The Role of Myocardial Fibrosis and Ventricular Mechanical Dyssynchrony in the Pathogenesis and Treatment of Contractile Myocardial Dysfunction

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Abstract

Structural and functional abnormalities of the left ventricle and atrium are important prognostic factors in patients with cardiovascular disease. Dysfunction of the left ventricle in heart failure exposes the left atrium to elevated pressures during diastole, which result in adverse left atrial remodelling and impairment.

Although the development of systolic left ventricular impairment has been linked with a number of causative factors, the pathophysiological cascade between these initiators of myocardial dysfunction and its overt manifestation has been incompletely characterised. Amongst the proposed intermediaries of systolic heart failure, recent attention has focussed on myocardial fibrosis and ventricular dyssynchrony. Myocardial fibrosis describes the extracellular deposition of collagen in response to an injurious process. This collagen deposition plays an important role in left ventricular remodelling, and may perpetuate myocardial dysfunction. Ventricular dyssynchrony refers to the incoordinate contraction of the ventricles: inter-ventricular dyssynchrony is the temporal uncoupling of left from right ventricular contraction, and intra-left ventricular dyssynchrony pertains to heterogeneity in the time to regional mechanical activation within the left ventricle. Ventricular dyssynchrony has also been implicated in the pathogenesis of systolic heart failure, and its treatment by cardiac resynchronisation has been proven efficacious in selected patients with systolic left ventricular dysfunction.

Despite emerging evidence implicating myocardial fibrosis and ventricular dyssynchrony in heart failure, their causal relationship with each other, and their relative importance in the pathogenesis of myocardial dysfunction have been poorly characterised. The aims of this thesis are to 1) characterise the role of myocardial

fibrosis and ventricular dyssynchrony in the development of left ventricular and atrial mechanical dysfunction, and 2) examine the importance of myocardial fibrosis and ventricular dyssynchrony in the response to therapy of patients with systolic heart failure using non-invasive imaging approaches.

The first study presented in this thesis in Chapter 3 explores the relationship between left atrial mechanical and left ventricular function by evaluating the effects on left atrial mechanical function of eliminating left ventricular function through the temporary induction of ventricular fibrillation in patients undergoing routine defibrillation threshold testing following implantable cardioverter-defibrillator insertion. In this mechanistic study, the dependence of left atrial function on left ventricular function is demonstrated. This finding establishes the context for the subsequent research in this thesis on the effects of left ventricular function on the left atrium in idiopathic dilated cardiomyopathy and cardiac pacing.

Chapter 4 presents research investigating the prevalence of myocardial fibrosis and ventricular dyssynchrony in patients with a first presentation of idiopathic dilated cardiomyopathy. The influence of these factors, amongst other recognised prognostic factors in heart failure, on recovery of left ventricular systolic function is examined. The key finding of this chapter is that myocardial fibrosis and ventricular dyssynchrony are independent predictors of improvement in left ventricular systolic dysfunction amongst these patients. These results relate directly to the chief aims of this thesis.

In Chapter 5, abnormalities in left atrial structure and function in patients with a first presentation of idiopathic dilated cardiomyopathy are explored. This research demonstrates that structural and functional abnormalities are prevalent early in the time course of this condition, but that these derangements are reversible following appropriate medical therapy. This chapter extends on the findings of the previous two

chapters to illustrate how disease processes primarily affecting the left ventricle can impact upon the left atrium.

Chapter 6 aims to further develop the evidence that left ventricular dyssynchrony promotes ongoing left ventricular dysfunction through the study of patients who had been enrolled in a randomised trial of right ventricular apical versus right ventricular outflow tract septal pacing for bradycardia. The major findings of this research are that right ventricular apical pacing is associated with greater ventricular dyssynchrony, poorer left ventricular function and worse adverse left ventricular remodelling than outflow tract septal pacing. Moreover, the adverse left atrial structural and functional effects of right ventricular apical pacing and ventricular dyssynchrony are demonstrated. These results lend support to the theme that ventricular dyssynchrony, in this instance induced by pacing site, adversely influences left ventricular function, which in turn impacts in a deleterious manner on left atrial structure and function.

In chapter 7, the final study conducted in this thesis, the intuitive question arising from the findings of chapter 6 is addressed, namely: if induction of ventricular dyssynchrony is deleterious, is its reversal therapeutic? This study randomised patients undergoing cardiac resynchronisation therapy for advanced heart failure to routine simultaneous bi-ventricular pacing, or echocardiographic optimisation of V-V timing during bi-ventricular pacing, with the goal of further reduction in ventricular dyssynchrony. This study was unable to demonstrate a benefit of routine V-V optimisation in recipients of cardiac resynchronisation therapy despite achieving less left ventricular dyssynchrony. A trend towards improved functional status was observed, however.

This thesis has led to an improved understanding of the mechanisms underlying the development and perpetuation of left ventricular and atrial dysfunction, and the determinants of their response to heart failure therapy. Work of this nature

may allow the identification of novel diagnostic and therapeutic approaches to heart failure in the future.

Declaration

This work contains no material which has been accepted for the award of any other degree or diploma in any university or other tertiary institution and, to the best of my knowledge and belief, contains no material previously published or written by another person, except where due reference has been made in the text.

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Darryl Leong

26th January, 2011

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Chapter 1

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Chapter 3

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Chapter 7

Manuscript awaiting supervisor approval for submission.

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Abbreviations

CHF = congestive heart failure

CMR = cardiovascular magnetic resonance

CRT = cardiac resynchronisation therapy

DCM = idiopathic dilated cardiomyopathy

HFNEF = heart failure with normal ejection fraction

HFREF = heart failure with reduced ejection fraction

IVMD = interventricular mechanical dyssynchrony

LA = left atrial

LAAEV = left atrial appendage emptying velocity

LAVI = left atrial volume index

LASEC = left atrial spontaneous echocardiographic contrast

LGE = late-gadolinium enhancement

LV = left ventricular

LVEDVI = left ventricular end-diastolic volume index

LVEF = left ventricular ejection fraction

LVESVI = left ventricular end-systolic volume index

NICM = non-ischaemic dilated cardiomyopathy

NT-pro-BNP = N-terminal pro-brain natiuretic peptide

NYHA = New York Heart Association

RV = right ventricular

RVA = right ventricular apical

RVEF = right ventricular ejection fraction

RVOT = right ventricular outflow tract

TAPSE = tricuspid annular plane systolic excursion

Chapter 1 – Background

1.1. INTRODUCTION

Heart failure is defined as a clinical syndrome that results from an impaired ability of the ventricle to fill with or eject blood(1). The diagnosis of heart failure is associated with a poor prognosis with a 50% 4-year mortality rate across population studies(2, 3). A first hospital admission for heart failure has been shown to confer a worse prognosis than a first admission for bowel or breast cancer(4). From a population health perspective, heart failure is a leading cause of morbidity and mortality in developed countries and an emerging one in the developing world(5, 6). Its prevalence in Western society is estimated to be 1-2%(7, 8). The prevalence increases with advancing age, exceeding 8% in those 75 years and older(8). The incidence also rises with advancing age, from 0.2 per 1000 person-years among those aged 45-55 years to 12.4 per 1000 person-years among those 85 years and older(9). Heart failure is the leading reason for hospital admission among patients over age 65 and the most costly cardiovascular disorder in Western countries(6, 10).

The development of heart failure is characterised by four stages(1). In Stage A, individuals are at elevated risk of heart failure but with no overt structural heart disease. Stage B is defined by the presence of subclinical abnormalities in cardiac structure. Patients in Stage C have or have had overt symptoms related to heart failure, whilst Stage D is characterised by refractory heart failure. The early identification of myocardial dysfunction is desirable to minimise patient morbidity from heart failure, and to permit prompt intervention to remedy causative factors. Moreover, understanding the pathophysiological events that culminate in myocardial dysfunction is important for the development of novel therapeutic approaches to the prevention and treatment of heart failure.

1.2. PATHOLOGY AND PATHOPHYSIOLOGY OF HEART FAILURE

The aetiology, pathology, and mechanisms underlying the clinical syndrome of heart failure are diverse. Pathophysiologically, heart failure can be dichotomised into heart failure with reduced or normal ejection fraction. Heart failure with reduced ejection fraction (HFREF) accounts for at least 50% of cases(11). The progression of HFREF features a process known as cardiac remodelling, which is characterised by left venrtricular (LV) chamber dilatation and change in its shape from elliptical to more spherical(12). These macroscopic changes are due to histological abnormalities that include myocardial fibrosis(13), increased fibrillar collagen(14), myocyte slippage and cardiomyocyte apoptosis(15). ***Myocardial fibrosis is thought to play a pivotal role in the pathophysiology of HFREF and its relentless progression.***

Several large randomised clinical trials have shown mortality and morbidity benefit from drug classes suppressing the renin-aldosterone system (angiotensin converting enzyme inhibitors, angiotensin receptor blockers, spironolactone) and adrenergic system (beta blockers)(16-20). These drugs form the cornerstone of medical management and have revolutionised the care of patients with congestive heart failure (CHF). Intriguingly these agents share the ability to reverse or attenuate LV remodelling in CHF. This drug response would appear to predict reduction in both mortality and morbidity in heart failure, whilst drugs that do not reverse remodelling do not alter prognosis, despite often improving symptoms (digoxin)(21). ***Notwithstanding these impressive advances with neurohumoral agents, the limits of this approach have already been encountered. Consequently, in order***

to identify new modes of treatment of CHF, a critical reassessment of fundamental cardiac pathophysiology is needed*.*

Cardiac resynchronisation therapy (CRT) has been demonstrated to confer benefit in patients with HFREF with moderate-severely depressed LV ejection fraction and electrocardiographic QRS prolongation, with respect to symptoms, LV systolic function and remodeling, and survival(22-25). These favourable effects support the emerging paradigm that posits that ventricular dyssynchrony itself has pathophysiological consequences rather than being an epiphenomenon to heart failure. The exact role of role of ventricular dyssynchrony and its relationship with myocardial fibrosis in the promotion of ongoing LV dysfunction remains poorly defined, however. An understanding of the pathophysiological influence of these factors might facilitate the development of novel avenues of therapy for heart failure.

1.3. HEART FAILURE AND SYSTOLIC LEFT VENTRICULAR FUNCTION

Global systolic LV function is well-recognised as a prognostic marker. Pocock *et al*. demonstrated that in 7599 patients with heart failure, reduced systolic LV function was among the most powerful predictors of adverse outcome(26). Among 518 subjects with and without cardiac disease, Wang *et al*. demonstrated that systolic LV function was an important predictor of mortality(27). In 512 patients with prior myocardial infarction, St John Sutton *et al*. found that reduced systolic LV function was an indicator of adverse cardiovascular prognosis(28). Gustafsson *et al*. reported that among patients with heart failure, global systolic LV function is a potent independent predictor of mortality(29). Older research suggested that HFREF – previously termed systolic heart failure – is associated with a poorer outlook than heart failure with normal ejection fraction (HFNEF) or diastolic heart failure(30). More

recent evidence indicates a similar outlook between the two categories of heart failure(31). Although these conflicting reports and the proposed explanations for the discrepant findings remain to be clarified, studies of pharmacotherapy and device therapy for heart failure have recruited participants on the basis of LV ejection fraction(19, 32). Thus the evidence base guiding therapeutic decisions hinges upon the evaluation of systolic LV function.

1.3.1. Echocardiographic Techniques for the Assessment of Systolic Left Ventricular Function

1.3.2.1. Fractional Shortening

Left ventricular (LV) systolic function may be measured by fractional shortening using either M-mode or 2-dimensional (2D) echocardiography. This method is of limited value in individuals with regional wall motion abnormalities, owing to its single plane of interrogation(33).

1.3.2.2. Left Ventricular Ejection Fraction

Left ventricular volumes for the calculation of the LV ejection fraction (LVEF) may be estimated by applying the modified Simpson's rule to 2D images of the left ventricle. This technique is currently the 2D method of choice for measurement of LVEF(33). The measurement of LVEF by 2D echocardiography is associated with three key limitations. First, it relies on clear endocardial definition, which is lacking in up to 31% cases(34), particularly when intravenous contrast is not utilised. Second, foreshortening of the correct imaging plane, either inadvertent or because of technically challenging echocardiographic windows, may result in biased estimation of LV chamber volumes. Third, 2D techniques assume uniform LV chamber

geometry, which may not be valid in the presence of LV aneurysm. Consequently, even in expert echocardiography laboratories, there is considerable variability in the estimation of LVEF(35). Furthermore, there is poor agreement between Simpson's bi-plane technique and cardiovascular magnetic resonance (CMR) imaging, the non-invasive gold standard for estimation of cardiac volumes, with Bland-Altman limits of agreement of up to ±20% in a sample of heart failure patients(34).

Three-dimensional (3D) echocardiography circumvents the second and third limitations of 2D echocardiography in the measurement of LVEF. In 3D echocardiography, data is acquired over 4-6 cardiac cycles then synthesised into a single so-called full-volume dataset. This can then be manipulated or cropped to obtain non-foreshortened planes through the left ventricle, thus permitting more accurate estimation of chamber volumes. Three-dimensional echocardiography boasts superior reproducibility and closer approximation to CMR than 2D echocardiography in the measurement of LVEF(36). Despite minimal bias compared with CMR, 3D echocardiography has slightly greater variability(37). This may relate to poorer spatial resolution and endocardial definition, which is sub-optimal in up to 20% of cases, and is associated with less reliable measurement of LV volumes compared with non-endocardial-dependent techniques(38). Three-dimensional echocardiography and CMR both require the patient to breath-hold during image acquisition, which can prove difficult in those dyspnoeic at rest.

Accurate and reproducible measurement of LVEF is not always feasible in practice. Obstacles such as the inability to adequately position bed-bound patients, ventilator-dependency in the intensive care unit, and co-morbidities such as chronic obstructive pulmonary disease and obesity frequently render accurate measurement of LVEF limited using conventional echocardiographic techniques. Contrast echocardiography and tissue Doppler imaging may potentially have a role to play in this setting. Jenkins *et al*. have shown in a cohort of 50 patients with prior myocardial

infarction that contrast-enhanced 2D echocardiography has similar accuracy to non-contrast 3D echocardiography in comparison with CMR(39). Contrast-enhanced 3D echocardiography demonstrated even superior results(39).

1.3.2.3. Tissue Doppler Imaging

The peak systolic tissue velocity measured at the septal mitral annulus is an index of global LV systolic function. Tissue velocity in this location represents an integral of longitudinal cardiac motion from base to apex. The advantage of tissue Doppler imaging is that it is less reliant on good 2D image quality and has good reproducibility.

Among 92 individuals with LV systolic function ranging from normal to depressed, peak systolic tissue velocity (Sm) by pulse wave tissue Doppler imaging of the mitral annulus has been shown to correlate with LVEF. Sm <7cm/s predicts LVEF <45% with sensitivity 93% and specificity 87%(40). A good linear correlation has been demonstrated between LV ejection fraction by 2D echocardiography and mean systolic mitral annular velocity from four sites(41). In a contrasting study of healthy individuals, the correlation between averaged mitral annular S_m and LVEF was weak, although statistically significant (r = 0.3)(42), raising the notion that the two indices are not interchangeable, and perhaps address different aspects of systolic function.

Tissue Doppler data may also be subject to post-processing to display strain and strain rate data. Lagrangian strain is defined as $(L-L_0)/L_0$, where L is the instantaneous myocyte fibre length and L_0 is its length under zero stress(43). In contrast, Natural strain is defined as $\log_e(L/L_0)$. In contrast to Lagrangian strain, Natural strain does not assume that myofibre cross-sectional area remains unchanged and that strain remains uniform along the fibre length. Strain rate is the first temporal derivative of strain.

Urheim *et al*. proposed and validated, using sonomicrometry in a canine model, that tissue Doppler-derived strain is representative of myocardial tissue deformation(44). A major advantage of strain imaging over tissue Doppler imaging is that tissue velocity is subject to the tethering effects of adjacent myocardial segments, whereas strain measurements are less susceptible to this bias. In a canine model, Greenberg *et al*. demonstrated that tissue Doppler-derived strain rate was more closely associated with peak LV elastance, as a gold standard measure of cardiac contractility, than tissue velocities(45).

1.3.2.4. Speckle Tracking Echocardiography

An important limitation of tissue Doppler-derived strain is its dependency on the angle of insonation(44). Speckle tracking technology provides another echocardiographic means to evaluate systolic LV function, but in contrast to tissue Doppler techniques, speckle tracking is not dependent of the angle of ultrasound insonation. It relies on tracking small myocardial regions of interest, each with a relatively unique appearance owing to its pattern of acoustic backscatter, through space from frame to frame. This then permits calculation of strain on a regional basis. Current software allows regional strain scores to be averaged to yield a global strain score. This score has been proven an accurate index of systolic LV function in patients with ischaemic heart disease(46, 47). Global strain has been demonstrated to confer addition prognostic information to conventional echocardiographic indices, including LVEF, in the prediction of adverse cardiovascular events(48). Mignot *et al*. reported that amongst patients with systolic LV dysfunction, global longitudinal strain by speckle tracking is the echocardiographic parameter that yields the greatest area under the receiver operating characteristic curve for the prediction of major adverse cardiovascular event(49). Owing to its angle independence, strain analysis permits interrogation of myocardial deformation in any cardiac axis. Wang *et al.* recently

demonstrated that longitudinal and radial systolic strains are reduced in HFNEF although LV twist is preserved(50). A further advantage of strain analysis is that it permits quantification of regional as well as global LV systolic function. Becker *et al*. have demonstrated close agreement between speckle-tracking strain imaging and CMR in the evaluation of regional wall function(51).

1.3.2. Cardiac Magnetic Resonance Techniques for the Assessment of Systolic Left Ventricular Function

CMR has rapidly become the imaging method of choice and the gold-standard in the assessment of systolic cardiac function of both normal and abnormal left ventricles(34). With regard to measurement of global LV systolic function, given its 3D nature and order of magnitude greater signal-to-noise ratio, CMR is highly superior to 2D echo(34). This imaging is typically performed in, although not limited to, the conventional short axis views and the 3 cardinal long-axis views. The ability of CMR to image in any plane without the need for optimal imaging windows allows for unprecedented flexibility for the interrogation of abnormal heart structures.

Cine images are obtained using steady state free precession sequences, which provide images of higher signal-to-noise (than older sequences such as gradient echo), and hence exceptional delineation of the blood–myocardium interface. This allows for accurate and reproducible quantitative assessment of chamber dimensions and systolic function using manual or semi-automated planimetry techniques.

CMR tagging is a technique by which a radiofrequency pulse is applied to LV myocardium in the form of grid lines. The tagged grid deforms as the saturated

myocardium moves throughout the cardiac cycle, allowing regional strain to be visualised and quantified. The tag is generally applied at the onset of systole, triggered by the ECG R wave, and fades during the cardiac cycle as the magnetisation recovers towards equilibrium as a result of spin-lattice, or T1, relaxation. Measurement of strain is suited to quantifying regional systolic LV function.

The tissue phase mapping technique allows the determination of three-dimensional velocity tensors over the cardiac cycle, i.e. for rotation, radial and longitudinal movement, with a pixel-by-pixel spatial resolution nearing that of “conventional” cine CMR(52). This has been investigated in clinical studies in both patients and volunteers, and newer navigator sequences (obviating the need for breath-holding, and hence with the potential for improving spatial resolution) have been developed. Displacement encoded imaging using stimulated echoes (DENSE) can also provide information on myocardial displacement, velocity and strain(53).

An important advantage of CMR is its ability to evaluate myocardial perfusion or ischaemia, and characterise tissue within the same examination. Tissue characterisation will be described subsequently. Assessment of myocardial ischaemia using CMR may be performed by intravenous contrast administration to detect a first-pass perfusion defect with adenosine stress (that is absent at rest), or by evaluation of segmental contractile reserve in response to intravenous dobutamine. Using these approaches, Hundley *et al*. demonstrated that the detection of LV systolic function and myocardial ischaemia by CMR are significant predictors of major adverse cardiovascular event, independent of traditional cardiovascular risk factors(54).

1.4. HEART FAILURE AND DIASTOLIC LEFT VENTRICULAR FUNCTION

Diastolic LV dysfunction is a frequent finding even in the general community(55). Amongst patients with organic heart disease, evaluation of diastolic function confers important prognostic value(56) and incremental prognostic information to systolic function(57). In patients with congestive heart failure, severe diastolic dysfunction has been reported as a potent predictor of cardiac death(58).

Diastolic dysfunction is characterised pathophysiologically by increased LV stiffness(59). Consequently with exercise, there is an inability to augment LV end-diastolic volume despite increasing LV end-diastolic pressure. The outcome of increased LV stiffness is reflected in the hemodynamic changes that are most widely used to assess diastolic function. In normal diastole, LV untwisting – a vigorous and active process – sucks blood from the left atrium into the left ventricle. Seventy to eighty percent of LV filling under these circumstances occurs in early diastole, with atrial contraction accounting for the remaining 20-30%. With the development of early diastolic dysfunction, the proportion of LV filling permitted to occur in early diastole is reduced. The relative importance of atrial contraction is thus increased – so-called grade I diastolic dysfunction. As diastolic dysfunction worsens, pressure mounts within the left atrium, such that immediately following mitral valve opening, blood is forced under positive pressure, rather than sucked by negative pressure, into the left ventricle. Although the proportion of LV filling occurring in early diastole returns to normal, the underlying physiology is not normal, hence the designation of pseudo-normal LV filling, or grade II diastolic dysfunction. Grade III diastolic dysfunction is characterised by very abrupt flow of blood from left atrium into left ventricle, but with reversibility with the Valsalva manoeuvre. Grade IV diastolic dysfunction is characterised by irreversibility with the Valsalva manoeuvre.

1.4.1. Echocardiographic Techniques for the Assessment of Diastolic Left Ventricular Function

Echocardiography is the imaging technique of choice in evaluation of diastolic function. Among the parameters available for echocardiographic assessment of diastolic function, trans-mitral flow velocities and tissue Doppler imaging are the quickest to acquire and have the lowest inter-observer variability(60). In healthy, young individuals most LV filling occurs in early diastole, resulting in a prevailing E wave. With ageing or diastolic dysfunction, increasing LV stiffness and impaired diastolic LV untwisting reduces early LV filling, thus resulting in a predominant A wave. As diastolic dysfunction progresses to pseudo-normality, left atrial (LA) pressure rises and early LV filling increases in proportion. Despite an E/A ratio >1, the pathophysiological distinction from normality is that early LV filling is from blood being forced in rather than being sucked in. In grade III diastolic dysfunction, the E/A ratio is >2 and deceleration time <140ms (Figure 1.1). Although the finding of a restrictive trans-mitral filling profile allows easy recognition of diastolic dysfunction, this pattern is only observed in 10% of cases of HFNEF(61). Occasionally a triphasic pattern of trans-mitral filling is observed (Figure 1.2) as an L wave: antegrade flow resulting in a Doppler signal between the E and A waves, during what is normally diastasis. Although not necessarily pathognomonic for severe diastolic dysfunction, the L wave has a predilection for occurrence in those with significant LV pathology, and thus may be supportive of diastolic dysfunction(62).

A challenge in diastology is the distinction of pseudo-normal filling from normal. Of assistance in this regard are (Table 1.1): 1) the Valsalva manoeuvre, which results in reversal in E/A ratio in pseudo-normality but not in normality (Figure

1.3B), 2) tissue Doppler imaging at the septal mitral annulus, where E' <7cm/s suggests diastolic dysfunction and E' <5cm/s strongly supports it (Figure 1.3C), 3) pulmonary venous Doppler (Figure 1.3D), 4) propagation of mitral in-flow towards the apex using colour M-mode(63), 5) systolic LV function – if impaired suggests concomitant diastolic dysfunction, 6) LV hypertrophy, which suggests diastolic dysfunction, and 7) LA dilatation, which also supports the diagnosis of diastolic dysfunction. Caution must be exercised relying solely on E/A ratio: following cardioversion or spontaneous reversion to sinus rhythm from atrial fibrillation the A wave is reduced owing to atrial stunning. This can give a misleadingly high E/A ratio. Moderate or greater mitral valve disease poses a similar caveat.

Peak early diastolic mitral velocity (E) is influenced by LA pressure, age and LV relaxation, whereas peak diastolic mitral annular tissue velocity (E') is governed by age and LV relaxation. Thus the E/E' ratio is theoretically a measure of LA pressure. E/E' has been shown to have a better correlation with LV end-diastolic pressure (LVEDP) than other echocardiographic indices, with a ratio >15 predicting elevated mean LVEDP(64). It is again important to be aware of a technique's limitations. If septal motion is abnormal, for instance as a result of right ventricular pacing or left bundle branch block, E/E' has been shown unreliable for the prediction of pulmonary capillary wedge pressure(65). Nonetheless in a study of patients 1.6 days following myocardial infarction, 42% of which were anterior, E/E' was a superior prognostic index to other clinical and echocardiographic parameters(66).

1.4.2. Cardiovascular Magnetic Resonance Techniques for the Assessment of Diastolic Left Ventricular Function

In contrast to the wealth of studies in LV systolic dysfunction, there is relative inexperience in CMR assessment of diastolic LV function. Nonetheless a number of CMR techniques have been used to evaluate diastolic function. Peak LV filling rates in early and late diastole can be measured by rates of change in chamber volume – a technique made possible by CMR's high spatial resolution. It has been demonstrated that their ratio decreases with age in healthy individuals, in a manner analogous to E/A ratio by trans-mitral Doppler echo(67). Volume-derived indices such as peak early and late LV filling rate and time to peak early LV filling have been promoted as sensitive markers of diastolic dysfunction(68), but their measurement remains highly time-consuming with present software and impractical from a clinical perspective.

Blood flow velocity can be measured by CMR. Phase-contrast imaging, in which the spin phase shift is used to estimate trans-mitral blood flow velocity, has demonstrated at least moderate correlation with echocardiography(69, 70), although 95% confidence limits on Bland-Altman analysis are wide. In a comparative study with echocardiographic E/E' and invasive pulmonary capillary wedge pressure, Paelinck *et al*. demonstrated the feasibility of phase-contrast-derived CMR E/E'(71). The use of this approach has also been restricted by the analysis time required. Recently, Bollache *et al*. have reported on a semi-automoated method for the measurement of diastolic parameters(72). The development of more rapid post-processing software may allow for translation of CMR diastolic evaluation into mainstream clinical practice.

Velocities measured by CMR tend to be lower than by echocardiography as a consequence of the lower temporal resolution of CMR. Temporal resolution may be improved by reducing number of views/segment, however this requires longer breath-hold times. Studies have employed myocardial grid tagging to demonstrate abnormalities in LV untwisting in diastole in conditions such as aortic stenosis(73). In a CMR study on the MESA cohort, Edvardsen *et al.* demonstrated that regional

diastolic strain rates were significantly reduced in asymptomatic individuals with LV hypertrophy compared to those without LV hypertrophy(74). To date the major limitation in myocardial grid tagging for the assessment of diastolic function has been the fading of grid lines over the course of the cardiac cycle. In a large population study of subjects without known cardiovascular disease, early diastolic strain rate (the first temporal derivative of strain) could be measured in 80% of segments analysed(74). Atrial-induced strain rate could be assessed in only 32% of patients. In the remainder, tag lines faded in intensity, precluding analysis. Although this study found early diastolic strain rate inversely proportional to indexed LV mass, it highlights the current limitations of CMR in assessing diastolic function. Imaging sequences with higher temporal resolution have been shown to increase the proportion of the cardiac cycle that can be analysed over older fast-gradient echo sequences. Three Tesla CMR has been shown to produce better tag persistence through the cardiac cycle than 1.5T and might have a role in the future(75). Furthermore, tagging measurement of strain is restricted in spatial resolution by the separation of the tag lines. Lastly, analysis of strain from the tagged dataset has limited availability on commercial CMR analysis software.

Velocity-encoded CMR or tissue-phase mapping has been used to evaluate regional systolic and diastolic tissue velocities in an analogous manner to echocardiography(76, 77). It has superior spatial resolution to grid tagging as the number of grid lines that can be placed on the myocardium limits the latter. Tissue-phase mapping also encompasses more of the cardiac cycle than grid tagging. Despite its feasibility tissue-phase mapping has not gained widespread popularity in the evaluation of diastolic function, mainly due to poorer temporal resolution and difficulty with the long breath-hold times required, which is of particular relevance in the heart failure population. Bergvall *et al*. have validated tissue-phase mapping

during free breathing against grid tagging(78). Fading of the grid lines in diastole limited the validation of diastolic tissue velocities, however.

In summary, although early studies show promise in CMR assessment of diastolic function, present limitations and the time-consuming nature of data acquisition restrict the widespread implementation of these techniques.

1.5. HEART FAILURE AND RIGHT VENTRICULAR STRUCTURE AND FUNCTION

The right ventricle is a structure of complex geometry. It curves around the left ventricle in a crescentic manner when viewed in short-axis. It is anatomically conceptualised in three components: an inlet (comprising of the tricuspid annular apparatus), the trabeculated apical myocardium, and the smooth-walled outlet(79). The right and left ventricles share a common wall – the interventricular septum – that plays an important role in right ventricular function(80). Thus right ventricular (RV) structure, and indeed function, is intimately linked with the left ventricle, a relationship referred to as ventricular interdependence.

The evaluation of RV structure and function is of prognostic value among patients with congestive heart failure(81, 82), however its complex three-dimensional geometry render this challenging in clinical practice.

1.5.1. Echocardiographic Techniques for the Assessment of Systolic Right Ventricular Function

Echocardiographic techniques for the evaluation of RV systolic function may be dichotomised into those involving measurement of change in RV geometry and those that measure physiological surrogates of RV contractile function. The former include tricuspid annular plane systolic excursion (TAPSE) in one dimension, fractional area change (FAC) in two dimensions, and three-dimensional techniques. The latter group includes RV strain and strain rate, RV myocardial performance index (MPI), and RV isovolumic acceleration (IVA)(83-87).

There have been a number of studies validating these echocardiographic indices of RV systolic function, and demonstrating their prognostic value. Among

patients with heart failure, Ghio *et al*. found that TAPSE <1.5cm added incremental prognostic information to New York Heart Association (NYHA) clinical class, LVEF, and mitral deceleration time(83). Anavekar *et al*. found that RV fractional area change correlated well with RV ejection fraction as measured by CMR(88). Amongst patients with LV systolic dysfunction following myocardial infarction, Zornoff *et al*. demonstrated that RV FAC was an independent predictor of total and cardiovascular mortality(89). RV volumes and ejection fraction measured by three-dimensional echocardiography has been shown to compare favourably with CMR(90).

Amongst the non-geometric indices of RV systolic function, tissue Doppler imaging has been shown to be an independent predictor of cardiovascular death among patients hospitalised for HFREF(91). Meluzin *et al*. found that a peak tricuspid annular tissue velocity during ejection of ≤10.8cm/s by pulse-wave tissue Doppler imaging was a significant predictor of adverse cardiovascular outcomes among patients with heart failure(84). Recently, Wahl *et al*. compared tissue Doppler imaging of the right ventricle with CMR right ventricular ejection fraction (RVEF)(92). Pirat *et al*. have demonstrated differences in speckle tracking parameters between patients with pulmonary arterial hypertension and controls(93).

1.5.2. Cardiovascular Magnetic Resonance Techniques for the Assessment of Systolic Right Ventricular Function

CMR allows highly reproducible 3-dimensional quantification of RV volumes(94, 95), and is regarded as the gold standard for estimation of RVEF(96). The most common technique for measurement of RV volumes utilises the same short axis cine stack of images acquired for measurement of LV volumes. These short axis images are orientated parallel to the atrio-ventricular valve plane. The major source of inter-observer variability using this technique is that the tricuspid valve is frequently not in-

plane, and thus the basal slice to be included in the RV volume is subject to uncertainty. Strugnell *et al*. undertook a comparison between this methodology and one involving a set of images in a plane perpendicular to a line from the centre of the pulmonary valve to the apex of the right ventricle(97). They reported closer agreement between the latter technique and stroke volume measured from the left ventricle compared with conventional measurement of the RV volume. Time constraints may limit the utility of this approach in routine clinical practice, however such a methodology may be of value when RV quantification is the primary indication for CMR.

