TISSUE DOPPLER IMAGING FOR THE ASSESSMENT OF LEFT VENTRICULAR FUNCTION IN AN OLDER POPULATION

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DECLARATION

This work presented in the thesis describes the results of research carried out in the Clinical Trials Unit and Academic Unit of Internal Medicine at The Canberra Hospital from January 2010 to December 2011.

The results presented in this thesis are my own work accomplished under the supervision of Professor Walter Abhayaratna. This material has not been submitted either in whole or in part for a degree at this or any other university.

Benjamin M. Jacobson

June 2015
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I thank Professor Frank Bowden for his assistance, which enabled me to undertake this research.

Most importantly I thank my family for their support and understanding which enabled me to complete this project.
PUBLICATIONS AND PRESENTATIONS RELATED TO THIS THESIS

Three manuscripts from this research have been prepared for publication in international peer-reviewed journals. The original scientific papers correspond directly to each of the study chapters in the thesis (chapters 3, 4, 5, 6 and 7).

Publications in peer-reviewed journals

Jacobson BM, Abhayaratna WP. The continuum between longitudinal and radial left ventricular “systolic” function: relationship to left ventricular filling pressure. *Under review in Heart*

Jacobson BM, Abhayaratna WP. Left ventricular systolic dyssynchrony; prevalence and determinants in a population-based cohort. *Under review in JACC imaging*

Jacobson BM, Abhayaratna WP. Mitral annular systolic velocity: clinical determinants and relationship to diastolic function in population-based subjects. *Under review in Am Journal of Cardiology*

Abstract presentations at national / international conferences

Jacobson BM, Abhayaratna WP. The continuum between longitudinal and radial left ventricular “systolic” function: relationship to left ventricular filling pressure.

*American College of Cardiology, San Francisco, March 2013*

*Cardiac Society of Australia and New Zealand, Gold Coast, August 2013*
Jacobson BM, Abhayaratna WP. Left ventricular systolic dyssynchrony; prevalence and determinants in a population-based cohort.

*American Heart Association, Chicago, 2010; oral presentation*

*Awarded top Australian abstract submission*

Jacobson BM, Abhayaratna WP. Mitral annular systolic velocity: clinical determinants and relationship to diastolic function in population-based subjects.

*American Heart Association, Chicago, 2010*

*Cardiac Society of Australia and New Zealand, Adelaide, August 2010*
ABSTRACT

Tissue Doppler Imaging (TDI) is an established tool in the echocardiographic assessment of cardiac function. Because of their subendocardial localisation, longitudinal fibres are particularly sensitive to fibrosis, hypertrophy and ischaemia, and impaired long-axis function can therefore provide a sensitive index for the assessment of systolic myocardial function. TDI derived measures have established prognostic utility however its use in the evaluation of left ventricular systolic function has largely been within selected populations.

This thesis is based on clinical and echocardiographic data from a population-based prospective cohort study of older adults in the Australian Capital Territory (ACT), the Canberra Heart Study. I review the epidemiology of heart failure (HF) and highlight the reasons as to why early diagnosis of HF (in Stage B) will be required to improve the prognosis of patients with HF, particularly those with normal ejection fraction (HFNEF) in whom the prognosis has not been improved by pharmacotherapy (Chapter 1). The rationale as to why TDI imaging may provide insights regarding the pathophysiology of HF, which may assist in the early detection of HF and reduce its increasing burden on the healthcare system.

The second chapter details study methodologies, including echocardiographic evaluation of cardiac function; and the assessment of cardiac biomarkers, specifically the aminoterminal component of pro-B-type natriuretic peptide (NT-proBNP) and high-sensitivity cardiac troponin T (hs-cTn).
In contrast to mitral annular diastolic velocities (e’), normal values for mitral annular systolic velocities (s’) and their clinical determinants are not well established, particularly using data from unselected populations. The clinical determinants of LV systolic function, as assessed by s’ were evaluated in a population-based study for the first time, and the results are presented in Chapter 3. Longitudinal LV systolic function declines with age and within this older population of adults, and s’ velocities were lower in females. Negative correlations were observed with clinical parameters associated with adverse LV loading conditions, systemic hypertension and increased pulse pressure.

The division of systolic and diastolic heart failure into distinct disease entities has been debated for some time. There is no physiological basis for dividing heart failure (HF) patients into groups based on an arbitrary cut-off value for LV ejection fraction (LVEF) (e.g. > 50%), and this approach has led to significant controversy and misunderstanding about the pathophysiology and progression of HF, in particular HFNEF. We assessed the relationship between LV systolic function using s’ and LV diastolic dysfunction (DD) and found the association to be independent of the effects of other echo-clinical factors, and the results are presented in Chapter 4. S’ is reduced according to the severity of DD. This data provides further support to the concept that diastolic and systolic dysfunction represent a continuum of the same disease.

We hypothesised that s’ may provide a more sensitive index than LVEF for assessing LV systolic function and that a continuum of systolic function could be observed in this unselected population. We examined the relationship between LV long axis systolic function using s’ and its association with LVEF,
a measure of global radial systolic function, and LV filling pressure, and the results are presented in Chapter 5. The illustration of a continuum between longitudinal and radial systolic function, in a predominantly asymptomatic population provides insights into the natural history of left ventricular dysfunction and cardiac failure. Reduced s’ velocities illustrate impaired LV systolic function despite a normal LVEF.

The findings in Chapter 5 are supported in Chapter 6 by our assessment of the relationship between cardiac biomarkers, NT-proBNP, hs-cTN, with s’, LVEF and LV filling pressure. Cardiac biomarkers increased significantly with increasing grades of LV dysfunction supporting the concept that adverse loading conditions and remodeling processes leading to myocyte loss are important mechanisms in the progression of HF.

LV dyssynchrony is a significant contributor to LV systolic dysfunction and has been linked to increased morbidity, mortality and arrhythmia susceptibility in patients with HF. Quantification of systolic dyssynchrony by the standard deviation of time-to-peak systolic myocardial velocity (Ts-SD) by TDI has previously been validated and reference limits have been evaluated in relatively small samples of clinic-based populations. Understanding the determinants of Ts-SD should facilitate a better understanding of the pathophysiology and natural history of LV dysfunction, and may provide insights to why this measure is a suboptimal marker for the selection of heart failure patients who benefit from cardiac resynchronisation therapy. The results of such an evaluation for the first time in a large, population-based cohort are presented in Chapter 7. LV systolic dyssynchrony, as assessed by
Ts-SD, was highly prevalent and determined by the opposing influences of aortic pulsatile load and ventricular preload, total systolic time, and intrinsic properties of LV structure and diastolic function.

