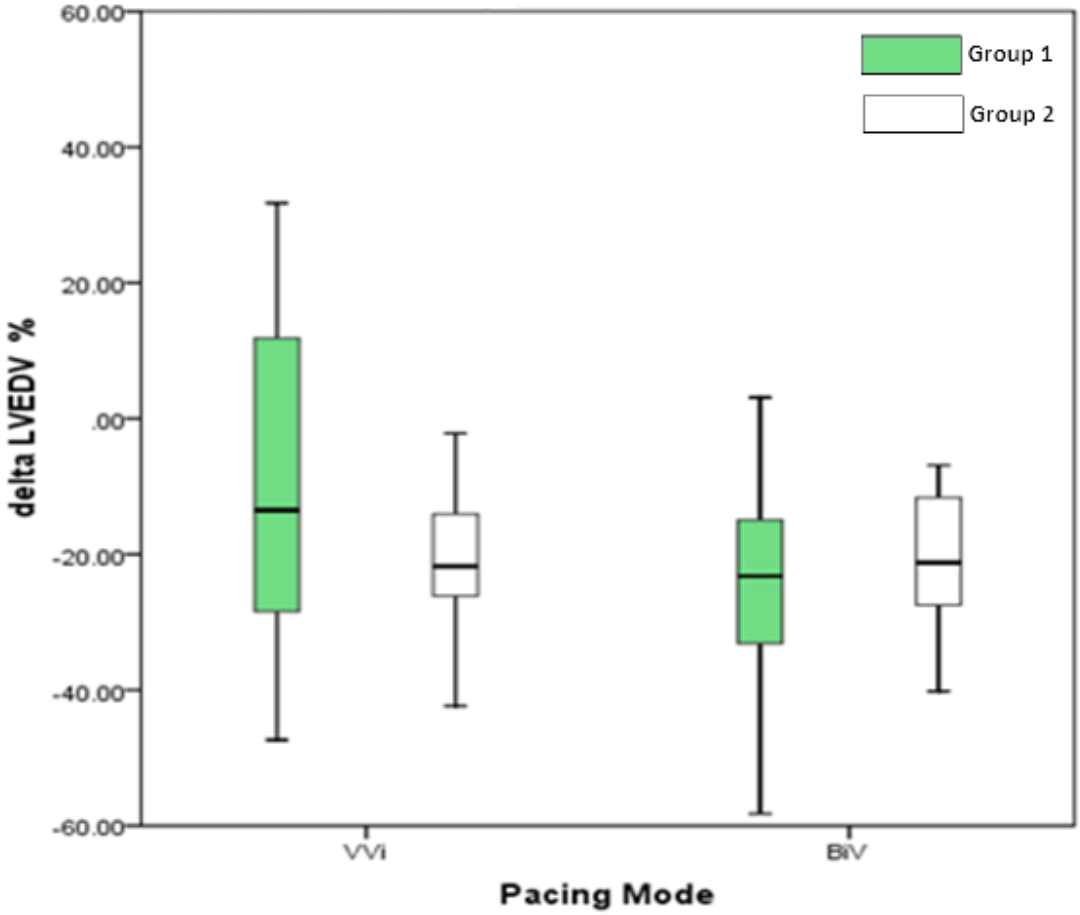

Figure 5.3 : This is a box whisker plot showing delta LVEDV following application of Lower Body Negative Pressure (LBNP) 30mmHg during sham pacing (VVi) and following active pacing (BiV) by Group, Group 1 n=15, Group 2 n=14

Discussion

In health, lower body negative pressure reduces left ventricular end-diastolic volume and stroke volume by approximately 20%, with no significant effect on end-systolic volumes[373]. Thus, in health LBNP significantly reduces preload and stroke volume, producing a Starling effect. In contrast, Atherton et al[4]. observed a paradoxical increase in LVEDV and, as might be expected, a decrease in RVEDV on application of LBNP in almost half of patients with severe chronic heart failure (Figure 1.14). These patients had evidence of increased right atrial (a surrogate for pericardial pressure[233]), pulmonary hypertension, and left sided filling pressures, at rest, which would set the scene for deleterious diastolic right and left ventricular interaction. It is suggested that volume off-loading the RV by LBNP, precipitates relief of diastolic ventricular interaction, suggested as the key mechanism underlying the paradoxical increase in LVEDV following LBNP in this group of patients.

We have shown for the first time, that following the application of LBNP in a group of highly symptomatic patients with non-obstructive HCM at rest, the majority of patients do not experience a paradoxical rise in LVEDV. This suggests that, at rest and when supine at least, the degree of deleterious diastolic ventricular interaction and pericardial constraint is not sufficiently marked as to impair LV filling sufficiently that it may be amenable to correction by LBNP. However, we identified 4 patients who did demonstrate this paradoxical increase in LVEDV following application of LBNP. In these 4 patients, it may be the relief of DVI and pericardial constraint by RV volume offloading by LBNP that results in increased preload recruitment of the LV, with an increase in measured LVEDV. Furthermore, we have shown, for the first time, that BiV pacing was able to correct this paradoxical increase in LVEDV in response to RV volume unloading in 3 of these 4 patients.

Previous studies by Frenneaux et al. has shown that patients with HCM have a markedly impaired ability to utilise the Starling mechanism to increase stroke volume during exercise (i.e. LVEDV fails to increase despite a substantial increase in pulmonary capillary wedge pressure) [10, 42, 244] and we see over half of our patients experiencing a fall in LVEDV on exercise (i.e. Group 1, see Chapter 4). Thus, the exercise data (Chapter 4) is suggestive of DVI development on exercise in many, but the LBNP data suggests its absence at rest in the majority of patients. All 4 patients in whom LVEDV paradoxically increased during application of LBNP (inferring presence of DVI at rest) were from Group 1.

Unpaced and on application of LBNP, Group 1 patients (i.e. who experienced a reduction in LVEDV on exercise, see Chapter 4), exhibited a lesser reduction in LVEDV as compared to those in Group 2 (i.e. who experienced an appropriate increase in LVEDV on exercise) (Table 5.1 and Figure 5.3), consistent with greater ventricular interaction in Group 1 patients.

Although the number of patients in which the overt 'correction' of the paradoxical increase in LVEDV to LBNP following BiV pacing was small (n=3), it is of note that during BiV pacing following application of LBNP, patients in Group 1(n=15) tended towards a similar reduction in LVEDV as that seen in Group 2, suggestive of amelioration of DVI by BiV pacing in this Group of patients (Table 5.1).

Left ventricular and BiV pacing has been shown to improve diastolic function in patients with heart failure in part by reducing the external constraint to LV filling with increased LVEDV with concomitant improvement in LV stroke volume[10]. The explanation suggested for this reduction in external constraint by LV pacing has been the thought that LV pacing induces a phase shift in LV filling relative to RV filling, as demonstrated in the LV pacing canine model[374], in

which LV relaxation and filling occurred relatively early compared with RV filling, allowing unimpeded LV filling.

On application of LBNP, we assume a reduction in RVEDV. It would have been ideal if we had demonstrated a decrease in RVEDV associated with an increase in LVEDV, with correction following BiV pacing. Unfortunately, due to decay of radionuclide activity, image quality was not sufficient to allow RV volume analysis. Increasing the dose radiation would be ethically difficult to justify.

Perhaps, lesser degrees of DVI may not have been observed because LBNP of -30mmHg may not have been great enough to sufficiently volume off load the right ventricle. Increasing the LBNP further causes nausea, making the procedure intolerable. A more acute reduction in central blood volume and RV pressure may be achieved by invasive inferior vena cava occlusion, using the balloon catheter method[10].

These studies were performed supine and at rest, we have shown earlier that it may be on exercise that this group of patients develops physiologically significant DVI. Volume off-loading the right ventricle, during exercise, may then manifest as a decrease in RVEDV and increase in LVEDV. Achieving this mechanically would be challenging. Pharmacological reduction in central volume maybe possible[375].

We report for the first time in the present study, that the majority of patients with HCM have an appropriate reduction in LVEDV following RV volume unloading, suggesting perhaps the absence of overt DVI in the majority of HCM patients at rest. However, our data suggests that in a small group of HCM patients there is an overt 'paradoxical' increase in LVEDV following LBNP, and that this response may be corrected by BiV pacing.

The Chronic Study

A randomized double blind cross-over trial

Chapter 6) *Effects of chronic biventricular (BiV) pacing on left ventricular dyssynchrony twist/untwist and strain in patients with non-obstructive Hypertrophic Cardiomyopathy (HCM)*

Chapter 7) *Effects of chronic BiV pacing on peak Oxygen consumption and quality of life in patients with exercise limited non-obstructive HCM.*

Chapter 6

The Chronic Study

The effects of chronic Biventricular pacing on left ventricular dyssynchrony, twist/untwist and strain in patients with non-obstructive Hypertrophic Cardiomyopathy.

Introduction

Dyssynchronous contraction in patients with HCM has been demonstrated using TDI[13] and Speckle tracking [12], as discussed in Chapter 1. A dyssynchronously contracting LV in patients with systolic heart failure portends an increased risk for developing ventricular tachyarrhythmia's and sudden death. In patients with systolic heart failure, myocardial dyssynchrony further impairs systolic function, perpetuates chamber inefficiency, increases morbidity and mortality.

Diastolic dysfunction is common in HCM patients and is manifest as a reduction in exercise capacity and breathlessness[42] commonly seen in the presence of normal or supranormal systolic function and absence of obstruction to outflow. Active relaxation is slower with typically reduced rates of diastolic filling at rest[376]. Frenneaux et al. have shown previously that there is a failure of the normal increase in the rate of active relaxation (as measured by TTPF) on exercise, indeed in a high proportion of patients there was a paradoxical slowing of active relaxation on exercise[42] i.e. deteriorating diastolic function just when needed most.