Although CMR is well suited to the global evaluation of RV systolic function, the peristaltic nature of RV contraction renders the assessment of regional deformation challenging. Youssef *et al.* have described the use of a novel SENC technique for measuring RV strain using CMR(98). The role of this approach to the quantification of RV function in clinical practice, and its reproducibility across institutions and machine vendors remains to be explored however.

1.6. HEART FAILURE AND LEFT ATRIAL STRUCTURE AND FUNCTION

1.6.1. Assessment of Left Atrial Structure and Remodelling

LA size has been demonstrated to be a powerful predictor of major adverse cardiovascular events among patients with heart failure independent of systolic and diastolic function(99-101). This may be attributable to the fact that the left atrium is directly exposed to LV pressure during diastole (except for isovolumic relaxation). Consequently, chronically elevated LV diastolic pressures manifest morphologically as LA dilatation. As such, LA size has been likened to the HbA_{1C} of diastolic LV function(102).

As with assessment of LV cavity size, echocardiographic quantification of LA size has progressed from single-dimension measurement by M-mode echocardiography to single-plane and bi-plane estimation of area and volume. Prognostic discriminatory power increases with each step's increase in data. Among 2D techniques used to assess LA volume Simpson's bi-plane and the area-length method have the closest correlation, whereas the prolate-ellipsoid technique underestimates LA volume(103). More recently, 3D echocardiography has been used to evaluate LA volume(104). This technique has superior test-re-test reliability and inter- and intra-observer variability to other echocardiographic techniques(105).

As a 3D imaging technique, CMR is well suited to the measurement of LA volume. Early studies determined reference ranges for LA dimensions and area(106). Subsequent studies have examined the accuracy of measurement of LA volume by either a modified bi-plane Simpson's technique from the horizontal and vertical long axes(107), or by measurement from a short axis stack(108). The inter- and intra-observer variability and inter-study variability tend to be greater when LA volume is

measured using the modified Simpson's technique(109). The appendage is generally included in the LA volume, but pulmonary veins are excluded. This approach contrasts with echocardiographic measurement of LA volume using either the Simpson's bi-plane or the area-length method, in which the LA appendage is excluded from atrial planimetry(103).

1.6.2. Assessment of Left Atrial Function

LA function may be divided into three phases: a reservoir phase coinciding with ventricular systole and isovolumic relaxation, a conduit phase during early ventricular diastole, and contractile phase in late diastole, which may contribute up to 20% of the LV stroke volume(110). A number of techniques and imaging modalities may be used to evaluate LA function. Phasic changes in LA volume may be measured echocardiographically, by cardiovascular magnetic resonance, or computed tomography(111, 112). Pulse-wave Doppler echocardiography at the tips of the mitral valve leaflets, and at the pulmonary vein ostia provides information on haemodynamics between the left atrium and ventricle, and upstream to the left atrium respectively. Peak trans-mitral A wave velocity and the velocity-time integral in late diastole have been used as indices of LA function. In a corollary manner, measurement of the late diastolic tissue velocity of the septal mitral annulus (A' velocity) has also been reported as an index of LA contractile function(113). Both A and A' velocities are rapidly acquired and reproducibly measured.

More novel indices for the assessment of LA function include measurement of LA strain, or deformation, and strain rate. These may be performed either by tissue Doppler techniques or speckle tracking echocardiography. Myocardial strain by tissue Doppler imaging is calculated from the difference in velocities of adjacent myocardial regions that are separated by a known distance. Tissue Doppler imaging

is limited, however, by its angle-dependence. In contrast, speckle-tracking echocardiography, which involves frame-to-frame tracking of small myocardial regions of interest, is not influenced by angle of insonation(114). Strain rate imaging of the left atrium is the first temporal derivative of strain. It has also been studied as an index of LA function(115, 116). At the present time, the optimal approach to the evaluation of LA function is uncertain. This is due to the complex nature of LA phasic deformation. In contrast to the wealth of evidence concerning the relationship between LA geometry and remodelling in heart failure, there is a relative paucity of research on LA function in this area. Donal *et al*. have demonstrated that end-diastolic mitral annular tissue velocity is able to predict exercise capacity among patients with congestive heart failure(117). Yu *et al*. reported that among cardiac resynchronisation therapy recipients, reverse LA remodelling was accompanied by improvements in LA contraction as measured by peak velocities and strain(118).

Transoesphageal echocardiography is the imaging gold-standard in the evaluation of LA mechanical function, and the identification of LA thrombus, the presence of which frequently co-exists with LA dysfunction. The presence of left atrial spontaneous echocardiographic contrast (LASEC), a swirling, echogenic appearance of blood flow, within the left atrium has been demonstrated to be a potent predictor of LA thromboembolism(119). Despite its important prognostic value, the exact nature of LASEC remains elusive(120). LASEC is classically evaluated by transoesophageal echocardiography, in which the close and unimpeded proximity of the probe to the left atrium permits optimal LASEC identification and quantification. Measurement of LA appendage emptying velocity using pulse-wave Doppler echocardiography has been demonstrated to be the strongest predictor of LA thrombus/LASEC(121).

In spite of the myriad approaches to assessment of LA function, as well as the recognition that LA dysfunction is frequently observed accompanying LV dysfunction(122), ***there is scant evidence concerning atrioventricular***

mechanical interdependence; that is, the extent to which LA mechanical function is directly related to LV mechanical function, independent of disease processes affecting both chambers' myocardium.

1.7. MYOCARDIAL DYSFUNCTION AND VENTRICULAR MECHANICAL DYSSYNCHRONY

Initial interest in the importance of ventricular synchrony began with the search for prognostic indices for patients with heart failure. Shamim *et al*. demonstrated that the degree of electrocardiographic intra-ventricular conduction delay was associated with risk of mortality among heart failure sufferers(123). At the same time, the quest for therapeutic alternatives for patients with severe heart failure led to the demonstration of acute haemodynamic benefit of LV and biventricular pacing(124, 125). These early observations were followed by clinical studies that have shown the benefits of bi-ventricular pacing for patients with severe systolic heart failure and evidence of ventricular dyssynchrony(22, 25, 126). Consequently, cardiac resynchronisation therapy (CRT) by bi-ventricular pacing has been adopted into treatment guidelines for patients with moderate-severe impairment in systolic LV function (LVEF ≤35%), moderate-severe heart failure symptoms (NYHA class III-IV), and evidence of ventricular dyssynchrony (QRS duration >120ms)(127, 128). More recent research has demonstrated the efficacy of CRT in reducing morbidity in patients with mild (NYHA II) heart failure symptoms, especially in patients with QRS duration ≥150ms and/or typical left bundle branch block(24, 129).

Notwithstanding the efficacy of CRT, a non-response rate of approximately 30% is consistently observed irrespective of the definition used to define therapeutic response(130, 131). It has been postulated that electrical ventricular dyssynchrony, as manifest by a prolonged QRS duration, may be an imperfect indicator of mechanical ventricular dyssynchrony, the pathophysiological mechanism targeted by CRT(132). Echocardiographic measures of mechanical ventricular dyssynchrony have been proposed as a means of identifying *a priori* those likely to respond to bi-ventricular pacing.

There was considerable early enthusiasm for these echocardiographic techniques following a large number of early publications, generally from single centres, reporting the ability of a particular methodology to distinguish CRT “responders” from “non-responders”. These studies largely failed to compare different approaches to echocardiographic assessment of dyssynchrony. The PROSPECT trial was a large, multi-centre study designed to evaluate echocardiographic dyssynchrony measures head-to-head(133). The major findings from this study were that no single parameter exceeded the others in its prognostic value, and that the echocardiographic assessment of dyssynchrony exhibited only modest sensitivity and specificity for the prediction of response. The PROSPECT study has been subject to considerable methodological criticism, and thus the role of echocardiographic evaluation of ventricular dyssynchrony remains to be clarified definitively(134, 135).

1.7.1. The Echocardiographic Evaluation of Interventricular Mechanical Dyssynchrony

The electromechanical coupling time of the right and left ventricles may be measured by the time interval from QRS onset to the beginning of antegrade blood flow on pulse wave Doppler echocardiography, in the right and left ventricular outflow tracts respectively. Interventricular mechanical dyssynchrony (IVMD) has been defined as the time difference between these values. In the CARE-HF study of patients with dilated cardiomyopathy (LVEF ≤35% and height-indexed LV end-diastolic diameter of 30mm) and NYHA class III or IV heart failure symptoms, patients exhibiting an intermediate QRS duration of 120-149ms were also required to demonstrate echocardiographic evidence of ventricular dyssynchrony in order to meet eligibility criteria(22). These echocardiographic parameters of ventricular dyssynchrony

included an IVMD of >40ms. Among patients from the CARE-HF trial, IVMD was shown to be a modest predictor of response to CRT(136).

The importance of IVMD was challenged by Bordachar *et al*. who studied CRT recipients echocardiographically at varying V-V intervals(137). In this study, there was no correlation between IVMD and cardiac output, whereas there were close correlations between variations in other echocardiographic indices of ventricular dyssynchrony and cardiac output. In a recent study by Gorscan *et al*. event-free survival among CRT recipients was significantly associated with IVMD, however after accounting for other confounding factors, including intra-LV dyssynchrony, IVMD was not demonstrated to be an independent predictor of event-free survival(138).

1.7.2. The Evaluation of Intra-Left Ventricular Mechanical Dyssynchrony

A number of techniques to evaluate mechanical dyssynchrony within the left ventricle have now been reported. The following is an overview of these approaches.

1.7.2.1. Septal-Posterior Wall Motion Delay

Septal-posterior wall motion delay (SPWMD) may be measured by M-mode echocardiography in the parasternal short axis view at the papillary muscle level. SPWMD is calculated as the shortest interval between the maximal posterior displacement of the septum and the maximal incursion of the posterior LV wall(139). Pitzalis *et al*. reported on sixty patients with severe heart failure and left bundle branch block. They found that SPWMD ≥130ms was highly predictive of response to CRT(140). In contrast to Pitzalis' findings, Sassone described forty-eight patients undergoing clinically-indicated CRT in whom SPWMD could not feasibly be measured in 33% because of absent septal inward motion, paradoxical septal motion, or presence of systolic deflection of the septum(141). Among those where it

could be measured, it was not predictive of response. Similarly, Marcus *et al*. found SPWMD to have poor feasibility: only 16% of the study cohort had clear incursion of both septum and posterior LV wall(142). They found that SPWMD failed to predict any clinical or echocardiographic endpoint. There were a number of differences between Pitzalis' and Marcus' studies. The most likely to have contributed to the disparity in their results was the preponderance of non-ischaemic cardiomyopathy among Pitzalis' cohort, in contrast to the preponderance of (143)among the latter may have contributed to their lower rate of technical feasibility in measuring SPWMD. When no discernible wall motion was present, Pitzalis' group designated a SPWMD of 0ms, in contrast to Marcus group, who recorded the SPWMD unmeasurable. Finally, Pitzalis *et al*. measured SPWMD in the parasternal short axis view at the level of the papillary muscles, whereas Marcus *et al*. measured SPWMD in the parasternal long axis view just beyond the mitral valve leaflet tips. Since these two manuscripts, further evidence has emerged on the utility of SPWMD. Among 67 patients undergoing CRT, Diaz-Infante *et al*. found that SPWMD was not able to distinguish responders from non-responders(144).

More recently, Suffoletto *et al*. demonstrated that SPWMD can be measured using speckle tracking strain imaging in the parasternal short axis view. They found that SPWMD ≥130ms by this technique was predictive of a favourable response to CRT.

1.7.2.2. Tissue Doppler Techniques

Tissue Doppler imaging is appealing in the evaluation of timing of regional myocardial mechanical activation owing to its high temporal resolution: frame rates in excess of 100 per second are typically achieved. Early studies using this approach employed pulse wave tissue Doppler imaging, which requires acquisition of data from different myocardial regions using different heart beats, thus potentially introducing

inaccuracy from beat-to-beat variation. Tissue velocity imaging, in which tissue Doppler data from an entire two-dimensional image is recorded, and from which regional tissue velocity measurements can be made offline, is therefore advantageous over pulse wave tissue Doppler imaging.

Using tissue velocity - or colour tissue Doppler - imaging, Bax *et al*. demonstrated that a 60ms or greater delay between basal septal and basal lateral wall tissue velocity peaks is associated with non-response to CRT(145). Van Bommel *et al*. subsequently validated a cut-off value of 65ms in a cohort of CRT recipients. They found that this parameter was an independent predictor of response to CRT(146). Yu *et al*. compared eighteen echocardiographic dyssynchrony parameters for their ability to predict reverse remodelling of the left ventricle following CRT(147). They reported that a dyssynchrony index, defined as the standard deviation of time-to-peak systolic tissue velocity measurements on a 12-segment model, was the most powerful predictor of reverse LV remodelling, exhibiting an area under the receiver operating characteristic curve of 0.94 (confidence interval 0.88-1.0). A cut-off value of 31.4ms for this index predicted significant reverse remodelling with a sensitivity of 96% and a specificity of 78%.

Penicka *et al*. attempted to incorporate inter- and intra-ventricular dyssynchrony into a dyssynchrony index. Among 49 patients undergoing CRT, they performed pulsed-wave tissue Doppler imaging at the basal lateral, septal and posterior segments of the left ventricle, and at the basal lateral segment of the right ventricle(148). Intraventricular asynchrony was measured as the difference between the shortest and longest delay in electromechanical coupling times in the left ventricular segments. Interventricular asynchrony was measured as the difference between the electromechanical coupling times of the basal lateral right ventricular segment and the most delayed LV segment. Sum asynchrony, defined as the sum of intra- and inter-ventricular asynchrony, was found to have sensitivity of 96% and

specificity 77% at predicting at 25% improvement in LVEF over 6 months' follow-up(148).

1.7.2.3. Speckle Tracking Strain Techniques

As previously described, Suffoletto *et al.* employed speckle tracking strain in the parasternal short-axis view to quantify intra-LV dyssynchrony(143). This finding was subsequently confirmed by Delgado, *et al(149)*. Haugaa *et al*. reported on mechanical dispersion of LV regional contraction using speckle-tracking strain in the long-axis amongst post-myocardial infarction patients(150). They found that mechanical dispersion was most pronounced in those patients with recurrent ventricular arrhythmia.

1.7.2.4. Three-Dimensional Echocardiographic Techniques

Three-dimensional echocardiography is appealing as an approach to the evaluation of intra-LV dyssynchrony because each 3D dataset is a synthesis of up to seven cardiac cycles. In contrast, two-dimensional echocardiographic assessment of intra-LV dyssynchrony relies on acquisition of images from different cardiac cycles and extrapolating myocardial event timing between images. The major limitation of 3D echocardiographic techniques with present ultrasound probes is the modest frame rate with which they can sample data. Limited temporal resolution may reduce the accuracy of detection of peak segmental contraction.

Among 23 patients undergoing CRT, real-time 3D echocardiography, with assessment of intra-LV dyssynchrony by the timing of regional wall volumetric change, was able to distinguish responders (those with sustained improvement in NYHA class) from non-responders(151). There was only weak correlation between systolic dyssynchrony evaluated from 3D data and dyssynchrony as assessed by

tissue velocity data, and there was no analysis to determine which approach is superior.

Among 49 patients undergoing CRT, measurement of the standard deviation of time to peak tissue velocity on as 12-segment model, using a new 3-V echo probe (which allows same-cycle acquisition of tissue velocity data from the entire myocardium), was the best predictor of acute volumetric response(152).

1.7.2.5. Comparison of Echocardiographic Techniques for Assessment of Ventricular Dyssynchrony

In contrast to the large number of studies reporting on the ability of single indices of ventricular dyssynchrony to predict CRT response, there is less research comparing indices with each other in a head-to-head manner.

The study by Yu *et al*. was among the first to do so, however did not include the use of M-mode or speckle tracking techniques(147). This report focussed on tissue Doppler-derived measures of myocardial mechanical activation. Tissue velocity as an index of myocardial contraction is limited, however, by the confounding effects of tethering of dysfunctional myocardial segments to more normally contracting segments. Furthermore, tissue Doppler data is influenced by the angle of insonation. In patients with heart failure with reduced ejection fraction, LV dilatation is a frequent finding, which may impact on the accuracy of tissue Doppler imaging.

As previously described, Gorscan *et al*. studied 229 CRT recipients to evaluate the prognostic value of tissue Doppler opposing wall delay ≥65ms, “Yu index” ≥32ms, radial strain septal-posterior wall delay ≥130ms, and interventricular mechanical delay ≥40ms(138). They found that on multivariate analysis, the Yu index (the standard deviation of time-to-peak systolic tissue velocity measurements on a

12-segment model) and radial strain septal-posterior wall motion delay were independently associated with major adverse cardiovascular events.

Delgado *et al*. compared speckle tracking strain analysis in the radial, circumferential, and longitudinal axes of cardiac contraction to determine which was most closely associated with CRT response(149). They found that radial strain was superior to the other types of strain measurement in this regard. Faletra *et al*. reported on the agreement between tissue Doppler, three-dimensional, and speckle-tracking approaches for the evaluation of intra-LV synchrony(153). They found poor agreement amongst these techniques.

In summary the role of echocardiographic assessment of ventricular dyssynchrony, particularly in the identification of patients likely to respond to CRT, remains controversial. There remains insufficient evidence to recommend routine use of these indices to deny individuals CRT when they meet guideline-supported criteria for bi-ventricular pacing. Existing evidence suggests that mechanical intra-LV dyssynchrony is an important pathophysiological phenomenon, and its measurement by echocardiography has yielded insight into the mechanisms underlying conditions associated with LV systolic dysfunction.

1.7.3. Post-Systolic Contraction

Post-systolic contraction – the continuation of myocardial contraction after aortic valve closure – may be observed in up to 30% of myocardial segments in healthy individuals, although this contraction is generally small in magnitude(154). A feature of the dyssynchronously contracting, impaired left ventricle may be an increase in the number segments exhibiting post-systolic contraction or the degree of post-systolic contraction occurring within individual segments. Exaggerated myocardial contraction against a closed aortic valve is disadvantageous because it fails to add to cardiac

output, while incurring an energetic cost. Such energetics appear to be ameliorated by cardiac resynchronisation(125).

Sogaard *et al*. reported that the extent of basal myocardial delayed longitudinal contraction predicted long-term efficacy of CRT(155). Among 48 patients undergoing CRT, the best echocardiographic predictor or response (defined as ≥15% reduction in LV end-systolic volume) was lateral wall post-systolic displacement by M-mode echocardiography(141). This study was limited, however, by lack of measurement of Doppler indices of intra-LV synchrony. A more compelling argument in favour of post-systolic contraction as a predictor of CRT response came from Porciani *et al*.(156). They reported that among recipients of CRT, a 12-segment model summing the total duration of post-systolic longitudinal contraction in each segment was a better predictor of response to CRT on volumetric grounds than the dyssynchrony index proposed by Yu *et al(147)*. This finding is in direct contradiction to that reported by Yu *et al(147)*.

1.7.4. Ventricular Mechanical Dyssynchrony in Right Ventricular Pacing

The right ventricular apex (RVA) has been the traditional site of implantation of the ventricular lead for permanent cardiac pacing, however long-term RVA pacing has been associated with impairment in systolic left ventricular (LV) function(157-159). Thambo *et al.* studied patients with complete congenital atrioventricular block paced long-term from the RV apex(157). They found that RVA pacing was associated with intra-LV dyssynchrony, adverse LV remodelling, and reduced functional capacity. In long-term follow-up of young patients permanently paced from the RV apex, a detrimental effect on LV systolic function was also noted by Tantengco *et al*(158). RVA pacing has been strongly associated with decline in LV ejection fraction in epidemiological data(159). Delgado *et al.* and Tops *et al.* have recently demonstrated

the adverse effects of RVA pacing on indices of LV synchrony(160-162). Among 58 patients paced from the RV apex over a 3.8-year period, intra-LV dyssynchrony as measured by septal-posterior wall motion delay was shown to develop in 57% of cases in spite of the absence of baseline dyssynchrony. The occurrence of dyssynchrony was associated with deterioration in LV systolic function(161). In 25 patients undergoing electrophysiological study, RVA pacing acutely induced intra-LV dyssynchrony and impairment in longitudinal LV strain(160). Wolber *et al.* utilised real-time three-dimensional echocardiography to measure the acute effects of RVA pacing on LV function(163). They found that pacing was associated with increased dyssynchrony as measured by the standard deviation of time to minimal regional volumes, and an altered sequence of mechanical activation of the left ventricle, from apex to base.

Pastore *et al*. sought to identify baseline factors that were predictive of the development of intra-LV dyssynchrony following RV pacing. They reported that the degree of intra-LV dyssynchrony induced was related to baseline LV chamber size, systolic function and intra-LV synchrony(164).

1.7.5. The Role of V-V Optimisation in Cardiac Resynchronisation Therapy

Early studies of echocardiographic V-V optimisation in CRT recipients demonstrated that stroke volume and indices of ventricular dyssynchrony could be individualised(165, 166). Among 21 recipients of CRT, it has been shown that the myocardial performance index can acutely be improved by optimising V-V offset over and above simultaneous biventricular pacing(167). Sogaard *et al*. studied twenty patients echocardiographically at eleven different V-V intervals after bi-ventricular pacemaker implantation(168). They reported that an optimised V-V interval was associated with a reduction in delayed longitudinal contraction compared with

simultaneous bi-ventricular pacing. A cohort of patients undergoing CRT with V-V optimisation (using cardiac output measured by echocardiography as the product of the left ventricular outflow tract area and aortic velocity-time integral) was compared with the treatment group from the MIRACLE study of CRT(169). The investigators found that 6-minute walk distance was greater amongst patients undergoing V-V optimisation, however there was no apparent benefit in terms of functional status or quality-of-life.

Subsequent randomised, controlled studies of echocardiographic V-V optimisation have yielded mixed results. Boriani *et al*. studied 121 patients randomised to simultaneous bi-ventricular pacing or VV-optimised pacing, in which echocardiographic stroke volume was maximised(170). They found no significant difference in the groups at 6 months follow-up. In a randomised, controlled study of echocardiographically optimised CRT, no benefit was observed at six months compared with CRT with simultaneous bi-ventricular pacing(171). In the largest randomised, controlled trial of V-V optimised versus simultaneous bi-ventricular pacing, little difference was observed between these two groups(172).

There is emerging evidence on the relationship between echocardiographic stroke volume and intra-LV synchrony. In a study of different V-V optimisation techniques, Bertini *et al*. demonstrated moderate concordance between methods that maximised LV outflow tract velocity time integral, tissue Doppler septal-lateral delay, and maximal temporal delay in mid-LV circumferential strain(173). Marsan *et al*. reported on sixty-nine CRT recipients who underwent echocardiography at seven different V-V intervals(174). They found a very strong concordance between the V-V interval providing the largest LV outflow tract velocity-time integral and the interval providing the least intra-LV dyssynchrony by tissue Doppler imaging. Duvall *et al*. have shown that both LV outflow tract velocity-time integral and three-dimensional LV ejection fraction may be increased above simultaneous bi-ventricular pacing by

altering V-V paving intervals(175). Importantly, however, these authors also demonstrated poor agreement between the two measures for selection of the optimal V-V pacing interval. They suggest that this finding may be due to the limited reproducibility of the echocardiographic indices used for optimisation. In contrast to those studies that employed echocardiography as the optimisation standard, this study by Rao *et al*. used an algorithm based on intra-cardiac electrograms obtained at the time of device implantation. This algorithm had previously been validated against acute, invasive haemodynamic parameters.

1.8. HEART FAILURE AND MYOCARDIAL FIBROSIS

The presence and extent of myocardial fibrosis are key determinants of response to therapy and prognosis in a number of cardiac conditions. Until recently, myocardial fibrosis could only be detected ante mortem by endomyocardial biopsy, which is associated with procedural risk and sampling error. The development of novel cardiac imaging techniques and serum assays now permits the accurate detection and quantification of myocardial fibrosis. These have yielded new insight into disease prognosis and response to therapy.

1.8.1. Pathogenesis of myocardial fibrosis

Myocardial fibrosis develops in response to a cardiac insult, which may include ischaemia, pressure- or volume-overload, viral infection, or genetically-mediated injury as in hypertrophic cardiomyopathy. Net collagen deposition results from an imbalance of its synthesis relative to degradation. A number of enzymes have been identified as potential mediators of myocardial extracellular matrix turnover. The matrix metalloproteinases (MMPs) are a family of at least 20 calcium-dependent endopeptidases that digest interstitial constituents. The various MMPs have different substrates – MMP-1 and -13 are collagenases and MMP-2 and -9 gelatinases. LV myocardial MMP activity in idiopathic dilated cardiomyopathy and ischaemic cardiomyopathy has been shown to be greater than in normal hearts(176). Abolition of MMP-9 synthesis has been associated with reduced myocardial fibrosis and improved LV function in a rodent model of pressure overload(177). The tissue inhibitors of matrix metalloproteinase (TIMPs) are a family of four proteins that bind to

and inhibit the effects of MMPs. TIMP-1 expression is reduced in explanted hearts from patients with both ischaemic and non-ischaemic cardiomyopathy(178).

Regardless of the aetiology and/or molecular cascade resulting in collagen deposition, the presence of myocardial fibrosis has both mechanical effects on cardiac function, mediated by increased myocardial stiffness, and electrophysiological effects, by acting as substrate for re-entry and arrhythmia.

1.8.2. Cardiac magnetic resonance (CMR) imaging and the evaluation of myocardial fibrosis

CMR is established as a major technique in clinical cardiology and cardiovascular research. Allied to its well-recognised role in accurate and reproducible measurement of LV volumes and mass, CMR offers an unprecedented ability to detect and quantify myocardial fibrosis. It provides exquisite 3-dimensional images allowing concurrent assessment of myocardial structure, function and tissue characterisation.

1.8.2.1. Late-gadolinium enhancement (LGE) technique

Gadolinium-DTPA (Gd-DTPA) is a paramagnetic contrast agent that is used to delineate areas of injured myocardium. Gd-DTPA reduces hydrogen-proton T1 relaxation times in proportion to its local concentration. In T1-weighted imaging, tissues with a shorter T1-relaxation time exhibit greater signal intensity than those with longer T1-relaxation times. Gd-DTPA equilibrates rapidly between intra-vascular and interstitial spaces, but is excluded from the intra-cellular compartment by the intact cell membrane(179). Following intra-venous administration, altered wash-in/wash-out kinetics and an increased volume of distribution in damaged tissue (owing to interstitial oedema and/or loss of cell membrane integrity), account for its pattern of appearance in these regions(180). Late or “delayed” imaging (after at least

5 minutes post-contrast) with T1-weighted inversion recovery sequences identifies conditions associated with expansion of the extra-cellular space.

1.8.2.2. Ischaemic Heart Disease

In the clinical realm, contractile abnormalities in patients with ischaemic heart disease may occur as a consequence of stunning, hibernation and scar, with the relative importance of these factors varying both between and within myocardial segments and dynamically over time. Detecting dysfunctional and scarred myocardium as opposed to dysfunctional but viable myocardium is of scientific and clinical significance and there is now a reasonable body of non-randomised evidence supporting revascularisation of hibernating myocardium(181).

In the setting of chronic ischaemic cardiomyopathy, to date there have been two single centre clinical studies examining the utility of the transmural extent of LGE in predicting recovery of contractile function. The first was performed by Kim e*t al*. in a cohort of 41 patients undergoing revascularisation by either percutaneous transluminal coronary angioplasty or coronary artery bypass grafting. They found that the likelihood of improvement in regional function after revascularisation decreased progressively as the transmural extent of LGE before revascularisation increased(182). This was subsequently confirmed in a study by Selvanayagam *et al*, which exclusively examined patients after surgical revascularisation(183). The ability of LGE-CMR to evaluate those segments that have severe dysfunction (and often the most difficult to evaluate with other imaging techniques) with high diagnostic accuracy is one of the strengths of the LGE-CMR technique. In addition, with excellent spatial resolution and contrast noise ratio, LGE-CMR has high sensitivity to detect viable myocardium and thus may provide more sensitive (albeit less specific) prediction of recovery of segmental function than inotropic contractile reserve. The analysis of what constitutes LGE positivity in human CMR studies of ischaemic

cardiomyopathy has been controversial. In earlier animal model studies performed by Kim *et al*., a signal intensity cut-off 2SD above normal myocardium identified accurately the extent of myocardial infarction(184). A recent elegant study by Amado *et al.* in a canine model of myocardial infarction demonstrated that the full-width at half-maximum technique for quantification of volume of myocardial enhancement was the most accurate(185). This method requires selection of a seed point within hyperenhanced myocardium. Software then identifies all pixels with signal intensity >50% of this point. The maximal signal intensity within this region is determined, and the final scar extent is defined as tissue exhibiting signal intensity >50% that of the maximal signal intensity. Quantifying scar size by tissue with signal intensity 2SD above normal myocardium, as originally described by Kim *et al*., was found to overestimate infarct size, whereas 5 and 6 SD thresholds were closer to histopathology.

Myocardial infarct size as quantified by the late-gadolinium technique has been demonstrated to be a powerful predictor of mortality and adverse LV remodelling – more powerful than LVEF(186, 187). Scar burden as quantified by CMR, or indeed SPECT imaging, has been shown to be a powerful predictor of response to cardiac resynchronisation therapy in ischaemic cardiomyopathy patients(188, 189).

Kwong *et al*. reported a high prevalence of myocardial fibrosis among diabetic patients with clinical features suspicious of coronary heart disease, but no history of or ECG findings consistent with prior myocardial infarction(190). The presence of LGE on CMR was associated with a high risk of future adverse cardiac events, whereas its absence portended a favourable 2-year outlook.

1.8.2.3. Non-Ischaemic Dilated Cardiomyopathy

Autopsy studies suggest that interstitial or replacement fibrosis is found in at least 57% of cases of non-ischaemic dilated cardiomyopathy (NICM) and that up to 20% of the LV myocardial mass may be scar in these cases(191). McCrohon *et al.* reported the CMR findings of 90 patients with systolic LV dysfunction, all of whom underwent coronary angiography(192). They observed 100% prevalence of late-gadolinium enhancement in either a subendocardial or transmural distribution among those with significant coronary disease. In contrast, late-gadolinium enhancement was absent in 59% of those with NICM, had a patchy, mid-wall distribution in 28% of cases, and displayed a subendocardial pattern indistinguishable from ischaemic cardiomyopathy in the remaining 13%. The authors suggested that LGE-CMR might be an acceptable alternative to coronary angiography in determining the aetiology of severe cardiomyopathy because of its non-invasive nature, and because the absence of luminal coronary abnormalities on angiography does not exclude an ischaemic cause of LV dysfunction. They postulate that some of those cases without severe coronary disease may represent re-canalised myocardial infarction. Assomull *et al.* found mid-wall LGE in 35% of patients with *established* NICM recruited from a large tertiary hospital setting(193). They reported that fibrosis extent (using a 2SD signal intensity threshold) was a significant predictor of the development of death or hospitalisation, and was superior to LV volumes and ejection fraction. More recently, Wu *et al*. reported that among 65 patients with NICM diagnosed a median of 4 years prior, 42% exhibited LGE, involving on average 10% of myocardial mass. In contrast to the earlier study, “fibrosis” was defined as signal intensity greater than the peak signal intensity of a remote normal region of myocardium(194). The presence of LGE on CMR was independently associated with a higher risk of the composite primary outcome of cardiac mortality, appropriate implantable cardioverter-defibrillator discharge, and hospitalisation for heart failure(194). Both these studies were

performed in large tertiary referral centres with patients evaluated often after years of treatment. It is unknown if the prevalence and extent of LGE-detected myocardial fibrosis is similar in an ambulatory population of patients with NICM and furthermore, if this is detected at first clinical presentation. Lastly, it is unclear if the presence of myocardial fibrosis on LGE CMR and/or its quantity influences the clinical response to medical and cardiac resynchronisation therapy in NICM.

Recently, in a cross-sectional study of patients with NICM, a significant correlation was identified between myocardial fibrosis, diastolic LV function, functional capacity and serum NT-pro-BNP concentration(195).