Finally, I provide a brief outline of future directions for research that may be guided by the results emanating from this thesis.
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ABBREVIATIONS

A = peak late mitral diastolic inflow velocity
ACT = Australian Capital Territory
AF = Atrial fibrillation
Am = mitral annular late diastolic velocity measured by TDI
BMI = Body mass index
BNP = B-type Natriuretic Peptide
BP = Blood pressure
BSA = Body Surface Area
CRT = Cardiac resynchronisation therapy
cTn = cardiac troponin
D = pulmonary vein diastolic flow velocity
DD = Left ventricular diastolic dysfunction
DT = deceleration time
E = peak early mitral inflow velocity
e’ = mitral annular peak early diastolic velocity measured by TDI
Ea = Effective arterial elastance
Ees = Ventricular systolic elastance
ESV = End systolic volume
HF = Heart Failure
HFNEF = Heart Failure with Normal Ejection Fraction
hs-cTn = high sensitivity troponin I
IVRT = Isovolumic relaxation time
LA = left atrium / left atrial
LAVI = left atrial volume indexed to body surface area
LV = Left ventricle
LVEF = left ventricular ejection fraction
LVEDP = left ventricular end diastolic pressure
LVEDV = Left ventricular end diastolic volume
LVESV = Left ventricular end systolic volume
LVMI = Left ventricular mass indexed to body surface area
MRI = Magnetic resonance imaging
NT-proBNP = Amino-N-terminal pro-B-type natriuretic peptide
PCWP = pulmonary capillary wedge pressure
PWTd = posterior wall thickness at end diastole
RWT = Relative wall thickness
SWTd = septal wall thickness at end diastole
S = pulmonary vein systolic flow velocity
s' = mitral annular peak systolic velocity measured by TDI
s'lat = s' at the lateral annulus measured by TDI
s'sept = s' at the septal annulus measured by TDI
s'ave = s'lat and s'sept averaged
SR = Strain rate
TDI = Tissue Doppler Imaging
3D = Three-dimensional
2D = Two-dimensional
Ts = Time-to-peak systolic myocardial velocity
Ts-SD = standard deviation of time-to-peak systolic myocardial velocity
This thesis is based on The Canberra Heart Study, a large population-based cohort of adults aged between 60 and 86 years. Echocardiographic and clinical data from 821 subjects assessed between February 2007 and June 2009 is examined.

TDI is an established tool in the echocardiographic assessment of cardiac function. The technology is readily available and enables the measurement of longitudinal myocardial velocities with very high temporal resolution. Because of their subendocardial localisation, longitudinal fibres are particularly sensitive to fibrosis, hypertrophy and ischaemia, and impaired long-axis function can therefore provide a sensitive index for the assessment of systolic myocardial function. TDI derived measures have established prognostic utility, however its use in the evaluation of left ventricular systolic function has largely been within selected populations.

There is still much controversy about the underlying pathophysiology and progression of heart failure (HF), and in particular, HF with normal ejection fraction (HFNEF). Left ventricular ejection fraction (LVEF) remains the mainstay for quantification of LV systolic function, however it is a nonspecific measure that does not provide information on intrinsic muscle performance and involves many assumptions about complex physiological aspects of cardiac performance, including the interactions between load, heart rate and nonuniformity. S’ measurements using TDI have the potential to provide more accurate assessment of LV systolic function than LVEF, but the echo-clinical determinants of this measure are not well characterised. S’ analysis in
a large cohort of older adults may provide insights into the natural history of left ventricular dysfunction. Left ventricular systolic synchrony can be assessed using TDI, quantitated as the standard deviation of time-to-peak systolic myocardial velocity (Ts-SD). LV systolic dyssynchrony reflects in part the concept of ventricular non-uniformity in the mechanical performance of the heart providing temporal and spatial information about mechanical performance of the ventricle. Identification of the determinants of Ts-SD should facilitate a better understanding of the pathophysiology and natural history of LV dysfunction, and may provide insights to why this measure is a suboptimal marker for the selection of HF patients who benefit from cardiac resynchronisation therapy.

HF is the most common cause of hospitalisation in patients over 65 years old. Despite a reduction in mortality for patients with systolic HF, there has not been a significant change in overall death rates and symptomatic HF has a worse prognosis than the majority of cancers. Further understanding of the pathophysiology of HF using novel echocardiographic indices may assist in the early detection of HF and ultimately help reduce its increasing burden on the healthcare system.
Chapter 1: LITERATURE REVIEW
1.1 HEART FAILURE EPIDEMIOLOGY

HF affects around 5.7 million people in the United States based on the latest data from the National Health and Nutrition Examination Study (NHANES) 2005 to 2008\(^1\). The prevalence increases sharply from 1% in 40 year olds to 10% in those 75 years and above. It is the most common cause of hospitalisation in patients over 65 years old\(^2-4\).

HF is a syndrome characterised by an impaired ability of the heart to fill with, and/or eject blood sufficient for metabolic requirements of the body, leading to a constellation of symptoms and signs of systemic and pulmonary congestion. It is now widely accepted that HF can occur in the presence of a normal or "preserved" ejection fraction (HFNEF). Recent studies estimate the prevalence of HFNEF at around 54\(^5\). Accurate estimations are inherently difficult due to lack of standardised diagnostic criteria and the potential for misdiagnosis\(^6\), however the "true" overall prevalence of HFNEF in the community is estimated at 1.1-5.5% of the general population\(^5\). Data from Olmsted County, Minnesota, showed the proportion of all HF patients with HFNEF increased from 38 to 54% between 1987 and 2001 in association with increases in the prevalence of hypertension, diabetes and atrial fibrillation\(^7\). During this same time period survival was found to improve in those with HF and reduced ejection fraction, but not in those with HFNEF, underscoring its importance as a major and growing health problem. With an ageing population and improved survival after HF onset we expect a dramatic increase in prevalence of HF in spite of stable incidence rates.
1.2 IMPORTANCE OF THE EARLY DIAGNOSIS OF HEART FAILURE

As a result of the increasing burden of HF on a limited healthcare system, the end-points of large randomised trials now include the effect of the various interventions on the rate of hospitalisations. Angiotensin-converting-enzyme inhibitors, angiotensin-receptor antagonists, beta-blockers, spironolactone, biventricular pacing, coronary bypass surgery and the use of multidisciplinary teams to treat HF have all been shown to reduce the rate of hospitalisations, as well as reduce mortality or improve functional status.

Despite a reduction in mortality for patients with systolic HF, there has not been a significant change in overall death rates. Symptomatic HF has a worse prognosis than the majority of cancers, with one-year mortality rates of approximately 45%. Although HF is a major and growing health problem, no screening efforts exist to detect the disease at its earlier stages. The factors that render a patient at high risk for the development of HF have recently been promulgated, and the American College of Cardiology and the American Heart Association have developed an approach to the classification of HF, emphasising its evolution and progression through four stages. The classification illustrates the fact that risk factors and structural cardiac abnormalities are necessary for the development of HF, recognises the progressive nature of the condition, and underscores the importance of treatment strategies for disease prevention. Stage A HF patients are at high risk for developing HF but are yet to develop demonstrable structural heart disease and are asymptomatic of congestive HF. Stage B HF patients are also asymptomatic, but have developed structural abnormalities of the heart.
### ACCF/AHA Stages of HF

<table>
<thead>
<tr>
<th>ACCF/AHA Stages of HF</th>
<th>NYHA Functional Classification</th>
</tr>
</thead>
<tbody>
<tr>
<td>A At high risk for HF but without structural heart disease or symptoms of HF</td>
<td>None</td>
</tr>
<tr>
<td>B Structural heart disease but without signs or symptoms of HF</td>
<td>I No limitation of physical activity. Ordinary physical activity does not cause symptoms of HF.</td>
</tr>
<tr>
<td>C Structural heart disease with prior or current symptoms of HF</td>
<td>II Slight limitation of physical activity. Comfortable at rest, but ordinary physical activity results in symptoms of HF.</td>
</tr>
<tr>
<td></td>
<td>III Marked limitation of physical activity. Comfortable at rest, but less than ordinary activity causes symptoms of HF.</td>
</tr>
<tr>
<td></td>
<td>IV Unable to carry on any physical activity without symptoms of HF, or symptoms of HF at rest.</td>
</tr>
<tr>
<td>D Refractory HF requiring specialized interventions</td>
<td>IV Unable to carry on any physical activity without symptoms of HF, or symptoms of HF at rest.</td>
</tr>
</tbody>
</table>

ACCF indicates American College of Cardiology Foundation; AHA, American Heart Association; HF, heart failure; and NYHA, New York Heart Association.