As discussed in Chapter 1 (Device Therapy) in the 1990s a pacemaker based therapy (Biventricular pacing) was introduced as a possible method with which to restore cardiac synchrony, by electrically stimulating both the right and left ventricles together. Biventricular pacing appears to have immediate effects on measures of dyssynchrony, reducing mitral regurgitation, and increasing cardiac output, all this without an increase in myocardial Oxygen consumption[377, 378]. Over a longer period of time, reverse remodeling ensues with a reduction in chamber size. BiV pacing therapy in patients with systolic heart failure has now been shown, repeatedly, to improve quality of life, exercise capacity[262] and most importantly reduce mortality[264], with this effect being most marked in those with evidence of dyssynchrony at baseline[347, 348]. Of note and particular relevance to the present study is that the ventricle pattern of

contraction and relaxation may be dyssynchronous even when there is apparently normal electrical conduction (narrow QRS complex) because of regional variation in myocardial function[379] , a feature which is particularly true of patients with HCM.

As discussed in the Chapter 1, a number of investigators have suggested the importance of the contribution made by myocardial twist and untwisting mechanics towards the efficient functioning of the myocardium[380]. During systole, myocardial deformation generates potential elastic energy, stored within the tissue of the myocardium, at end of active contraction this stored elastic energy is converted to kinetic energy, manifest as rapid untwisting[80, 188] that is seen in early diastole. This untwist contributes to the generation of a pressure gradient from atria to ventricle, so 'sucking' blood in during diastole, contributing to more efficient diastolic myocardial function.

Speckle tracking has been recently been validated, by comparison with MRI, as a feasible, relatively easily applicable non-invasive method with which to measure myocardial strain and rotation[199]. When viewed from the apex, the left ventricle twists as a result of counter clockwise rotation of the apex and clockwise rotation of the base, and the opposite during diastole, resulting in untwisting. Further work has suggested that the rate of untwist may be a measure of diastolic function that is largely independent of preload [187].

A synchronously contracting and relaxing ventricle may then conceivably result in improvement of systolic parameters including twist and strain, and likewise a mechanically synchronous diastolic phase may result in improvement in untwist. In this study, we hypothesised that chronic BiV pacing would improve systolic and diastolic dyssynchrony, with concomitant improvements twist and untwist rates and strain in patients with symptom limited non-obstructive HCM.

Methods

See Chapter 2 (section i) Study design, and Figure 2.1.

This was a randomised, double blind, cross-over study of active Biventricular pacing *vs.* sham (VVI30) pacing (4 months in each limb). 31 HCM patients (20 males mean age 55years), were selected according to the inclusion and exclusion criteria described in Chapter 2 (section ii). In brief transthoracic echocardiographic studies were carried out at rest, lying in the left lateral decubitus position, at cross over and at completion of study. To allow retrospective speckle tracking analysis B mode images, at a minimum frame rate of 60fps were acquired from the apical and parasternal short axis windows, as described in Chapter 2, section viii. Color coded tissue doppler images with a minimum frame rate of 90fps were obtained from the apical long axis and four and two chamber views, as described in Chapter 2 section viii.

Speckle tracking software was used to measure radial strain, and time to peak radial strain. From which 2 indices of radial dyssynchrony were derived as described in Chapter 2 (section viii). Speckle tracking software was used to measure rotation and rotation rates at the apex and base. From which were calculated LV twist and untwisting rates, as described in Chapter 2 section viii.

Post image acquisition analysis of color coded tissue doppler images from the apical window, was carried out to measure the time to peak systolic and diastolic velocity in twelve segments of the LV. From this data, 2 indices of systolic and 1 of diastolic dyssynchrony were calculated, as described in Chapter 2 (section viii). These analyses were carried out for the 29 patients who completed the trial. The programming of the biventricular pacemaker was as described in Chapter 2 (section iii).

Statistical analysis

See Chapter 2 (section xi) Statistical analysis Data were analyzed using SPSS version. 17.0 for Window and Microsoft Office Excel 2010, and expressed as mean ± standard error (sem). Comparison of the measured variables between active pacing (BiV), and sham pacing (VVI30), was performed using repeated measures analysis of variance. Statistical significance was set at $p< 0.05$.

A retrospective analysis for inequality of carry-over effects was carried out using a repeated measures analysis of variance [381], $P >0.05$ suggests no significant carry-over.

Results

The clinical and cardiopulmonary characteristics of the patient cohort are shown in Table 3.1. Of the 31 patients enrolled, 29 patients were able to complete the study.

As indicated in Chapter 2 (section ii), these patients had a significantly reduced exercise capacity, with significant symptoms. Baseline QRS interval was not prolonged. Over half the patients were on rate limiting medications (beta blockers and/or calcium channel blockers). 29 patients were able to tolerate active BiV pacing. 1 patient was unable to tolerate sustained BiV pacing because of diaphragmatic twitching, despite attempts at LV lead repositioning and a further patient was unable to tolerate cross over from active BiV pacing to sham pacing. Both patients have been excluded from all analysis.

Dyssynchrony

See Table 6.1. Using TDI two indices of LV systolic dyssynchrony were derived, the global Yu index, and a more basal focused systolic dyssynchrony index. Both demonstrated a trend towards reduction following BiV pacing but neither achieved statistical significance.

A measure of diastolic intraventricular dyssynchrony using TDI (Te-SD) did not significantly change following chronic BiV pacing. Interventricular dyssynchrony was measured using two different techniques with conventional pulse wave doppler and TDI. Neither measure demonstrated any significant change following BiV pacing (Table 6.1). Analysis for inequality of carry-over effect, suggests no significant sequence-order effect (Figure 6.1).

Speckle tracking has advantages over TDI in being a direction independent, non-doppler method of measuring ventricular mechanics. Using this technique 2 different speckle tracking indices of systolic intraventricular dyssynchrony were derived. $SDt_{6S,}$ a more global index and AS-P delay, both showed a tendency towards reduction in dyssynchrony (Table 6.1). Neither index achieved statistical significance.

Strain

See Table 6.2. Chronic BiV pacing (4months) did not significantly alter apical radial strain ($p=0.13$) and strain rate ($p=0.29$), papillary radial strain ($p=0.83$) or strain rate ($p=0.76$) or basal radial strain ($p=0.24$) or basal strain rate ($p=0.81$). Similarly, circumferential peak strain and strain rates were not significantly altered by BiV pacing at apical, papillary or basal levels. Longitudinal peak strain and strain rates, measured from the apical 4 chamber view, were not significantly altered by chronic BiV pacing (Table 6.2).

Twist

See Table 6.3. Following 4 months of BiV pacing no significant effect was seen in basal peak rotation (p=0.18) nor peak rotation rate (p=1.00). No significant change was seen in apical peak rotation (p=0.82), nor peak rotation rate (p=0.72). Four months of active BiV pacing (BiV) did not significantly alter peak twist (p=1.00), time to peak twist (p=1.00), peak twist rate (p=1.00) and time to peak twist rate (p=1.00). Peak untwist rate and time to peak untwist was unchanged following BiV pacing (p=0.89 p=0.58 respectively). Despite peak untwist rates being unaffected, untwist was more rapidly completed, with a significant reduction in time taken to complete 25% untwist (p=0.015) and 50% untwist (p=0.009) (Table 6.3, Figure 6.2, Figure 6.3).

Table 6.1 Effect of Chronic BiV pacing on inter and intraventricular dyssynchrony

		Chronic Pacing Mode		
	Baseline	**VVI30**	**BiV**	***p***
Intraventricular dyssynchrony n=29				
[178]SDt_{6s} (s) (ste)	0.058±0.007	0.045±0.009	0.037±0.007	1.00
[178]AS-P delay by RS (s) (ste)	0.11±0.01	0.08±0.02	0.05±0.01	0.58
[173]Yu index by TDI (s)	0.07±0.009	0.048±0.003	0.04±0.004	0.25
[14]Basal systolic dyssynchrony TDI (s)	0.10±0.01	0.08±0.009	0.07±0.01	0.84
[151]Diastolic dyssynchrony Te-SD (s)	0.049±0.006	0.051±0.008	0.04±0.006	1.00
Interventricular dyssynchrony n=29				
Qa-Qp (ms)	14.27±3.24	16.69±4.98	16.50±2.56	0.976
LV-RV asynchrony by TDI(s)	0.08±0.01	0.049±0.009	0.058±0.012	0.504

SDt_{6s}: Standard Deviation time to peak systolic radial strain for six segments papillary level. ste: speckle tracking. AS-P delay by RS: Anteroseptal – Posterior wall delay in time to peak Radial Strain. Basal systolic dyssynchrony TDI: Maximum delay between peak systolic longitudinal velocities basal level four walls. Te-SD: Standard deviation 12 segments to peak early diastolic velocity (e). Qa-Qp: Pre-ejection interval difference aortic and pulmonary flow. Ts LV-RV: Time interval (Ts) to peak longitudinal systolic velocity basal wall lateral left ventricle (LV) and basal free wall right ventricle (RV). Values are mean ± sem. p values are for BiV *vs.* VV130.