1.8.2.4. Hypertrophic Cardiomyopathy

Hypertrophic cardiomyopathy (HCM) is a genetic disorder characterised by the development of cardiac muscle fibre disarray, dysplasia of small intramural coronary arterioles, and myocardial fibrosis. It must be distinguished from hypertensive LV hypertrophy and athlete's heart, particularly in its early stages. Moon *et al.* reported the ability of LGE-CMR to accurately identify and quantify replacement fibrosis in HCM(196). A cross-sectional study of 21 HCM patients demonstrated fibrosis by the LGE technique in 81% of cases(197). Scarring was patchy but occurred predominantly within hypertrophied segments (typically observed at the junction of the right ventricle and inter-ventricular septum). Findings from another series corroborate this pattern of LGE in HCM(198). The presence of LGE has been shown to be associated with the incidence of ventricular tachycardia in HCM patients(199).

1.8.2.5. Valvular Heart Disease

Chronic valvular heart disease may impose either a volume-load (in the case of mitral or aortic incompetence) or pressure-load (in the case of aortic stenosis) on the left ventricle. These two pathophysiological processes result in different patterns of chamber remodelling: volume-overload results in eccentric remodelling, in which wall thickness is reduced relative to chamber volume, whereas pressure-overload causes concentric remodelling, where wall thickness is maintained or increased relative to chamber size. Myocardial fibrosis is a feature of long-standing valvular heart disease irrespective of the mechanism. CMR has demonstrated sensitivity of 74% and specificity of 81% for detection of myocardial fibrosis in patients with severe aortic valve disease(200). Fibrosis quantity was associated negatively with LV ejection fraction. Rudolph *et al*. reported a 62% prevalence of late-gadolinium enhancement in patients with aortic stenosis and LV hypertrophy(198). Weidemann *et al.* confirmed that myocardial fibrosis is common in patients with severe, symptomatic aortic

stenosis, and could be detected accurately by CMR(201). Not surprisingly, they found that myocardial fibrosis was not reversible following aortic valve replacement.

1.8.2.6. Other Conditions

Myocardial fibrosis may also be seen in a number of other cardiac conditions, such as sarcoidosis and arrhythmogenic right ventricular cardiomyopathy. The ability of CMR to identify fibrofatty replacement and/or infiltration, as well as to provide images of high spatial resolution in any plane, permit it a role in their diagnosis.

1.8.2.7. T1 Mapping

The major limitation of LGE CMR in the detection of myocardial fibrosis is its reliance on difference in signal intensity between scarred regions and adjacent normal myocardium. It thus has reduced sensitivity for the detection of diffuse myocardial fibrosis, which is the pathological hallmark of NICM and volume-overloaded conditions. T1 mapping, the calculation of a post-contrast myocardial T1-time by imaging a given plane with sequentially increasing inversion times, has been validated in animal studies as showing a good correlation with *ex vivo* fibrosis content. Reproducibility has been defined, and more recently this technique has been able to discriminate heart failure patients from healthy controls even after excluding myocardial segments displaying late gadolinium enhancement(202). In this study, Iles *et al*. performed CMR on 25 patients with heterogeneous causes of heart failure, and 20 healthy controls. The mid-chamber short-axis slice was imaged at a range of inversion times 15 minutes following the administration of 0.2mmol/kg gadolinium-DTPA. The average T1 in regions of interest was measured using specialised software. They found a significant difference in T1 time between LGE positive and negative myocardium among heart failure patients (330±30ms v. 429±22ms

respectively, p=0.02) and a significant difference in T1 time between the LGE negative myocardium of heart failure patients and healthy controls (429±22ms v. 564±23ms respectively, p<0.001). Although more work needs to be done on the robustness of the technique, especially with respect to multi-centre, multi-vendor application, this technique shows promise in the quantitative evaluation of diffuse myocardial fibrosis, and hence may have a potentially wide array of applications in heart failure, cardiomyopathy and valvular heart disease.

1.8.3. Echocardiography and the evaluation of myocardial fibrosis

Myocardial composition influences its acoustic properties. Collagen is an important cause of ultrasound scattering and attenuation. The measurement of peak integrated backscatter and cyclic variation in integrated backscatter may thus reflect degree of myocardial fibrosis. Hoyt *et al*. demonstrated a linear relationship between myocardial hydroxyproline content as a marker of fibrosis and magnitude of echocardiographic integrated backscatter in autopsy specimens from victims of myocardial infarction(203). Among a cohort of hypertensive patients, integrated backscatter decreased and cyclic variation in integrated backscatter increased following treatment with blood pressure-lowering agents(204). Bertini *et al*. studied the relationship between myocardial fibrosis as measured by calibrated integrated backscatter and response to cardiac resynchronisation therapy(205). They reported that myocardial ultrasound reflectivity was an independent predictor of CRT response. Ohtsuka *et al*. reported on the relationship between echocardiographic backscatter indices and serum markers of myocardial angiogenesis among patients with idiopathic dilated cardiomyopathy(206). They found that calibrated integrated backscatter was significantly lower and cyclic variation in integrated backscatter significantly greater amongst cardiomyopathy patients compared with controls. They

also observed significant relationships between backscatter parameters and serum interleukin-13 and vascular endothelial growth factor concentrations.

Myocardial scar, as defined by 2D echocardiographic wall thickness <6mm, was associated with increased acoustic reflectance, and predicted response to cardiac resynchronisation therapy among patients with ischaemic cardiomyopathy(207). This technique has a limited role in the assessment of fibrosis in non-ischaemic cardiomyopathies.

Myocardial strain refers to its degree of deformation through the cardiac cycle. Strain may be measured by either tissue Doppler imaging or speckle tracking. The latter technique relies upon echocardiographic software recognition of myocardial points by their acoustic characteristics and measurement of their displacement over the cardiac cycle. Given the effect of collagen deposition on myocardial deformation, strain measurement may be well suited to indirect evaluation of myocardial fibrosis. Gjesdal *et al.* and Roes *et al*. have both demonstrated a high sensitivity and specificity for longitudinal strain scores to predict extent of myocardial scar among patients with ischaemic LV dysfunction as compared with contrast-enhanced CMR(46, 208). Weidemann *et al.* quantified myocardial fibrosis histologically in biopsies from the LV outflow tract in 58 aortic valve prosthesis recipients for severe, symptomatic aortic stenosis(201). Patients underwent comprehensive echocardiographic evaluation (including radial and longitudinal strain and strain rate imaging using tissue Doppler) pre-operatively and 9 months post-operatively. The authors demonstrated uniform improvement in these parameters only among subjects with no or mild fibrosis. Baseline radial LV function and LVEF were similar irrespective of myocardial fibrosis burden, whereas longitudinal indices of LV function were significantly reduced in those with more extensive fibrosis. This study suggests that quantitative evaluation of longitudinal LV function may be a sensitive tool for detection of the mechanical effects of myocardial fibrosis.

1.8.4. Nuclear imaging and the evaluation of myocardial fibrosis

Cardiac nuclear imaging encompasses the techniques of positron emission tomography (PET) and single photon emission computed tomography (SPECT), and with these techniques there is now a wealth of evidence in the assessment of myocardial viability and therefore indirectly of scarred and fibrotic myocardium. Evaluation of viability by PET involves simultaneous measurement of resting myocardial perfusion (with ^{82}Rb or ^{13}N ammonia) and glucose metabolism (using 18-fluorodeoxyglucose). The observation of perfusion-metabolism mismatch (normal metabolism in the absence of perfusion) is a highly accurate indicator of myocardial viability. According to one pooled analysis, the sensitivity, specificity, postive and negative predictive values of PET in the identification of myocardial viability (the improvement of myocardial contractile function following revascularisation) were 92%, 63%, 74% and 87% respectively(209).

SPECT approaches involve administration of ^{99}Tc or ^{201}Tl radioisotopes for evaluation of myocardial perfusion both with stress and at rest. Myocardial uptake of these tracers is dependent on both regional perfusion and on cell membrane integrity and viability(210). In a pooled analysis, SPECT was associated with lower positive and negative predictive values for myocardial viability compared with PET(211), although the greater availability of SPECT have ensured its ongoing clinical use.

In patients with ischaemic cardiomyopathy, scar tissue as detected by PET has been shown to be a good predictor of lack of recovery of left ventricular systolic function after coronary artery bypass surgery, though precise individual prognostication is difficult(212, 213). Also, as expected, PET provides for information on outcome. In a meta-analysis of 10 such studies (1,046 patients) annualised

mortality rates were 4% for those with viable myocardium who underwent revascularisation *vs*. 17% for those with viability who did not(214). If no viability was demonstrated with PET, revacularisation was not associated with changes in mortality rates (annual mortality rates of 6-8%). Such evidence has encouraged studies in which treatment is based on PET findings, but so far the studies have only been partly successful. In the PARR-2 trial, treatment based on ^{18}F-FDG PET findings was equivalent to standard care after one year of follow up(215). In a post-hoc analysis of the PARR-2 trial data, however, the patients with ischaemic cardiomyopathy with larger amounts of perfusion-metabolism mismatch (more than 7%) did have improved outcome with revascularisation(216), and PET may find a place to assess outcome in patients with critical ischaemic cardiomyopathy in whom surgery is of risk.

The *water-perfusable tissue index* has emerged as a candidate for *in vivo* detection of myocardial fibrosis by PET (217). Briefly, the ratio of the water perfusable tissue fraction to the anatomic tissue fraction is determined using the tracers $H_2{}^{15}O$ and $C^{15}O$. In normal individuals, the perfusable tissue index should be 1.0, but fibrotic tissue is unable to exchange water rapidly and hence the tissue index decreases in fibrotic myocardium. In dogs a reduction of the perfusable tissue index correlates well with the extent of fibrosis after infarction. In humans, comparisons have been made to LGE CMR in different patient populations. In patients with scarring due to myocardial infarction, late gadolinium enhancement was indeed negatively correlated (r=-0.65) with the perfusable tissue index(218), but the water-perfusable tissue index systematically underestimates the amount of scar tissue if the latter becomes extensive(219). With respect to replacement fibrosis in patients with hypertrophic cardiomyopathy (HCM) where Gd late-enhancement was seen, the perfusable tissue index was essentially unaffected. The perfusable tissue index was slightly lowered in the LV free wall of patients with HCM, but not at all in the septum

where myocardial disarray, oedema and later fibrosis predominantly takes place. The authors suggest that hyperenhancement by LGE-CMR may not be solely governed by fibrosis but also (especially so early in the natural history of HCM) by oedema, but in light of missing histology, the finding may equally well be attributed to a lack of sensitivity by the perfusable tissue index technique.

In clinical practice, SPECT is still the more robust and more often applied technique and a wealth of evidence testifies to its ability to demonstrate (larger) viability defects and provide for important prognostic information. In comparison with PET, SPECT has more limited spatial resolution. In a study by Wagner *et al (220)* that compared LGE-CMR with ^{99m}Tc-SPECT in a canine model of myocardial injury CMR identified 92% of all subendocardial infarcts whereas SPECT only identified 28%. The relative lack of spatial resolution with SPECT can potentially lead to erroneous conclusions with respect to viability. Thus, in dysfunctional segments, transmural LGE of 9%, 33%, and 80% respectively, corresponds to segments that by combined ^{99}Tc SPECT/^{18}F-FDG PET (and accepted cut-off values) are classified as normal, mismatched (hibernating) and matched (fibrotic)(221). The classification of “hibernating” versus “fibrotic” myocardium by combined ^{99}Tc SPECT/^{18}F-FDG PET may have to do more with the extent of transmurality of scar and appropriateness of chosen cut-off values for flow (by SPECT) and glucose metabolism (by PET).

1.8.5. Biomarkers of myocardial fibrosis

In comparison to cardiac imaging, serum biomarkers of myocardial fibrosis have yet to achieve general acceptance in clinical practice. This may relate to the semi-quantitative nature of measurement techniques, and to inferior specificity in a general population, in whom collagen turnover may be increased due to co-morbid conditions. Nonetheless serum biomarkers of myocardial fibrosis are conceptually

appealing as they allow measurement of diffuse fibrosis, the quantification of which remains elusive using current imaging techniques.

Martos *et al.* found higher concentrations of serum carboxy-terminal telopeptide of procollagen type I, amino-terminal propeptide of procollagen type III, MMP-1, -2, and -9, and TIMP-1 in patients with HFNEF compared with those without(222). Serum TIMP-1 concentration has been associated with echocardiographic indices of diastolic dysfunction in hypertensive patients(223). This study demonstrated that serum MMP-2 concentration as the most sensitive and specific biomarker of heart failure with preserved ejection fraction, superior to B-type natiuretic peptide(224). Based on this finding, the authors propose an adjunctive role for MMP-2 in the diagnosis of this condition, although this is yet to gain widespread clinical acceptance.

In a cross-sectional study of 1069 subjects from the Framingham Heart Study, serum TIMP-1 concentration was positively related to LV mass, end-systolic diameter, and LA diameter after adjustment for age, sex and height(225). although adjustment for further clinical covariates attenuated the strength of association between TIMP-1 concentration and echocardiographic measures, the authors concluded that this evidence supports the hypothesis that cardiovascular risk factors promote LV remodelling by influencing turnover of the extracellular matrix.

In a study by Yan *et al.* of HFREF patients, serum MMP-9 concentration was demonstrated to have a positive linear relationship with LV end-systolic volume and a negative association with LVEF(226). Over 43 weeks follow-up, there was a negative relationship between change in serum MMP-9 concentration and change in LV ejection fraction. In contrast, Vorovich *et al*. have recently shown that serum MMP-9 concentration is a poor marker of LV remodelling and clinical outcome compared with brain natiuretic peptide(227).

At the present time, although associations between serum fibrosis biomarker concentration and indices of myocardial disease have been demonstrated, the clinical role of serum analysis of biochemical markers remains to be defined. Moreover, the robustness of these assays outside of research laboratories is unknown.

1.9. SUMMARY

Heart failure is a cause of considerable morbidity and mortality whose pathogenesis remains incompletely characterised. Novel imaging techniques now permit the evaluation of aspects of cardiac structure and function, such as myocardial fibrosis and ventricular contractile dyssynchrony, that previously could not be assessed *in vivo*. These approaches may therefore allow greater insight into the mechanisms underlying heart failure, thus offering new diagnostic and therapeutic opportunities.

Amongst emerging paradigms in heart failure evaluation, assessment of myocardial fibrosis and ventricular dyssynchrony appear particularly promising, however it remains incompletely established whether these factors are causative or perpetuating factors in heart failure, or whether (and if so to what extent) these are purely epiphenomena. Novel imaging approaches not only allow characterisation of of these potentially pathological processes, but also permit evaluation of left ventricular and left atrial structural remodelling and function, which have been shown to be important surrogates for clinical endpoints.

The goal of this thesis is then to employ these developing imaging techniques in humans to further the understanding of the relationship between myocardial fibrosis, ventricular mechanical dyssynchrony, and left ventricular and left atrial structural remodelling and function.

Table 1.1(228)

Echocardiographic classification of grades of diastolic dysfunction

Parameter	Normal	Mild dysfunction (grade 1)	Moderate dysfunction (grade 2)	Severe dysfunction (grade 3)	Severe dysfunction (grade 4)
Trans-mitral PW Doppler					
E/A	1-1.5	<1	1-1.5	>2	>2.5
DT (ms)	140-250	>250	140-250	<140	<140
TDI					
Septal E' (cm/s)	≥7	<7	<7	<5	<5
Valsalva	Negative	Positive	Positive	Positive	Negative
LAVI (mL/m^2)	22 ± 6	>28	>28	>35	>40
Pulmonary venous flow	S ≥ D	S >> D	S < D	S << D	S << D
Mitral in-flow propagation velocity (cm/s)	≥50	<50	<50	<50	<50

PW = pulse-wave, E/A = ratio of E to A wave velocities, DT = deceleration time, TDI = pulse-wave tissue Doppler imaging at the septal mitral annulus, LAVI = LA volume indexed to body surface area

Figure 1.1

Doppler Evaluation of a Patient With Restrictive Left Ventricular Filling.

A) Trans-mitral pulsed wave Doppler at mitral valve leaflet tips demonstrating E/A ratio >2 and brief deceleration time (arrows). B) Pulsed wave Doppler at the ostium of the right upper pulmonary vein showing S-wave << D-wave. E/A = ratio of E- to A-wave velocities.

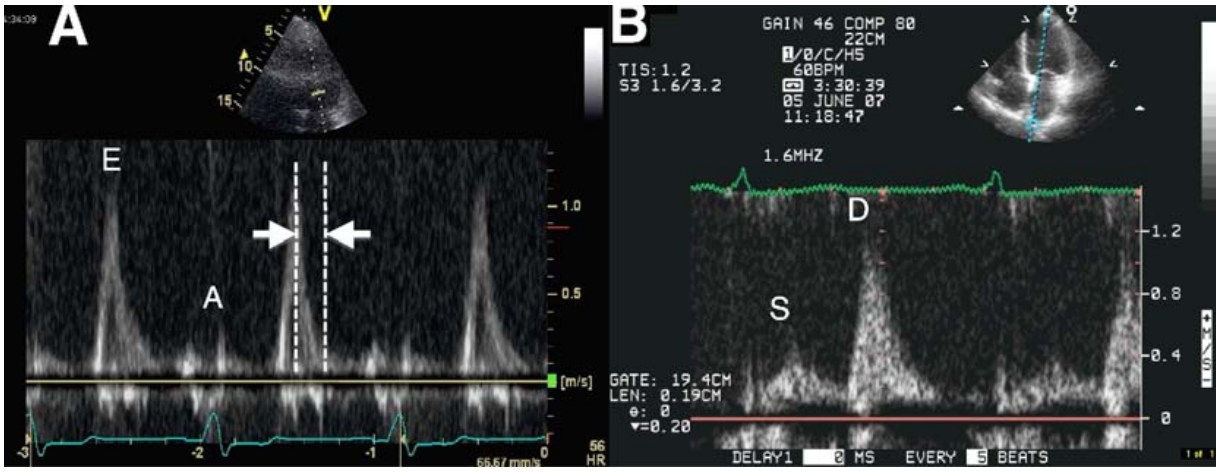


Figure 1.2

Diastolic L-Wave on Trans-Mitral Doppler Echocardiography.

Transmitral pulsed wave Doppler at mitral valve leaflet tips in a patient with pseudo-normal left ventricular filling. An L-wave is seen as antegrade flow occurring between the E and A waves

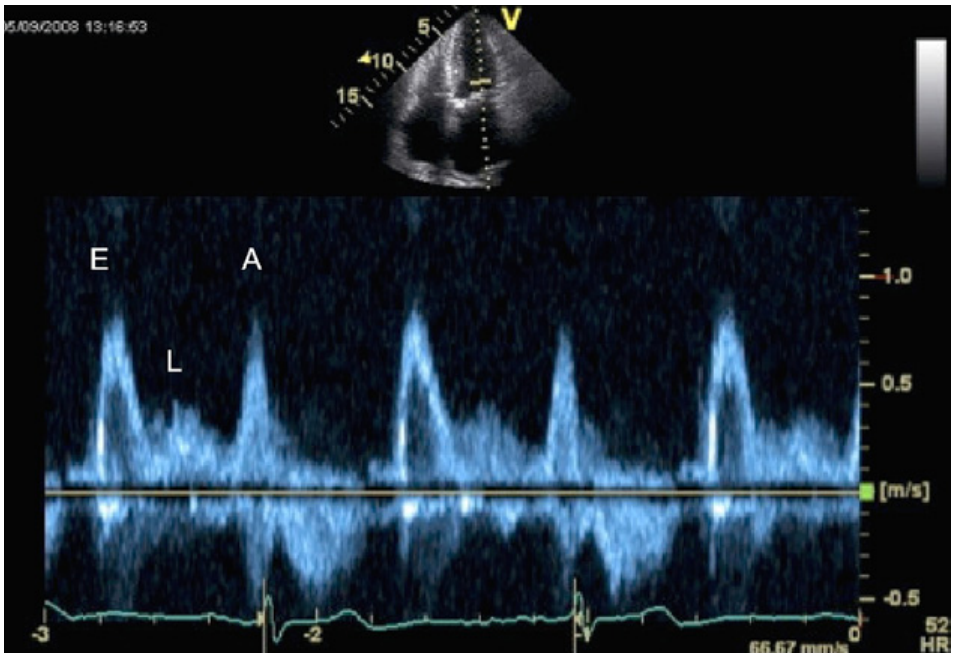
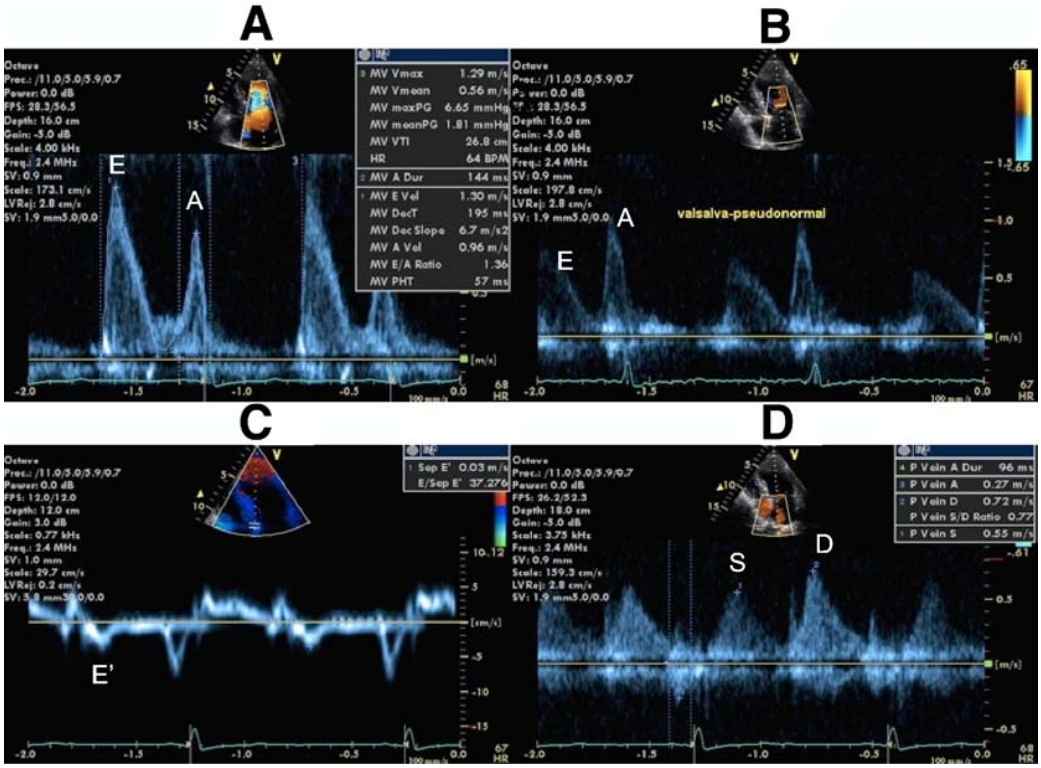


Figure 1.3

Doppler Evaluation of a Patient With Pseudo-Normal Left Ventricular Filling

A) Trans-mitral pulsed wave Doppler at mitral valve leaflet tips. B) Trans-mitral pulsed wave Doppler at mitral valve leaflet tips during Valsalva manoeuvre illustrating E/A reversal. C) Pulsed-wave tissue Doppler imaging at the septal mitral annulus demonstrating reduced diastolic E' velocity. D) Pulsed-wave Doppler at the ostium of the right upper pulmonary vein showing S-wave < D-wave.



Chapter 2 – Methods

2.1. INTRODUCTION

Chapters 3-7 feature the evaluation of left ventricular and LA structure and function in different patient groups. This chapter contains the protocol for transthoracic echocardiographic and cardiovascular magnetic resonance image acquisition and analysis. In addition, general statistic analytical methods are described.

2.2. TRANSTHORACIC ECHOCARDIOGRAPHIC IMAGE ACQUISITION

Patients were imaged in the left lateral decubitus position using a commercially available system (Vingmed Vivid Seven or Vivid i, General Electric Healthcare, Horten, Norway). Images were obtained using a 3.5-Mhz transducer, at a depth of 16 cm in the apical views. Grey-scale images of the left ventricle were acquired in three apical views with the depth and sector width adjusted to achieve frame rates exceeding 70 per second. Grey-scale imaging of the left atrium was performed in the apical 2- and 4-chamber views with the sector width adjusted to achieve frame rates exceeding 70 per second. For the Tissue Velocity imaging, the sector width was adjusted to obtain a frame rate of at least 100 frames per second. Tissue Velocity imaging of the left ventricle was performed in the three apical views (Figure 2.1). Pulse wave Doppler recordings were taken with the sample volume in the right ventricular outflow tract in the parasternal short axis view, and in the LV outflow tract in the apical 5-chamber view (Figure 2.2). Transmitral blood flow velocities (E and A wave) were measured by pulse wave Doppler at the mitral valve leaflet tips. TAPSE was measured by M-mode echocardiography of the lateral tricuspid annulus. A minimum of three consecutive cardiac cycles was recorded for each image. Images

were recorded digitally in cine-loop format and analysed off-line with commercial software (EchoPac version 7.0.0 General Electric-Vingmed).

2.3. TRANSTHORACIC ECHOCARDIOGRAPHIC IMAGE ANALYSIS

2.3.1. Left Ventricle

The following analysis was performed of left ventricular structure and function:

(i) Left ventricular end-diastolic and end-systolic volumes were measured from apical 4- and 2-chamber images using Simpson's biplane method of discs(33) (Figure 2.3).

(ii) The peak systolic tissue velocity of the mitral annulus during LV ejection was measured offline from Tissue Velocity Images. Velocities were recorded at 6 points from the 3 apical views, and then averaged (Sm).

(iii) LV strain profiles were derived by speckle-tracking (2D strain): following manual tracing of the endocardial border and adjustment of region of interest width to encompass the LV myocardium, strain versus time curves were obtained for 18 segments from 3 apical views. The peak systolic strain was measured from the 18 segments and averaged (LV longitudinal strain score) (Figure 2.4).

(iv) Cardiac dyssynchrony was assessed using offline Tissue Velocity and 2D strain images. The time from QRS onset to peak systolic tissue velocity during LV ejection was measured at the mid-point of 12 myocardial segments (6 basal and 6 mid). The tissue Doppler dyssynchrony index (TD DI) was defined as the standard deviation of these values (Figure 2.1). The time from QRS onset to peak systolic strain was measured in 18 segments

from 3 apical views using speckle-tracking data. The strain dyssynchrony index (SDI) was defined as the standard deviation of these values (Figure 2.4).

(v) Using pulse wave Doppler measurements in the RVOT and LV outflow tract, IVMD was calculated as the difference in time-to-onset of ejection from the right and left ventricles measured from the beginning of the QRS complex (Figure 2.2).

(vi) Diastolic E' velocity was measured offline from Tissue Velocity images as the peak tissue velocity of the septal mitral annulus in early diastole.

2.3.2. Left Atrium

The following analysis was performed of LA structure and function:

(i) LA volume was estimated from apical 4- and 2-chamber images from the frame prior to mitral valve opening using the modified Simpson's rule(33), and was indexed to body surface area, which was estimated using the Mosteller formula(229).

(ii) LA strain profiles were derived in both apical 4- and 2-chamber views and peak strain scores averaged to determine LA strain(230) (Figure 2.5).

2.4. CARDIOVASCULAR MAGNETIC RESONANCE IMAGE ACQUISITION

CMR was performed using commercially available 1.5T machines (Siemens Avanto, Erlangen, Germany or Philips Intera, Best, The Netherlands).

Electrocardiographically-gated steady-state free precession imaging of the left ventricle in the short-axis plane was undertaken (TE/TR, 1.5/3.0ms; flip angle 60^0)

with slice thickness 6mm and 4mm inter-slice gap. A T2-weighted triple inversion recovery sequence was applied in three short axis slices (basal, midventricular, and apical) and in three long axis views to exclude myocardial oedema. T1-weighted contrast-enhanced imaging was then undertaken 10 minutes following intravenous administration of gadolinium-DTPA 0.1mmol/kg using an inversion-recovery segmented gradient echo sequence. Inversion times were adjusted to null normal myocardium (260 to 400ms) with voxel sizes of 1.9x1.4x7.0mm (Figure 2.6). To exclude artefact, cross-cut images and imaging with another phase-encoding direction were performed.

2.5. CARDIOVASCULAR MAGNETIC RESONANCE IMAGE ANALYSIS

LV volumes and mass were measured as previously described(109), using commercially available software (CAAS MRV Version 3.3, PIE, Netherlands). End-diastolic and end-systolic phases were identified as those corresponding with the largest and smallest LV cavity sizes respectively. The basal short-axis LV slice was identified in both end-diastole and end-systole as that in which in which at least 50% of the blood volume was surrounded by myocardium. The apical short-axis slice was defined as the most caudal slice containing intra-cavitary blood pool. The endocardium and epicardium was manually traced at end-diastole and end-systole for each LV slice in order to measure LV end-diastolic and end-systolic volumes, and LV myocardial volume. Myocardial mass was calculated as the product of end-diastolic LV myocardial volume and 1.05g/cm^3 (the specific density of myocardium).

The presence of myocardial oedema was excluded by visual inspection of the T2-weighted images. The presence and distribution of LGE in a 16-segment model were determined by two experienced, independent observers blinded to patient

outcomes. Each segment was awarded 0 for LGE absence and 1 for LGE presence, yielding a fibrosis score out of 16. Regions in which fibrosis was identified by LGE were manually planimetered to measure fibrosis mass, which was calculated for each slice as the product of the planimetered area, the slice thickness and the specific density of myocardium (1.05g/cm^3), then summed over the left ventricle. A third blinded observer adjudicated cases of disagreement.

Figure 2.1

Tissue Velocity imaging in the apical 4-chamber view illustrating tissue velocity profiles of the basal-septal (yellow) and basal-lateral (blue) left ventricular segments.

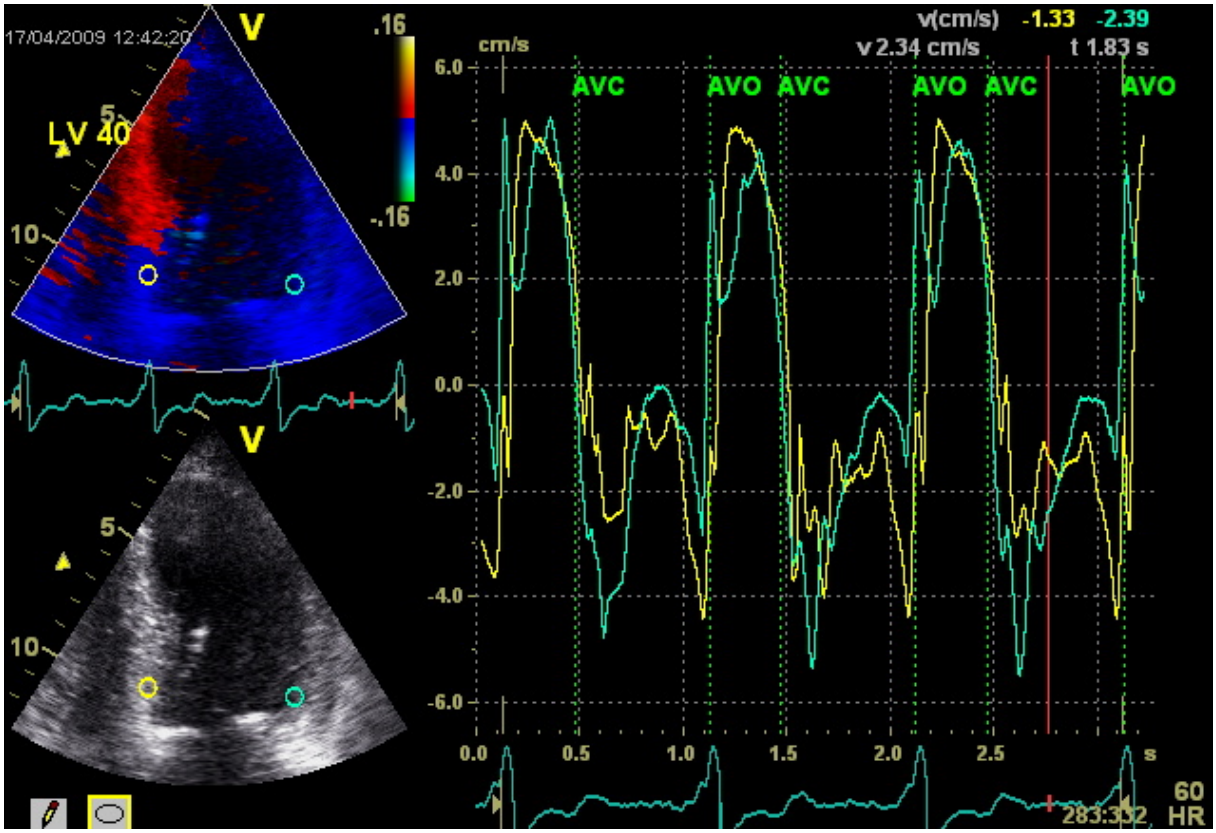


Figure 2.2

Pulse-wave Doppler imaging in the left ventricular outflow tract (A) in the apical 5-chamber view, and the right ventricular outflow tract (B) in the parasternal short-axis view. Times from QRS onset to onset of antegrade flow are displayed.