Stage C patients have current or previous symptoms of HF with structural abnormalities of the heart and stage D patients have end-stage symptoms of HF that are refractory to standard treatment.

Control of risk factors in stage A (e.g., hypertension, coronary artery disease and diabetes mellitus) has a favorable effect on the incidence of later cardiovascular events. The goal of treatment at this stage is to prevent cardiac remodeling. Clinical trials have shown that effective treatment of hypertension decreases the occurrence of LV hypertrophy and cardiovascular mortality, reducing the incidence of HF by 30 to 50%\(^9\),\(^10\). The use of ACE Inhibitors in asymptomatic, high-risk patients with diabetes or vascular disease has resulted in significant reductions in rates of death, myocardial infarction and stroke\(^11\).

Whether the burden of clinically overt HF can be effectively reduced by screening efforts remains to be determined. Pharmacotherapy for patients with reduced LVEF has been shown to reduce morbidity and mortality, however the prevalence of the condition in the community is too low to justify a screening program in an unselected population. Evidence from community-
based studies suggests a change in the epidemiology of HF with an increasing proportion of patients with HF having a preserved LVEF\textsuperscript{7}. As opposed to HF with reduced LVEF, pharmacotherapy with a number of neurohumoral modulating agents has not been found to be effective in reducing morbidity and mortality in patients with preserved LVEF\textsuperscript{7}.

1.3 THE ROLE OF IMAGING IN THE DIAGNOSIS AND ASSESSMENT OF HEART FAILURE

Noninvasive imaging has a crucial role in understanding the pathophysiological mechanisms of HF, developing effective therapies, and selecting patients who might benefit from these therapies, as well as guiding therapeutic interventions.

Haemodynamics

Doppler and tissue Doppler echocardiography are currently the best-suited modality for the noninvasive quantification of haemodynamic parameters because of their ability to capture data at high frame rates. Improvements in haemodynamics have not translated into improvements in clinical end-points in HF trials. Haemodynamic measurements have a primary role in diagnosing HF and in particular, LV diastolic function, however provides only a limited mechanistic insight into a particular therapy for HF. The accuracy of noninvasive quantification of LV filling pressure has recently been challenged\textsuperscript{12}. Simultaneous invasive (e.g., pulmonary artery catheter) and noninvasive (echocardiography) techniques for pressure-volume analysis can add sophistication to assessment in trial settings.
Cardiac structure and remodelling

Echocardiography, due to its relatively high availability and low cost is the principal noninvasive modality used to evaluate cardiac structure and remodeling. Two-dimensional (2D) echo-derived volumes and mass are less reliable in the presence of distorted ventricles or wall motion abnormalities, and are based on geometric assumptions. Three-dimensional (3D) echo provides a true volumetric assessment, however depends on high image quality, requires additional post-processing time and is less accurate in the presence of irregular cardiac rhythm. Analysis of left atrial (LA) volumes can provide information on LV filling pressures over time. Cardiac magnetic resonance imaging (MRI) is especially useful for detecting small changes in cardiac structure over time due to its high spatial resolution, high reproducibility and decreased variability. Limitations include its relatively high cost, limited availability, the effect of magnetism resulting in limitations in pacemaker patients, and increased variability depending on analyst experience and differing results based on technique used for determining the boundaries of the LV.

Left ventricular systolic function

LV ejection fraction remains the most widely used parameter to assess LV systolic function. Using echocardiography, a biplane volumetric technique is most accepted. 3D echo or cardiac MRI provides more accuracy. Regional myocardial systolic function can be examined using longitudinal, radial and circumferential fibre shortening in a quantitative, reliable and reproducible way. Available methods include TDI (pulsed or colour TDI), and tissue
tracking imaging (echocardiography and cardiac MR). TDI using pulsed wave Doppler is easy to acquire with faster interpretation and higher frame rates, however only provides information on a single region of interest. Colour tissue Doppler allows for post processing of images, potentially improving the reliability of tissue Doppler velocity, strain and strain rate (SR) measurements. Tissue tracking uses computerised algorithms to track pixels of imaging data (obtained by echo or cardiac MRI) to quantify displacement, velocity and strain of the myocardium. This method is not angle dependent, a limitation with Doppler imaging techniques, which requires optimal alignment of the Doppler beam, or velocities will be underestimated. Tissue tracking using both echo and cardiac MRI has lower temporal resolution compared to Doppler. Echocardiographic tissue tracking requires high-quality images, however 3D tissue tracking is being developed and will potentially overcome this issue. LVEF, tissue velocities, and strain are all load-dependent. Pressure-volume analysis could assist in determining whether changes in these parameters are due to intrinsic myocardial contractile properties or simply due to changes in preload and/or afterload.

**Left ventricular diastolic function**

Left ventricular diastolic dysfunction (DD) is increasingly being identified as a powerful predictor of poor outcome in a variety of cardiac diseases including HF\(^{13}\). Echocardiographic diastolic parameters include transmitral flow; E velocity (peak early mitral inflow velocity, E/A ratio (ratio of peak early mitral inflow velocity to peak late mitral diastolic inflow velocity), deceleration time (DT), isovolumic relaxation time and pulmonary vein flow. TDI and tissue
tracking imaging provide information on diastolic stiffness, however it is important to recognise that all these parameters are load dependent. Further discussion on the echocardiographic analysis of LV diastolic function follows in section 1.7.

Coronary perfusion and myocardial viability

The assessment of coronary perfusion and myocardial viability are very important components in the management of HF patients. Modalities available include stress echocardiography, single positron emission computerised tomographic (SPECT) imaging, cardiac MRI, and positron emission tomography (PET). Combined modality imaging such as cardiac computerised tomography (for noninvasive coronary angiography) with PET imaging (for perfusion) can be used in some centres. Adenosine SPECT, PET and cardiac MRI have the advantage of being able to quantify the amount of perfusion. High-spatial resolution myocardial perfusion is a newer modality that is highly accurate for the detection of coronary artery disease and may allow assessment of right ventricular perfusion. Cardiac MRI has been found to be superior to SPECT imaging for the assessment of myocardial viability and is the current reference standard for quantitative assessment of nonviable myocardium.