Whole group n=29			Baseline	VVI30	BiV	*p*
Base	**Peak Radial strain %**		19.55±2.49	22.35±2.49	18.01±2.53	0.24
	Radial strain rate s^{-1}	S	1.49±0.12	1.49±0.12	1.53±0.13	0.81
		E	-0.92±0.09	-1.12±0.09	-1.40±0.10	0.10
		A	-1.00±0.11	-1.06±0.11	-0.72±0.11	0.02
	Peak Circumferential Strain %		-12.85±0.92	-13.722±0.92	-13.85±0.93	0.92
	Circumferential strain rate s^{-1}	S	-1.35±0.07	-1.34±0.06	-1.46±0.07	0.29
		E	1.23±0.08	1.29±0.08	1.37±0.08	0.36
		A	0.69±0.05	0.72±0.05	0.61±0.05	0.16
PM (Papillary Muscle)	**Peak Radial Strain %**		20.17±2.19	20.00±2.15	19.38±2.19	0.83
	Radial strain rate s^{-1}	S	1.30±0.45	1.40±0.51	1.46±0.82	0.76
		E	-1.11±0.103	-1.35±0.10	-1.36±0.10	0.97
		A	-1.13±0.09	-0.85±0.09	-0.77±0.09	0.50
	Peak Circumferential Strain %		-14.44±1.02	-17.90±1.00	-17.19±1.02	0.62
	Circumferential strain rate s^{-1}	S	-1.38±0.07	-1.50±0.07	-1.45±0.07	0.66
		E	1.22±0.09	1.59±0.09	1.41±0.09	0.19
		A	0.86±0.06	0.93±0.07	0.71±0.06	0.03
Apex	**Peak Radial strain %**		14.16±2024	13.60±2.20	8.79±2.28	0.13
	Radial strain rate s^{-1}	S	1.10±0.11	1.15±0.11	0.96±0.11	0.29
		E	-1.01±0.14	-1.06±0.13	-0.98±0.13	0.66
		A	-0.59±0.45	-0.60±0.57	-0.37±0.46	0.10
	Peak Circumferential Strain %		-15.26±1.30	-17.13±1.30	-17.77±1.35	0.74
	Circumferential strain rate s^{-1}	S	-1.37±0.09	-1.45±0.09	-1.48±0.09	0.85
		E	1.26±0.14	1.48±0.14	1.50±0.15	0.94
		A	0.79±0.07	0.81±0.07	0.71±0.08	0.33
Longitudinal	**Peak Strain %**		-12.25±0.077	-11.92±0.77	-11.07±0.78	0.43
	Strain Rate s^{-1}	S	-0.93±0.03	-0.90±0.03	-0.93±0.04	0.52
		E	0.90±0.05	0.88±0.05	0.93±0.06	0.55
		A	0.82±0.05	0.78±0.05	0.71±0.05	0.31

Table 6.2 Effects of Chronic BiV pacing on STE derived measures of myocardial strain and strain rates. Values are mean±sem. P values are for BiV *vs.* VV130.

Whole group n=29				Pacing Mode			
				Baseline	**VVI30**	**BiV**	***p***
Rotation	**Apex**	**Rotation Peak (deg)**		6.30±1.17	6.84±1.09	7.08±0.993	0.82
		Rotation Rate (deg/s)	S	50.26±9.71	47.25±8.21	50.73±7.42	0.72
			E	-42.26±9.67	-40.11±8.76	-48.39±9.45	1.00
			A	-20.95±6.18	-27.17±6.49	-22.76±3.91	1.00
	Base	**Rotation Peak (deg)**		-4.17±1.13	-6.37±0.70	-5.38±0.78	0.18
		Rotation Rate (deg/s)	S	-46.84±9.00	-62.62±4.56	-64.76±6.40	1.00
			E	46.41±9.43	62.63±4.81	56.53±5.43	1.00
			A	39.90±7.40	51.72±3.35	34.29±4.20	1.00
Twist	**Peak Twist deg**			13.08±1.11	11.69±1.11	12.67±1.13	1.00
	Time to peak Twist (RR=1s)			0.37	0.35	0.36	1.00
	Peak Twist Rate deg/sec			89.05±6.71	85.68±6.83	90.65±6.48	1.00
	Time to Peak Twist Rate (RR=1s)			0.18±0.017	0.20±0.017	0.20±0.017	0.58
Untwist	**Peak Untwist Rate deg/sec**			-81.60±8.9	-77.99±7.82	-83.34±8.24	0.89
	Time to Peak Untwist Rate (RR=1s)			0.53±0.01	0.51±1.87	0.53±0.02	1.00
	% Untwist @25% of total untwist duration			22.95±2.82	23.79±2.68	33.08±3.25	0.015
	% Untwist @50% of total untwist duration			53.26±3.58	48.16±3.30	64.48±4.36	0.009

Table 6.3 Effects of Chronic BiV pacing on myocardial Rotation, Twist and Untwist. Values are mean±sem. p values are for BiV *vs.* VV130.

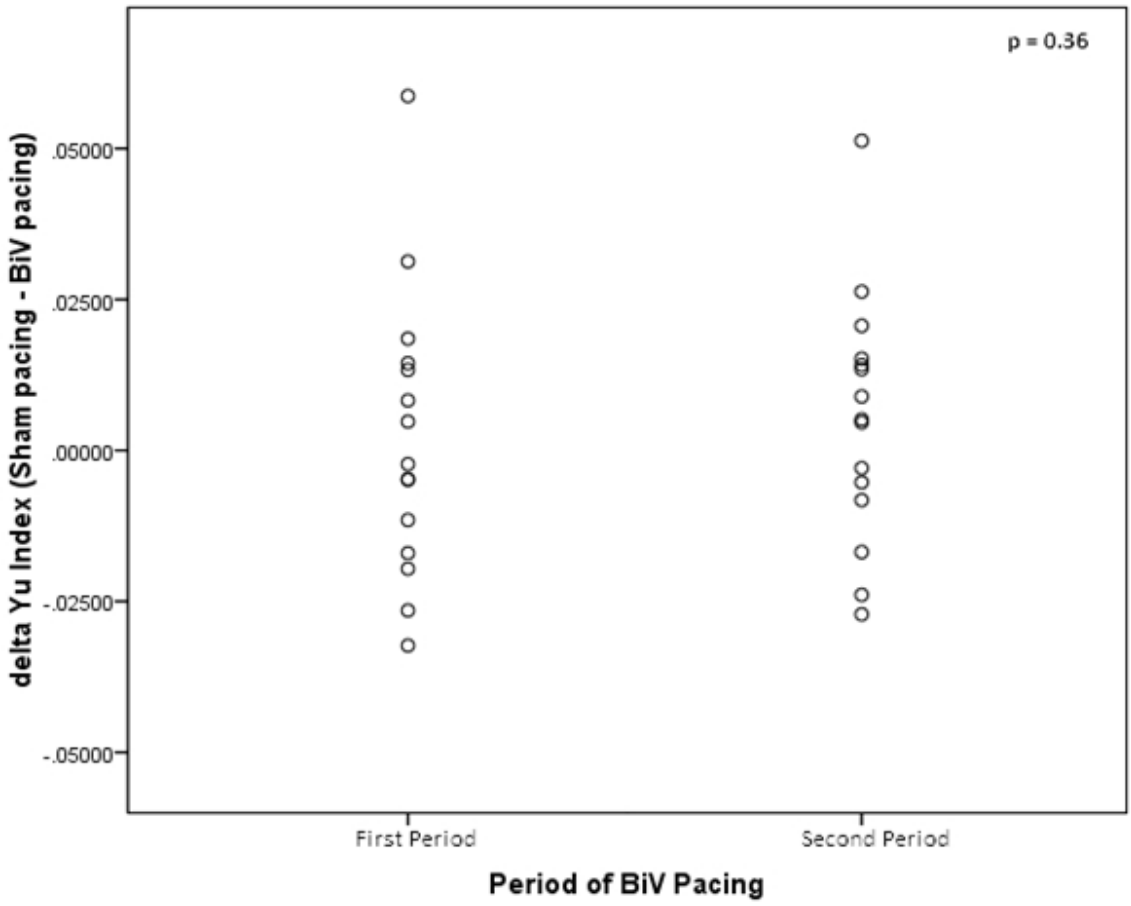

Figure 6.1 : No inequality of carry-over effects on the Yu index for patients experiencing active pacing for the first four months compared to those who received active pacing during the second four months, p=0.36.