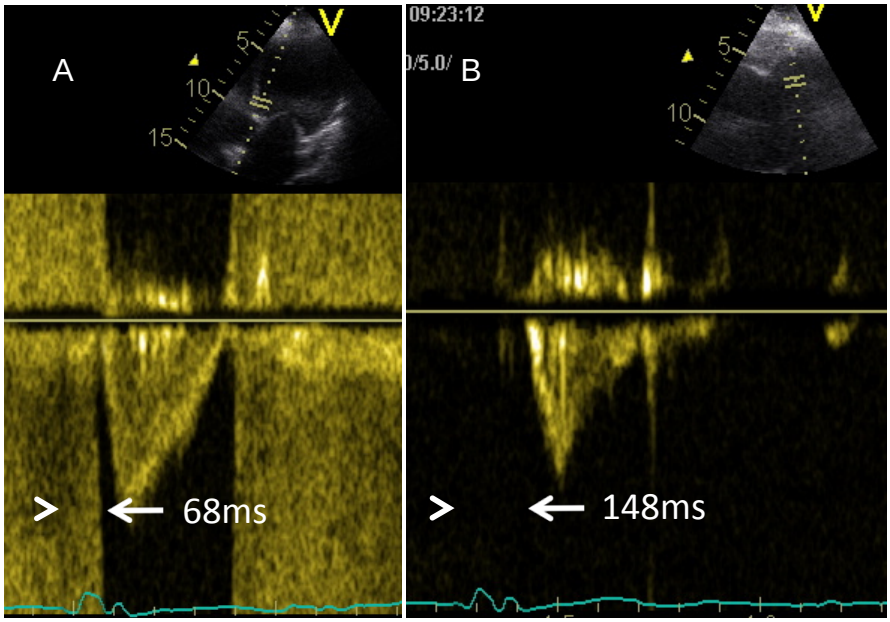


Figure 2.3

Measurement of left ventricular end-diastolic volume by Simpson's bi-plane method of discs, using the apical 4-chamber and 2-chamber views.

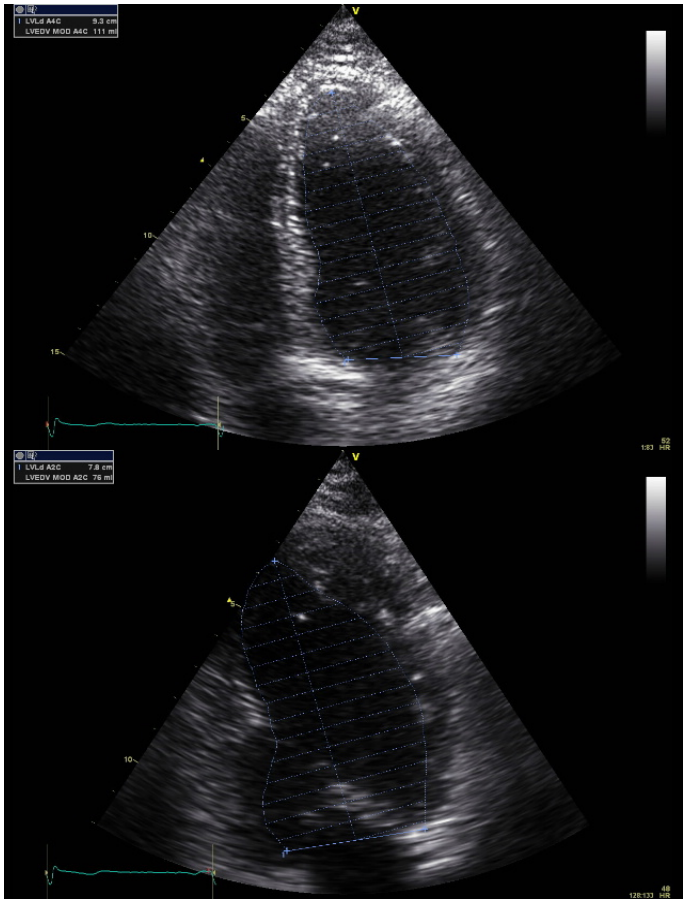


Figure 2.4

Representative offline analysis of 2D longitudinal strain in the apical 4-chamber view, demonstrating systolic shortening profiles of the basal septal (yellow) and lateral (red), mid-septal (pale blue) and mid-lateral (dark blue), and apical septal (green) and lateral (magenta) segments. AVC = aortic valve closure.

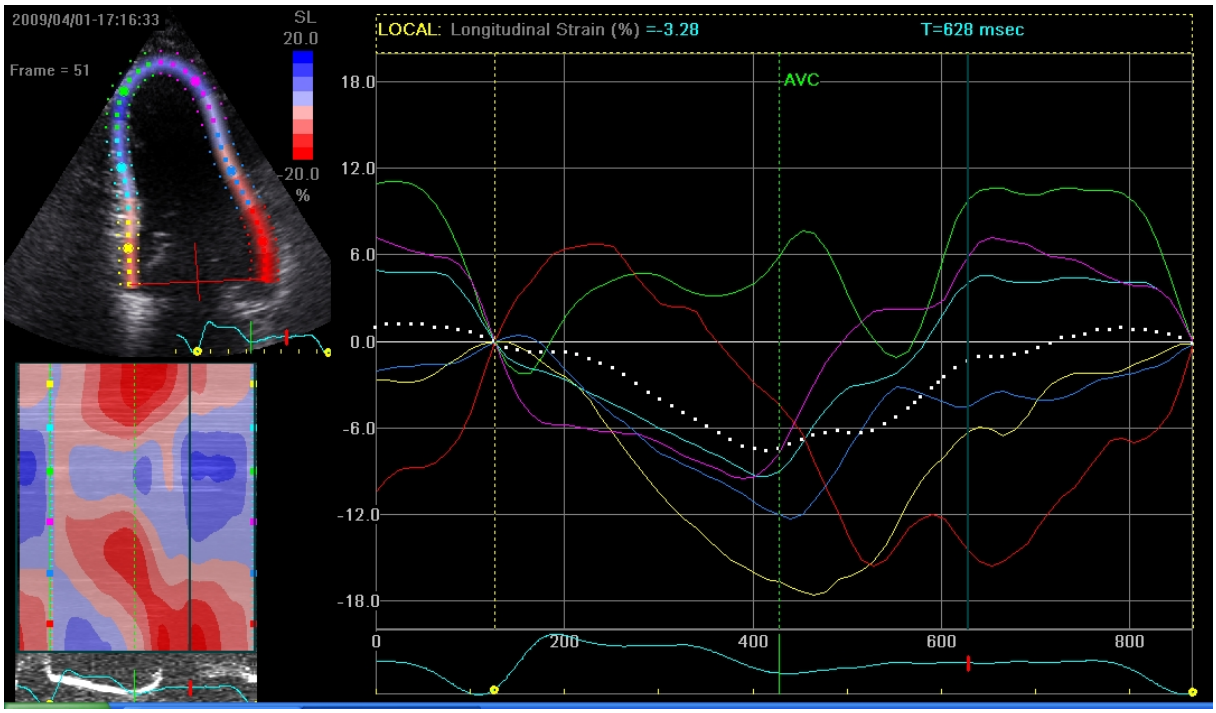


Figure 2.5

Speckle-tracking strain image of the left atrium in the apical 4-chamber view. The dotted white curve represents the average of segmental strain curves from this view.

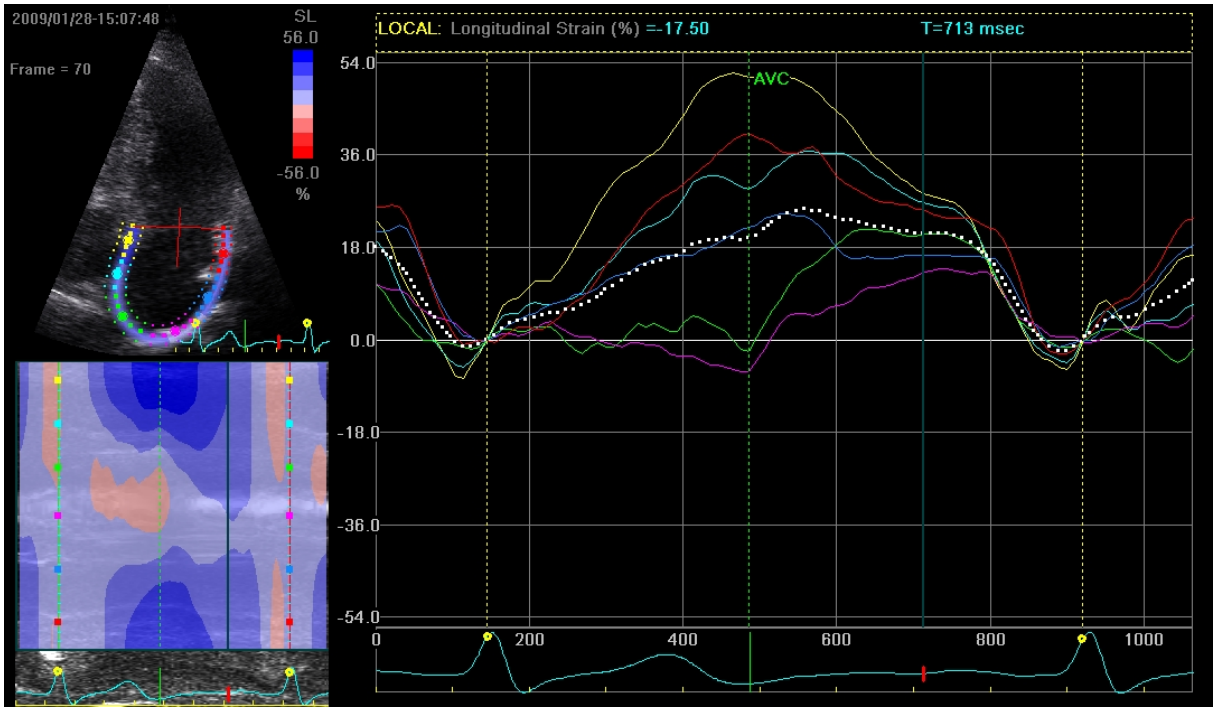
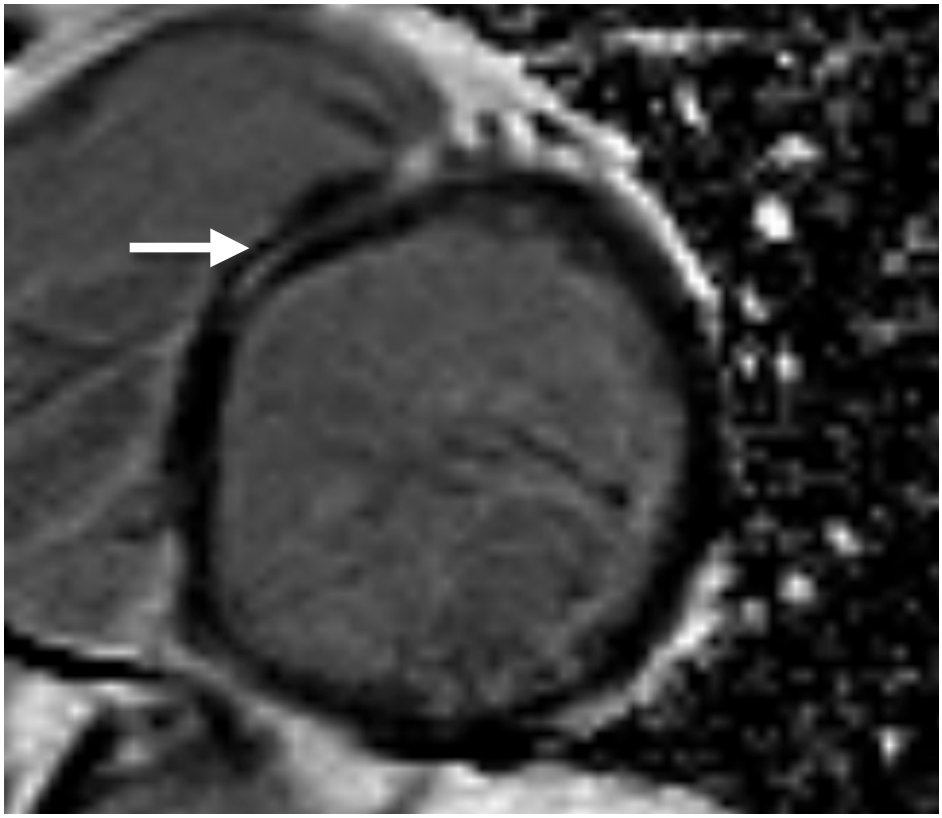


Figure 2.6

T1-weighted late-gadolinium enhancement image in the short axis view illustrating mid-wall late-enhancement (arrow).



Chapter 3 – The Ventricular Dependence of Left Atrial Mechanical Function

3.1. BACKGROUND

Atrial mechanical function is considered an important determinant of the risk of thromboembolic cardiovascular complications(121, 231). The function of the left atrium has many potential determinants – volume status, autonomic function, heart rate and possibly ventricular function. In patients with chronic atrial arrhythmia, there is evidence of a functional, recoverable component as evidenced by atrial stunning following cardioversion(232, 233). The duration of this arrhythmia may influence the extent of recovery of LA function(234). LA contractile function has been estimated to contribute up to 30% of left ventricular (LV) stroke volume in healthy individuals(235). This may increase in importance under pathological states in which early diastolic LV filling is impaired.

Abnormalities in LA structural and electrophysiological properties have been demonstrated in heart failure patients(236). LA contractile dysfunction has also been associated with both advancing systolic and diastolic LV function(237, 238), although its relationship with diastolic function is inconsistent(239). An understanding of the mechanisms underlying LA contractile dysfunction in heart failure may lead to the refinement of existing therapies or the development of novel approaches for the reduction of thromboembolic risk. ***It is unclear, however, whether LA dysfunction is an epiphenomenon, sharing the same cause as the LV impairment, or whether it is a direct result of the LV dysfunction. There is a paucity of evidence on the interdependence of left ventricular and left atrial function.***

Transoesophageal echocardiography is the imaging gold standard in the identification of LA thrombus and the evaluation of surrogate markers of

thromboembolic risk. LASEC within the left atrium has been demonstrated to be a potent predictor of LA thromboembolism(119). Despite its important prognostic value, the exact nature of LASEC remains elusive(120). LA appendage emptying velocity (LAAEV) using pulse-wave Doppler echocardiography is an important index of LA contractile function, and has been demonstrated to be the strongest predictor of LA thrombus/LASEC(121, 240).

The aim of this study was therefore to characterise, using transoesophageal echocardiography, the relationship between LV function and LA contractile function by observing the effects on LA function of ceasing effective LV mechanical activity.

3.2. METHODS

3.2.1. Subject Characteristics

Sixteen subjects who had undergone insertion of an implantable cardioverter defibrillator (ICD) within the previous month, and in whom defibrillation threshold testing (DFT) was scheduled, were prospectively recruited. Exclusion criteria included severe native valvular heart disease, the presence of prosthetic cardiac valves, New York Heart Association class III or IV heart failure, and the identification of LA or LA appendage thrombus. All patients provided written informed consent to the study protocol, which was approved by the Human Research Ethics Committees of the Royal Adelaide Hospital and the Flinders Medical Centre, Adelaide, Australia.

3.2.2. Study Protocol

In order to evaluate the impact of ventricular function, LA function was evaluated before, during and after an episode of ventricular fibrillation (VF). VF was induced during DFT testing by a pacing train of 10 cycles at 400ms intervals followed by the

delivery of a shock in the T wave vulnerable period. Termination of VF was by defibrillator discharge.

3.2.3. Transthoracic echocardiogram protocol

Immediately prior to defibrillation threshold testing, subjects underwent transthoracic echocardiography as previously described (see Chapter 2). Specific measurements included LV and LA volumes, transmitral mitral E and A wave velocities, and Tissue Velocity imaging of the septal mitral annulus as described in Chapter 2.

3.2.4. Trans-oesophageal echocardiogram protocol

Following induction of general anaesthesia and endotracheal intubation, a trans-oesophageal echocardiogram probe was inserted into the upper oesophagus. Baseline imaging included: 1) 2-dimensional imaging of the left atrium and LA appendage with gain and filter settings optimised for the detection and quantification of LASEC 2) pulse-wave Doppler imaging of the LA appendage with the sample volume positioned 1cm into the orifice of the appendage for measurement of the LAAEV (Figure 3.1), and 3) continuous-wave transmitral Doppler imaging for the measurement of E and A wave velocities. Following the induction of VF, 2-dimensional imaging of the left atrium for quantification of LASEC and pulse-wave Doppler imaging of the LA appendage were performed during VF with each image looped over a 2 second interval rather than being gated to QRS complex. Post-VF images were recorded 10 minutes after defibrillation, with the same parameters acquired as for the baseline images. All data were stored digitally for offline analysis. Baseline and post-VF measurements were averaged over 5 cardiac cycles if in sinus rhythm and over 10 cardiac cycles if in atrial fibrillation. LASEC was quantified on a scale of 0 to 4 as previously described(241):

- 0 – absence of LA echogenicity
- 1 – minimal echogenicity, imperceptible at “normal” gain settings, detectable only transiently during the cardiac cycle
- 2 – more dense echogenicity detectable without increased gain settings
- 3 – dense, swirling echogenicity detectable throughout the cardiac cycle in the LA appendage, with lesser intensity in the main LA cavity
- 4 – intense echodensity with very slow, swirling appearance of similar severity in the LA appendage and main LA cavity

3.2.5. Statistical Analysis

Continuous data are presented as mean ± SD. The change in echocardiographic parameters before, during, and after VF was evaluated by repeated measures analysis of variance. A second, blinded observer repeated LAAEV and LASEC measurements for 5 randomly selected subjects pre-, during and post-VF. Inter-observer variability for the measurement of LAAEV was assessed by Lin’s Concordance Correlation Coefficient(242) and by the coefficient of variation (calculated as the standard deviation of the differences between two sets of measurements divided by the mean value of the parameter under consideration), and are expressed as bias and 95% limits of agreements of limits as described by Bland and Altman(243). Inter-observer variability for the measurement of LASEC was evaluated by the kappa statistic.

3.3. RESULTS

3.3.1. Subject Characteristics

Baseline and echocardiographic characteristics are presented in Table 3.1 and Table 3.2 respectively. Subjects' mean age was 60 ± 11 years, and 14 of the 16 were male. ICD indication was for primary prevention of sudden cardiac death in all but one case; subject 4 was the survivor of ventricular fibrillation cardiac arrest. The mean LVEF was 36 ± 12% and mean LA volume was 91 ± 34mL. The mean A wave velocity was 51 ± 14cm/s and mean A' velocity was 6.0 ± 3.3cm/s. Two subjects (12 and 15) were found to have LA appendage thrombus at trans-oesophageal echocardiogram, and so defibrillation threshold testing was not undertaken. One subject (16) withdrew consent immediately prior to induction of general anaesthesia, and so did not undergo trans-oesophageal echocardiography. The following analysis was performed on the remaining 13 subjects.

3.3.2. Effects of Ventricular Fibrillation and Defibrillation on Left Atrial Appendage Emptying Velocity

The mean LAAEV at baseline was 34.0 ± 24.4cm/s. VF was successfully induced in the first instance in all patients. The LAAEV fell to 15.6 ±12.2cm/s ($p<0.05$) during VF. Defibrillation was successful on the first occasion in all subjects. Ten minutes following defibrillation, the LAAEV returned to baseline (35.8 ± 24.5cm/s, p = NS compared with baseline) (Figure3.2).

3.3.3. Effects of Ventricular Fibrillation and Defibrillation on Left Atrial Spontaneous Echocardiographic Contrast

Baseline LASEC score was 1.0 ± 0.9. LASEC score increased during VF to 3.9 ± 0.3 ($p<0.05$). Ten minutes following defibrillation, the LASEC score returned to baseline (1.4 ± 1.2, p = NS).

3.3.4. Effects of Ventricular Fibrillation and Defibrillation on Trans-Mitral Doppler Parameters

E wave velocities were no different pre- and ten minutes post-VF (66 ± 19 v. 68 ± 20cm/s, p = 0.6). A wave velocities were also no different pre- and ten minutes post-VF (54 ± 15 v. 49 ± 14cm/s, p = 0.8).

3.3.5. Atrial Rhythm During Ventricular Fibrillation

Ten subjects had dual-chamber ICDs implanted, and thus had atrial electrograms available for analysis. Nine of these were in sinus rhythm immediately prior to induction on VF, and one was in atrial fibrillation. The individual in atrial fibrillation at baseline (subject 4) remained in atrial fibrillation during VF, but reverted to sinus rhythm following defibrillation. Of the nine subjects in sinus rhythm at baseline for whom atrial electrograms were available, two developed atrial fibrillation when VF was induced (subjects 8 and 11). They reverted to sinus rhythm following defibrillation. Subject 8 demonstrated substantial decline in LAAEV (36 to 10cm/s) and increase in LASEC (grade 1 to 4) during VF/atrial fibrillation, which improved 10 minutes after defibrillation (LAAEV 25cm/s and LASEC grade 1). Subject 11 exhibited no major change in LAAEV or LASEC during or following VF. When analysis was limited to the seven individuals who maintained sinus atrial rhythm

during VF, the pattern of significant decline in LAAEV (from 35 ± 24cm/s to 16 ± 12cm/s, $p<0.05$) and increase in SEC grade (from 0.9 ± 0.8 to 3.8 ± 0.4, $p<0.05$), followed by recovery to baseline persisted.

3.3.6. Inter-Observer Variability

For LAAEV, Lin's Concordance Correlation Coefficient was 0.99 (95% CI 0.99 – 1.0), and the coefficient of variation was 7.4. Bland-Altman limits of agreement were -5.3 and 4.3cm/s. For SEC, the kappa statistic was 0.74.

3.4. DISCUSSION

3.4.1. Major Findings

In this prospective cohort study of patients undergoing defibrillator threshold testing, the acute relationship between LA contractile function and LV function was evaluated. When LV function was eliminated by the induction of ventricular fibrillation, there was a significant decline in LA contractile function as reflected by reduction in LA appendage emptying velocity and increase in spontaneous echo contrast. Within ten minutes of successful defibrillation there was a return to normal LA contractility.

This is a first-in-human study of the effect of elimination of ventricular function on atrial function. During VF both systolic and diastolic ventricular function is abolished. The marked reduction in LA function with the elimination of ventricular function occurred despite the atrial rhythm in the majority of these subjects remaining in sinus rhythm.

3.4.2. Mechanistic Implications

This study furthers the understanding of the relationship between ventricular and atrial function. Although previous evidence suggested an association between the two, it has been uncertain whether this association was merely an epiphenomenon of the disease process that resulted in ventricular dysfunction. The association between LA contractility and LV function exhibited in the present study is consistent with the premise that the relationship between atrial and ventricular dysfunction is in fact a direct causal one. The interdependence of the left and right ventricles has longed been recognised(244). The present study elaborates on this model of cardiac function by raising the possibility of atrioventricular interdependence.

In an acute pacing canine model of LV dysfunction, Hoit *et al*. demonstrated a compensatory increase in atrial booster pump function(245). This finding together with those of the present study suggests that the relationship between LA contractility and LA afterload may not be linear. Increase in LA booster pump function may help to compensate for impaired LV function until LA contractility is unable to overcome excessive resistance, at which point LA contraction enters a failure arm.

In the clinical realm, reports of LA function in the setting of chronic heart failure are mixed, with evidence of both impaired and augmented LA contractility(246, 247). Whilst the present study has examined the effects of acute LV dysfunction on LA contraction, the rate at which LV dysfunction develops and its chronicity are likely to influence LA functional response in chronic heart failure.

3.4.3. Clinical Implications

The profound deterioration in LA mechanical function observed during VF may have implications for those resuscitated from cardiac arrest or successfully defibrillated from VF by an implantable cardioverter-defibrillator. In the present study, LAAEV declined and LASEC increased dramatically during a brief episode of VF. These indices have been shown to be important markers of thromboembolic risk. It is tempting to speculate that some of the adverse neurological sequelae of cardiac arrest may be thromboembolic in origin.

The findings of the current study complement those illustrating the impact of loss of atrial mechanical function, from atrial fibrillation, on cardiac output. The relationship between LA and LV function would appear consistent with current understanding of the importance of atrioventricular synchrony.

3.4.4. Study Limitations

This study featured a small number of patients with heterogeneous cardiac diseases. The quantification of LA contractile function during VF was by necessity limited to the use of only two echocardiographic indices. The brief duration of VF before defibrillation precluded further imaging of the left atrium during this critical period. The use of intra-cardiac manometry would have provided corroborative information to the data collected, but the additional risk to the patients to perform this was felt excessive. In the absence of LV and/or LA pressure measurement during VF it is possible that the decline in LA contractility observed in this study is merely consequent upon an abrupt and large increase in LA afterload. Most subjects in the present study suffered systolic left ventricular impairment. Whether the same relationship between LA and LV function would be observed among those with normal systolic LV function remains uncertain.

3.4.5. Conclusion

Ventricular function may have a significant impact on atrial mechanical function. With the elimination of ventricular function, during ventricular fibrillation, there is a marked decrease in LA emptying and an increase in LASEC; both important negative prognostic indicators. Whilst this relationship has been demonstrated in an acute setting, Chapters 4 and 5 will explore the relationship between LA remodelling and function, and LV function in a more persistent disease state, namely newly-presenting idiopathic dilated cardiomyopathy.

Table 3.1

Subject	Age	Gender	Diagnosis	Beta-blocker	Amiodarone	Digoxin
1	68	Female	ARVC	No	Yes	No
2	73	Male	NICM	Yes	No	Yes
3	64	Male	Ischaemic cardiomyopathy	No	No	No
4	65	Male	NICM	Yes	No	No
5	57	Male	NICM	Yes	No	Yes
6	37	Male	HCM	Yes	No	No
7	55	Male	NICM	Yes	No	No
8	78	Male	Ischaemic cardiomyopathy	Yes	No	No
9	63	Male	Ischaemic cardiomyopathy	Yes	No	No
10	46	Female	Ischaemic cardiomyopathy	Yes	No	Yes
11	54	Male	NICM	Yes	No	No
12	53	Male	NICM	Yes	No	No
13	63	Male	NICM	Yes	No	Yes
14	66	Male	Ischaemic cardiomyopathy	Yes	No	Yes
15	74	Male	Ischaemic cardiomyopathy	Yes	No	No
16	55	Male	HCM	Yes	No	No

Table 3.1 continued

Subject	ACE-I/ ARB	Other AAD	Warfarin	Co-morbid conditions
1	No	No	No	Obesity, obstructive sleep apnoea
2	No	No	Yes	Atrial fibrillation, stroke
3	Yes	No	No	Obesity, DM, hypertension
4	Yes	No	No	DM
5	Yes	No	Yes	Atrial fibrillation, DM
6	No	No	No	None
7	Yes	No	No	None
8	Yes	No	No	Paroxysmal atrial fibrillation
9	Yes	No	No	DM, hypertension, obesity
10	Yes	No	No	DM, hypertension, obesity
11	Yes	No	Yes	Paroxysmal atrial fibrillation
12	Yes	No	Yes	Paroxysmal atrial fibrillation
13	Yes	No	No	DM
14	Yes	No	Yes	Atrial fibrillation
15	Yes	No	No	Hypertension
16	No	No	No	Paroxysmal atrial fibrillation, hypertension

ARVC = arrhythmogenic right ventricular cardiomyopathy; NICM = idiopathic dilated cardiomyopathy; HCM = hypertrophic cardiomyopathy; ACE-I = angiotensin converting enzyme inhibitor; ARB = angiotensin receptor blocker; AAD = anti-arrhythmic drug; DM = diabetes mellitus

Table 3.2

Subject	Heart rhythm	LVEF (%)	LA volume (mL)	E wave velocity (cm/s)	A wave velocity (cm/s)	E' velocity (cm/s)	A' velocity (cm/s)
1	Sinus	56	57	39	67	2.8	6.4
2	AF	30	167	74	.	4.3	.
3	Sinus	33	71	84	82		
4	Sinus	36		32	56	6.7	10
5	AF	34	106	105	.	4.7	.
6	Sinus	62	93	72	50	4	5.5
7	Sinus	35	96	79	22	6	1
8	Sinus	26	60	78	74	4.5	8
9	Sinus	29	91	73	98	6	10.5
10	Sinus	32	57	74	92	4	6
11	Sinus	20	63	61	46	3.6	5.4
12	Sinus	30	132	86	.	6.5	.
13	Sinus	25	68	93	19	2.7	1.4
14	AF	30	125	70	.	6	.
15	Sinus	35	119	99	20	6.2	1.4
16	Sinus	55	64	76	71	6	9.2

Figure 3.1

Pulse-wave Doppler imaging acquired at the same scale, 1cm into the orifice of the LA appendage at baseline (A), during ventricular fibrillation (B), and 10 minutes after defibrillation to sinus rhythm (C), illustrating profound reduction in LA appendage exit velocity during ventricular fibrillation (VF).