1.4 PHYSIOLOGIC-CONCEPTUAL APPROACHES TO CARDIAC PERFORMANCE

Three main schools of thought have emerged over the last century to characterise and quantify cardiac performance. Brutsaert illustrated these views as (i) a hydraulic input-output system, (ii) a ventricular haemodynamic
(compression) pump or (iii) a ventricular muscular pump (Figure 1-2). Each one of these concepts has led to measurements or indices that derive from that specific approach, and continue to be used in present day for the evaluation of patients with HF (Figure 1-3).

Ernest Starling was one of the leading figures to begin analysing cardiac performance as a **hydraulic input-output system**, and was followed by many others including Arthur Guyton\(^{14}\). This approach to the cardiovascular system was then applied to the left ventricle (LV) by Sarnoff and Mitchell with the construction of ventricular function curves\(^{15,16}\). The Swan-Ganz catheter,
through measurement of pulmonary capillary wedge pressure (PCWP) enables the calculation of cardiac output, stroke work and LV end-diastolic pressure (LVEDP) and remains one of the best ways to express the ability of the heart to pump blood (Figure 1-2 left).

Otto Frank constructed ventricular pressure volume loops and this allowed the application of concepts derived from physics and engineering to the heart as a *haemodynamic compression pump*. The elimination of time as part of

Figure 1-3 Indices of cardiac performance

<table>
<thead>
<tr>
<th>INDICES of CARDIAC PERFORMANCE</th>
<th>CARDIAC INPUT–OUTPUT SYSTEM</th>
<th>VENTRICULAR HEMODYNAMIC PUMP</th>
<th>VENTRICULAR MUSCULAR PUMP</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cardiac Input–Output System</strong></td>
<td><strong>Ventricular Hemodynamic Pump</strong></td>
<td><strong>Ventricular Muscular Pump</strong></td>
<td></td>
</tr>
<tr>
<td>- cardiac output (CO)</td>
<td>- ventricular PRESSURE-VOLUME curves</td>
<td>I. CONTRACTION</td>
<td></td>
</tr>
<tr>
<td>- stroke volume (SV) x HR</td>
<td>- ventricular wall stress-strain (Laplace Law)</td>
<td>myocaridal (ventricular) contractility = ?</td>
<td></td>
</tr>
<tr>
<td>- arterial pressure (Pa)</td>
<td>- LVEDV; LVESV; LV mass</td>
<td>II. RELAXATION</td>
<td></td>
</tr>
<tr>
<td>- peripheral resistance (Rt)</td>
<td>- LVEDP / LVESV ratio</td>
<td>- time to onset of relaxation</td>
<td></td>
</tr>
<tr>
<td>- arterial elastance (EA)</td>
<td>- LV Ejection Fraction = (LVEDV - LVESV) / LVEDV</td>
<td>[r-end ejection; l-(r)dp/dt; Echo-Doppler or MRI time intervals]</td>
<td></td>
</tr>
<tr>
<td>- stroke work (SW) = Pa x SV</td>
<td>- LVEDV/LVESV ratio</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Pwpr (r str P; LVEDP)</td>
<td>- peak(-)dp/dt; peak(-)dp/dt; tau</td>
<td>III. UNIFORMITY</td>
<td></td>
</tr>
<tr>
<td>- SW vs PCWP (LVEDP)</td>
<td>- peak(-)dp/dt; peak(-)dp/dt; tau</td>
<td>- ventricular twisting untwisting</td>
<td></td>
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<tr>
<td>(ventricular function curve)</td>
<td>- LV ejection rate; LV power (reserve)</td>
<td>- regional ventricular torsion</td>
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<td></td>
<td>- time-varying elastance</td>
<td>- mitral annular shortening</td>
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<td></td>
<td>- systolic time intervals; time interval ratio</td>
<td>- mitral annular shortening velocity (Em)</td>
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<td></td>
<td></td>
<td>- PEP/ET</td>
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<td></td>
<td>- arterial impedance</td>
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<td></td>
<td>- Echo-Doppler IVRT; early mitral inflow</td>
<td></td>
</tr>
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<td></td>
<td></td>
<td>- velocity E; deceleration time DT; A wave</td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td>Adapted from Brutsaert et al.177</td>
</tr>
</tbody>
</table>

the analysis of cardiac performance was opposed by Robert Rushmer who proposed that cardiac pump performance should be derived from recording time traces of pressure, volume and flow17. A number of measurements that characterise the heart as a haemodynamic compression pump are listed in Figure 1-3 (middle), both inside and outside the time domain. LVEF remains
the most convenient and sensitive measure of haemodynamic pump performance, however the elimination of the time dimension in evaluating cardiac performance has resulted in ongoing controversy with respect to the definition and diagnosis of HF, and in particular, HFNEF. Haemodynamic pump performance remains compensated for a substantial time, and this makes this measure inappropriate for the evaluation of systolic function of the ventricular muscle pump, which is essential in understanding the early phases of HF, and particularly HFNEF.

In 1959 Abbott and Mommaerts and then in 1962 Sonnenblick proposed that the heart should be viewed as a muscular pump rather than a hydraulic or haemodynamic pump. This led to the evaluation of cardiac muscle concepts in the contraction phase of the cardiac cycle and then in the 1970's to cardiac relaxation.

1.5 THE CARDIAC CYCLE

In the first half of the 20th century the prevailing concept of cardiac performance, as a haemodynamic pump led to Wiggers proposed subdivision of the cardiac cycle into systole and diastole. In the next half of the century the heart was rethought of as a muscular pump, however, despite this, Wiggers subdivision of the cardiac cycle has continued to be widely used. This approach has led to the ongoing confusion and controversy about so-called HFNEF. Because this concept of the cardiac cycle has barely been questioned since its beginnings (1883-1963), there have been missed opportunities in cardiovascular research on a number of levels. Emphasis on more current insights into cardiac physiology such as myocardial energetics,
excitation-contraction-relaxation coupling processes, and biochemical and hormonal mechanisms has been lacking has been, and until recently have been ignored.

1.6 ECHOCARDIOGRAPHY FOR THE DETECTION OF SUBCLINICAL LV DYSFUNCTION

LV morphology and diastolic dysfunction

Community-based studies have repeatedly demonstrated that 40% to 50% of individuals with HF have normal EF. This has previously been referred to as “diastolic HF” because of the presence of LV diastolic dysfunction evident from slow relaxation and increased LV stiffness21. HFNEF being increasingly adopted as preferred terminology. The distinction between diastolic HF and systolic HF is increasingly being challenged22, 23, although the issue is not resolved. Many consider HF to be a single syndrome characterised by a progressive decline in systolic performance. This concept is supported by the unimodal distribution of LVEF in large HF trials that recruited patients with normal and reduced LVEF24 and can be appreciated better by tissue Doppler velocities than LVEF25-28. Abnormalities in systolic function have repeatedly been demonstrated in patients with DD using TDI, strain imaging and speckle tracking echocardiography (discussed below). Support for the argument that systolic and diastolic HF are separate syndromes comes from structural, functional and molecular findings, however detailed discussion of these issues is beyond the scope of this thesis and is discussed elsewhere3.