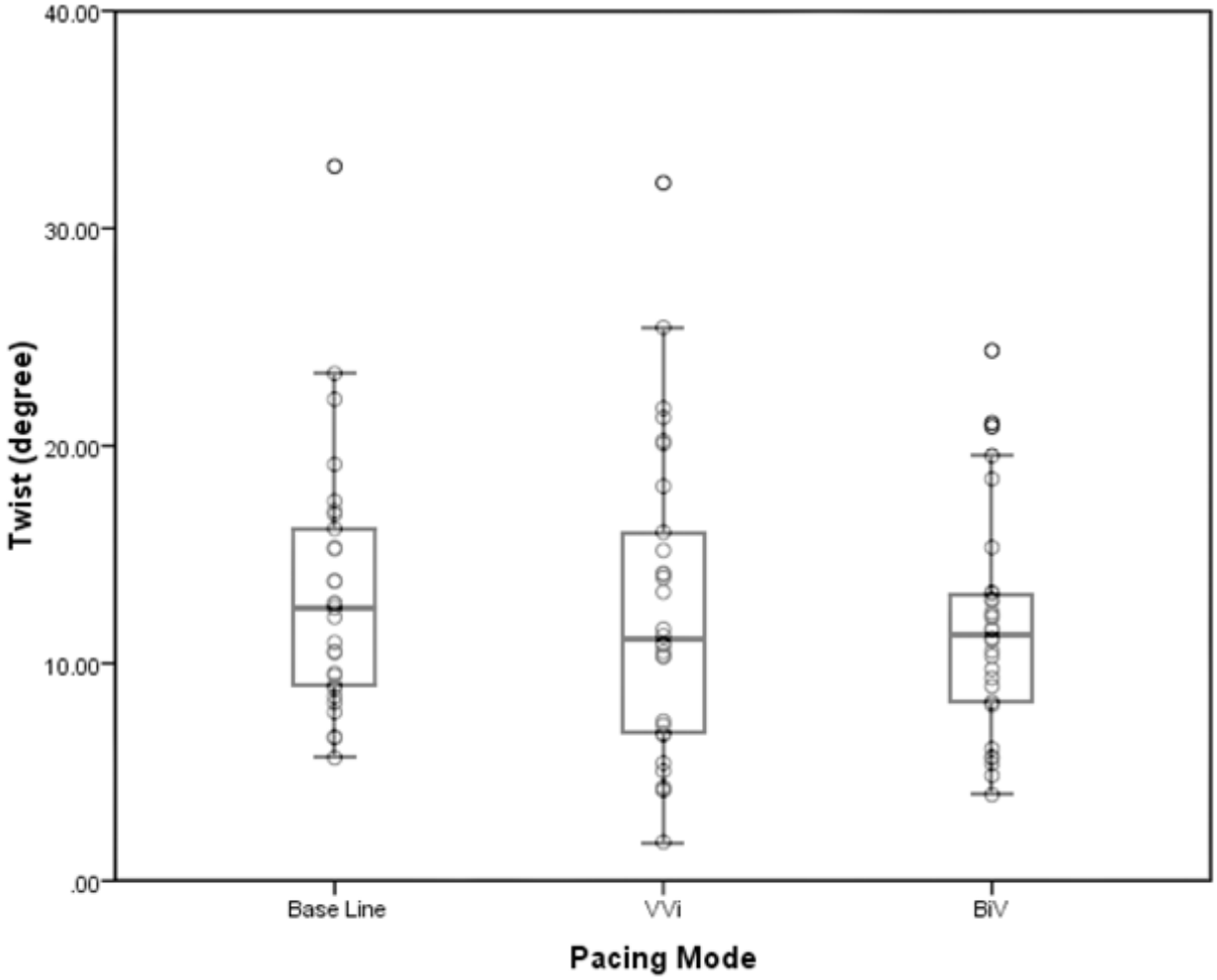

Figure 6.2 : Box-whisker plot showing myocardial Twist at baseline, following sham pacing (VVi) and chronic Active pacing (BiV) in 29 patients. Open circles are values for individual patients, bold line is median. p=ns for difference between sham pacing(VVi) or BiV and baseline and between BiV and sham pacing (VVi).

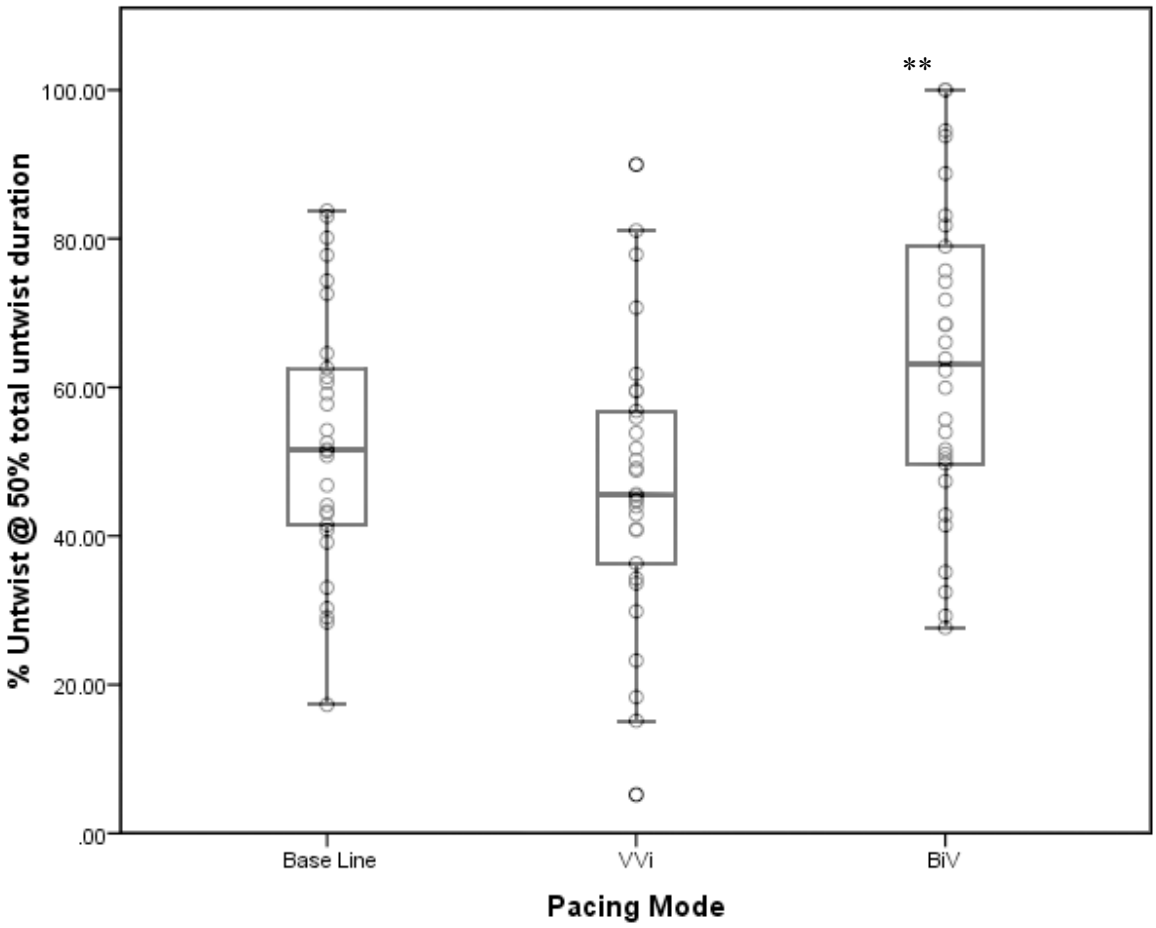

Figure 6.3 : Box-whisker plot showing the percentage of total untwist completed at the 50% of total untwist duration. This is shown at baseline, following sham pacing (VVi) and chronic active pacing (BiV). Open circles are individual patients; bold line is median. **p= 0.009: BiV *vs.* VVi.

Discussion

We found that following 4 months of active BiV pacing in patients with symptomatic non-obstructive HCM, transthoracic echocardiographic-derived measures of intraventricular and interventricular systolic and diastolic dyssynchrony, at rest, were not significantly different compared to sham pacing. Thus, the improvements seen acutely in the measures of dyssynchrony, described in Chapter 3 were not sustained. In the present study, we demonstrated that in contrast to patients with left ventricular systolic heart failure[382], BiV pacing had no measurable effect on strain and strain rate in multiple planes in patients with non-obstructive HCM, when measured with STE. We show that unlike patients with systolic heart failure[383] chronic BiV pacing in HCM patients does not significantly alter rotation or rotation rates at the apex or base, and that peak twist and twist rates are essentially unchanged following 4 months of BiV pacing. Despite lack of effect on peak values, BiV pacing does however appear to reduce the duration of time taken in which completion of untwisting takes place (Figure 6.2, Figure 6.3).

As discussed in Chapter 1 there was reason to speculate that myocardium affected with HCM may be more dyssynchronous in its mechanical function than normal healthy myocardium.

We hypothesised that chronic BiV pacing would ameliorate dyssynchronous contraction of the myocardium in patients with HCM, speculating that a synchronously contracting ventricle may improve myocardial strain and rotation.

A reduction of interventricular dyssynchrony measured as the difference between RV and LV pre-ejection intervals has been shown to be associated with reduction in LVEDV and improved systolic function in patients with systolic heart failure[183]. In patients with HCM this index was essentially unaffected by BiV pacing both acutely and chronically. The minimal impact of BiV pacing therapy on interventricular dyssynchrony may perhaps be a reflection of there being

insufficient baseline interventricular dyssynchrony. Though data is scant regarding normal interventricular dyssynchrony intervals, as measured using pre-ejection delays, Matsushita et al.[352] report interventricular delay post BiV pacing, in patients with conventional indication for BiV therapy to be 16.2±47.4ms. Given that our HCM patients had a pre BiV paced interventricular delay of 15.63±2.73ms, room for further reduction using BiV pacing may have been limited.

As discussed in Chapter 1, the majority of work on dyssynchrony has been focused on intraventricular dyssynchrony. The Yu index a robust measure of global dyssynchrony has been shown to be predictive of reverse remodeling in patients with conventional indication for CRT therapy[161, 167]. In the present study, we report a tendency for improvement in the Yu index, following 4 months of BiV pacing, suggestive of amelioration of intraventricular dyssynchrony. However, unlike acute BiV pacing (Chapter 3), statistical significance was not achieved, perhaps reflecting attrition of the initial acute impact of BiV pacing. Similarly, improvements in TDI derived measures of basal LV systolic synchrony, following acute BiV pacing, failed to be sustained following four months of BiV pacing.

As discussed in the Chapter 1, to overcome shortcomings inherent of tissue doppler, Speckle tracking [178] has been used to assess mechanical myocardial mechanics. In the present chronic study, we used STE to derive two indices of radial dyssynchrony (SDt_{6s} and AS-P delay), (Table 6.1). We find that despite 4 months of BiV pacing ('resynchronisation therapy'), patients with HCM did not show a significant change in either index, findings consistent with those seen in following acute BiV pacing (see Chapter 3), though there was a tendency for reduction in both.

Diastolic dyssynchrony has been reported in patients with HCM[11, 203] and has been shown to be ameliorated by Verapamil[147]. In the present study using tissue doppler imaging we derived indices of diastolic dyssynchrony as described in Chapter 2. We found, that similar to acute BiV

pacing, that chronic BiV pacing had a limited if any impact on this TDI derived measure of diastolic dyssynchrony. Perhaps not so surprising given the marginal effects seen on systolic dyssynchrony.