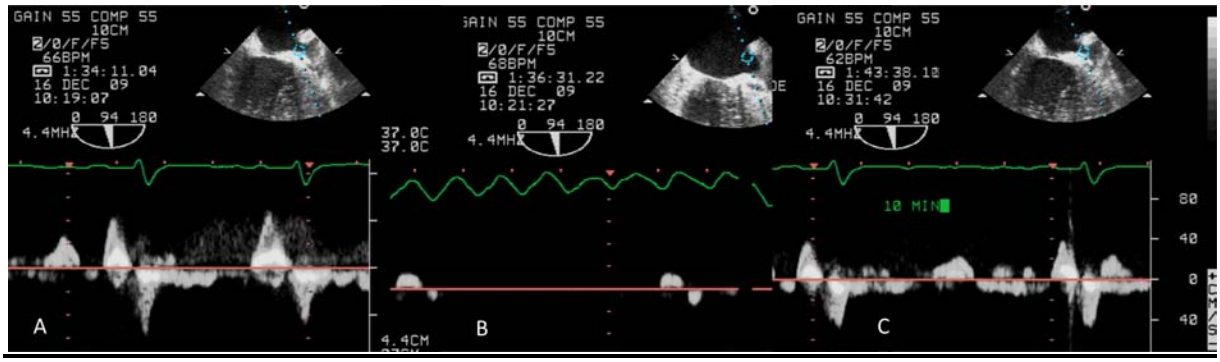


Figure 3.2

Graph illustrating the change in LA appendage emptying velocity from baseline to ventricular fibrillation (VF) to 10 minutes post-VF

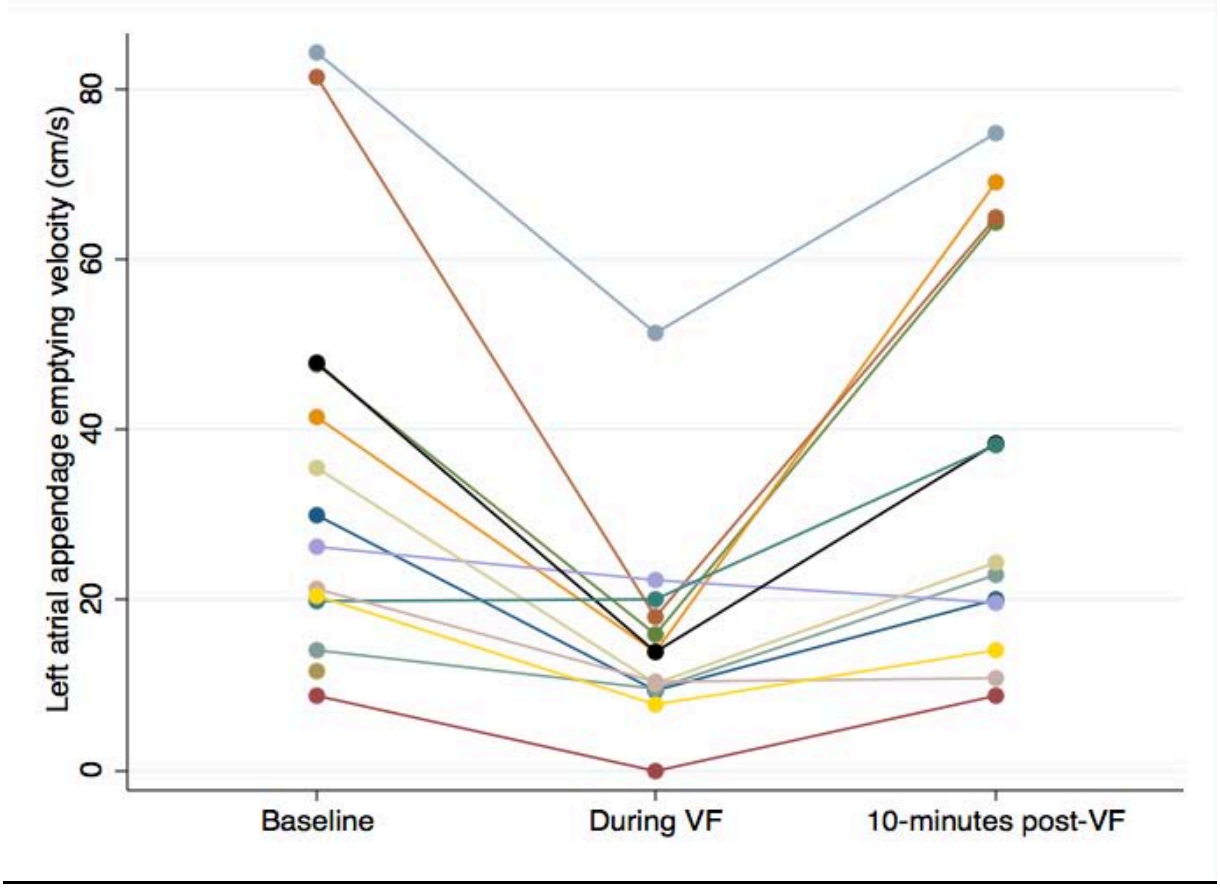
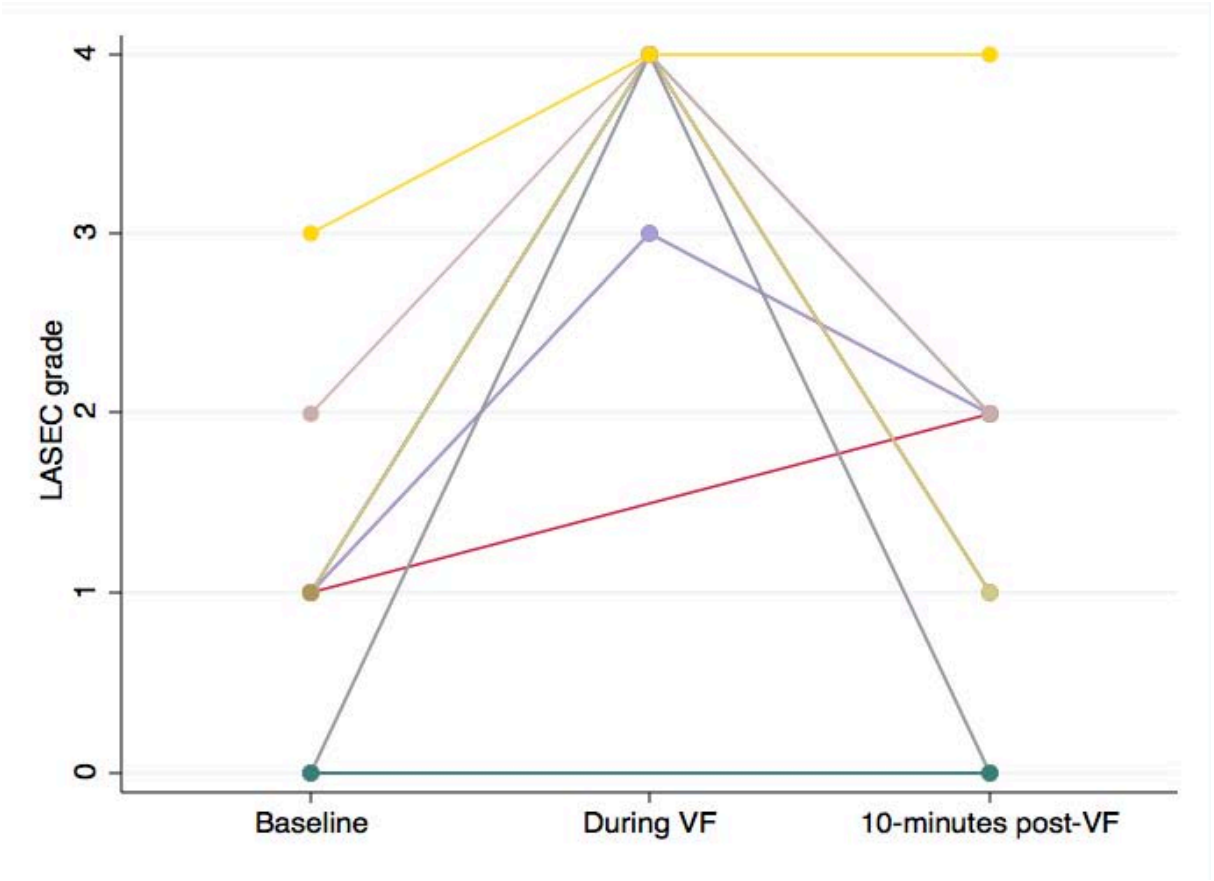


Figure 3.3

Graph illustrating the change in LASEC grade from baseline to ventricular fibrillation (VF) to 10 minutes post-VF. There is overlap of datapoints and connecting lines for several individuals.



Chapter 4 - Effects of Myocardial Fibrosis and Ventricular Dyssynchrony on Response to Therapy in New-Presentation Idiopathic Dilated Cardiomyopathy: Insights From Cardiovascular Magnetic Resonance and Echocardiography

4.1. BACKGROUND

Chapter 3 examined the association between LA nd LV function. This chapter will characterise patients with idiopathic dilated cardiomyopathy (DCM), a condition featuring impairment in systolic LV function following a poorly defined myocardial insult. Th research undertaken in this chapter was performed in concert with that of Chapter 5, in which the relationship between LV dysfunction and LA function is further developed, however the findings were separated into the two chapters in the interests of clarity.

A hallmark of DCM is myocardial fibrosis(248), whose presence (as detected by late-gadolinium enhancement cardiovascular magnetic resonance imaging; LGE-CMR) portends an adverse prognosis(193, 194). Additionally, dyssynchronous ventricular contraction is a frequent finding in DCM patients(249) and its presence (using echocardiographic tissue Doppler criteria) has been strongly associated with adverse cardiovascular events(250).

Despite this emerging evidence, reports of DCM disease course vary widely, both with respect to patient outcomes and to prognostic factors(193, 194, 250, 251). Previous studies have focussed on patients with established cardiomyopathy; however the presence and extent of myocardial fibrosis at presentation of DCM and

its effect on subsequent response to medical therapy is unknown. Furthermore, the prevalence of ventricular dyssynchrony at presentation in DCM is uncertain and its role in perpetuating adverse LV remodelling remains unclear. Those studies of individuals with long-standing DCM did not characterise patients early in the disease course, and may not have included those with significant improvement in LV function. Thus factors contributing to LV recovery are uncertain. The identification of such predictors of improvement is of particular value with the advent of the implantable cardioverter-defibrillator, whose role at the time of diagnosis in DCM is unclear(252).

The aims of this study was therefore to 1) determine the prevalence of myocardial fibrosis as detected by LGE-CMR, and ventricular dyssynchrony by echocardiography in patients early following a first presentation with DCM, and 2) examine the relationship between the extent of myocardial fibrosis, ventricular dyssynchrony, and improvement in LV systolic function as measured by LVEF following institution of medical therapy. The primary hypotheses were that the degree of myocardial fibrosis as detected by LGE-CMR, and ventricular dyssynchrony by echocardiography are independent predictors of failure of improvement in systolic LV function in patients with newly diagnosed DCM. Secondary endpoints were LA volume and function (as measured by speckle tracking strain echocardiography).

4.2. METHODS

4.2.1. Subject Characteristics

Consecutive patients were recruited from the Royal Adelaide Hospital, Flinders Medical Centre, and Modbury Public Hospital from April 2008 to December 2009. All patients had a new diagnosis of DCM made within the preceding two weeks. The inclusion criterion was the presence of LV ejection fraction ≤45% at baseline echocardiography or CMR. Exclusion criteria included the diagnosis of significant coronary artery disease (defined as the presence of >70% luminal stenosis in an epicardial coronary artery at angiography, non-invasive stress imaging suggestive of ischaemia, or prior myocardial infarction), severe valvular heart disease, thyroid dysfunction, infiltrative cardiomyopathy or extra-cardiac systemic features to suggest sarcoidosis or amyloidosis, chemotherapy-induced cardiomyopathy, and myocarditis. Myocarditis was excluded in potential DCM cases by the absence of classic clinical features, the presence of normal serum troponin I concentration at presentation, and by the lack of evidence of myocardial oedema on T2-weighted CMR(254). Exclusion from the CMR arm of the study was mandated by patient claustrophobia, renal impairment (eGFR <60mL/min), or the presence of prostheses, including cardiac devices, which were CMR incompatible. Control subjects were a sample of health volunteers with no history of cardiac disease, hypertension, or diabetes mellitus. All subjects provided written, informed consent to the study protocol, which complies with the Declaration of Helsinki and was approved by the Human Research Ethics Committee at each participating institution.

4.2.2. Treatment of Heart Failure

Heart failure therapies were administered in accordance with current guidelines(127), using angiotensin converting enzyme inhibitors or angiotensin receptor blockers (ACE-I/ARB), beta-blockers and when clinically indicated, aldosterone antagonists. These therapies were initiated and titrated to maximum tolerated doses by the treating physician.

4.2.3. Study Protocol

Patients were recruited and studied within two weeks of presentation with new-onset DCM when clinically stable. Patients in whom the diagnosis of DCM was made as an outpatient were studied as soon as possible following diagnosis, but within two weeks following presentation. Any patient ineligible for CMR but consenting to the remainder of the protocol underwent these other study investigations. The study protocol consisted of the following baseline investigations: blood sampling, LGE-CMR, echocardiography, 6-minute-walk testing, Minnesota Living with Heart Failure Questionnaire, and cardiopulmonary exercise testing. To minimise variability due to loading conditions, imaging (CMR and echocardiography) was performed in immediate succession for each individual. Patients underwent repeat echocardiography, 6-minute-walk testing, Minnesota Living with Heart Failure Questionnaire, and cardiopulmonary exercise testing a median 5 months (interquartile range 4-7 months) later. Follow-up echocardiography was performed at the same time of day as baseline imaging to correct for effect of loading conditions of ventricular function.

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4.2.4. Cardiovascular Magnetic Resonance Protocol

Refer to Chapter 2.4 and 2.5 for image acquisition and analysis specifics (Figure 4.1).

4.2.5. Echocardiography Protocol

Imaging acquisition and analysis was performed as described in Chapter 2. In addition, TAPSE was measured by M-mode echocardiography of the lateral tricuspid annulus. A minimum of three consecutive cardiac cycles was recorded for each image. Data were stored digitally for subsequent analysis (Figure 4.1).

4.2.6. Exercise Testing Protocol

Cardiopulmonary exercise testing was conducted on stationary cycle ergometer to measure peak oxygen uptake ($VO_{2\ PEAK}$) according to current recommendations(255). $VO_{2\ PEAK}$ has previously been shown to be an important predictor of outcome in non-ischaemic systolic heart failure patients(256). Six-minute walk test was also performed to assess its prognostic value for LVEF, given its recognised ability to predict heart failure hospitalisation and mortality(257). Both these indices of functional capacity were evaluated for their ability at baseline to predict improvement in LVEF.

4.2.7. Blood Samples

Venous blood specimens were collected, immediately centrifuged for 10 minutes at 3000rpm, and the serum aliquoted and stored at -80^0C for batch analysis of NT-pro-BNP, whose concentration has recently been shown to have prognostic value in

stable heart failure patients(258), and so was included in the model for follow-up LVEF prediction.

4.2.8. Statistical Analysis

Data from controls were compared with patients by the Student's t-test for continuous variables and the χ^2 test for categorical variables. We performed two multivariate regression analyses. Firstly, change in continuous variables from baseline to follow-up, and the predictive value of baseline covariates for changes in LVEF, from baseline to follow-up were evaluated by mixed effects modelling. For univariate analysis, the covariate of interest and subject visit, and the covariate*visit interaction were modelled as fixed effects, with subject identity as a random effect to account for repeated measures within patients. For significant covariate*interaction terms *post hoc* testing was performed at baseline and follow-up visits. For the multivariate model, any covariate with significant visit-dependent association with LVEF on univariate analysis, and any covariate whose main effect on LVEF independent of visit exhibited a p-value <0.2 was included. Backward elimination was used to identify independent predictors of change in LVEF.

In the second analysis, we determined whether incremental prognostic value was added by the stepwise inclusion of echo markers of ventricular dyssynchrony and LGE-CMR to evaluation of DCM patients by routinely acquired information (age, QRS-duration, NT-pro-BNP concentration), using the likelihood-ratio test.

Finally, the influence of LGE presence on change in echocardiographic dyssynchrony indices from baseline to follow-up was examined by mixed effects modelling.

All statistical tests were two-sided and a p-value <0.05 considered significant. Statistical analysis was performed with STATA 11 (Stata Corp, College Station, Texas).

4.2.9. Inter-observer variability

Inter-observer agreement was assessed in 20 randomly selected cases, in which a second blinded observer measured strain and dyssynchrony parameters. Inter-observer agreement was evaluated by the method of Bland and Altman. The inter-observer variability for the quantification of LGE using a 16-segment model was evaluated by Spearman correlation coefficient.

4.3. RESULTS

Eighty-two patients presenting with new-onset heart failure were screened for enrolment, of whom 14 were ineligible. The study cohort thus consisted of 68 patients, which were compared with 19 healthy volunteers (Figure 4.2). One DCM patient (2%) was intolerant of ACE-I/ARB due to hypotension. Three patients (4%) were intolerant of beta-blockers due to hypotension or bradycardia. All other patients were treated with both ACE-I/ARB and beta-blockers at maximum tolerated doses.

4.3.1. Baseline Characterisation of Idiopathic Dilated Cardiomyopathy Patients

Initial patient evaluation was performed a median of 12.5 days (interquartile range, IQR 7-23 days) following their first presentation with symptoms of heart failure. The baseline characteristics of patients and controls are displayed in Table 4.1. The median duration of patient symptoms prior to presentation was 9 weeks (IQR 2-26 weeks).

There was no difference in baseline age and gender between patients and controls. Compared to this healthy reference population, patients with DCM exhibited the following: poorer functional capacity as measured by six-minute walk distance and $VO_{2\ PEAK}$ ($p<0.001$); a trend towards greater QRS-duration ($p = 0.05$); and higher serum NT-pro-BNP concentration ($p = 0.01$).

On CMR analysis, DCM patients displayed greater LV mass ($p<0.001$). Twelve (24%) DCM patients exhibited late-gadolinium enhancement by CMR, whereas LGE was absent in all controls ($p = 0.03$). The mean fibrosis score among DCM patients was 0.57±1.3, and the mean fibrosis mass was 0.54±1.1g. Among patients with LGE, the mean fibrosis mass was 2.2±1.3g. LGE was typically found as mid-wall striae or as foci at the junction points of the right ventricular free wall and the

interventricular septum. No DCM patient exhibited LGE in a subendocardial or transmural distribution.

Echocardiographic analysis revealed significantly lower LVEF and global longitudinal strain (GLS) among DCM patients compared with controls, and greater LV volumes ($p<0.001$). DCM patients also demonstrated worse diastolic function, and adverse LA structural remodelling and function ($p<0.001$). Assessment of ventricular synchrony displayed significantly greater inter- ($p = 0.03$) and intraventricular ($p<0.001$) dyssynchrony than controls.

4.3.2. Response to Heart Failure Therapy

Patient follow-up was performed a median of 5 months (interquartile range 4-7 months) after first presentation. Changes over follow-up are displayed in Table 4.2. There was significant improvement in left and right ventricular function with favourable LV remodelling ($p<0.001$). There was also significant improvement in LA function ($p\leq0.03$) and reduction in LA volume ($p<0.001$). Six-minute walk distance improved over follow-up ($p<0.001$), however despite these functional and structural changes, indices of ventricular dyssynchrony and $VO_{2\ PEAK}$ failed to improve significantly. Minnesota Living with Heart Failure questionnaire scores were significantly lessened with treatment ($p<0.001$).

4.3.3. Predictors of Response to Medical Therapy

The following parameters were evaluated to determine the ability of their baseline value to predict improvement in LV ejection fraction: age, gender, QRS-duration, 6-minute walk distance, $VO_{2\ PEAK}$, markers of intra-LV (Tissue Doppler dyssynchrony index and strain dyssynchrony index), and interventricular mechanical dyssynchrony, E/E', LA volume, NT-pro-BNP concentration, fibrosis mass by LGE-

CMR. Of these, QRS-duration, NT-pro-BNP concentration, strain dyssynchrony index, and fibrosis mass at baseline were significant univariate predictors of improvement in LVEF (Table 4.3). On multivariate analysis, strain dyssynchrony index, and fibrosis mass were independent predictors of change in LVEF over time ($p \leq 0.001$) (Table 4.3). The influence of LGE presence on LVEF and GLS is displayed in Figure 4.3. Baseline LVEF was similar between those without and with LGE (29 ± 7% in both groups, $p = 0.9$), however at follow-up, those without initial LGE demonstrated improvement in LVEF to 48 ± 13%, whereas LVEF amongst those with initial LGE was 33 ± 8% at follow-up ($p<0.001$). These findings were supported by a similar predictive value of LGE for GLS.

LGE status also influenced changes in LA volume: baseline LA volume was similar between those without and with LGE (103±32mL and 92±25mL respectively, $p=0.3$). At follow-up, those without initial LGE experienced reduction in LA volume to 67±19mL, whereas those with baseline LGE exhibited no change in LA volume (93±31mL, $p=0.03$ compared with the LGE negative group). Baseline absence of LGE was also predictive of improvement of LA function as measured by two-dimensional LA strain. Baseline LA strain was similar between those without and with LGE (13±6% v. 14±7%, $p=0.7$). In those without initial LGE, LA strain increased to 21±6%, whereas in those with baseline LGE, LA strain remained 15±8% ($p=0.02$ compared with the LGE negative group). However, baseline LGE status was not predictive of change in A'.

In the second multivariate analysis, compared to a model containing patient age (as a referent variable), QRS-duration, and serum NT-pro-BNP concentration, the strain dyssynchrony index did not add further value to the model, however the fibrosis mass as determined by LGE-CMR did significantly add incremental prognostic value for follow-up LVEF (Figure 4.4).

4.3.4. Baseline LGE and Ventricular Dyssynchrony

Absence of baseline LGE was predictive of improvement in both intra-LV and interventricular dyssynchrony. At baseline, the TD DI was similar between those without and with baseline LGE (41±14 v. 42±15ms, p=0.9). At follow-up those without baseline LGE exhibited improvement in TD DI to 34±18ms; those with baseline LGE experienced progression in TD DI to 49±21ms (p=0.01). There was no significant difference in IVMD between those without and with baseline LGE (31±23ms v. 33±28ms, p=0.9). At follow-up, those without baseline LGE had stable IVMD (29±31ms), whereas those with baseline LGE displayed worsening of IVMD (57±39ms, p=0.01). LGE presence was not predictive of change in strain dyssynchrony index (p=0.3).

4.3.5. Inter-Observer Agreement

Bland-Altman biases (95% limits of agreement) were 0.5ms (-8 to 9ms) for the TD DI, -6 (-11 to 23ms) for the SDI, 1.6% (-1.8 to 5.0%) for GLS, and -1.5% (-6 to 3%) for LA strain. The Spearman correlation coefficient for the 16-segment quantification of LGE was 0.81 ($p<0.001$).

4.4. DISCUSSION

4.4.1. Major Findings

This prospective, multi-centre study of *newly diagnosed* idiopathic dilated cardiomyopathy (DCM) patients demonstrated for the first time that: (1)Myocardial fibrosis at initial presentation, as detected by LGE-CMR, and intra-LV dyssynchrony by speckle tracking strain analysis were, among a broad range of physiologic covariates, independent predictors of failure in improvement in LVEF at 5 months follow-up. The performance of LGE-CMR added incremental prognostic value in a multivariate model for prediction of follow-up LVEF. (2)The presence of LGE at first presentation was associated with adverse outcomes with respect to global LV strain, LA remodelling and function, and interventricular and intra-LV dyssynchrony. Thus, our findings have important implications for the clinical management of newly diagnosed DCM patients and for understanding the relationship between myocardial fibrosis and ventricular dyssynchrony.

4.4.2. The Prognostic Significance of CMR Late-Gadolionium Enhancement in DCM

In a study of patients with established DCM of at least 12 months duration, Assomull *et al*. showed that LGE was the sole independent predictor of death or cardiovascular hospitalisation(193). Wu *et al*. reported similar findings among a cohort of patients with established non-ischaemic cardiomyopathy referred for implantable cardioverter-defibrillator insertion(194). Neither of these studies included QRS-duration, echocardiographic indices of ventricular dyssynchrony, or NT-pro-BNP concentration, despite their reported prognostic value(250, 259). In contrast, the present study included a variety of novel and established indices in the prognostic model. LGE

status at initial presentation was shown to be an independent predictor of improvement in LV function even accounting for these. Assomull and Wu reported a prevalence of LGE of 30 and 42% respectively. The prevalence of LGE in the current study was slightly less, at 24%. This most likely reflects the exclusive recruitment of consecutive patients with *newly* diagnosed DCM in our study, in whom the prevalence of myocardial fibrosis may be less than when compared to the rates amongst patients with long-standing disease. Park *et al*. previously studied 46 patients with non-ischaemic cardiomyopathy, and found that LGE status predicted improvement in LVEF(260). It was unclear, however, whether this study was performed in consecutive cardiomyopathy patients and most importantly, if CMR was performed at diagnosis and at the commencement of medical therapy. The reported 52% prevalence of LGE substantially exceeds that described in other series of non-ischaemic cardiomyopathy, including our the present one, reflecting that theirs was likely a cohort with long-standing dilated cardiomyopathy.

Cho *et al*. have recently shown that global two-dimensional strain may confer additive prognostic value to routine echocardiographic indices, including LVEF, in systolic heart failure patients(48). In the current study, the absence of myocardial fibrosis by LGE-CMR at presentation was associated with improvement in global LV strain, whereas its presence is associated with failure to improve. In a cohort of patients with ischaemic LV dysfunction (i.e. focal scar), Roes *et al*. have shown that speckle-tracking strain is able to identify regions of heavy myocardial fibrosis by CMR LGE(208). Whether speckle-tracking strain measurement also reflects the burden of diffuse myocardial fibrosis is uncertain.

Atrial dysfunction and subsequent atrial fibrillation is a major clinical event in the course of DCM. This study has demonstrated that there is significant LA structural remodelling and functional improvement following therapy for newly diagnosed DCM. I have also shown that baseline absence of LGE is predictive of

these changes in LA volume and function. These findings corroborate the favourable prognosis portended by the lack of fibrosis by LGE-CMR.

4.4.3. The Prognostic Significance of Ventricular Dyssynchrony

Neither intra-LV nor interventricular dyssynchrony was shown to decrease with medical therapy despite significant improvement in all other major indices of cardiac structure and function. These findings are in contrast with those of Takemoto *et al*. who reported that beta-blocker therapy improves intra-LV synchrony in a small cohort of patients with DCM(261). However, this study cohort did not comprise consecutive patients with DCM and follow-up dyssynchrony data was only obtained in 15 of 25 DCM patients. Furthermore, since assessment of ventricular dyssynchrony was not combined with direct assessment of myocardial fibrosis the authors were unable to relate these two parameters in response to medical therapy. In contrast, the current study indicates that the presence of myocardial fibrosis as detected by LGE-CMR at presentation in patients with newly diagnosed DCM is associated with subsequent deterioration in indices of ventricular synchrony.

This study found that among echocardiographic indices of ventricular dyssynchrony, only strain measures were independently predictive of change in LVEF. Despite its reported ability to identify responders to cardiac resynchronisation therapy, tissue Doppler dyssynchrony was not predictive of response to medical therapy in our cohort. Tethering of poorly contractile segments to adjacent viable segments may influence tissue velocities. This may account for the observed superior prognostic value of strain imaging. Tigen *et al*. have recently reported an association between fibrosis extent in DCM patients and intra-LV dyssynchrony(262). The present study extends on these findings to demonstrate that the presence and

quantity of myocardial fibrosis by LGE-CMR influences the magnitude of improvement in both LV function and ventricular synchrony.

4.4.4. Clinical Implications

The findings from the current study may have important implications for the clinical management of newly diagnosed DCM patients. Although implantable-defibrillator use has been shown to reduce cardiac mortality in patients with LVEF ≤35%, uncertainty exists over the optimal timing of insertion following diagnosis with DCM(263). A substantial proportion of newly diagnosed DCM patients will experience improvement in LVEF to >35% following medical therapy. Thus, routine device implantation at the time of diagnosis, purely based on LVEF at presentation, is likely to result in insertion in many who would no longer qualify after 5 months' medical therapy. The present study strongly suggests a role for LGE-CMR as a risk-stratifying investigation in cases of newly diagnosed DCM, given its additive prognostic value. Furthermore, the identification of individuals at high risk of non-response to heart failure treatment may permit more aggressive observation and more targeted medical and device therapy.

4.4.5. Study Limitations

Patients were recruited and studied within two weeks of initial diagnosis with DCM. The duration of LV dysfunction prior to enrolment could not be precisely determine, and hence it is likely that patients were presenting at different time points in disease course. It is therefore uncertain whether the reported findings are influenced by the chronicity of cardiomyopathy. This study remains highly clinically relevant however, as it reflects real-life practice, in which identifcation of patients with subclinical DCM

is not feasible, and those presenting with DCM do so at varying stages of disease duration owing to inter-individual variation in symptom threshold and tolerance.

CMR could not be performed in all patients at recruitment. This limits the generalisability of the study's findings. The LGE technique is limited in its ability to detect diffuse myocardial fibrosis because it relies on the contrast between more fibrotic tissue and relatively normal myocardium. T1 mapping is a CMR technique that has shown promise in the quantification of diffuse myocardial fibrosis, and may be of value in this setting(202), although the necessary CMR sequence was not available for the present study. Myocardial biopsy was not undertaken as routine in the present cohort of patients. The practice of exclusion of myocarditis by clinical, laboratory and CMR findings is standard of care in the participating institutions. The presence of inflammatory myocardial infiltrate suggestive of myocarditis could not be excluded.

This study was limited in its ability to delineate the causal relationship between myocardial fibrosis and dyssynchrony: both were independently predictive of change in LV function. Further research on the influence of cardiac resynchronisation in this cohort is likely to be informative, in those patients with baseline myocardial fibrosis.

4.4.6. Conclusion

Using novel and complementary imaging techniques, the presence of myocardial fibrosis has been shown to be independent predictors of a negative response to medical therapy in new-presentation DCM. Identification of individuals at high risk of non-response to initial heart failure treatment may permit more targeted treatment.

This thesis' theme of integrating LV and LA functional evaluation is continued in the following chapter, in which the LA effects of the LV abnormalities described in the present chapter are explored further.

Table 4.1

Subject characteristics

Characteristic (±SD)	Patients	Controls	p-value
Age (years)	59±14	54±7	0.2
Gender, male (%)	44 (65)	9 (47)	0.2
Diabetes mellitus, n (%)	14 (21)	0 (0)	0.03
Hypertension, n (%)	23 (34)	0 (0)	0.001
QRS-duration (ms)	115±30	91±23	0.05
Six-minute walk distance (m)	420±96	589±90	<0.001
$VO_{2\ PEAK}$ (mL/kg/min)	20±6	30±10	<0.001
NT-pro-BNP (ng/L)	2776±4408	50±41	0.01
Cardiovascular magnetic resonance			
LVEF (%)	26±9	68±6	<0.001
LVEDVI (mL/m^2)	126±28	76±18	<0.001
LVESVI (mL/m^2)	94±27	24±8	<0.001
LV mass index (g/m^2)	81±20	49±11	<0.001
Late-gadolinium positive, n (%)	12 (24)	0 (0)	0.03
Echocardiogram			
LVESVI (mL/m^2)	60±22	16±4	<0.001
LVEDVI (mL/m^2)	83±24	49±10	<0.001
LVEF (%)	29±8	67±6	<0.001
Global longitudinal strain score (%)	12±2	21±2	<0.001
Diastolic grade	2.3±1.2	0.3±0.5	<0.001
E/A	1.5±1.1	1.4±0.5	0.8
E/E’	25±15	10±3	<0.001

LAVI (mL/m^2)	48±14	31±8	<0.001
TAPSE (cm)	1.8±0.5	2.4±0.4	<0.001
Strain dyssynchrony index (ms)	79±33	38±14	<0.001
Tissue Doppler dyssynchrony index (ms)	41±14	25±14	<0.001
IVMD (ms)	31±24	17±12	0.03

Table 4.2

Comparison of Baseline and Follow-up Parameters in DCM Patients

Characteristic (±SD)	Baseline	Follow-up	p-value
Minnesota Living with Heart Failure Score	44±24	29±20	<0.001
QRS-duration (ms)	114±29	115±32	0.4
Six-minute walk distance (m)	420±96	472±95	<0.001
$VO_{2\ PEAK}$ (mL/kg/min)	20±6	22±6	0.09
N-terminal pro-brain natiuretic peptide (ng/L)	2776±4408	1359±2180	0.02
Echocardiogram			
LV end-systolic volume (mL)	119±38	90±43	<0.001
LV end-diastolic volume (mL)	165±42	152±45	0.01
LV ejection fraction (%)	29±8	43±13	<0.001
Global longitudinal strain score (%)	12±2	16±4	<0.001
Diastolic grade	2.3±1.2	1.3±0.9	<0.001
E/A	1.5±1.1	1.0±0.7	0.02
E/E’	25±15	20±17	0.1
LA volume index (mL/m^2)	48±14	35±11	<0.001
TAPSE (cm)	1.8±0.5	2.1±0.4	0.004
Strain dyssynchrony index (ms)	79±33	79±28	0.5
Tissue Doppler dyssynchrony index (ms)	41±14	38±19	0.07
IVMD (ms)	31±24	39±34	0.3

Table 4.3

Univariate and Multivariate Predictors of Change in LVEF Following Therapy

Variable	Univariate model		Multivariate model	
	Coefficient (95% CI)	p-value	Coefficient (95% CI)	p-value
Age	-0.06 (-0.3 to 0.2)	0.8		
Gender	-4 (-10 to 3)	0.8		
6-minute walk distance (m)	0.03 (-0.01 to 0.08)	0.3		
$VO_{2\ PEAK}$ (mL/kg/min)	0.3 (-0.7 to 1.3)	0.6		
Tissue Doppler dyssynchrony index (ms)	-0.07 (-0.3 to 0.2)	0.7		
E/E’	0.04 (-0.2 to 0.3)	0.8		
LA volume (mL)	-0.02 (-0.1 to 0.1)	0.8		
TAPSE (cm)	-1 (-10 to 7)	0.7		
IVMD (ms)	-0.1 (-0.3 to 0.05)	0.3	0.3 (-0.06 to 0.6)	0.1
NT-pro BNP (µg/L)	-1 (-2 to -0.09)	0.007	-0.2 (-2 to 1)	0.8

QRS-duration (ms)	-0.14 (-0.3 to -0.02)	0.004	-0.3 (-0.7 to 0.1)	0.2
Strain dyssynchrony index (ms)	-0.1 (-0.2 to -0.06)	0.04	-0.1 (-0.2 to -0.04)	<0.001
Fibrosis mass (g)	-7 (-11 to -3)	<0.001	-7 (-11 to -4)	<0.001

Figure 4.1

Panels A and B: horizontal long-axis and short-axis T1-weighted late-gadolinium cardiac magnetic resonance images respectively, both acquired from an individual 7 days after presentation with new onset idiopathic dilated cardiomyopathy. These demonstrate mid-wall septal enhancement (solid arrows). Panel C: baseline Tissue Velocity Imaging of the same individual in the apical 4-chamber view: peak systolic ejection tissue velocity occurs simultaneously in the basal septal and basal lateral segments (dashed line). Panel D: follow-up Tissue Velocity Imaging of the same individual in the apical 4-chamber view: difference in time-to-peak systolic tissue velocity in the basal septal and basal lateral segments is shown to have increased from baseline (dashed arrows). Panel E: baseline speckle tracking strain imaging of the same individual in the apical 4-chamber view (dotted line represents the mean 4-chamber longitudinal strain). Panel F: follow-up speckle tracking strain imaging of the same individual in the apical 4-chamber view demonstrating no improvement in longitudinal strain.