Echocardiographic diagnosis of LV-DD is determined by considering a number of variables examining LV geometry, blood flow and tissue Doppler
variables and LA dimensions. Guidelines have been established for the
diagnosis and grading of LV diastolic function, although the
recommendations will continue to evolve to achieve consensus and
widespread adoption in clinical laboratory reporting\textsuperscript{29}.

A high incidence of HF events has been observed among individuals with
subclinical abnormalities in cardiac structure and function (stage B HF). LV
remodeling describes the process by which the heart changes its size,
geometry, and function over time. The most common form of adverse LV
remodeling is increased LV mass which has been associated with incident
HF for many years\textsuperscript{30}. Increased LV mass can result from a number of
different remodeling patterns. The most common pattern observed in
normally aging individuals is concentric LV remodeling in which LV wall
thickness progressively increases and LV cavity dimensions decrease in the
setting of a preserved LVEF\textsuperscript{31}. The rate of increase in relative wall thickness
(RWT) is more pronounced in women than in men across all ages, especially
later in life, and may account for the higher prevalence of concomitantly
increased ventricular and vascular stiffness observed in community-based
studies\textsuperscript{32}. Concentric LV remodeling is a potential surrogate for direct
evidence of LV-DD and a precursor to LV hypertrophy. The presence of
conventional risk factors for HF modifies this typical remodeling pattern. In
patients with obesity, hypertension and diabetes, LV wall thickness increases
but cavity dimensions do not decrease proportionately with age\textsuperscript{31}. Further
research is required to clarify the functional changes that occur as LV
geometry evolves over time.
Blood flow Doppler assessment of mitral inflow and pulmonary venous flow are established methods to determine the presence of LV-DD. Isovolumic relaxation time (IVRT), E/A ratio, DT, and ratio of pulmonary vein systolic (S) and diastolic (D) flow velocities have variable predictive value and have been scrutinised in a number of studies\textsuperscript{33, 34}. The use of these measures is no longer a first-line diagnostic approach, but is useful when tissue Doppler velocities are non-diagnostic. LA volume measurements are strongly associated with the severity and duration of LV diastolic dysfunction\textsuperscript{35,36}. In a population-based study, the LA volume indexed to body size, progressively increased according to the severity of diastolic dysfunction\textsuperscript{37}.

The progression of HF is likely to be a multiorgan, multisystem process\textsuperscript{38}. Abnormalities in pulmonary function\textsuperscript{39}, renal function, albumin\textsuperscript{40} and haemoglobin\textsuperscript{41} have been associated with HF risk and/or worse HF outcomes. In a large community based sample, a lower ratio of forced expiratory volume in the first second to forced vital capacity ratios (FEV\textsubscript{1}/FVC), haemoglobin and higher serum creatinine were each associated with a 30% increased risk of incident HF after adjustment for conventional risk factors. The strongest risk factors were asymptomatic LV-SD and LV-DD respectively\textsuperscript{42}.

LA volume measurements are strongly associated with the severity and duration of LV-DD\textsuperscript{35, 36}. In a population-based study the LA volume index (LAVI) progressively increased according to the severity of DD\textsuperscript{37}. 

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Tissue Doppler Imaging

TDI was adapted by Isaaz, McDicken and Sutherland to assess tissue (myocardial) velocities. In contrast to “classic” Doppler echocardiography which measures high-frequency, low-amplitude signals from rapidly moving red blood cells, TDI uses colour flow mapping to filter out signals reflected from slow moving structures such as the myocardium and detects low-frequency, high-amplitude signals of myocardial tissue motion. The motion of the myocardium is a complex three-dimensional deformation process resulting in longitudinal shortening, radial thickening and circumferential shortening of myocardial muscle.

Pulsed wave TDI is measured online, measuring instantaneous myocardial velocities with very high temporal resolution (250-300 samples/sec or a temporal resolution of 3-4ms). Colour-coded TDI requires post-processing on an echocardiographic platform or using a dedicated workstation. TDI velocities are superimposed on grey-scale, two-dimensional images.

The peak systolic (s’) mitral annular velocity and early diastolic (e’) mitral annular velocities are considered to be sensitive markers of LV systolic and diastolic function. Multiple studies have documented abnormalities in both systolic and diastolic function using TDI in a variety of disease states, as discussed below. Systolic mitral annular velocities are a sensitive marker of longitudinal LV systolic function and are impaired in many conditions where the LV ejection fraction remains normal. Early diastolic annular velocities (e’) are significantly associated with LV relaxation in both animal and human studies. The ratio of early mitral valve flow velocity (E) divided by e’ (E/e’)

36
correlates closely with LV filling pressures\textsuperscript{43}. E/e’ is a powerful predictor of survival after myocardial infarction and if elevated, measures a superior prognostic markers than clinical or other echocardiographic variables\textsuperscript{44}.

Table 1-1 Practical differences between pulsed-wave and colour-coded tissue Doppler imaging

<table>
<thead>
<tr>
<th>Pulsed wave TDI</th>
<th>Colour-coded TDI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Advantages</strong></td>
<td><strong>Advantages</strong></td>
</tr>
<tr>
<td>Available on most high-end machines</td>
<td>Post hoc repositioning of sample volumes possible</td>
</tr>
<tr>
<td>High temporal resolution</td>
<td>Simultaneous comparison of multiple segments</td>
</tr>
<tr>
<td>Online visualisation of velocity curves</td>
<td></td>
</tr>
<tr>
<td><strong>Disadvantages</strong></td>
<td><strong>Disadvantages</strong></td>
</tr>
<tr>
<td>Post hoc repositioning of sample volumes not possible</td>
<td>Myocardial velocities 10-20% lower than with pulsed wave TDI</td>
</tr>
<tr>
<td>Simultaneous comparison of multiple segments impossible</td>
<td>Online depiction of myocardial velocity curves not possible</td>
</tr>
</tbody>
</table>

There are both technical and clinical limitations with TDI. Technical factors are minimised with experience, and the measures are highly reproducible with low variability. The location of the sample size, correct gain and filter settings and minimal angulation are all important. In normal subjects e’ velocity is positively correlated to preload and the E/e’ may not provide a reliable estimate of LV filling pressures, therefore clinical factors and other aspects of cardiac structure (e.g. LV geometry, LA size) need to be considered. In subjects with significant annular calcification, surgical rings,
mitral stenosis, and prosthetic mitral valves e’ velocities are reduced, whereas moderate to severe mitral regurgitation increases e’ velocity and constrictive pericarditis increases septal e’ velocities. E/e’ should be cautiously interpreted in these clinical settings. In decompensated advanced systolic HF, E/e’ showed a poor correlation with LV filling pressures, especially in the presence of large LV volumes, worse cardiac indices and in the presence of cardiac resynchronisation therapy\textsuperscript{45}.

**Systolic mitral annular velocity**

Mitral annular velocities reflect the longitudinal function of the ventricle. Longitudinally directed myocardial fibres are found in the subendocardium\textsuperscript{46}, and during early systole, shortening of these fibres precedes shortening of circumferential fibres\textsuperscript{47}. Because of their subendocardial localisation, longitudinal fibres are particularly sensitive to fibrosis, hypertrophy and ischaemia, and impaired long-axis function can therefore provide a sensitive index for the assessment of systolic myocardial function\textsuperscript{27,48–51}.