The reasons for there being no measurable change in current measures of dyssynchrony may be several-fold. Perhaps most importantly, the substrate may not have been amenable to resynchronisation by BiV therapy. Recent studies have demonstrated that the only consistently reliable predictor of outcome to BiV therapy is the prolonged QRS interval on the surface ECG. Notably, those with the greatest prolongation were shown to be the most likely to benefit, so that today a Class 1[384] indication for BiV therapy mandates a QRS interval ≥150ms. Our HCM patients had QRS (98.82±4.05ms) duration well within limits of normality. So, from an electrical dyssynchrony viewpoint (as measured using surface ECG), these patients did not have the electrical substrate for dyssynchrony, and given that BiV therapy is first an electrical resynchronisation therapy, at first glance, it may not be surprising that there was no effect. That said this statement may be an oversimplification, as the reduction in QRS width following BiV is not particularly sensitive (18%) in predicting of response to BiV therapy[385], and there is some evidence that suggests that there is a group of patients with a narrow QRS interval who do respond to BiV pacing[285, 386]. Furthermore, almost a third[387] of patients, despite having the prerequisite prolonged QRS interval who do not respond to BiV therapy, and often in this group it is the 'paradoxical' lack of mechanical dyssynchrony that is cited as the cause for this lack of response[388].

It may be that despite patchy fibrosis, ischemia, and regional variability in mechanical function, a critical dyssynchrony threshold was not crossed for it to become amenable to the effects of resynchronisation using the modality of BiV pacing. Indeed, our findings demonstrate pre-BiV pacing indices of dyssynchrony which are of the order of magnitude often found following BiV pacing in patients with systolic heart failure.

Myocardial twist as measured using STE, in humans, shows good correlation and agreement with MRI[177, 199], the gold standard. The relative ease of application of Speckle tracking has allowed interrogation of rotational dynamics in a broader cohort of patients.

Reports of the effect of BiV pacing on rotational mechanics in patients with systolic heart failure has been variable with some investigators reporting an acute improvement[383] following BiV pacing with others reporting no effect[389] even in patients otherwise seen to be responding to BiV pacing[390]. We found no reports on the effect of BiV pacing on rotation/twist in patients with non-obstructive HCM.

The important role of myocardial rotation to systolic and diastolic function has now been borne out by several studies[380 391]. Kim et al.[392] report a strong correlation between dP/dt_{max} (a marker of contractility) and LV twist, consistent with our findings where we show that BiV pacing does not alter LV systolic elastance (a marker of contractility) or LV twist.

Ischemic myocardium has been shown to reduce systolic rotation and delay untwisting using MRI[393], the same has been shown using Speckle tracking[394]. Though overt epicardial coronary disease is not a feature of HCM, microvascular ischemia is[341]. We have previously demonstrated the loss of the normal inverse relationship of LV TTPF with increasing heart rates in patients with HCM[42]. Similar has been shown with myocardial ischemia[395]. Myocardial contraction during systole, results in the storage of elastic energy in compressed giant molecules of titin[396] and transmural shear between myofibril sheets[397]. This stored energy is rapidly released, predominantly during the isovolumic relaxation phase, generating intraventricular pressure gradients[80], which contributes to suction of blood from atria to ventricle[391] and enhanced ventricular filling. It is conceivable then that patients with HCM may have loss of this untwist function, with reports of delayed untwist in HCM[83, 195, 196], with consequent loss of this suction effect, resulting in the delays

in times peak filling and consequent diastolic inefficiency. The results of this study show that BiV pacing has no statistically significant effect upon peak twist rates, or peak untwist rates, but we find that BiV pacing reduced the time taken for completion of untwisting, possibly via a more uniformly increased untwisting velocity throughout diastole rather than changes in peak values alone. This would require further study to prove. Although the present study was at rest, if the same were to hold true on exercise, this might contribute to the restoration of the normal inverse relationship between heart rate and time to peak filling, and ability to increase stroke volume on exercise[42] in this patient subset.

Perhaps reassuring is that we report chronic BiV pacing was not deleterious to myocardial rotational mechanics, as was demonstrated by Delgado et al.[398] who using RV apical pacing in 25 healthy volunteers demonstrated significant reduction in LV twist.

In the present study, we have also demonstrated that chronic biventricular pacing does not have a significant effect on systolic or diastolic, longitudinal, circumferential or radial strain and strain rates in patients with non-obstructive HCM at rest.

Despite systolic function as measured by ejection fraction being preserved or even supra-normal, subtle abnormalities in myocardial deformation are increasingly recognised in patients with HCM. Investigators have reported reduced strain and strain rate[201], indeed asymptomatic, phenotypically normal carriers of sarcomeric mutations have been identified as having impaired diastolic function, with reduced early diastolic velocities, using deformation imaging[205]. In this study, we measured circumferential, radial and longitudinal peak systolic and diastolic strain and strain rates at multiple distinct planes (apex, papillary and basal). Though strain and strain rate have been reported as reduced in patients with HCM[205], we show that BiV pacing is unable to

significantly alter these at rest, in distinction to the impact of BiV pacing on strain in patients with systolic heart failure, in whom BiV pacing has been shown to improve myocardial strain.[382]

These studies were performed with the patient lying down at rest. All of the patients were asymptomatic in this position. It was on exertion that patients manifest symptoms. A dyssynchronously contracting myocardium, that is playing a significant role in limiting exercise tolerance may be unmasked on exertion [399]. Furthermore, it may be on exercise that the degree of dyssynchrony is severe enough for BiV pacing to effect significant re-synchronisation. The present study did not examine the effect of BiV pacing on dyssynchrony during exercise.

In summary, our data do not support our initial hypothesis that chronic BiV pacing would significantly ameliorate systolic, diastolic or interventricular dyssynchrony in patients with HCM. We thus report for the first time that chronic BiV pacing has no significant effect on resting measures of systolic and diastolic dyssynchrony in patients with non-obstructive HCM. Furthermore, we report for the first time that BiV pacing does not alter peak twist and untwist velocities at rest, but does affect a more rapid completion of untwist. Whether this contributes to amelioration of diastolic dysfunction reported in patients with HCM, with consequent improvement in exercise capacity requires further study.

Chapter 7

The Chronic Study

The effects of chronic Biventricular pacing on peak Oxygen consumption and quality of life in patients with exercise limited non-obstructive Hypertrophic Cardiomyopathy.

Introduction

Patients with HCM frequently experience exertional breathlessness. In the variant of HCM where there is no obstruction to the out flow of blood from the LV, as in our cohort of patients, symptoms are often cited to be as a result of diastolic dysfunction[7], as discussed in Chapter 1. In this group of patients' treatment options are few, in the main consisting of rate limiting medications with the hope of improving diastolic filling. However, these strategies are frequently met with limited beneficial effects. Although we have recently shown the beneficial effects of Perhexiline, utilizing a novel approach, in this group of patients, there remains a pressing need for further treatment options for these patients.

Biventricular pacing has been shown to improve morbidity and mortality in patients with systolic heart failure. BiV pacing is now a Class 1 indication with level of evidence A, in patients who have LV systolic heart failure, with refractory symptoms, and a broad QRS interval on surface ECG. In this group of patients BiV pacing has been shown to improve peak Oxygen consumption by up to 1-2ml/kg/min.

Commonly the mechanism of improvement with BiV pacing, as discussed in Chapter 1, is thought to relate to a reduction in dyssynchronous contraction, with improved myocardial efficiency, though earlier in this study (see Chapter 6) we report that the effect of BiV pacing on parameters of dyssynchrony were limited, at rest at least, in this group of patients. In patients with systolic heart failure Frenneaux et al. have shown that that BiV pacing may be operating through a mechanism in addition to mechanical resynchronization, via amelioration of deleterious diastolic ventricular interaction[10].

There is reason to believe that patients with symptomatic HCM may have deleterious diastolic ventricular interaction, particularly on exercise, consequential on the development of

elevated pulmonary artery pressure, elevating RV end diastolic pressures, as discussed in the Introduction. This may then be amenable to BiV pacing as per analogy with systolic heart failure. In Chapter 4, we show that indeed there is evidence in some patients with HCM for deleterious diastolic ventricular interaction, particularly on exercise and that this may be relieved by BiV pacing, with a consequent improvement in stroke volume.

Whether this change in myocardial function following BiV pacing would translate into improved symptom status and exercise tolerance remained unanswered. The effect of BiV pacing on symptom status and on exercise tolerance in patients with non-obstructive HCM has not been previously reported.

To answer the above questions, we undertook a randomized cross over trial (4 months in each limb) to assess the effects biventricular pacing (BiV) *vs.* sham pacing (VVI30) on exercise capacity and symptom status in patients with marked exercise limitation due to non-obstructive HCM.

Methods

See Chapter 2 (section i) for study design and patient inclusion and exclusion criteria. The baseline clinical characteristics and cardiopulmonary exercise test results of the HCM patients are shown in Table 3.1. 31 patients were enrolled into the study. Two patients discontinued at the crossover phase of the study, both these patients were excluded from all analysis. Data are therefore presented for the 29 patients that completed both arms of the chronic cross over study. The Biventricular pacemaker was programmed as described in Chapter 2 (section iv). Symptom status assessments were carried out using the Minnesota living with heart failure questionnaire, see

Chapter 2 (section ix). Exercise tolerance was assessed using peak Oxygen consumption measurements (VO_{2max}) see Chapter 2 (section x).

Statistical analysis

Data were analyzed using SPSS version. 17.0 for Window and Microsoft Office Excel 2010, and expressed as mean ± standard error (sem). Comparisons of BiV pacing and sham pacing modes were performed using repeated measures analysis of variance. Statistical significance was set at $p< 0.05$.