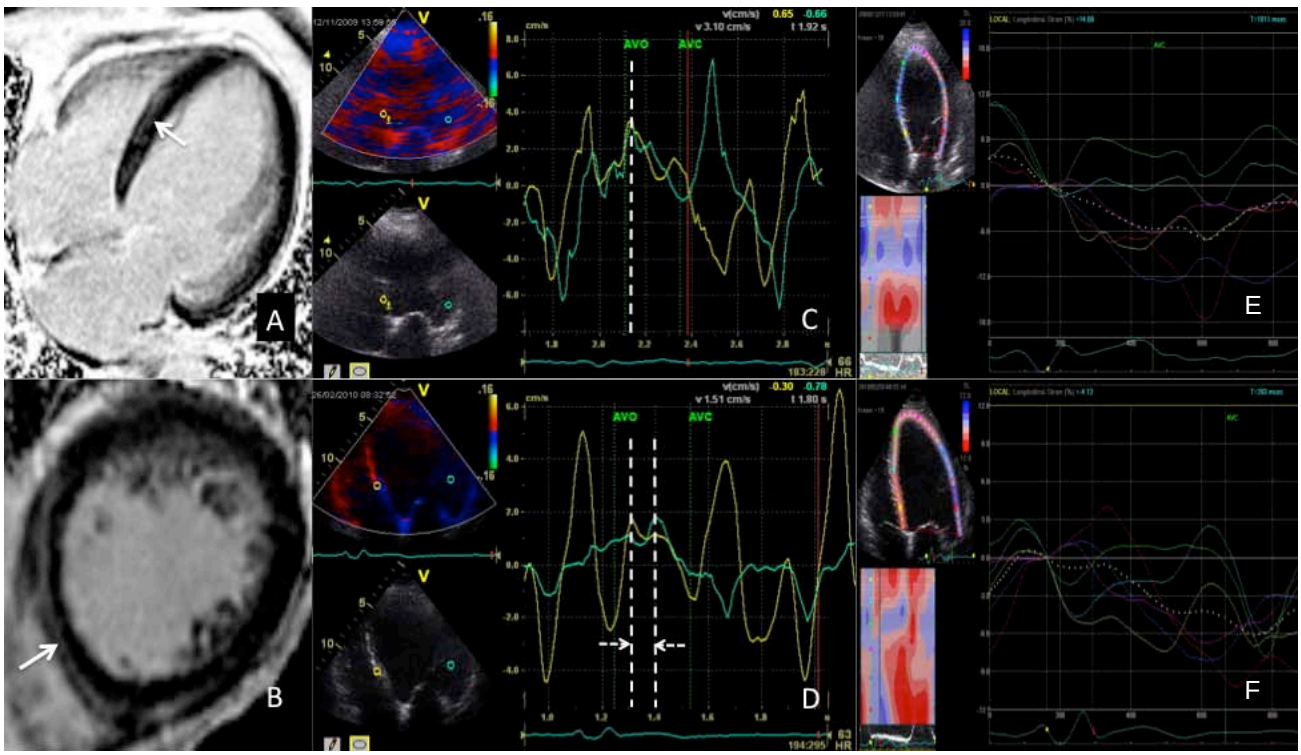


Figure 4.2

Flow diagram illustrating the numbers of participants undergoing CMR during the study. All consenting subjects underwent echocardiography at baseline and follow-up irrespective of their eligibility for CMR.

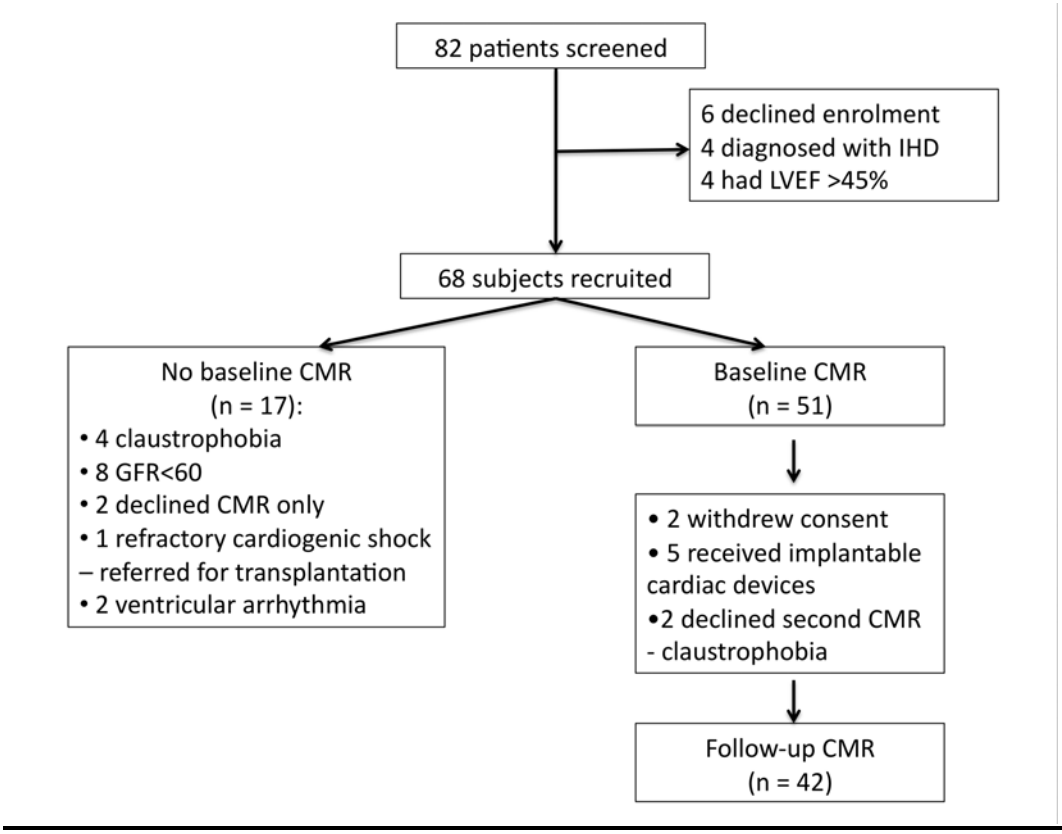


Figure 4.3

Graphs illustrating the influence of baseline LGE status on (A) LVEF, (B) global longitudinal left ventricular strain score.

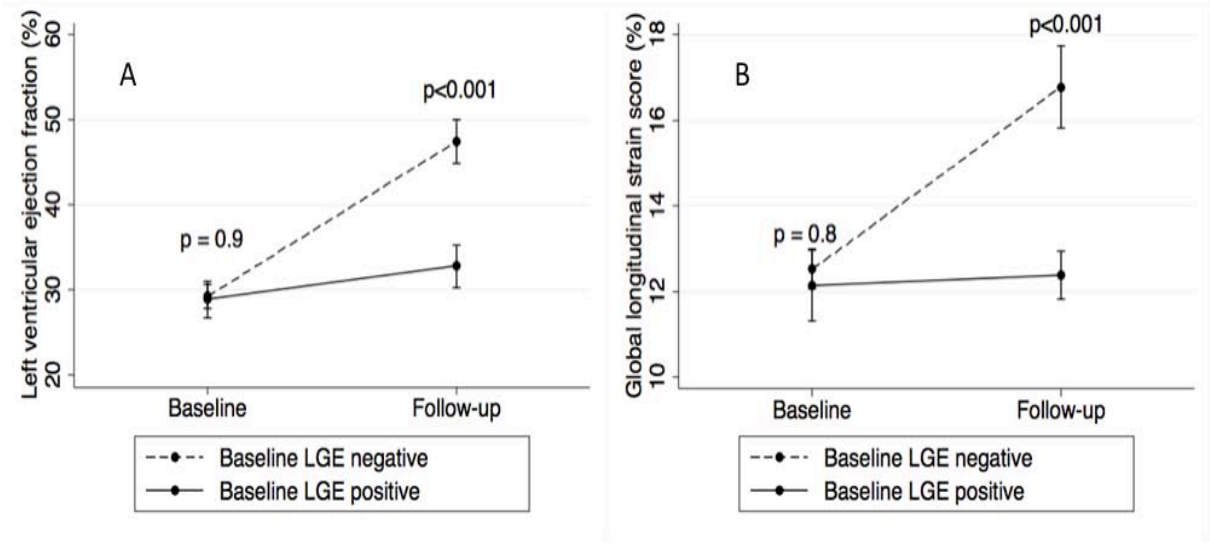
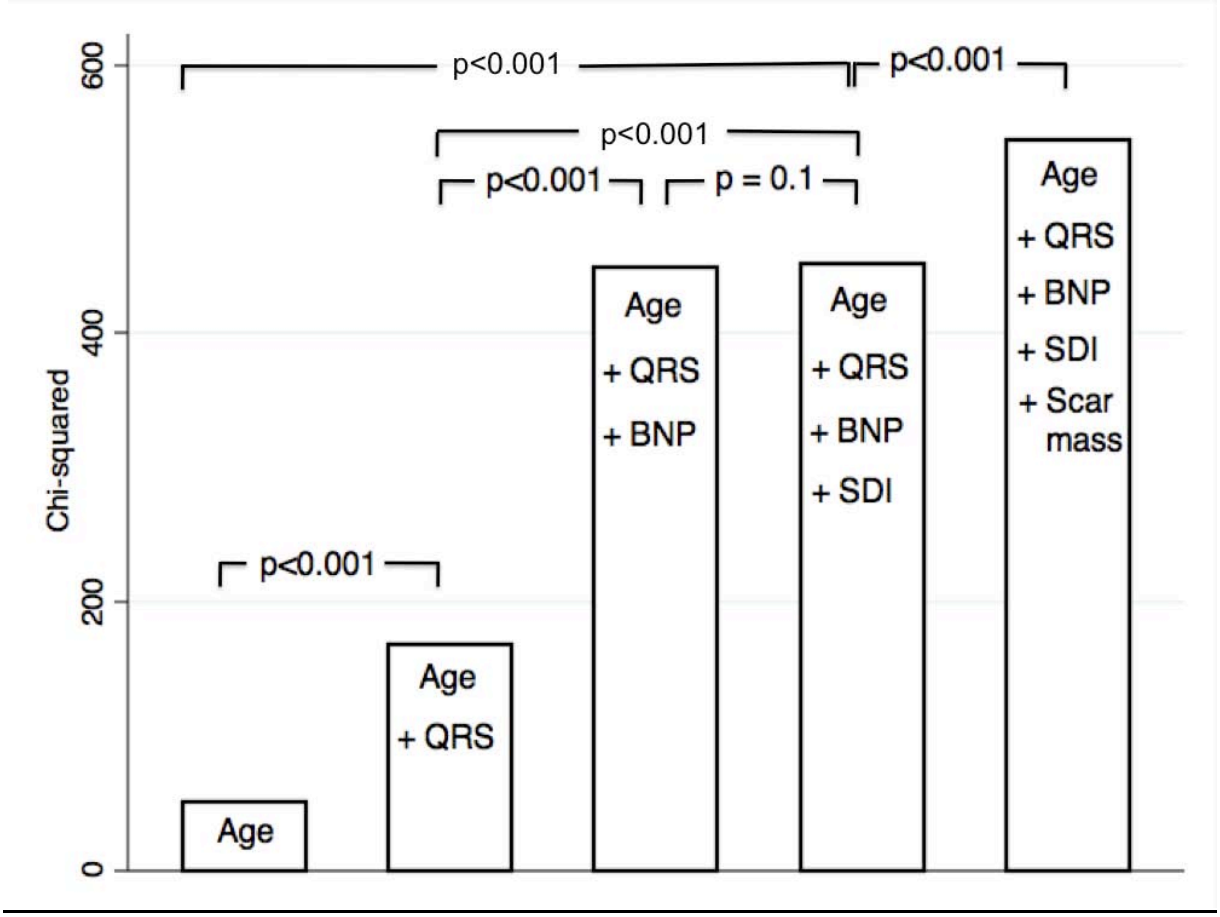


Figure 4.4

Multivariate analysis illustrating the incremental value of LGE-CMR to the prediction of improvement in LVEF.



Chapter 5 – Left Atrial Remodelling and Reverse-Remodelling With Therapy in New-Presentation Idiopathic Dilated Cardiomyopathy

5.1. INTRODUCTION

There is a strong association between heart failure and both adverse LA remodelling and impairment in LA function. Amongst patients with heart failure, LA size has been shown to be a powerful predictor of outcome(100). In a population study, congestive heart failure was among the most potent risk factors for the development of atrial fibrillation(264). Atrial dilatation and stretch may be important mediators of atrial fibrillation in this setting(236, 265).

Successful treatment of heart failure (with cardiac resynchronisation therapy) has been associated with significant improvement in LA booster pump function(118). To date, existing research has focussed on established heart failure, and there is a paucity of data on the extent of adverse LA remodelling or functional impairment early in the course of heart failure, as well as on their response to medical therapy.

Amongst techniques available to evaluate LA function, the measurement of LA strain by speckle-tracking echocardiography is a new approach that has shown particular promise in the assessment of both regional and global LA contractility. The measurement of LA strain by speckle-tracking echocardiography has been demonstrated to be feasible in individuals without cardiac disease and with heart failure, and to correlate with other indices of LA function(266-269). In comparison with tissue Doppler-derived strain measurements, speckle-tracking echocardiography

is attractive for the evaluation of tissue deformation because of its independence of angle of ultrasound insonation(44).

In this context, the primary aim of this study was to explore the relationship between LA structure and function, and therapeutic response following administration of optimal heart failure therapy. This research is an extension of the work presented in the previous chapter and permits a more comprehensive evaluation of the cardiac abnormalities present in patients early in the course of DCM, and their response to medical therapy.

5.2. METHODS

The design and participants for the present study are the same as for the study presented in Chapter 4. This study represents a pre-specified analysis of change in LA structure and function, and its determinants among patients with a first presentation idiopathic dilated cardiomyopathy.

5.2.1. Subject Characteristics

Consecutive patients were recruited from the Royal Adelaide Hospital, Flinders Medical Centre, and Modbury Public Hospital from April 2008 to December 2009. All patients had a new diagnosis of DCM made within the preceding two weeks. The inclusion criterion was the presence of LV ejection fraction ≤45% at baseline echocardiography or CMR. Exclusion criteria included the diagnosis of significant coronary artery disease (defined as the presence of >70% luminal stenosis in an epicardial coronary artery at angiography, non-invasive stress imaging suggestive of ischaemia, or prior myocardial infarction), severe valvular heart disease, thyroid dysfunction, infiltrative cardiomyopathy or extra-cardiac systemic features to suggest sarcoidosis or amyloidosis, chemotherapy-induced cardiomyopathy, and myocarditis. Myocarditis was excluded in potential DCM cases by the absence of classic clinical features, the presence of normal serum troponin I concentration at presentation, and by the lack of evidence of myocardial oedema on T2-weighted CMR(254). Exclusion from the CMR arm of the study was mandated by patient claustrophobia, renal impairment (eGFR <60mL/min), or the presence of prostheses, including cardiac devices, which were CMR incompatible. Control subjects were a sample of health volunteers with no history of cardiac disease, hypertension, or diabetes mellitus. All subjects provided written, informed consent to the study protocol, which complies

with the Declaration of Helsinki and was approved by the Human Research Ethics Committee at each participating institution.

5.2.2. Treatment of Heart Failure

Heart failure therapies were administered in accordance with current guidelines(127), using angiotensin converting enzyme inhibitors or angiotensin receptor blockers (ACE-I/ARB), beta-blockers and when clinically indicated, aldosterone antagonists. These therapies were initiated and titrated to maximum tolerated doses by the treating physician.

5.2.3. Study Protocol

Patients were recruited and studied within two weeks of presentation with new-onset DCM when clinically stable. Patients in whom the diagnosis of DCM was made as an outpatient were studied as soon as possible following diagnosis, but within two weeks following presentation. Any patient ineligible for CMR but consenting to the remainder of the protocol underwent these other study investigations. The study protocol consisted of the following baseline investigations: blood sampling, LGE-CMR, echocardiography, 6-minute-walk testing, Minnesota Living with Heart Failure Questionnaire, and cardiopulmonary exercise testing. To minimise variability due to loading conditions, imaging (CMR and echocardiography) was performed in immediate succession for each individual. Patients underwent repeat echocardiography, 6-minute-walk testing, Minnesota Living with Heart Failure Questionnaire, and cardiopulmonary exercise testing a median 5 months (interquartile range 4-7 months) later.

5.2.4. Cardiac Magnetic Resonance Protocol

Refer to Chapter 2.4 and 2.5.

5.2.5. Echocardiography Protocol

Refer to Chapter 2.2. and 2.3.

5.2.6. Statistical Analysis

Continuous variables are presented as mean±SD where normally distributed. Categorical data are summarised as frequencies and percentages. Overall change in LA volume index and speckle-tracking strain was evaluated using repeated measures analysis of variance. Mixed effects modelling was employed to evaluate determinants of change in both LA volume index and LA strain following medical therapy, and also to examine whether LA strain at baseline was associated with subsequent degree of improvement in LVEF. The covariate of interest and subject visit, and the covariate*visit interaction were modelled as fixed effects, with subject identity as a random effect to account for repeated measures within patients. For significant covariate*interaction terms *post hoc* testing was performed at baseline and follow-up visits. All statistical tests were two-sided and a p-value <0.05 considered significant. Statistical analysis was performed with STATA 11 (Stata Corp, College Station, Texas).

5.3. RESULTS

Eighty-two patients presenting with new-onset heart failure were screened for enrolment, of whom 14 were ineligible. The study cohort thus consisted of 68 patients, which were compared with 19 healthy volunteers (Figure 4.2).

5.3.1. Baseline Characterisation of LA Structure and Function in Idiopathic Dilated Cardiomyopathy Patients

Initial patient evaluation was performed a median of 12.5 days (interquartile range, IQR 7-23 days) following their first presentation with symptoms of heart failure. The baseline characteristics of patients and controls are displayed in Table 4.1. The median duration of patient symptoms prior to presentation was 9 weeks (IQR 2-26 weeks). Despite this relatively brief history of heart failure symptoms, there was significant LA dilatation observed amongst DCM patients compared with controls (LAVI 48±14 vs. 35±11mL/m^2, p<0.001). There was also significant reduction in LA speckle-tracking strain in DCM patients at presentation compared with controls (13±6 vs. 26±7%, p<0.001).

5.3.2. LA Remodelling and Functional Changes Following Heart Failure Therapy

Patient follow-up was performed a median of 5 months (interquartile range 4-7 months) after first presentation. Changes over follow-up are displayed in Table 4.2. There was significant improvement LA remodelling; the LAVI decreased from 48±14 to 35±11mL/m^2 (p≤0.001). This was accompanied by significant increase in LA speckle-tracking strain from 13±6 to 19±7% (p<0.001).

5.3.3. Predictors of LA Reverse Remodelling

The following co-variates were evaluated as potential univariate predictors of reverse LA remodelling: age, gender, QRS duration, six-minute walk distance, $VO_{2\ PEAK}$, delta LVEF (defined as LVEF at follow-up – LVEF at baseline), E/E', interventricular mechanical delay, tissue Doppler dyssynchrony index, strain dyssynchrony index, and fibrosis mass (Table 5.1). Although none were significant, fibrosis mass exhibited a trend towards predictive value (p=0.1).

5.3.4. Predictors of Change in LA Strain

The following co-variates were evaluated as potential univariate predictors of change in LA strain following medical therapy: age, gender, QRS duration, six-minute walk distance, $VO_{2\ PEAK}$, delta LVEF, E/E', interventricular mechanical delay, tissue Doppler dyssynchrony index, strain dyssynchrony index, and fibrosis mass (Table 5.1). Although none were significant, fibrosis mass exhibited a trend towards predictive value (p=0.08).

5.3.5. LA Strain and LVEF Response to Medical Therapy

Baseline LA strain was not associated with degree of change in LVEF following medical therapy.

5.4. DISCUSSION

5.4.1. Major Findings

This study has demonstrated that: 1) early in the course of idiopathic dilated cardiomyopathy, there is marked adverse LA remodelling as manifest by increased LA volume index, and impairment in LA function as measured by speckle-tracking LA strain, and 2) these deleterious changes exhibit considerable capacity for reversal following appropriate medical therapy.

The findings of the present study are consistent with those of Yu *et al*, who reported that cardiac resynchronisation therapy for the treatment of heart failure may result in reverse LA remodelling and improvement in LA mechanical function, particularly in those with significant reverse LV remodelling(118). The current study extends on these findings, however, to explore the determinants of such changes in LA structure and function.

5.4.2. Clinical Implications

In a large observational study of patients with heart failure, Rossi *et al*. demonstrated that LA size confers independent and additive prognostic value to clinical parameters and indices of left ventricular systolic and diastolic function(100). The reversal in LA dilatation observed in the present study strongly suggests that early intervention in idiopathic dilated cardiomyopathy may attenuate the pathophysiological processes observed in long-standing heart failure. Given the well-recognised relationship between LA dilatation and atrial fibrillation, prompt heart failure therapy may thus prevent the development of atrial fibrillation.

The finding of a trend towards predictive value of left ventricular myocardial fibrosis for reverse LA remodelling and improvement in LA strain prompts speculation

that stiffening of the left ventricle with more advanced fibrosis exposes the left atrium to elevated diastolic pressures, which may compromise LA function and promote LA dilatation.

5.4.3. Study Limitations

The duration of follow-up in this study does not provide information on the long-term course of LA remodelling and function in DCM. The sample size of the present study may have limited the power to detect significant predictors of reverse LA remodelling or improvement in LA strain.

5.4.4. Conclusions

In Chapters 3-5, the relationship between LV structure, function and contractile dyssynchrony, and adverse LA remodelling and function have been explored. Chapter 6 extends upon this research to examine whether different sites of right ventricular pacing are associated with induction of different degrees of LV dyssynchrony, and whether such effects are correlated with distinct patterns of LV and LA adverse remodelling and dysfunction.

Table 5.1

Univariate Predictors of Change in LA Volume Index and LA Strain Following Therapy

Variable	LA Volume Index		LA Strain	
	Coefficient (95% CI)	**p-value**	**Coefficient (95% CI)**	**p-value**
Age (years)	0.04 (-0.2 to 0.3)	0.7	-0.01 (-0.1 to 0.1)	0.8
Female gender	-1.4 (-8.3 to 5.4)	0.7	1.4 (-1.9 to 4.8)	0.4
QRS duration (ms)	0.1 (0.01 to 0.3)	0.2	0.03 (-0.02 to 0.08)	0.3
6-minute walk distance (m)	-0.02 (-0.06 to 0.02)	0.3	0.01 (-0.01 to 0.03)	0.2
$VO_{2\ PEAK}$ (mL/kg/min)	-0.1 (-1 to 0.8)	0.9	-0.2 (-0.6 to 0.3)	0.5
Delta LVEF (%)	-0.1 (-0.4 to 0.1)	0.3		
E/E’	-0.1 (-0.3 to 0.1)	0.3	0.0 (-0.1 to 0.1)	0.9
IVMD (ms)	-0.02 (-0.2 to 0.1)	0.8	0.04 (-0.03 to 0.1)	0.3
Tissue Doppler dyssynchrony index (ms)	0.1 (-0.1 to 0.3)	0.4	0.05 (-0.07 to 0.1)	0.5

Strain dyssynchrony index (ms)	-0.04 (-0.1 to 0.05)	0.4	0.0 (-0.04 to 0.05)	0.9
Fibrosis mass (g)	6 (0.7 to 12)	0.1	-3 (-6 to -0.4)	0.08

Chapter 6 – Long-Term Mechanical Consequences of Permanent Right Ventricular Pacing: Effect of Pacing Site

6.1. BACKGROUND

Right ventricular pacing has been implicated in the development of dyssynchronous left ventricular (LV) contraction, and in the long term, impairment in systolic LV function(157-160). The right ventricular apex (RVA) has been the traditional site of implantation of the ventricular lead for permanent cardiac pacing, however the advent of active fixation leads and steerable stylets/delivery systems has allowed permanent pacing at alternate sites, such as the right ventricular outflow tract (RVOT). Head-to-head comparisons between RVA and RVOT pacing have been limited to short-term studies employing acute hemodynamic surrogate endpoints. These suggest a small but statistically significant advantage with RVOT pacing(270). There is a paucity of long-term comparative data and the effects of RVOT pacing on intra-LV synchrony remain unclear. Moreover the long-term consequences of right ventricular (RV) pacing site on LA structure and function are unknown.

Novel software now allows the assessment of cardiac systolic function and synchrony by measurement of regional tissue velocity and strain. These techniques have demonstrated prognostic value in the prediction of response to cardiac resynchronisation therapy(143, 147), and have been used to illustrate that intra-LV dyssynchrony is acutely induced by RVA pacing(160).

Using a cohort of patients who were prospectively randomised to long-term pacing either from the RVA or RVOT, the aim of the present study was to determine the mechanical consequences of ventricular pacing site on cardiac function. In particular, this study aimed to determine whether long-term RVOT pacing is

associated with superior LV systolic function and less intra-LV dyssynchrony than RVA pacing. In addition, the role of RV pacing site and intra-LV synchrony on LA structure and mechanical function was examined. This study adds to the work presented to this point within this thesis, in which it has been shown that recovery of LV function in DCM patients is associated with degree of LV dyssynchrony at presentation, by addressing the relationship between LV dyssynchrony and LV function from a different perspective. It seeks to determine whether different degrees of induced LV dyssynchrony may be observed between RVA and RVOT septal paced patients, and whether these induced physiological differences are subsequently associated with differences in LV and LA structure and function.

6.2. METHODS

6.2.1. Patient Characteristics

Patients were recruited from a cohort of patients who had previously participated in a prospective, randomised, controlled study of RVOT septal versus RVA pacing (PASSES study; Australian New Zealand Clinical Trials Registry Number 12608000593336). The PASSES study enrolled patients who had a conventional indication for pacing. Exclusion criteria included previous pacemaker implantation and indication for cardiac resynchronisation therapy.

For the current study, all consecutive consenting patients from two participating centres underwent one-off evaluation. A total of 92 subjects were screened for recruitment into this echocardiographic substudy. Patients were excluded for the following reasons: 6 were deceased, 2 had had the device explanted due to infection, 2 had previously withdrawn consent to participate in the PASSES study, 1 was lost to follow-up, 17 were in atrial arrhythmia and therefore could not reproducibly be assessed by echocardiography and 6 declined to be involved. Thus 58 patients paced for a mean 29±10 months (range 11-53 months) were studied: 32 RVOT-paced and 26 RVA-paced.

Ventricular lead position was confirmed at the RVOT septum at the time of implant using left anterior oblique, right anterior oblique and antero-posterior fluoroscopic images. An independent observer blinded to subject outcome subsequently verified lead position: both posterior lead tip orientation on fluoroscopy in the left anterior oblique 40^0 projection, and a predominantly negative QRS complex in lead I of a surface 12-lead ECG were required for confirmation of RVOT septal lead location(271). Baseline characteristics of these groups are presented in Table 6.1.

All patients provided written informed consent to the study protocol, which was approved by the clinical research and ethics committee of each participating institution.

6.2.2. Echocardiogram Protocol

Subjects underwent clinically indicated echocardiography at baseline for the evaluation of left ventricular systolic function. For the present echocardiographic substudy a detailed standardised transthoracic echocardiogram protocol (outlined below) was performed during A-V synchronous pacing on a single occasion. Imaging and offline analysis were performed as described in Chapter 2. In addition, LA function was further assessed by septal A', which was measured as the peak tissue velocity at the septal mitral annulus in late-diastole.

6.2.3. Statistical Analysis

Continuous variables are presented as mean±SD. Categorical data are summarised as frequencies and percentages. RVOT pacing and RVA pacing were compared the Student's t-test and chi-square test for continuous and categorical variables, respectively. The nature of the association between continuous variables was examined using linear regression. Mixed effects models were constructed for axial LV myocardial sections (base, mid and apex) for their time to-peak contractions. Group (RVOT-paced and RVA-paced) and section main effects, and the section*group interaction were modelled as fixed terms, with subject identity as a random effect to account for the multiple myocardial segments within patients. Inter-observer agreement was assessed in 10 randomly selected cases, in which a second blinded observer measured strain and dyssynchrony parameters. Inter-observer agreement was evaluated by Lin's concordance correlation coefficient.

Statistical analysis was performed with STATA 10 (Stata Corp, College Station, Texas) and SPSS Version 16 (SPSS Inc, Chicago, Illinois). All statistical tests were 2-sided and a p-value <0.05 considered significant.

6.3. RESULTS

6.3.1. Patient Characteristics

The baseline characteristics of the patients in each group are presented in Table 6.1. RVOT- and RVA-paced patients were well matched except for QRS duration during pacing, which was greater in RVA-paced subjects (156±21ms vs. 139±20ms, p=0.008).

Patients were followed-up for 29±10 months (range 11-53 months) following device implantation. At 6-month follow-up 30 patients were paced 100% and 37 were paced >50% of the time in the ventricle.

6.3.2. Left Ventricular Analysis

Figure 6.1 and Table 6.2 demonstrate the differences in indices of LV systolic function and remodelling.

6.3.2.1. Left Ventricular Volumes and Ejection Fraction

There was a significant difference in LVEF (60±7% vs. 52±9%, p<0.001) and LV end-systolic volume (30±12mL vs. 45±26mL, p=0.007) between RVOT- to RVA-paced patients. There was however no significant difference in LV end-diastolic volume between RVOT- and RVA-paced subjects 74±24mL vs. 88±39mL, p=0.1).

6.3.2.2. Left Ventricular Strain and Tissue Velocity

A total of 1044 LV myocardial segments were evaluated for longitudinal 2D strain characteristics. Ninety-two (8.8%) of these were excluded due to poor tissue tracking. Peak systolic tissue velocity was measurable in all segments. There was a non-significant trend towards greater longitudinal strain (17.4± 2.9% vs. 15.8±3.7%,

p=0.07) and greater peak systolic tissue velocity (5.0±1.3cm/s vs. 4.5±1.3cm/s, p=0.08) among RVOT-paced patients compared with RVA-paced patients.