Colour-coded TDI and pulsed wave TDI s’ have been validated with established invasive indices of LV contractility in animal models\textsuperscript{52,53}. Tissue Doppler derived myocardial velocities are strongly dependent on both the number of myocytes and the myocardial beta-adrenergic receptor density in patients with coronary disease\textsuperscript{54}. Down-regulation of beta-adrenergic receptor density in cardiac failure occurs predominantly in the subendocardium\textsuperscript{55}.

The prognostic value of s’ has been documented in patients with HF, mitral regurgitation and ischaemic heart disease\textsuperscript{56–58}. S’ was shown to correlate
with B-type natriuretic peptide (BNP) levels better than other standard echocardiographic measurements including LVEF and mitral inflow patterns\textsuperscript{59}.

Abnormal left ventricular long axis systolic function assessed using s’ has been detected in those with normal EF in patients with DD or “isolated” diastolic HF\textsuperscript{25, 27, 28, 60-63}, diabetic subjects\textsuperscript{64} and those with LV hypertrophy\textsuperscript{65}. A number of studies have shown a graded association between s’ velocities and cardiac function, being highest in normal controls, with progressive reduction in subjects with diastolic dysfunction, diastolic HF and lowest values in those with systolic HF\textsuperscript{25, 27, 28, 62, 63, 66}. In population-based subjects reductions in s’ velocities have been found with increasing diastolic dysfunction\textsuperscript{67}. In contrast to e’, normal values for systolic velocities and their echo-clinical determinants are not well established.

**Standard deviation of time to peak systolic velocity: Ts-SD**

Ts-SD using TDI has been used to quantify the extent of LV systolic dyssynchrony and has previously been validated\textsuperscript{68}. Reference limits have been established in relatively small samples of clinic-based populations\textsuperscript{69}. LV dyssynchrony has been shown to be prevalent in various clinical and subclinical cardiac diseases including LV hypertrophy\textsuperscript{70}, myocardial ischemia\textsuperscript{71}, myocardial infarction\textsuperscript{72}, HF\textsuperscript{73}, and with right ventricular pacing\textsuperscript{74}.

Using a 12 segment model of the LV, a normal cutoff value for Ts-SD of <33ms (2 standard deviations above "control" subjects), has been established in clinic-based populations, with elevated levels purported to predict a favorable response to cardiac resynchronisation therapy (CRT)\textsuperscript{75}.  

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However, selection of patients for CRT based on the current guidelines\textsuperscript{76} results in approximately 30\% not responding to therapy despite the use of TDI to predict a favorable response therapy\textsuperscript{77}. Accordingly Ts-SD is no longer recommended for the assessment of LV dyssynchrony to select patients who may benefit from CRT\textsuperscript{78}.

LV dyssynchrony reflects in part the concept of non-uniformity in the mechanical performance of the heart. This has been considered one of the key determinants of cardiac performance for a long time\textsuperscript{79}, along with load and activation-inactivation. The non-uniform behaviour of load (volume and/or pressure) and activation-inactivation in time and space regulates the function of the normal ventricle, and may become imbalanced and increased in diseased states\textsuperscript{80}. Identification of the determinants of Ts-SD in unselected populations should facilitate a better understanding of the pathophysiology and natural history of LV dysfunction, and may provide insights to why this measure is a suboptimal marker for the selection of HF patients who benefit from cardiac resynchronisation therapy.

**Strain and strain rate imaging**

Conventional TDI quantifies myocardial tissue velocity but is affected by tissue translation and tethering. Strain imaging circumvents this by measuring deformation and velocity relative to a myocardial reference frame. A regression calculation performed on velocity data from adjacent sites within a region of interest creates a strain rate (SR) curve: $\text{SR} = \text{spatial derivative of velocity at 2 points in the myocardium} = \text{Va} - \text{Vb}/d$. SR integrated over time yields strain, which is a dimensionless index reflecting total myocardial
deformation, or change in length during the cardiac cycle. Global and regional cardiac function can be analysed using strain and SR imaging. Regional radial and longitudinal strain and SR can be analysed as well as circumferential-radial shear strain, describing the local torsion and twisting/untwisting. The precise interaction of changes in SR/strain with alterations in preload and afterload has not been determined in clinical practice. SR has been found to be less dependent on load variations than strain, and has been applied clinically. These techniques require further study for use in the evaluation of LV-DD. An important problem that may confound regional SR/strain calculation is the presence of signal noise in the data set. The SR curve is derived by comparing two myocardial Doppler velocity data sets, and this calculation amplifies any noise component. High frame rate data acquisition (>170/sec) and the use of data averaging techniques during post processing reduce the random noise component.

Despite these limitations, the sensitivity of SR has made it an effective tool in the evaluation of subclinical heart disease. It has been valuable in the detection of myocardial involvement in non-cardiac diseases such as amyloidosis, diabetic heart disease and Friedreich's ataxia, and in the distinction of hypertrophy caused by hypertension and cardiomyopathy. Strain has been used to examine the effects of treatment response in hypertensive heart disease, diabetes and Fabry disease. However, it is unclear whether there is incremental advantage in using SR in preference to tissue velocity. In the assessment of diabetic heart disease, tissue e’ velocity was at least as sensitive as SR imaging markers.
Speckle tracking

Speckle tracking echocardiography is based on analysis of the spatial dislocation (tracking) of speckles (spot generated by the interaction of ultrasound beams and myocardial fibres) on routine 2-D sonograms. It allows for the assessment of regional and global myocardial function that is angle independent and not affected by translational movements. Longitudinal, radial and circumferential strain can be measured and has been validated with sonomicrometry and tagged MRI showing high reproducibility and feasibility\(^9_1\). Limitations include its dependence on high frame rates and high quality 2-D images, which are required to obtain optimal definition of the endocardial border.

1.7 B-TYPE NATRIURETIC PEPTIDES

BNP is secreted primarily by atrial and ventricular cardiomyocytes. Like atrial natriuretic peptide it has vasodilator, lusitropic and natriuretic actions. In addition, it inhibits cardiac sympathetic traffic, renin-angiotensin-aldosterone activity and cardiac fibrosis\(^9_2\). Increased ventricular or atrial wall stress, reflecting volume or pressure overload, is the primary driver of myocyte stretch-mediated secretion of BNP. Ischaemia, neurohormones and cytokines can also stimulate or modify BNP gene expression.