Results

At baseline (Table 3.1), all patients experienced symptoms of exercise limitation due to breathlessness that significantly impacted activities of daily living. The Minnesota living with heart failure quality of life score was 49 ± 4 (≈ NYHA II-III). At baseline, echocardiographic examination the maximal wall thickness was 18.65 ± 0.88 mm. No patient had a peak left ventricular outflow tract gradient of greater than 30mmHg at rest or during exercise. No patient had more than mild mitral regurgitation. The mean baseline exercise duration was 422 ± 25s. The peak Oxygen consumption achieved at baseline was 17.89 ± 0.78ml/Kg/min (42.99 ± 1.41 % of age and gender predicted). Heart rhythm was normal sinus in all patients, with mean resting heart rate 67.82±2.7bpm and peak exercise heart rate 119±4.44bpm.

As described in Chapter 4, those patients who experienced a decrease in LVEDV on exercise were classed as Group 1and those who experienced an increase in LVEDV on exercise were classed as Group 2.

i) Effects of Biventricular pacing on exercise capacity

In the whole group, Table 7.1, peak $VO_{2\ max}$ was higher (by 1.16ml/kg/min) during BiV pacing *vs.* sham pacing (p=0.02). At baseline, peak $VO_{2\ max}$ was significantly lower in Group1 (16.42± 0.87ml/kg/min) *vs.* Group2 (19.46±1.14ml/kg/min) (p=0.043), (Table 7.1). The increase in peak VO_{2max} was also significantly greater during BiV pacing in Group1 (by 1.4ml/kg/min; p= 0.032) but not in Group2 (p=0.13). Treadmill exercise duration was significantly (p=0.02) increased following BiV pacing (465±18s) than that achieved following sham pacing (437±19s) and compared to baseline (422 ± 25s). This increase was significant in Group1 (p= 0.008) but not in patients in Group2 (p=1.00), as might be anticipated from the $VO_{2\ max.}$

The mean peak exercise heart rate (HR) at baseline was 119±4.44 bpm, and following 4 months of sham pacing and BiV pacing, 120±4.47bpm and 121±4.28bpm respectively. Peak exercise HR did not significantly differ between Group1 and Group2 at baseline (p=0.09), following sham pacing (VVI30) (p=0.07) or when BiV paced (p=0.54). Heart rate and blood pressure responses to exercise during BiV pacing were not significantly different compared with exercise tests performed at baseline and during sham pacing. All patients achieved a respiratory quotient of 1.0 or more. The VE/VCO_2 slope following 4 months of BiV pacing (35.55±1.06) did not significantly differ from sham pacing (VVI30) (35.22±1.59) or from baseline (35.53±1.08).

ii) Effects of chronic BiV pacing on Symptom Status.

See Table 7.1. The Minnesota Living with heart failure questionnaire (MLHFQ) score, was significantly lower with BiV (36.72± 4.08) compared to sham pacing (VVI30) (47.52± 4.08) or baseline (49.07±4.08) in the whole group (p=0.001), and in Group1 (p=0.02), with the difference being of borderline significance in Group2 (p=0.049).

Table 7.1 Effect of Chronic BiV pacing on exercise capacity and quality of life

	Pacing Mode			
	Baseline	**VVI30 (sham)**	**BiV**	***p***
Whole group follow up n=29				
HR (beats/min) Rest	67.82±2.7	64.93±2.19	63.10±2.08	0.64
Peak HR	119±4.44	120±4.47	121±4.28	1.00
SBP (mmHg) Rest	129.48±3.47	124.69±3.39	123.31±3.91	1.00
Peak SBP	167.58±5.17	158.68±4.83	165.93±4.42	0.368
QOL score Minnesota	49.07±4.08	47.52±4.08	36.72±4.08	0.001
Exercise duration(sec)	422±25	437±19	465±18	0.023
RER	1.07±0.017	1.09±0.017	1.09±0.017	1.00
VE/VCO_2	35.53±1.08	35.22±1.59	35.55±1.06	1.00
VO_2 max % of max. predicted	42.99±1.41	43.67±1.56	46.56±2.07	0.01
VO_2 ml/kg/min	17.89±0.76	18.0 ±0.80	19.17±1.01	0.02
Group 1 follow up n=15				
HR(beats/min) Rest	60.2±2.87	62.66±2.86	59.06±2.09	0.28
Peak HR	112±6.13	111±5.82	118±5.65	0.50
SBP (mmHg) Rest	131.13±5.54	122.86±4.79	123.73±5.41	1.00
Peak SBP	164±6.67	158±7.58	163±6.71	1.00
QOL score Minnesota	48.6 ±6.78	49.73±5.05	35.26±5.89	0.02
Exercise duration (sec)	424±45	409±26	461±25	0.008
RER	1.07±0.03	1.09±0.03	1.09±0.02	1.00
VE/VCO_2	35.57±1.71	34.26±2.85	35.99±1.60	1.00
VO_2 max % of max. predicted	41.34±2.34%	41.37±2.49	44.93± 3.23	0.027
VO_2 ml/kg/min	16.42±0.87	16.22±0.94	17.62±1.25	0.032
Group 2 follow up n=14				
HR (beats/min) Rest	76.00±3.70	67.35±3.33	67.42±3.41	1.00
Peak HR	127±6.43	128±6.84	123±6.47	0.56
SBP (mmHg) Rest	127.71±4.19	126.64±4.92	122.85±5.78	1.00
Peak SBP	171.28±8.14	159.14±6.14	168.28±5.87	0.48
QOL score Minnesota	49.57±5.54	45.14±6.16	38.29±5.49	0.049
Exercise duration (sec)	420±29	462±28	469±28	1.00
RER	1.07±0.01	1.08±0.02	1.09±0.02	1.00
VE/VCO_2	35.49±1.36	36.26±1.35	35.09±1.44	0.82
VO_2 max % of max. predicted	44.77±1.44%	46.13±1.66	48.31±2.59	0.11
VO_2 ml/kg/min	19.46±1.14	19.92±1.14	20.83±1.51	0.13

Values are mean±sem. Group 1 and 2 as defined in Chapter 4. p values are given for BiV *vs*. VV130.

iii) Sequence order effect

A repeated measures analysis of variance examining for carryover effects was carried out [381]. The analysis suggests there was no statistically significant sequence order effect affecting peak Oxygen consumption (p=0.28), (Figure 7.1) or Minnesota symptom scores(p=0.83) (Figure 7.2).

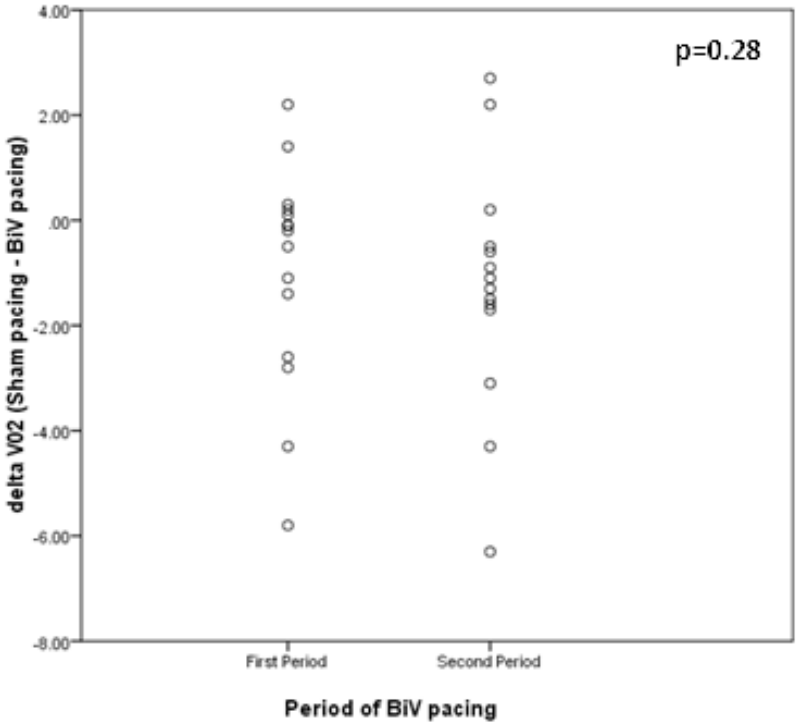

Figure 7.1 : Sequence order effect on $VO_{2max.}$

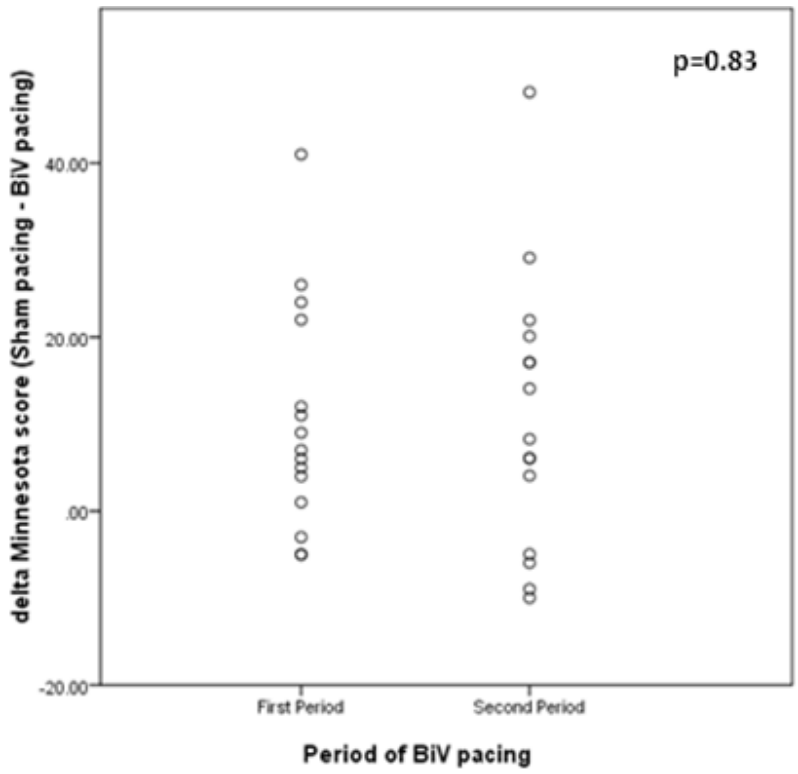

Figure 7.2 : Sequence order effect on symptom score

iv) Drug effect

A repeated measure of analysis of variance revealed no significant difference in exercise tolerance (VO_{2max}) following BiV pacing, whether on Calcium channel blocker or on beta blocker therapy (p=0.68) (Figure 7.3).