Dyskinesis was considered present in a given myocardial segment if it displayed positive strain on longitudinal 2D strain analysis for greater than 50% of the systolic phase of the cardiac cycle prior to aortic valve closure. There was a total of 7 dyskinetic segments in 6 of the RVOT-paced subjects and 9 dyskinetic segments in 9 of the RVA-paced subjects (p=0.2).

The left ventricle was divided into three axial sections - basal, mid, and apical - to evaluate its spatiotemporal pattern of mechanical activation. The time-to-peak contraction for each section was calculated as the average of time-to-peak systolic longitudinal strain values for its constituent segments. In RVA-paced patients, mechanical activation commenced at the LV apex and propagated towards the base of the heart. In RVOT-paced patients, mechanical activation also commenced at the LV apex and propagated towards the base of the heart, however the time required for activation of the left ventricle was significantly less than in RVA-paced patients (Figure 6.2) (p=0.01).

6.3.2.3. Cardiac Synchrony Analysis

Table 6.2 summarises the differences in indices of cardiac synchrony between the groups. There was a significant difference in SDI between RVOT- and RVA-paced subjects (65±18ms vs. 76±21ms, p=0.02). Interventricular mechanical delay was also significantly less in the RVOT group compared with the RVA group (13±32ms vs. 35±23ms, p=0.007). There was a non-significant trend towards a smaller TD DI among RVOT-paced patients than among RVA-paced patients (40±19ms vs. 48±20ms, p=0.09).

6.3.3. Left Atrial Analysis

Table 6.2 summarises the differences in indices of LA structure and function between the groups. LA volume was significantly lower amongst RVOT- than RVA-paced subjects (66±27mL vs. 86±34mL, p=0.02) (Figure 5.3). There was a significant linear association between septal A' velocity as an index of LA function and the TD DI as a marker of LV dyssynchrony, such that the greater the dyssynchrony, the poorer the LA function (p=0.02) (Figure 6.4). The relationship between septal A' velocity and SDI did not reach statistical significance.

6.3.4. Influence of Duration and Percentage of Time Paced

There was no significant relationship between the follow-up time and either LV ejection fraction or SD DI. There was however a modest positive linear association between the follow-up time and the TD DI (r=0.26, p=0.04). Longer duration of pacing was more closely related to LA remodelling. There was a significant positive linear association between follow-up time and LA volume (r=0.41, p=0.003). There was no significant relationship between septal A' and follow-up duration.

Although there was no significant relationship between LV ejection fraction and percentage V-paced, there was a modest positive linear association between the percentage V-paced and LV end-systolic volume (r=0.28, p=0.04) and a similar trend between the percentage V-paced and LV end-diastolic volume (r=0.25, p=0.07). The percentage V-paced was not significantly related to indices of LA structure or function.

Thirty subjects (17 RVOT-paced and 13 RVA-paced) were V-paced >75% of the time. When analysis was limited to this subgroup, the significant difference in LVEF (58±7% vs. 48±9%, p=0.002) and LV end-systolic volume (33±16mL vs. 60±29mL, p=0.004) between RVOT- and RVA-groups persisted, however the

difference in LA volume between the groups no longer reached statistical significance (72±31mL vs. 92±40mL, p=0.1). Indices of inter-ventricular and intra-left ventricular synchrony also failed to differ significantly between the RVOT- and RVA-groups when the analysis was limited to those V-paced >75% of the time.

6.3.5. Inter-Observer Agreement

The following values for Lin's concordance correlation coefficient (±95% CI) were obtained, suggesting good reproducibility of strain and dyssynchrony parameters: LV longitudinal strain score 0.97 (0.92 – 1.0), strain dyssynchrony index 0.89 (0.76 – 1.0), tissue Doppler dyssynchrony index 0.98 (0.94 – 1.0).

6.4. DISCUSSION

6.4.1. Major Findings

In this clinical study evaluating atrial and ventricular mechanical function in patients randomly allocated to ventricular pacing from the RVA or RVOT septum the following were observed:

(i) This study objectively demonstrates a superiority of RVOT septal-pacing over RVA-pacing in LV ejection fraction and remodelling in the long-term follow-up of chronically paced patients.

(ii) RVOT septal-pacing is associated with less interventricular and intra-LV dyssynchrony than RVA-pacing.

(iii) Long-term RVA-pacing is associated with greater adverse LA remodelling than RVOT septal-pacing.

(iv) Septal A' were adversely affected by intra-LV dyssynchrony.

6.4.2. Implications of Right Ventricular Pacing Site for Left Ventricular Function

Chronic RVA pacing has been associated with deleterious effects. Thambo *et al.* studied patients with complete congenital atrioventricular block paced long-term from the RV apex(157). They found that RVA pacing was associated with intra-LV dyssynchrony, adverse LV remodelling, and reduced functional capacity. In long-term follow-up of young patients permanently paced from the RV apex, a detrimental effect on LV systolic function was also noted by Tantengco *et al*(158). RVA pacing has been strongly associated with decline in LV ejection fraction in epidemiological data(159). Delgado *et al.* and Tops *et al.* have recently demonstrated the adverse effects of RVA pacing on indices of LV synchrony(160, 161). Among 58 patients paced from the RV apex over a 3.8-year period, intra-LV dyssynchrony as measured

by septal-posterior wall motion delay was shown to develop in 57% of cases. The occurrence of dyssynchrony was associated with deterioration in LV systolic function(161). In 25 patients undergoing electrophysiological study, RVA pacing acutely induced intra-LV dyssynchrony and impairment in longitudinal LV strain(160).

Comparisons of alternate-site pacing with RVA pacing have been limited largely to short-term studies that have used hemodynamic parameters as endpoints. Victor *et al.* performed a prospective, randomized cross-over study of sixteen patients with chronic atrial tachyarrhythmia and atrioventricular block, in which subjects were sequentially RVA and RVOT-paced for 3-month intervals(272). They found no significant difference between pacing sites, however their study may have had limited power to detect a difference in LV ejection fraction given the small number of participants. Moreover 3-month follow-up may not have been sufficient for the detrimental effects of RVA pacing to become apparent. Ng *et al.* recently described 17 patients paced from the RV septum and 17 paced from the RV apex(273). They found septal-paced patients to have poorer LV ejection fraction and intra-LV synchrony. They also reported the incongruous findings of less interventricular mechanical delay and shorter QRS duration in the septal-paced group. This study was limited by the confounding effects of heterogeneity in septal positioning of the RV lead. In contrast, subjects in the present study were only included in the RVOT-paced group if strict radiographic and electrocardiographic criteria for lead location were met according to a blinded, independent observer. Pacing specifically in the RVOT septum was required. Our study's findings of longer QRS duration, lower LV ejection fraction, and greater interventricular mechanical delay and intra-LV dyssynchrony in the RVA-paced group appear more congruous and biologically plausible.

Recently, Yu *et al*. reported on 177 patients requiring permanent pacing randomised to RVA or bi-ventricular pacing(274). Subject baseline characteristics

and LV ejection fraction were similar to our patient cohort. These authors demonstrated a similar reduction in LV ejection fraction over 12 months to our subjects among RVA-paced patients, which was prevented by bi-ventricular pacing. Our study is the first however to demonstrate a superiority of RVOT-pacing over RVA-pacing in LV ejection fraction in the long-term follow-up of chronically paced patients. This was associated with the finding of smaller LV end-systolic volumes in RVOT-paced patients. Yu *et al.* have previously shown that change in LV end-systolic volume is the most powerful predictor of outcome among recipients of cardiac resynchronisation therapy(275). It remains unknown whether alternate-site RV pacing is not inferior to bi-ventricular pacing.

This study has yielded new information about the spatiotemporal sequence of LV myocardial contraction RV-paced patients. RVOT-paced patients had more synchronous LV contraction than RVA-paced patients by longitudinal strain and had less interventricular mechanical dyssynchrony. When conceptualised in 3 axial sections, among RVA-paced patients the LV apex was the first section to contract as anticipated from the lead position. A wave of myocardial shortening was then demonstrated to propagate towards the base of the heart. Although a similar spatial pattern of contraction occurred among RVOT-paced patients, significantly less time was required for this wavefront of contraction to reach the base of the heart from the apex. The finding that RVOT pacing results in initial LV apical contraction, which then progresses in a basal direction, is surprising. It may be explained by the distinction between electrical activation as defined by myocyte depolarisation and mechanical coupling as represented by myocardial shortening.

6.4.3. Implications of Permanent Pacing for Left Atrial Structure and Function

LA size has been shown to have prognostic value in a variety of cardiac conditions(110, 276). Little is known to date about the effects of permanent pacing for bradycardia indications on LA structure and function. This study is the first to demonstrate more deleterious LA remodelling in RVA-paced compared with RVOT-paced patients. Moreover, the negative relationship between septal A' as an index of LA function and LV synchrony raises the possibility that LV dyssynchrony per se adversely affects LA function and promotes undesirable LA remodelling. Yu *et al.* have demonstrated that among responders to cardiac resynchronisation therapy, there is improvement in LA volume and contractile function, and that improvement in LA function is associated with a reduced risk of atrial fibrillation and death(118, 277). While I have demonstrated that the RVOT pacing is associated with less atrial remodelling when compared to RVA pacing, whether the site of RV pacing can influence incidence of atrial fibrillation remains to be demonstrated.

6.4.4. Study Limitations

The mean percentage ventricular pacing was only approximately 50% in both RVOT- and RVA-paced patients. Had a greater proportion of subjects been pacemaker-dependent, one would have expected a more profound contrast between pacing groups; the limited percentage ventricular pacing diluted the difference in ventricular synchrony parameters between groups.

Baseline echocardiographic data are limited to measurement of LVEF. Analysis of ventricular strain and synchrony at randomisation was not performed. Whether these changes observed at late evaluation were present at baseline seems unlikely given the absence of a difference in ejection fraction but cannot be excluded.

In addition, given that the study cohort were prospectively randomised to RVA or RVOT pacing a difference between these groups at baseline would seem less likely.

Although a significant difference in LV ejection fraction, strain DI, IVMD and LA volume was demonstrated between groups, the difference in other indices of LV function, intra-LV synchrony, and LA function did not reach statistical significance. Furthermore, when the analysis was restricted to only those V-paced >75% of the time, differences in inter- and intra-ventricular synchrony did not differ significantly between groups. This study may have been underpowered to detect such uniform differences however, as study numbers were constrained by the original PASSES study cohort. Furthermore 34 of 92 patients screened for involvement in this study were ineligible. This contributed to the limited power of the study as well as its generalisability.

Evaluation of the pattern of electrical activation of the left ventricle by electroanatomical mapping was outside the scope of this study, but would provide insight into the complex nature of electromechanical coupling.

Although RVOT pacing was associated with superior LV systolic function, intra-LV and interventricular synchrony than RVA pacing, the causal relationship between LV function and cardiac synchrony could not be established. Bleeker *et al.* have shown that restoration of cardiac synchrony is the most important predictor of response to cardiac resynchronisation therapy(132). The results of this study are consistent with the corollary – that the development of greater dyssynchrony promotes greater decline in systolic LV function.

6.4.5. Conclusions

This mechanistic study suggests that RVOT septal pacing may be associated with superior LV systolic function, less adverse LA remodelling, and less LV dyssynchrony

compared with apical right ventricular pacing. These findings require confirmation in larger, randomised, controlled studies that are powered to detect differences in clinical endpoints between respective pacing sites.

Chapter 7 is a logical extension to chapter 6 in examining whether minimising LV dyssynchrony in patients undergoing bi-ventricular pacing may similarly be associated with superior LV systolic function and less adverse LA remodelling.

Table 6.1

Baseline Characteristics

	RVOT-paced (n = 32)	RVA-paced (n = 26)	p-value
Age, years	73 ± 12	77 ± 8	0.2
Gender, M/F	18/14	16/10	0.4
Indication			
• sick sinus syndrome	14	12	0.8
• AV-block	18	14	
NYHA Class	1.3 ± 0.7	1.4 ± 0.8	0.7
Coronary artery disease, n (%)	5 (16)	5 (19)	0.6
Diabetes mellitus, n (%)	2 (6)	2 (8)	0.4
Hypertension, n (%)	8 (25)	6 (23)	0.6
Frusemide, n (%)	4 (13)	4 (15)	0.4
ACE-I/ARB*, n (%)	11 (34)	12 (46)	0.6
Beta-blocker, n (%)	5 (16)	2 (8)	0.1
LVEF, %	61 ± 9	60 ± 6	0.3
Duration paced, years	2.3 ± 1	2.5 ± 1	0.2
Paced QRS duration, ms	139 ± 20	156 ± 21	0.008
Percentage RV-paced, %	56 ± 48%	49 ± 42%	0.6

* ACE-I/ARB = Angiotensin-converting enzyme inhibitor/ Angiotensin receptor blocker

Table 6.2

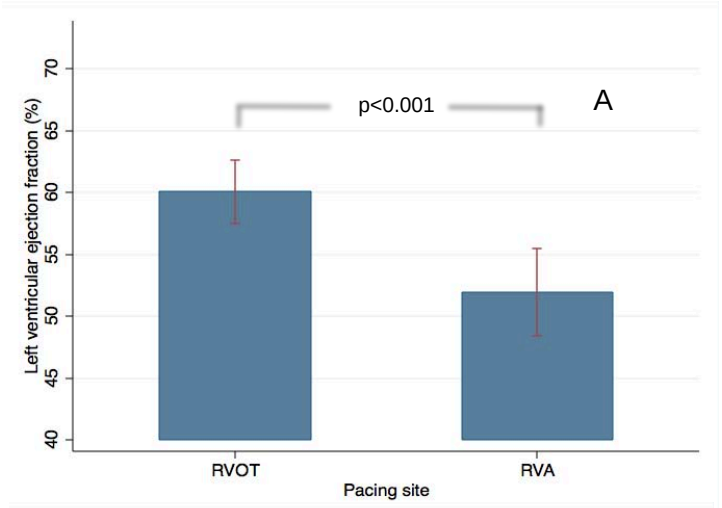
The Effects of Right Ventricular Pacing and Pacing Site on Indices of Cardiac Structure and Function

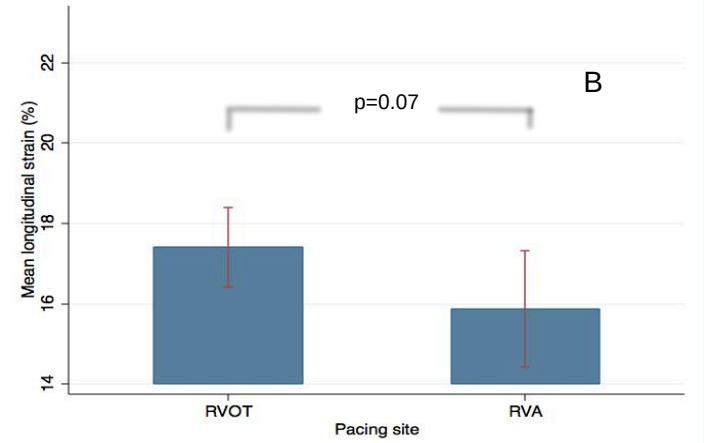
Parameter	RVOT-Paced Patients	RVA-Paced Patients	p-value
Left Ventricular Systolic Function			
LVEF, %	60±7	52±9	<0.001
Mean longitudinal strain, %	17.4±2.9	15±4	0.07
Mean Sm, cm/s	5.0±1.3	4.5±1.3	0.08
Left Ventricular Remodelling			
LVESV, mL	30±12	45±26	0.007
LVEDV, mL	74±24	88±39	0.1
Cardiac Synchrony			
IVMD, ms	13±32	35±23	0.007
SDI, ms	65±18	76±21	0.02
TD DI, ms	40±19	48±20	0.09
LA Structure and Function			
LA volume, mL	66±27	86±34	0.02
Septal A', cm/s	6.5±2.0	6.6±2.1	0.8

LVEDV = left ventricular end-diastolic volume, LVESV = left ventricular end-systolic volume, SDI = strain dyssynchrony index, Sm = systolic mitral annular tissue velocity, TD DI = tissue Doppler dyssynchrony index

Figure 6.1

Comparison of left ventricular functional parameters in RVOT- and RVA-paced patients. Bar graphs illustrating the differences in (A) LVEF, (B) mean longitudinal strain on an 18-segment model and (C) peak systolic mitral annular tissue velocity (Sm) on a 6-point model between controls, RVOT-paced and RVA-paced patients at the time of study echo.


A
p<0.001
Left ventricular ejection fraction (%)
70
65
60
55
50
45
40
RVOT
RVA
Pacing site


B
p=0.07
Mean longitudinal strain (%)
22
20
18
16
14
RVOT
RVA
Pacing site

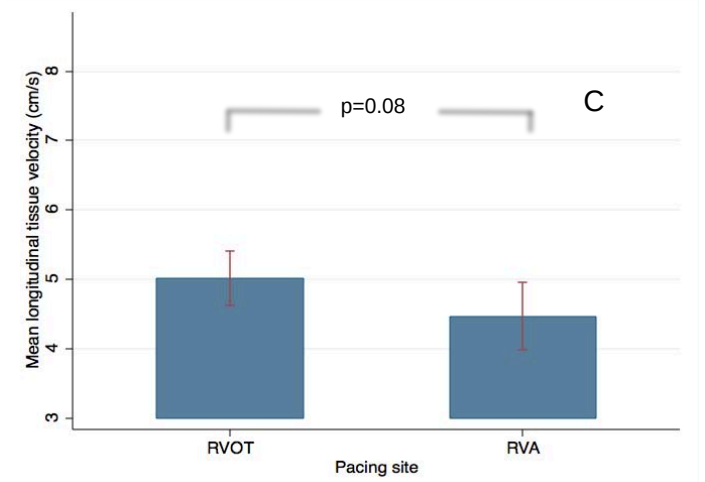

C
p=0.08
Mean longitudinal tissue velocity (cm/s)
8
7
6
5
4
3
RVOT
RVA
Pacing site

Figure 6.2

Wavefront of mechanical left ventricular activation. Dot plot demonstrating mean time-to-peak systolic strain of 3 axial myocardial sections in RVOT- and RVA-paced patients (p=0.01 for RVOT- vs. RVA-paced patients by mixed effects modelling).

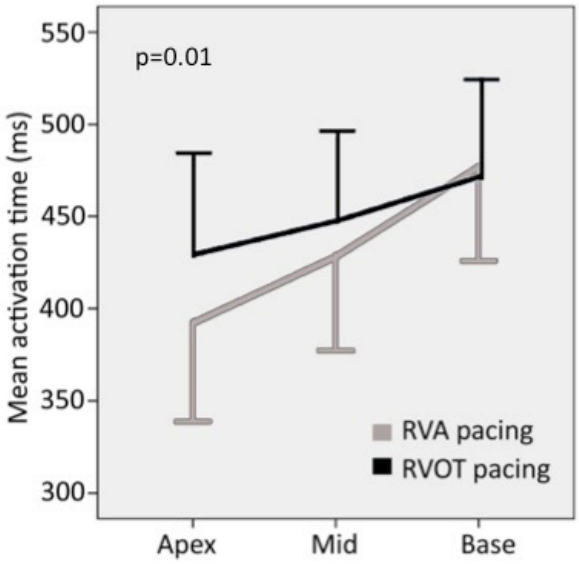


Figure 6.3

Bar graph demonstrating the difference in LA volume between RVOT- and RVA-paced subjects.

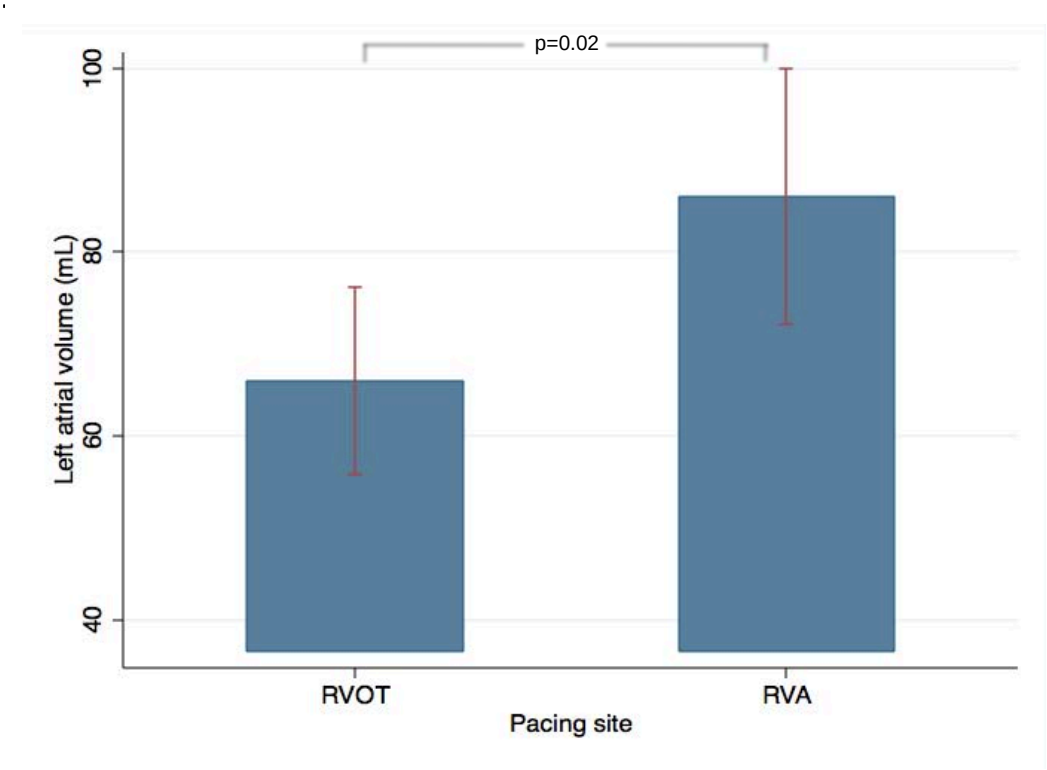
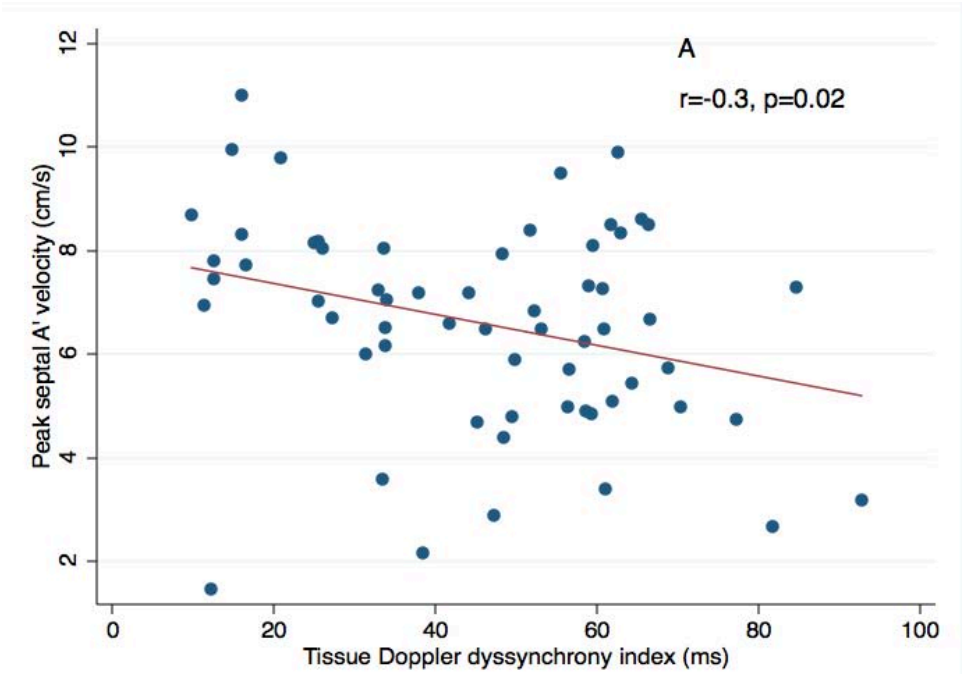
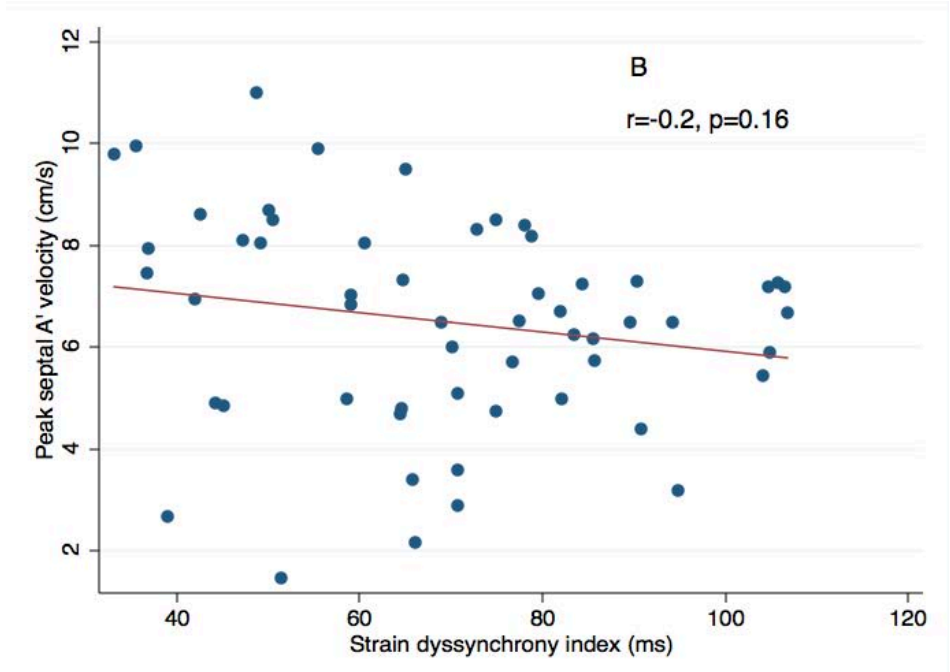


Figure 6.4

LA function is associated with left ventricular synchrony. Scatter plots demonstrating the associations between (A) septal A' velocity and the tissue Doppler dyssynchrony index, and (B) septal A' velocity and the strain dyssynchrony index.





Chapter 7 – A Long-Term Prospective Randomised Evaluation of V-V Delay Optimisation to Reduce Intra-Left Ventricular Dyssynchrony in Cardiac Resynchronisation Therapy

7.1. INTRODUCTION

Cardiac resynchronisation therapy (CRT) is of proven benefit among patients with moderate-severe impairment in systolic left ventricular (LV) failure with evidence of ventricular dyssynchrony as manifest by a prolonged QRS duration(22, 23). Notwithstanding the efficacy of CRT, a non-response rate of approximately 30% is consistently observed, irrespective of the definition used to define therapeutic response(130, 131). Hence further refinement in CRT delivery is desirable to maximise recipient benefit. Optimisation of V-V timing has been studied as a means of enhancing CRT efficacy(170, 171). This is conventionally performed by maximising LV stroke volume as measured by transthoracic echocardiography. This technique of CRT V-V optimisation has yielded variable results, however. Bordachar *et al*. demonstrated that acute V-V optimisation displayed a close association between indices of ventricular synchrony and echocardiographically measured cardiac output(137). Despite observing similar acute haemodynamic benefits, Boriani *et al*. showed no significant benefit from V-V optimisation in a small, randomised, controlled study(171).

Bleeker *et al*. have demonstrated that improvement in ventricular dyssynchrony is an important pre-requisite for CRT response(132). This study therefore sought to determine whether V-V optimisation with the goal of minimising intra-LV dyssynchrony would confer additional benefit beyond routine simultaneous

bi-ventricular pacing. Our primary hypothesis was that echocardiographic V-V optimisation to minimise intra-LV dyssynchrony would be associated with significant improvement in LV ejection fraction compared with simultaneous bi-ventricular pacing among CRT recipients for conventional indications. Our secondary hypothesis was that V-V optimisation would result in reduction in major adverse cardiovascular events over and above simultaneous bi-ventricular pacing. The findings from this thesis to this point are suggestive that LV dyssynchrony has a deleterious influence on LV function. The present study thus aims to determine whether LV dyssynchrony can be minimised on an individual basis, over and above routine simultaneous bi-ventricular pacing, and whether such direct treatment of LV dyssynchrony influences patient outcomes.

7.2. METHODS

7.2.1. Patient Characteristics

Consecutive patients scheduled for implantation of a new bi-ventricular pacemaker with or without defbrillators at the Royal Adelaide Hospital and the Flinders Medical Centre were recruited. Inclusion required the following to be present: 1) LV ejection fraction ≤35%, 2) QRS duration >120ms with left bundle branch block, and 3) NYHA class III/IV symptoms despite at least 6 months' optimal medical heart failure therapy. Exclusion criteria included previous CRT and unsuccessful bi-ventricular pacemaker implantation. During pacemaker implantation the right ventricular lead was implanted at the right ventricular apex and the right atrial lead in the right atrial appendage. The LV lead was positioned where possible in the vein closest to the mid-lateral left ventricular wall with the greatest excursion from the right ventricular lead. All patients provided written, informed consent for enrolment in the study, which was approved by the Human Research Ethics Committees of the Royal Adelaide Hospital and the Flinders Medical Centre, Adelaide, Australia.

7.2.2. Study Design

Prior to bi-ventricular pacemaker implantation, participants underwent echocardiography for evaluation of systolic LV function, electrocardiography, six-minute walk testing, and Minnesota Living With Heart Failure Questionnaire. At the time of bi-ventricular pacemaker implantation patients were randomised in a 1:1 manner to simultaneous bi-ventricular pacing (with V-V delay = 0ms) or echocardiographically optimised bi-ventricular pacing. Within four weeks of bi-ventricular pacemaker implantation patients underwent transthoracic echocardiography as described subsequently. Echocardiography (and V-V

optimisation in the treatment group), six-minute walk testing, and Minnesota Living With Heart Failure Questionnaire were repeated at 6 months, and final echocardiography performed at 18 months (Figure 7.1).

7.2.3. Echocardiography Protocol

At each visit patients underwent standardised echocardiography as described in Chapter 2. The specific images acquired included two-dimensional images of the left ventricle and atrium in the apical 4-, 2- and 3-chamber views, Tissue Velocity Imaging of the left ventricle in the apical 4-, 2- and 3-chamber views, and pulse-wave Doppler recordings in the LV outflow tract in the apical 5-chamber view and at the mitral valve leaflet tips. In addition, a parasternal long-axis view for measurement of LV outflow tract diameter (D) was recorded.

7.2.4. CRT Optimisation Protocol

In all patients, A-V optimisation was undertaken using an iterative technique to maximise LV filling time. Grey-scale and Tissue Velocity Images in the apical 4-, 2- and 3-chamber views were then acquired during pacing at the following V-V intervals: +80ms, +40ms, +20ms, +10ms, 0ms, -10ms, -20ms, -40ms, -80ms, and LV pacing only. The sequence in which these V-V intervals were tested was randomly determined to avoid any bias from a stereotypical protocol. Images for each V-V interval were acquired after at least 6 cardiac cycles at that timing interval.

7.2.5. Echocardiography Analysis

Echocardiography images were analysed offline using commercially available software (EchoPac version 7.0.0 General Electric-Vingmed). Endpoint data were analysed by a single observer blinded to patient outcome and randomisation group as follows. Left ventricular end-diastolic and end-systolic volumes were measured from apical 4- and 2-chamber images using Simpson's biplane method of discs(33). LA volume was estimated from apical 4- and 2-chamber images from the frame immediately prior to mitral valve opening, using the modified Simpson's rule(33). LV stroke volume was calculated as LV outflow tract velocity-time integral x π x $D^2/4$. E' velocity was measured offline from Tissue Velocity images as the peak early diastolic septal annular velocity. Intra-LV synchrony was evaluated by a Tissue Doppler dyssynchrony index (TD_DI), defined as the standard deviation of values of time measurements from QRS onset to peak systolic ejection tissue velocity on a 12-segment model, as previously described(278). This was performed at each V-V interval for every patient in order to determine the timing interval associated with the greatest intra-LV synchrony. This V-V interval was programmed for patients randomised to the optimised group.