Plasma levels of BNP and NT-proBNP increase with age and are lower in men than in women\(^9_3\). There is an inverse relationship to body mass index (BMI) and lean mass, and increase with worsening glomerular filtration rate.
BNP and echocardiographic indices of cardiac function

BNP is primarily synthetised by cardiomyocytes and therefore the greatest secretion of BNP is from the LV. Plasma levels are positively correlated with LV dimensions, volumes and mass, and inversely with LV ejection fraction. In subjects with LV hypertrophy and clinical HF, levels are further elevated\textsuperscript{94-98}. BNP increases with greater severity of diastolic dysfunction and occurs independently of LVEF, age, sex, BMI and renal function. The highest levels are present in those with restrictive filling patterns. Level reflect indexes of filling pressure, including E/e'. Positive correlations have been found with LA volume, particularly in the general population and in patients with HFNEF\textsuperscript{93,99}. There is a modest relationship between BNP levels and LV filling pressures, which reflects the complexity of factors influencing secretion and clearance\textsuperscript{100}. Aside from the effects of age, gender, renal function and neurohormonal or cytokine status\textsuperscript{101}, the right ventricle and LA contribute to peptide levels. Dilated ventricles secrete more peptides for a given filling pressure due to greater wall stress and mass. Low BNP levels however have a high negative predictive value for an elevated filling pressure in most settings\textsuperscript{102}. Doppler echocardiography is widely validated method to accurately assess LV filling pressures. These indices have been validated with BNP for detection of PCWP >15mmHg in patients admitted to the intensive care unit. In patients with cardiac disease, BNP levels >400pg/ml had a similar
sensitivity (91%), but poorer specificity (51% vs. 91%) and overall accuracy than Doppler indices such as E/e’ for detecting a PWCP >15mmHg \( ^{103} \).

1.8 CARDIAC TROPONIN CONCENTRATIONS

Pathologic changes in cardiac myocytes are an important cause of cardiac remodelling. Cardiac troponin (cTn) is a three-unit complex located in the actin filament, comprising troponin I, T and C. Along with tropomyosin it is essential for the regulation of calcium-mediated contraction of the skeletal and cardiac muscles. cTn, T and I are highly sensitive and specific markers of myocardial injury and have replaced the MB fraction of creatine kinase as the gold standard for the diagnosis of acute myocardial infarction.

Detectable circulating cTnI is rare in the general population using assays available prior to 2013. More recently commercially available high-sensitivity (hs) assays allow the measurement of low concentrations of cTn with high precision. In the Val-HeFT study of over 4000 patients, hs-cTn was detectable in 92% of patients, compared to only 10.4% using the standard cTnT assay \(^{104} \).

Mechanisms of troponin release in heart failure

cTn release occurs in patients with and without obstructive coronary disease. Potential contributing mechanisms have been proposed, including subendocardial ischaemia leading to myocyte necrosis, cardiomyocyte damage from inflammatory cytokines or oxidative stress, hibernating myocardium or apoptosis \(^{105-109} \). cTn can be released from injured but viable myocardium as a result of increased membrane permeability or by a stretch-
related mechanism mediated by integrins\textsuperscript{110-112}. Altered calcium handling resulting from increased preload has been found to activate intracellular proteolytic enzymes that degrade cTn, releasing cTn fragments into the circulation, which may have epitopes with an affinity for the cTnl immunoassays\textsuperscript{113}.

**Significance of troponin release in heart failure**

Multiple studies have documented an association between elevated circulating cTn concentrations and adverse clinical outcomes in various HF populations\textsuperscript{114}. A large observational study in Europe has shown associations between low levels of cTn and the future development of HF in asymptomatic subjects, similar to observations with BNP\textsuperscript{115}. Both cTnT and cTnl are prognostic indicators in patients with acute and chronic HF. In addition, when added to other biomarker considerations, may provide insight into mechanisms of transition from compensated to decompensated HF. Persistently increased cTn concentrations during compensated phases of HF suggest ongoing myocyte injury and cardiac remodeling resulting in further deterioration in ventricular function and worse clinical outcomes\textsuperscript{116, 117}. In a study comparing BNP, cTn and markers of ventricular remodelling in patients with acute HF, stable HF and control subjects; acute HF patients had significantly higher cTn, markers of collagen biosynthesis and markers of extracellular matrix remodelling\textsuperscript{118}. 

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1.9 CONCLUSIONS

HF is a major and growing health problem and has become a leading cause for hospitalisations and death. HFNEF is more common than HF with reduced EF but disease identification remains challenging. The current recommended diagnostic criteria lack sensitivity and specificity for the disease, and this difficulty is compounded by the high rates of co-morbid cardiovascular and non-cardiovascular diseases in the elderly. The mortality rates for HFNEF have not significantly changed, in contrast to HF with reduced EF.

Improvements in understanding the natural history of disease will assist in identifying patients as high-risk for developing HF. Stage B HF patients are the most prevalent group, and are at high risk for the development of symptomatic HF\textsuperscript{119}. These patients often go undetected and untreated.

TDI provides information on preclinical LV dysfunction, and may provide insights as to the promoters of impaired myocardial function and physiological continuum between “normal” LV function and the development of quantifiable LV dysfunction during diastole and systole. Echocardiography and the use of cardiac biomarkers can potentially be used for screening, early diagnosis and the assessment of the effects of pharmacologic therapy in asymptomatic LV dysfunction.
Chapter 2: METHODOLOGY
2.1 DEVELOPMENT OF THE STUDY PROTOCOL

The data for my thesis were collected as part of the Canberra Heart Study, which is the first Australian population-based study to evaluate the epidemiology of HF and LV dysfunction. The thesis design and methodology were developed under the supervision of Professor Walter Abhayaratna, who is the principal investigator of the Canberra Heart Study.

2.2 SOURCES OF FUNDING

The Canberra Heart Study follow-up assessment, commencing in 2007, was funded through a project grant awarded to Dr Abhayaratna from the National Heart Foundation of Australia. Dr Ben Jacobson was funded through an Australian National University Medical School Fellowship, awarded in 2010.

2.3 STUDY POPULATION

The methods for the Canberra Heart Study, a population-based prospective cohort study of adults of age 60 to 86 years, have been previously described67. For the original research related to this thesis, we report data from 821 subjects (mean age 75.3 ± 5.8yrs, 52% women) who attended the assessment clinic between February 2007 and June 2009. The Canberra Heart Study was approved by the Human Research Ethics Committees of the Australian National University and Australian Capital Territory Health. Subjects provided written and informed consent for the study.
2.4 CLINICAL DATA

A self-administered questionnaire was used to gather data on a history of cardiac failure, myocardial infarction, angina, hypertension, diabetes, and alcohol consumption. Brachial artery systolic and diastolic blood pressures (BP) were measured after 10 minutes of rest in a seated position and two recordings were averaged for each participant. Hypertension was defined as systolic BP ≥140mmHg, diastolic BP ≥90mmHg or the use of medical therapy for hypertension. Height and weight were measured while the subject was wearing light clothing without shoes. Body surface area (BSA) in meter squared was calculated by the square root of height in cm times weight in kilograms divided by 3600. A self-reported history of clinical HF was verified by a review of the subject’s medical records. Study participants were consulted by a cardiologist (Professor Walter Abhayaratna), who was blinded to the echocardiography findings and past medical history. They were asked about symptoms of dyspnoea, orthopnoea, paroxysmal nocturnal dyspnoea or dependant oedema; and examined for the presence of a raised heart rate, raised jugular venous pressure, displaced apex beat, added heart sounds, cardiac murmurs, lung crepitations or peripheral oedema. HF status was determined according to the Framingham criteria for the diagnosis of HF\textsuperscript{120}.