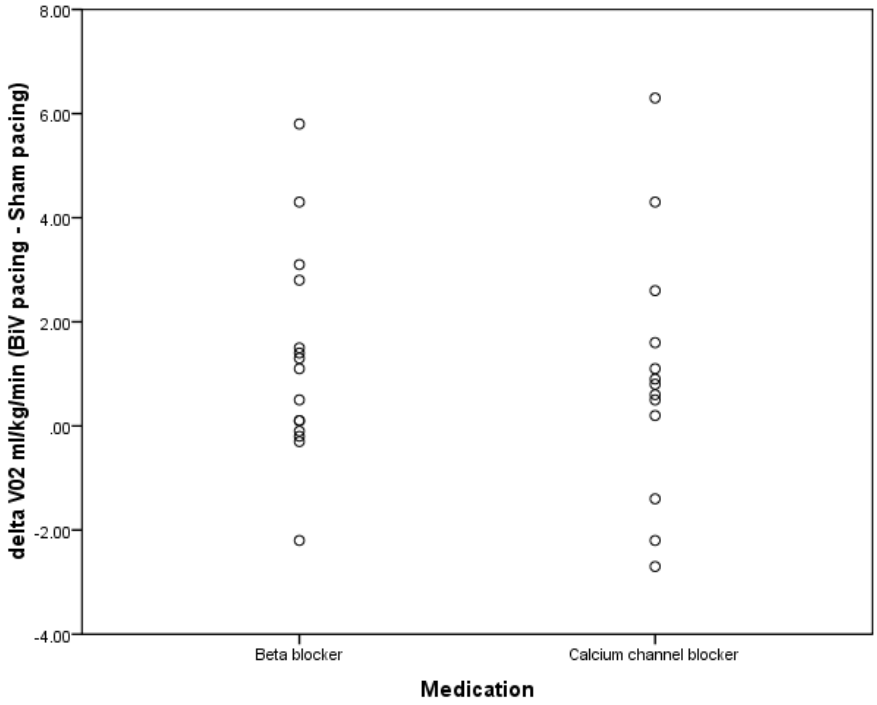

Figure 7.3 : Effect of medical therapy on response to BiV pacing

Discussion

This present pilot study shows that Biventricular pacing can improve exercise capacity and quality of life in patients with non-obstructive hypertrophic cardiomyopathy who have severe exercise limitation due to breathlessness despite being on optimal tolerated standard therapies (non-dihydropyridine calcium channel blockers or beta blockers).

Patients with HCM frequently experience a reduction in exercise tolerance and breathlessness on exertion. In the subgroup of patients that we studied, HCM without outflow tract obstruction, therapies have been to date limited, mostly based on a small number of studies, and are often empirical[108, 400]. Therapies studied have mainly been focused around use of beta blockers[97, 401] and calcium channel blockers[103, 106, 108, 402], the benefits frequently modest with little objective improvement in exercise capacity[105, 403]. Recently, our group has shown that Perhexiline, a metabolic modulator has a beneficial effect on symptoms and exercise tolerance in this group of patients, unfortunately it requires assessment of plasma levels of to avoid toxic effects. The treatment of refractory symptoms in patients with the non-obstructive variant of HCM remains unsatisfactory.

We found that, except for one patient who experienced diaphragmatic twitching following BiV pacing, this was a well-tolerated therapy in patients with non-obstructive HCM, with a low complication rate.

Measuring peak Oxygen consumption ($VO_{2\ max}$) is now considered the gold standard for the estimation and monitoring of relative exercise intensity[404], having the ability to provide highly reproducible metrics of exercise capacity[405]. Furthermore, numerous studies have demonstrated the prognostic utility of measuring peak Oxygen consumption and the VE/VCO_2 slope in patients with heart failure[406, 407]. In the present study we have demonstrated that peak Oxygen consumption

increased by over 1ml/kg/min in the group as a whole, which is comparable to the order of magnitude seen in patients who have BiV pacemaker therapy for systolic heart failure (1-2ml/kg/min) [408], with no significant increase in peak Oxygen consumption following BiV pacing in Group 2, and by 1.4ml/kg/min in Group1, i.e. those patients with most marked diastolic dysfunction.

Symptom status was assessed using the Minnesota living with heart failure questionnaire (MLHFQ) at baseline, cross over and at exit from study. A 10.8 point reduction in mean score was seen as a whole group, though more marked in Group1 (-14.47 points). This is comparable to patients who receive BiV pacing therapy for conventional indications who report an average 10 point reduction in MLHFQ score[408]. Borderline reduction in MLHFQ was seen in Group 2. Pacemakers have been used in Hypertrophic Cardiomyopathy before. When assessing subjective symptom status it is important to bear in mind that that in the early 1990s initial trials of dual chamber pacemakers in patients with the obstructive variant of HCM, demonstrated clinical improvement[119] but that subsequent trials demonstrated that a significant element of the benefit seen was in perceived subjective improvement, a placebo effect associated with having a device, with little impact on objective exercise capacity[122, 127, 409]. Our cross over study which employed sham (VVI30 backup) pacing excludes such an effect.

As discussed earlier, cross-over trials may be limited by carry-over effect, potentially blunting the effect seen of the therapy under scrutiny. A washout period between the two limbs would have been ideal to mitigate against this effect. In the absence of a washout period in this study, an analysis looking for carry-over effect of BiV pacing suggests that this was not a significant factor in the results seen (Figure 7.1, Figure 7.2).

Thus, for the first time we have shown that BiV pacing objectively improves exercise tolerance in patients with non-obstructive hypertrophic cardiomyopathy. Furthermore, we show that patients with the most marked diastolic dysfunction (Group1), as opposed to dyssynchrony, derive most benefit.

Chapter 8

General Discussion

The aims of this PhD were broadly two-fold. Firstly, to examine the possible pathophysiological mechanisms involved in exercise limitation in patients with non-obstructive hypertrophic cardiomyopathy, and the acute impact on myocardial function of Biventricular pacing in this patient group. Secondly, we appraised the potential role of chronic Biventricular cardiac pacing, as a treatment strategy for severely exercise limited patients with HCM.

In brief this study has shown that BiV pacing can improve exercise capacity and the quality of life of patients with non-obstructive hypertrophic cardiomyopathy who have severe exercise limitation due to breathlessness despite optimal tolerated standard therapies (non- dihydropyridine calcium channel blockers or beta blockers).

In patients with systolic heart failure, the predominant mechanism of improvement of cardiac performance following BiV pacing has traditionally been considered to be the relief of mechanical dyssynchrony. However, the degree of resting systolic mechanical dyssynchrony present in the patients in this study was much less marked than is seen in patients with systolic heart failure who undergo Biventricular pacemaker implants [264]. Furthermore, in these patients with HCM, QRS duration was normal and in all patients left ventricular ejection fraction was at least 50% at rest. Although following BiV pacing we saw acute improvement in TDI derived parameters of dyssynchrony, these gains were not sustained, with no significant changes in echocardiographic measures of systolic or diastolic dyssynchrony (at rest) being observed with chronic biventricular pacing (using tissue doppler and speckle tracking techniques). Perhaps, measuring dyssynchrony during exercise would have given a different result, as it is on exercise that patients develop symptoms. It may be then that we would have seen dyssynchrony[410], pronounced enough for BiV pacing to have its resynchronisation effects. However, we measured dyssynchrony at rest only. Applying TDI during exercise is difficult since TDI measures only the vector of motion that is

parallel to the direction of the ultrasound beam from the echo probe, and maintaining alignment during exercise is challenging.

The translational movement artifact limitation of TDI may be countered by using speckle tracking analysis, as described in Chapter 2. Optimal STE analysis requires acquisition of digital routine gray-scale cineloops with high quality images, again this may be difficult to achieve in the exercising subject. The ideal frame rate for STE currently appears to be 60–80 Hz. Frame rates that are too high (>100 Hz) result in excessive signal noise, but higher frame rates would be necessitated in order to maintain temporal resolution. Furthermore, increased mechanical movement during exercise would contribute to greater through plane movement of the myocardium during image acquisition leading to further degradation in STE.

In addition to the marginal effects on parameters of dyssynchrony, BiV pacing had no significant effect on LV ejection fraction or on LV end systolic elastance, (a relatively load independent measure of LV contractile function) at rest or on exercise. These findings argue against a substantial beneficial effect of BiV pacing on LV contractile function that might explain the improved stroke volume response on exercise and the increase in exercise capacity observed. However, there was a modest reduction in the duration of systole suggesting that there may have been a subtle improvement in contractile function, potentially related to reduced mechanical dyssynchrony on exercise, but we only have dyssynchrony data at rest.