7.2.6. Evaluation of Outcomes

Patient status was determined by regular 6-monthly follow-up by an investigator blinded to patient randomisation group. The following endpoints and their dates of first occurrence were recorded: death, ventricular arrhythmia requiring device therapy (ventricular tachycardia or fibrillation), hospitalisation, diuretic dose increase for worsening heart failure, and atrial fibrillation. The primary endpoint was a composite of these events. Only the first occurrence of one such endpoint was considered. Pre-

defined secondary endpoint included change in six-minute walk distance and change in Minnesota Living with Heart Failure Questionnaire.

7.2.7. Statistical Analysis

Continuous variables are presented as mean±SD where normally distributed. Categorical data are summarised as frequencies and percentages. All analysis was performed on an intention-to-treat basis. Change in continuous variables was analysed using mixed-effects modelling. Randomisation group and subject visit, and the randomisation*visit interaction were modelled as fixed effects, with subject identity as a random effect to account for repeated measures within patients. For significant randomisation*interaction terms *post hoc* testing was performed at baseline and follow-up visits Time-to-event analysis was undertaken using the Kaplan-Meier method, and difference between groups was tested by the logrank test. Statistical analysis was performed with STATA 11 (Stata Corp, College Station, Texas). All statistical tests were 2-sided and a p-value <0.05 considered significant. This sample size had 76% power to detect an absolute difference in 18-month LV ejection fraction of 6% between groups at α=0.05. Inter-observer variability for the tissue Doppler dyssynchrony index was evaluated in a subset of 10 randomly selected patients using Lin's Concordance Correlation Coefficient(242).

7.3. RESULTS

Sixty-nine consecutive patients scheduled to undergo CRT were prospectively screened for enrolment. Four patients declined to participate and in one individual the LV lead could not be implanted. The following analysis thus pertains to the remaining sixty-four consenting participants. Baseline characteristics of patients randomised to the simultaneous and optimised bi-ventricular pacing groups are displayed in Table 7.1. Patients underwent echocardiographic V-V optimisation a median 11 days (inter-quartile range, IQR 6-24 days) following bi-ventricular pacemaker implantation. V-V optimisation was repeated at 7 months (IQR 6-9 months) and 18 months (IQR 15-23 months).

7.3.1. Cardiac Function and Remodelling

Changes in indices of cardiac structure and function are presented in Table 7.2. Following CRT there was significant, progressive reduction in LV end-systolic volume ($p<0.001$). There was similar improvement in LV ejection fraction ($p<0.001$). A significant reduction in E/E' was observed by 18-month follow-up ($p=0.04$), however LA volume did not change over the study period (p=NS). No significant difference in cardiac output was observed over the course of follow-up (p=NS).

7.3.2. Patient Functional Status

Six-minute walk distance and Minnesota Living With Heart Failure score both improved significantly at 7 months, however plateaued at 18 months (Table 7.2)

7.3.3. Effects of V-V Optimisation

The distribution of optimum V-V intervals over the study period is displayed in Figure 7.2. Acutely, echocardiographic optimisation of V-V timing by minimising intra-LV dyssynchrony resulted in improvement in Tissue Doppler dyssynchrony index beyond simultaneous bi-ventricular pacing (31±16ms vs. 41±16ms, p<0.001). Acutely, the optimum V-V interval was associated with similar cardiac output to simultaneous bi-ventricular pacing (4.0±1.4L/min vs. 3.9±1.5L/min, p=0.2). The optimum V-V interval for each individual changed from baseline to first follow-up in fifty-nine patients, and remained unchanged in five individuals.

At both interim and final follow-up, V-V optimisation performed at each patient's prior visit did not result in subsequent improvement in LV ejection fraction (p=0.9) (Figure 7.3) or LV end-systolic volume (p=0.4) over simultaneous bi-ventricular pacing. Similarly, no difference between groups was observed with respect to E/E' (p=0.7), LA volume (p=0.4), or Minnesota Living With Heart Failure Questionnaire (p=0.8). A trend towards improvement in six-minute walk distance was seen amongst those with optimised V-V pacing, however (p=0.05, Figure 7.4).

7.3.4. Time-to-Event Analysis

Patients were observed for a median 18 months. During this time, fourteen individuals in the simultaneous pacing group and fifteen in the optimised group experienced an endpoint event. There was no difference in the development of a first primary endpoint between the simultaneous and optimised pacing group (p=0.5) (Figure 7.5).

7.3.5. Inter-Observer Variability

Lin’s concordance correlation coefficient (±95% CI) for the Tissue Doppler dyssynchrony index is 0.98 (0.94 – 1.0), reflecting good inter-observer variability.

7.4. DISCUSSION

7.4.1. Major Findings

In this prospective, randomised, controlled study of simultaneous versus echocardiographically optimised CRT, in which for the first time optimisation was performed by minimising intra-LV dyssynchrony, no significant benefit from routine V-V timing optimisation was demonstrated. However, there was a trend to improved functional status as measured by six-minute walk distance in the optimised compared to simultaneous bi-ventricular pacing groups.

7.4.2. Previous Studies

The findings from the present study are in keeping with previous reports of V-V optimisation, which have failed to show a clinically significant benefit with routine use in CRT recipients. The major distinction of the current study is that V-V optimisation was undertaken by identifying the interval associated with the least intra-LV dyssynchrony as measured by the Tissue Doppler dyssynchrony index. This index has been well validated as an index of intra-LV dyssynchrony, and has been shown to be highly predictive of response to CRT(147). The achievement of cardiac resynchronisation has been reported to be an important requirement for bi-ventricular pacing efficacy(132). It would therefore seem intuitive that individualisation of V-V interval to minimise intra-LV dyssynchrony is desirable.

Previous studies of echocardiographic V-V optimisation have used LV stroke volume as the arbiter of optimal V-V timing(170, 171, 279), however this technique is subject to variation in the position of the echocardiographic sample volume within the LV outflow tract, in alignment of the Doppler beam, and in patient respiration if not adequately suspended. There is emerging evidence on the relationship between

echocardiographic stroke volume and intra-LV synchrony. These studies report disparate findings, with some investigators identifying a close relationship, and others a weak one(173-175). Duvall *et al*. have shown that both LV outflow tract velocity-time integral and three-dimensional LV ejection fraction may be increased above simultaneous bi-ventricular pacing by altering V-V paving intervals(175). Importantly, however, these authors also demonstrated poor agreement between the two measures for selection of the optimal V-V pacing interval. They suggest that this finding may be due to the limited reproducibility of the echocardiographic indices used for optimisation. Bertini *et al*. demonstrated moderate concordance between methods that maximised LV outflow tract velocity time integral, tissue Doppler septal-lateral delay, and maximal temporal delay in mid-LV circumferential strain(173). Marsan *et al*. reported on sixty-nine CRT recipients who underwent echocardiography at seven different V-V intervals(174). They found a very strong concordance between the V-V interval providing the largest LV outflow tract velocity-time integral and the interval providing the least intra-LV dyssynchrony by tissue Doppler imaging.

In the present study, the approach employed to V-V optimisation that sought to address dyssynchrony as a mediator of LV dysfunction, found no benefit to routine V-V optimisation. Possible explanations for the lack of long-term benefit by echocardiographic V-V optimisation include: 1) frequency of optimisation – the high incidence of change in optimal V-V interval in the present study, as well as previous studies suggests that optimal V-V timing may be very dynamic, requiring intensive repetition of optimisation(280) and 2) precision of echocardiographic optimisation techniques. The PROSPECT study highlighted the variability of echocardiographic measures of ventricular dyssynchrony, and the resulting limitation of these indices as clinical tools(133).

Other investigators have explored the possibility of non-echocardiographic methods of V-V optimisation, including electrocardiography(281) and invasive haemodynamic measures(282). These various techniques are subject to similar limitations to echocardiography, and have not been shown to confer clinically significant intermediate or long-term benefit in CRT recipients in randomised studies.

7.4.3. Clinical Implications

The results of this study strongly argue against the use of echocardiographic optimisation as a routine in patients undergoing CRT therapy. However, the trend towards functional improvement with optimisation seen in this study, together with the data on response in non-responders of simultaneous CRT therapy, suggests that there may be a role of echocardiographic optimisation in selected patients.

7.4.4. Study Limitations

Echocardiographic V-V optimisation using the present technique is time-consuming and may be of limited practicality in clinical practice, however the purpose of the current study was a proof of concept. Although the current study does not support the routine performance of echocardiographic V-V optimisation in CRT recipients, it remains unclear whether optimisation may be beneficial in selected patients, such as CRT non-responders. In addition, the role of dynamic optimisation or electrical optimisation was not evaluated in this study.

Table 7.1

Baseline Characteristics

Parameter (mean ±SD)	Simultaneous Bi-Ventricular Pacing (n=32)	Optimised Bi-Ventricular Pacing (n = 32)	p-value
Age (years)	74±10	70±13	0.2
Gender (M/F)	25/7	26/6	0.8
Ischaemic Aetiology, n (%)	18 (56)	21 (66)	0.4
ACE-I/ARB, n (%)	32 (100)	31 (97)	0.3
Beta-blocker, n (%)	29 (91)	31 (97)	0.3
Spironolactone, n (%)	14 (44)	12 (38)	0.6
Frusemide, n (%)	22 (69)	20 (63)	0.6
QRS duration (ms)	163±22	151±18	0.1
6-minute walk distance (m)	375±100	347±138	0.5
Minnesota Living With Heart Failure Score	52±21	50±21	0.7
LV end systolic volume (mL)	211±155	172±77	0.3
LV ejection fraction (%)	27±10	26±8	0.8
Cardiac output (L/min)	3.7±1.3	3.9±1.7	0.7
E/E’	26±12	25±23	0.8
LA volume (mL)	90±33	84±24	0.5
Tissue Doppler Dyssynchrony Index (ms)	40±19	45±13	0.3

Table 7.2

Response to CRT

Parameter (mean±SD)	Baseline	7 months	18 months
Six-minute walk distance (m)	360±121	424±103*	414±73
Minnesota Living With Heart Failure Score	51±21	31±21*	38±19*
LV end-systolic volume (mL)	195±128	145±139*	101±44*
LV ejection fraction (%)	27±9	36±13	42±9
Cardiac output (L/min)	3.8±1.5L	3.6±1.5L	3.8±1.4
E/E’	26±17	25±11	17±6*
LA volume (mL)	87±30	90±42	77±29

* $p<0.05$ compared with baseline

Figure 7.1

Flow diagram illustrating the study protocol.

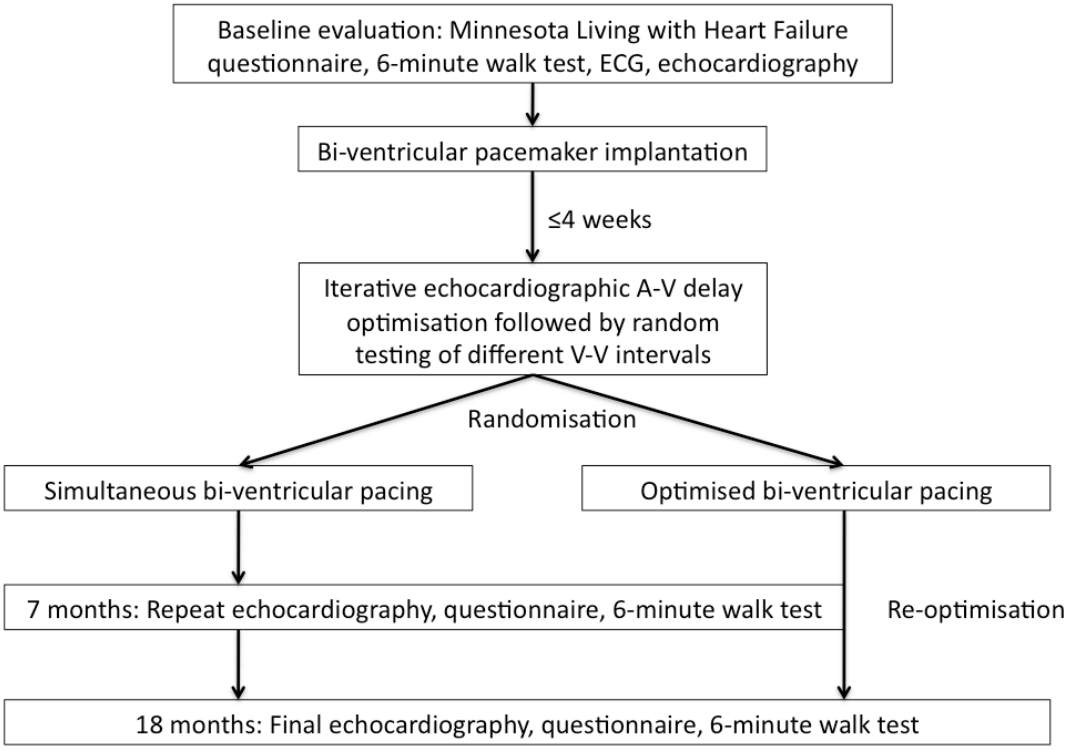


Figure 7.2

Histogram illustrating the frequency with which each V-V interval was found to be optimal

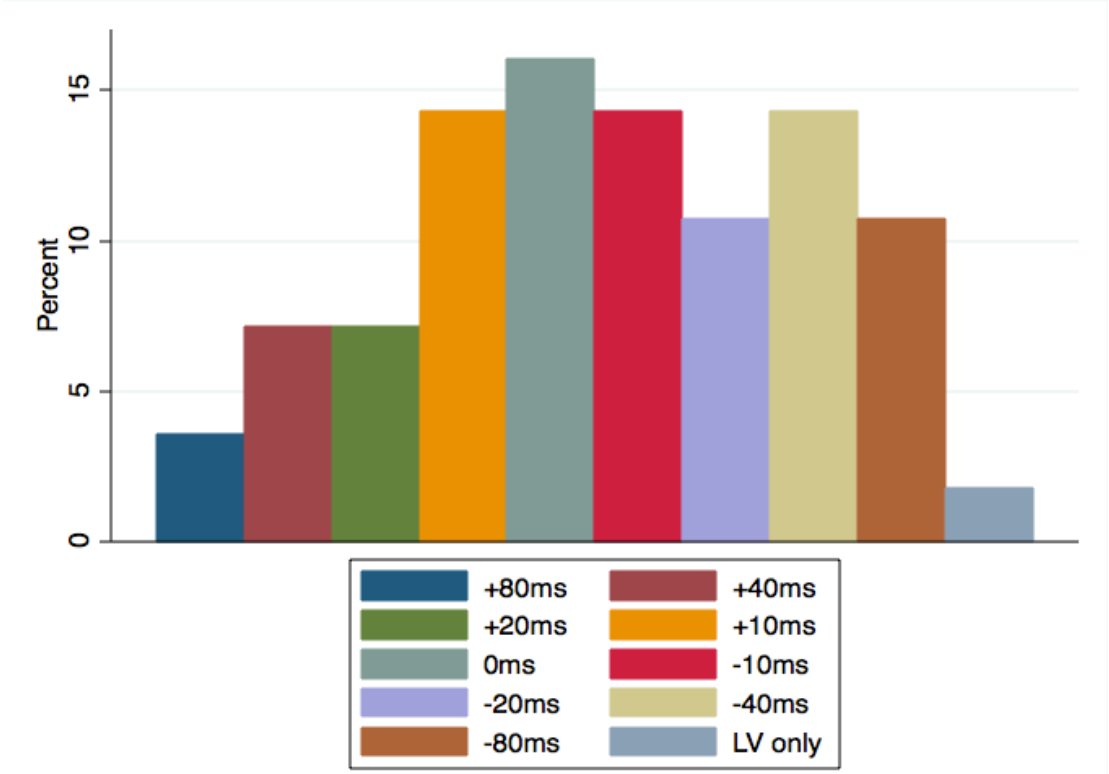


Figure 7.3

Graphs illustrating change in left ventricular ejection fraction during follow-up in simultaneous and optimised groups.

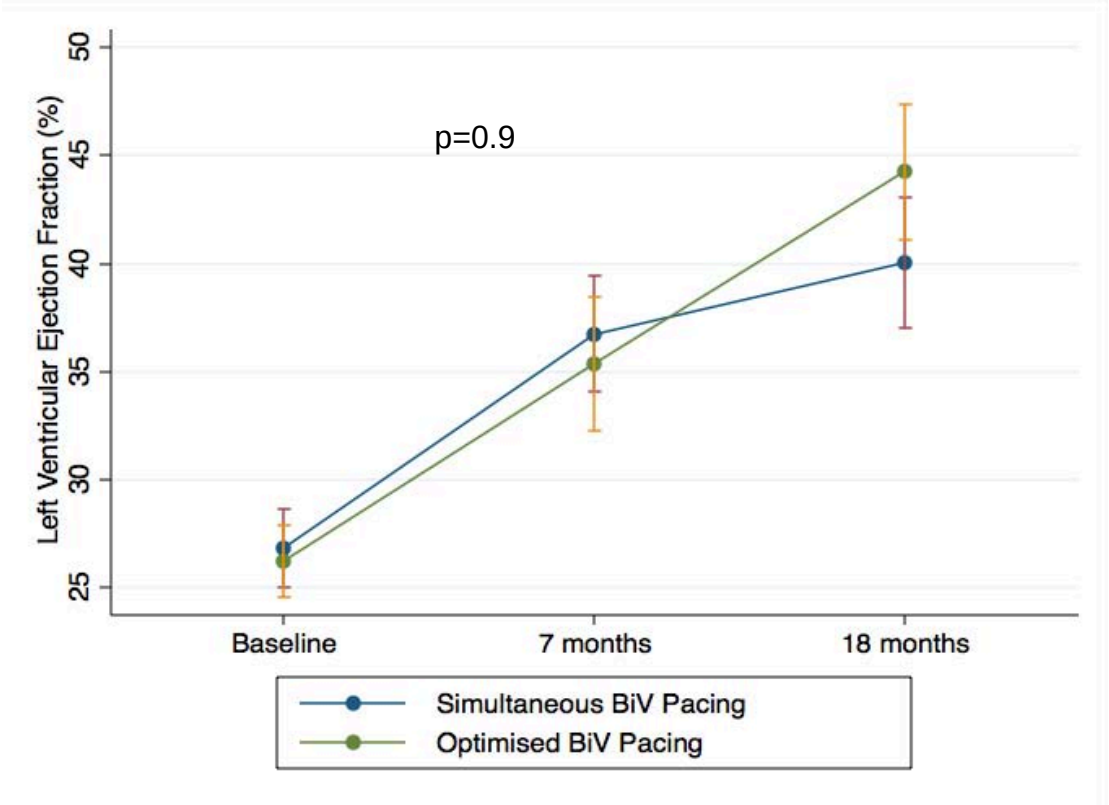


Figure 7.4

Graphs illustrating change in six-minute walk distance during follow-up in simultaneous and optimised groups

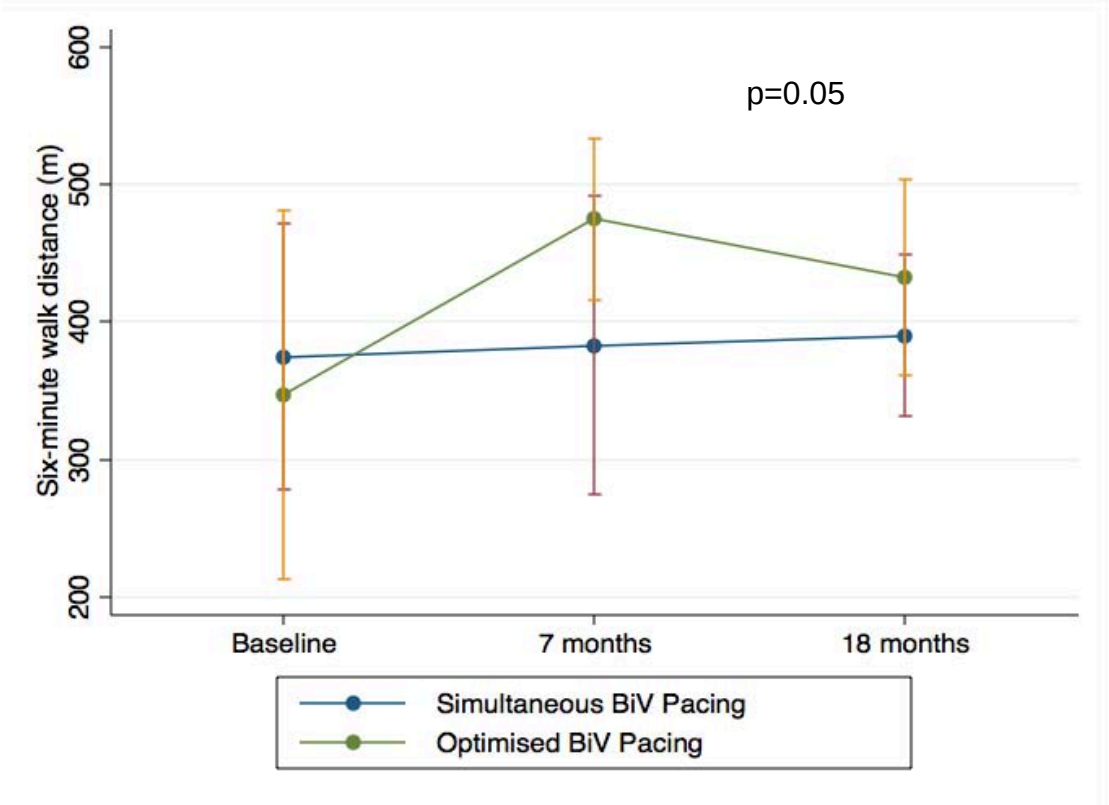
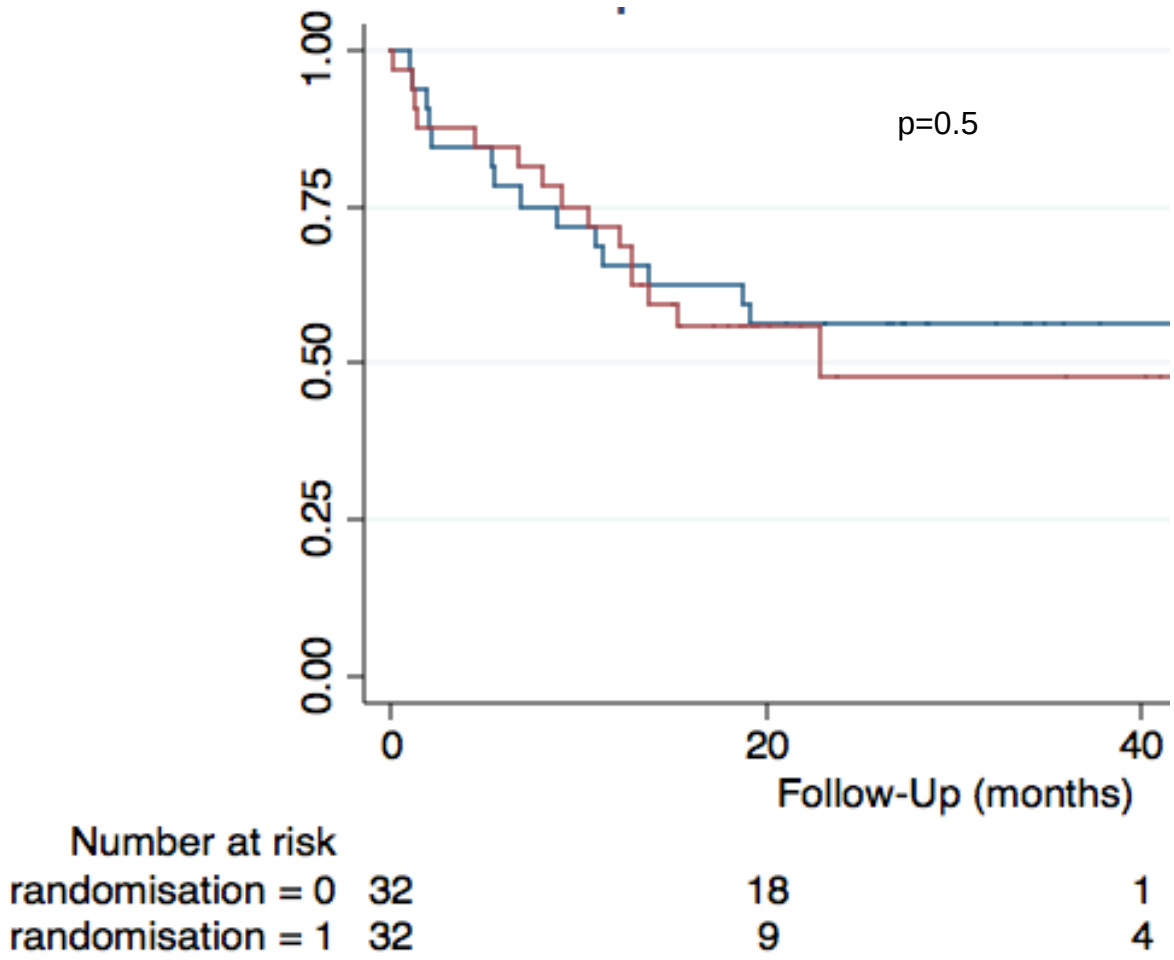


Figure 7.5

Kaplan-Meier estimates of time-to-primary endpoint for VV-optimised patients (red) and controls (blue)



Chapter 8 – Final Discussion

This thesis has explored the complex relationship between ventricular dyssynchrony, myocardial fibrosis, and left ventricular and atrial mechanical dysfunction. Systolic left ventricular function is a key determinant of cardiovascular morbidity and mortality, and is closely linked with LA mechanical function. Ventricular, and in particular intra-left ventricular dyssynchrony is also strongly associated with systolic left ventricular impairment. Myocardial fibrosis plays an important role in left ventricular remodelling and in the pathogenesis of congestive heart failure. This thesis has examined the role of ventricular dyssynchrony and myocardial fibrosis in the perpetuation of systolic left ventricular dysfunction, which in turn strongly influences LA mechanical function.

Left ventricular filling and thus function is in part dependent on LA contractile function, and conversely, LA mechanical function may be adversely affected by left ventricular dysfunction. The nature of the inter-dependence between left atrium and ventricle remains incompletely understood, in particular in heart failure, where the extent to which LA impairment is the result of left ventricular dysfunction - as opposed to the underlying disease process - is unknown. In Chapter 3, the dependence of LA contraction on left ventricular mechanical function is demonstrated. Temporary abolition of left ventricular function during ventricular fibrillation is associated with marked impairment in LA contractility. This observation is consistent with reports of impaired LA function in the setting of chronic left ventricular dysfunction, and with the notion that it is the left ventricular impairment causing the LA dysfunction.

In heart failure with reduced systolic left ventricular function, both intra-ventricular mechanical dyssynchrony and myocardial fibrosis have been shown in

separate studies to be prevalent and associated with adverse outlook. This research has focussed on individuals with long-standing heart failure. Thus, the prevalence of ventricular mechanical dyssynchrony and myocardial fibrosis early in the time course of heart failure with impaired left ventricular systolic function are uncertain. Furthermore, factors contributing to the early recovery of patients following heart failure therapy are incompletely understood. In addition, the causal relationship of ventricular mechanical dyssynchrony and myocardial fibrosis remains to be examined. Chapter 4 was a prospective, observational study of patients early following their first presentation of idiopathic dilated cardiomyopathy. Using cardiovascular magnetic resonance to evaluate myocardial fibrosis and echocardiography to assess ventricular dyssynchrony, the prevalence and degree of these factors was evaluated in this cohort. It was shown that both these processes are independent predictors of change in left ventricular systolic function in response to optimal medical therapy. This finding is suggestive of a pathophysiological role for both myocardial fibrosis and intra-left ventricular dyssynchrony in the perpetuation of systolic heart failure. An important limitation of Chapter 4 is that the relationship between duration of LV dysfunction and the extent of myocardial fibrosis could not be determined. It is possible that the presence of myocardial fibrosis in patients with a first presentation of DCM merely reflects a longer pre-clinical disease course. Nonetheless, this study is still of clinical relevance as it is a reflection of current practice with respect to these patients at their initial diagnosis.

The importance of intra-left ventricular dyssynchrony in causing left ventricular dysfunction was further examined in Chapter 6. In a cohort of patients randomised to right ventricular or right ventricular outflow tract septal pacing for bradycardia, it was demonstrated that septal pacing was associated both with less intra-left ventricular dyssynchrony, and with superior global systolic left ventricular function at long-term follow-up. This study provides further evidence to support the contention that it is

dyssynchrony that promotes left ventricular dysfunction, rather than being merely an epiphenomenon.

Cardiac resynchronisation therapy is of proven efficacy in patients with moderate-severe systolic heart failure and evidence of ventricular dyssynchrony. The logical extension of this observation and the findings from Chapters 4 and 6 is that optimisation of ventricular synchrony in systolic heart failure may result in maximal improvement in systolic left ventricular function. The study presented in Chapter 7 is a randomised, controlled trial to address this hypothesis. While this evaluation failed to demonstrate superior efficacy of the approach of echocardiographic optimisation of V-V timing to minimise intra-left ventricular dyssynchrony, this study suffered from methodological limitations. These shortcomings are of clinical relevance as the study protocol was designed as a template for clinical practice, however they do restrict the ability of this trial to confirm the findings from Chapters 4 and 6 of this thesis, with respect to the causal role of ventricular dyssynchrony.

Chapter 9 - Future Directions

Although the observations made in the course of this thesis have yielded some understanding of the mechanisms underlying the pathogenesis and perpetuation of contractile left ventricular and LA dysfunction, they have led to further questions, some of which are described in the following text.

The finding in Chapter 4 that the degree of myocardial fibrosis and ventricular mechanical dyssynchrony are predictive of lack of improvement in systolic left ventricular function despite routine medical therapy prompts speculation that evaluation of these factors should be part of routine assessment of patients presenting with dilated cardiomyopathy. The value of such a strategy would be the early identification of “non-responders” to medical therapy, who may be more aggressively treated with respect to intensity of follow-up, pharmacotherapy and device therapy. The ideal test of the merits of this approach to new-presentation dilated cardiomyopathy would be a clinical trial in which participants are randomised to early CMR and evaluation of dyssynchrony versus routine care. Those featuring high-risk characteristics for non-response to medical therapy would be prescribed a more aggressive therapeutic regimen.

The in vivo quantification of myocardial fibrosis, particularly when diffusely distributed within the heart, is challenging. The late-gadolinium technique is dependent on the contrast between areas of greater collagen content and more normal myocardium. This approach to the evaluation of fibrosis is limited in the setting of homogenous, diffuse fibrosis. Techniques such as T1 mapping by cardiovascular magnetic resonance and calibrated integrated backscatter have shown promise in the measurement of diffuse myocardial collagen content, and may prove fruitful in further examining the relationship between ventricular dyssynchrony, myocardial fibrosis, and the perpetuation or progression of heart failure.

The development of non-invasive techniques to accurately quantify diffuse myocardial fibrosis may enable evaluation of anti-fibrotic therapies for heart failure. Successful identification of such agents would contribute to the evidence supporting the role of myocardial fibrosis in perpetuating left ventricular dysfunction, and may open a novel therapeutic strategy for heart failure.

This thesis was unable to reach a conclusion as to whether myocardial fibrosis causes intra-ventricular dyssynchrony or vice versa. Indeed the possibility that each pathological process promotes each other in a vicious cycle must also be entertained. The nature of the relationship between ventricular dyssynchrony and myocardial fibrosis is likely to remain an elusive one to clarify because, be it human or animal study, the confounding factor of left ventricular dysfunction, which is associated with both dyssynchrony and fibrosis, is difficult to control for.

There is a wealth of research to support the prognostic importance of ventricular dyssynchrony in large patient cohorts. More controversial is the role of evaluation of dyssynchrony in clinical practice to guide decision-making for the individual patient(133). Existing techniques for the assessment of ventricular dyssynchrony are limited by their inter-observer variability, and the development of a robust and reproducible means of dyssynchrony evaluation remains highly sought-after.

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