Biventricular pacing however, did have marked effects on the filling of the left ventricle. In health, LV end diastolic volume increases during exercise, and thereby the Starling mechanism contributes to the increase in stroke volume[364]. This is a consequence of both an increase in the rate of LV active relaxation during exercise[280, 281] and of translocation of blood from the venous compartment to the central compartment due the effects of the muscle pump and to active

vasoconstriction in the intestinal and splenic venous capacitance beds[366]. We have previously shown that the rate of LV active relaxation paradoxically slows during exercise in many patients with HCM on exercise, and that amelioration of the marked cardiac energetic impairment with the metabolic modulator Perhexiline reverses this abnormality[95]. In approximately 50% of the patients in the present study there was an abnormal fall in LV end diastolic volume during exercise, and an associated fall in stroke volume (Group 1). This pattern was associated with more severe exercise limitation and with worse symptoms than in those patients in whom LVEDV increased on exercise (Group 2). Biventricular pacing substantially corrected these abnormal responses in Group 1 patients (indeed overall there was a modest mean increase in LVEDV during exercise during BiV pacing) with no significant effect observed on the increase in LVEDV during exercise seen in Group 2 patients. This was associated with a significant increase in LV stroke volume during exercise with BiV pacing in Group 1, but not in Group 2 patients and during the chronic study a significant increase in peak VO_2 was also observed with BiV pacing in Group 1, but not in Group 2 patients. These findings argue that the improved cardiac performance on exercise and the resulting increase in exercise capacity is in large part related to a partial restoration of the ability to use the Starling mechanism to increase stroke volume on exercise.

How might this have been achieved? Potential mechanisms might include an increase in the rate of LV active relaxation on exercise or a reduction in intrinsic left ventricular stiffness, an increase in diastolic filling time or a reduction in external constraint to left ventricular filling. Diastolic dyssynchrony has been reported in HCM[11, 367] and a reduction in the degree of diastolic dyssynchrony by BiV pacing (especially on exercise) might translate into more rapid LV active relaxation and reduced LV stiffness. However, at least at rest, we observed no significant effect of BiV pacing on measures of diastolic dyssynchrony. Furthermore, BiV pacing was associated with

a reduction in first third filling fraction at rest and on exercise, which argues against this being an important mechanism. External constraint to left ventricular filling by the pericardium[368] (pericardial constraint) and by the right ventricle through the interventricular septum (diastolic ventricular interaction) is observed in experimental models associated with acute RV volume and/or pressure overload[216 214]. We have shown that these phenomena are seen in an experimental model of chronic heart failure[367] and in those patients with chronic heart failure who have elevated left ventricular end diastolic pressures (typically >15mmHg)[4].

Bleasdale et al. have previously shown that in patients with severe chronic heart failure, both biventricular and left ventricular pacing reduced this external constraint to left ventricular filling and thereby recruited LV preload, presumably by shifting the timing of LV *vs.* RV filling[10]. We report in the present study, a paradoxical increase in left ventricular diastolic volumes during application of lower body negative pressure in 4 patients (all of whom were in Group 1), suggesting the presence of significant DVI in these patients. In 3 of these patients this paradoxical increase in LVEDV during application of LBNP was normalised by BiV pacing, suggesting alleviation of DVI. Although only a minority of patients with HCM have pulmonary hypertension and markedly raised LVEDP at rest, both PA pressure and LVEDP markedly rise during exercise in many patients with symptomatic HCM[239] . Therefore *a priori*, DVI might be expected to be a frequent occurrence on exercise in these patients. We suggest that the restoration of the Starling mechanism on exercise by BiV pacing in Group 1 patients is the most likely explanation for our findings. Diastolic ventricular interaction is typically associated with a restrictive LV filling pattern[236] in which rapid early filling then ceases with the onset of external constraint. Of note, BiV pacing reduced the rate of early filling but markedly increased filling in the later part of diastole during exercise, consistent with our assertion.

The anatomical position of the septum makes it an ideal surrogate of the diastolic interactions between the two ventricles, akin to a membrane separating two fluid volumes[411], as described in earlier Chapter 2 (section vii). The normal shape of the intraventricular septum (convex to the RV[412]) is dependent on the presence of a positive LV - RV pressure gradient. In 10 patients with hypertrophic cardiomyopathy, we show that during sham pacing, on exercise there was a tendency for septal flattening (with an increased Rs p=0.08), as might be anticipated with the development of adverse DVI. Furthermore, we see that during BiV pacing on exercise there was a reduction in the degree of septal flattening (reduction in Rs). We suggest that this is due to the phase shift in ventricular filling following BiV pacing, allowing the LV to fill unimpeded by RV, (in distinction to RV pacing by Kingma et al.[370]), with the development of an appropriate transeptal gradient, restoring the normally concave to the left conformation of the ventricular septum. These findings lend further weight to the argument for the development of DVI during exercise, and its correction following BiV pacing.

Biventricular pacing markedly increased the diastolic filling period on exercise in Group one, but less so in Group 2 patients. This may also be an important mechanism contributing to improved LV filling. This may in turn be a consequence of reduced ventricular interaction resulting in a longer period of filling and/or (by reduced LVEDP) reducing pre-systolic mitral regurgitation on exercise. Alternatively, it might in part be related to the shortening of systolic duration observed.

These findings would have been more conclusive of DVI development if we had been able to measure simultaneous RV and LV volumes. On exercise a simultaneous increase in right ventricular (RV) end diastolic volume with associated fall in LV end diastolic volume, and on application of LBNP, a reduction in RV end diastolic volumes with a simultaneous increase in LV end diastolic volumes would argue strongly for the presence of DVI. However, our image quality

was not good enough to analyse RV volumes with sufficient fidelity, and further increasing already significant radiation doses (1:3300 fatality) to achieve this would be ethically difficult. We demonstrated the potential development of DVI in only 50% of patients on exercise, when exercised to only 50% of heart rate reserve. Likely the number demonstrating potential DVI would have been larger, and effects of DVI more dramatic, at greater workloads due to associated increase in pulmonary artery pressures. However, maintaining gated radionuclide ventriculography data integrity at high workloads is challenging, due to difficulties in maintaining constant heart rates (patient fatigue) and movement artefact, seriously degrading statistical reliability of systolic and diastolic indices measured.

Conclusion

In this pilot study, we have shown for the first time that Biventricular pacing can improve symptoms and exercise capacity in patients with non-obstructive Hypertrophic Cardiomyopathy. As this was a crossover study there is always the concern of carryover effect. However previous investigators have demonstrated that the symptomatic benefits and the effects of reverse modelling of BiV pacing begin to diminish within a week of halting BiV pacing, and have completely reversed back to baseline by 3 months[161].

The benefit we report was most marked in those patients with the most marked diastolic impairment during exercise. We suggest that the mechanism of improvement is primarily through the relief of DVI, a mechanism not previously described in HCM patients, with consequent improvement in the ability to utilize the Starling mechanism to increase stroke volume. We have shown that there is a subset of patients with HCM who may derive particular benefit from BiV pacing however this group is small, 15 patients. To show more definitively the benefits of BiV

therapy it would be better to recruit potential patients for a trial of this therapy by screening for deleterious DVI pre-implantation.

Chapter 9

Future Direction

This pilot study has shown that there may be a role for BiV pacing in patients with symptomatic, exercise limited non-obstructive Hypertrophic Cardiomyopathy. However, we show that this benefit was restricted to those patients with the most marked diastolic dysfunction on exercise. We have argued that one of the mechanisms contributing to this is diastolic ventricular interaction. Atherton et al.[4] showed that almost 50% of patients with chronic heart failure had evidence of DVI at rest. Furthermore, they showed, using transthoracic echocardiography, that a restrictive transmitral LV filling pattern at rest was associated with DVI in patients with chronic heart failure[236]. We show that at rest most non-obstructive HCM patients do not have evidence of DVI, however over half had evidence suggestive of the development DVI on exercise. It then follows that a restrictive LV filling pattern on exercise in patients with non-obstructive HCM may, similarly to patient with chronic heart failure, be able to identify patients with DVI. Transmitral doppler maybe a simple non-invasive tool for identifying HCM patients who may benefit from BiV pacing. A further study would be required to establish the relationship between restrictive LV filling patterns on exercise and the development of DVI on exercise in patients with non-obstructive HCM.

Geske et al.[413] in a retrospective analysis of 321 patients with HCM, showed that those with most marked pulmonary hypertension had the greatest elevations in brain natriuretic peptide (BNP) and in n-terminal BNP. Information which may lend additional support for the presence of significant DVI. A future full scale study of BiV pacing in patients with NOHCM may then be restricted to those who are most likely to benefit, identified with easily available blood tests, and straight forward transthoracic echocardiography.

The relief of DVI, allows an increase in LVEDV and utilization of the Starling mechanism. On exercise this should manifest as an increase in cardiac output. Peak Oxygen consumption,

a powerful prognostic index[414], is an indirect measure of cardiac output, is influenced by peripheral factors[415, 416]. The Innocor rebreathing system, a relatively easy to apply, non-invasive method, by using the Fick principle is able to measure cardiac output, both rest and on exercise[417]. A future study may incorporate this technique to provide direct evidence for improvement in cardiac output following BiV pacing.

Myocardial mechanical dyssynchrony is an appealing and relatively easy idea to grasp, qualitatively is often easily recognised, but to quantify has proven to be far more challenging then initial reports suggested[289, 418]. As imaging technology rapidly advances with the advent of techniques such as 3D Speckle tracking[419] and MRI, measures of dyssynchrony[420] are likely to be developed that are more robust, sensitive, and easily applied. Utilising these future measures, it would be useful to study and quantify the role mechanical dyssynchrony is playing in producing cardiac dysfunction in patients with HCM, particularly on exercise. Furthermore, if ameliorating mechanical dyssynchrony by therapies such as BiV pacing offers benefit to patients.

More recently investigators have reported changes in molecular and cellular function induced by BiV pacing, going beyond the traditional mechanical and hemodynamic effects[421]. In animal models, BiV pacing has been shown to have a positive impact on mitochondrial function, altering expression of at least 30 different proteins within the mitochondrial proteome[302]. Recently, we have shown using magnetic resonance spectroscopy, that Perhexiline a metabolic modulator improved myocardial performance in patients with HCM. With increasing availability of MRI compatible BiV pacemakers (Medtronic SureScan device series), it would be of interest to see if both, BiV pacing and Metabolic manipulators such as Perhexiline share common metabolic end pathways in patients with HCM, different means to the same ends!

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