2.5 TRANSTHORACIC ECHOCARDIOGRAPHY

One of three experienced sonographers obtained images according to the guidelines of the American Society of Echocardiography (ASE) using transthoracic echocardiography (Vivid 7; Vingmed-General Electric) according to a standardised protocol\textsuperscript{29, 121}.
2.6 CHAMBER QUANTIFICATION

Quantification of the left ventricle

Linear measurements at end-diastole of the interventricular septal wall thickness (SWTd) and posterior wall thickness (PWTd) plus LV internal dimensions in end-diastole and end-systole (LVIDd and LVIDs) were obtained from 2D images made from the parasternal long axis acoustic window. Measurements were taken at the level of the mitral valve leaflet tips. End-diastole was determined by taking the frame after mitral valve closure, and end-systole as the frame preceding mitral valve opening.

Figure 2-1 LV chamber measurement

LV mass was measured according to the ASE recommendations\textsuperscript{121} using a formula based on linear dimensions that has been validated in necropsy studies:
LV mass = 0.8x\{1.04[(LVIDd + PWTd + SWTd)^3 - (LVIDd)^3]\} + 0.6g

Where LVIDd is the LV internal diastolic diameter and PWTd and SWTd are posterior wall thickness at end-diastole and septal wall thickness at end-diastole, respectively. LV mass was indexed to BSA. The presence of LV hypertrophy was confirmed if indexed LV mass was >95g/m² in women and >115g/m² in men (Figure 2-2).

Relative wall thickness (RWT) was calculated by the formula (PWTd + SWTd)/LVIDd, and an increase in LV RWT was categorised as either concentric (RWT > 0.42) or normal (RWT ≤ 0.42). Left ventricular hypertrophy was classified as concentric if an increase in indexed LV mass was associated with an increased RWT and eccentric if the increased LV mass was associated with normal RWT (RWT ≤0.42).

**Figure 2-2 Assessment of LV remodeling**
LV volumes and ejection fraction

The modified Simpson's rule (biplane method of disks) was used to measure LV volume and ejection fraction. Total LV volume is calculated from the summation of a stack of elliptical disks. The height of each disk is based on the longer of the two lengths from the 2- and 4-chamber views. The cross-sectional area of the disk is based on the two diameters obtained from the 2- and 4-chamber views. Left ventricular end-diastolic volume (LVEDV) and end-systolic volume (LVESV) are measured and EF calculated by: ejection fraction = (LVEDV − LVESV)/LVEDV (Figure 2-3).

Figure 2-3 LV volume and EF by the biplane method of disks
Left atrial volume measurements

LA volume was measured using Simpson’s rule (Figure 2-4) according to the ASE recommendations and indexed to body surface area (BSA)\(^{121}\). Simpson’s algorithm divides the LA into a series of stacked oval disks. The volume of the disks is derived from the disks height (h) and orthogonal minor and major axes, \(D_1\) and \(D_2\): \(\text{Volume} = \frac{\pi}{4}(h) \sum (D_1)(D_2)\) was calculated by the online software package.

Figure 2-4 LA volume based on the biplane method of disks

2.7 ASSESSMENT OF LEFT VENTRICULAR DIASTOLIC FUNCTION

Transmitral pulsed wave Doppler

Pulsed-wave (PW) Doppler was performed in the apical 4-chamber view to obtain mitral inflow velocities and assess LV filling. A 1mm to 3mm sample volume was placed between the mitral leaflet tips to record the velocity profile. The sweep speed was 100mm/s, at end-expiration and averaged over
3 consecutive cardiac cycles. The E velocity, A velocity, E/A ratio and DT of mitral inflow were measured.

Figure 2-5 Mitral inflow by PW Doppler

Pulsed wave tissue Doppler velocities

Pulsed wave TDI was performed in the apical views to acquire mitral annular velocities. The sample volume was positioned at or within 1cm within the septal and lateral insertion sites of the mitral leaflets and adjusted to cover the longitudinal excursion of the mitral annulus in both systole and diastole. The velocity scale was generally set at 20cm/s above and below the zero-velocity baseline. The sample plane of the ultrasound beam was aligned with the minimal angulation achievable to the plane of cardiac motion. The sweep speed was set at 50 to 100mm/s, recorded at end-expiration and averaged over 3 to 5 cardiac cycles. The systolic (s’), early diastolic (e’) and late diastolic (a’) mitral annular velocities were measured at the septal and lateral annular sites.
Grading of LV diastolic function.

LV diastolic function was graded according to the ASE guidelines into four categories\(^{122}\) (Table 2.1). Doppler evaluation of the mitral and pulmonary venous inflow and TDI at the lateral mitral annulus velocity was used.

### Table 2-1 Grading of LV diastolic function

<table>
<thead>
<tr>
<th>Grade</th>
<th>Mitral inflow</th>
<th>Pulmonary venous inflow</th>
<th>TDI (E/e')</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>0.8 &lt; E/A &lt; 1.5 DT &gt;160ms</td>
<td>S&gt;D MV Adur &gt; PV A dur</td>
<td>&lt;10</td>
</tr>
<tr>
<td>Grade 1 DD</td>
<td>E/A &lt;0.8 DT &gt;240ms</td>
<td>S&gt;D MV Adur &gt; PV A dur</td>
<td>&lt;10</td>
</tr>
<tr>
<td>Grade 2 DD</td>
<td>0.8 &lt; E/A &lt; 1.5 DT &gt;160ms</td>
<td>S&lt;D MV Adur + 30ms &lt; PV A dur</td>
<td>≥10</td>
</tr>
<tr>
<td>Grade 3/4 DD</td>
<td>E/A &gt;1.5 DT &lt;160ms&lt;</td>
<td>S&gt;D MV Adur + 30ms &lt; PV A dur</td>
<td>≥10</td>
</tr>
</tbody>
</table>

At least two Doppler criteria consistent with moderate to severe left LV-DD were required to distinguish from normal diastolic function. A, peak mitral filling velocity at atrial contraction; D, peak velocity of pulmonary venous forward flow during diastole; DT, deceleration time of mitral E wave; E, peak early mitral inflow filling velocity; e', peak velocity of lateral mitral annulus motion during diastole; MV Adur, duration of mitral A wave; PV Adur, duration of pulmonary venous reversal wave at atrial contraction; S, peak velocity of pulmonary venous forward flow during systole.
2.8 ASSESSMENT OF LV SYNCHRONY

Colour tissue Doppler imaging; myocardial velocity curves

Colour TDI was recorded from the apical four-chamber, two-chamber and long-axis views with the images optimised to achieve a frame rate >150Hz. At least three consecutive beats were stored and the images analysed offline using customised software (EchoPac-PC, version 6.1.0; Vingmed General Electric). Myocardial velocity curves were reconstructed offline using a six basal segment model (septal, lateral, anteroseptal, posterior, anterior and inferior segments) of the LV. Investigators performing the measurements were blinded to the clinical information. The basal segments were sampled one centimetre above the annulus. Ts (time to peak myocardial systolic velocity during the ejection period) was measured from the beginning of the QRS complex to peak velocity and the standard deviation between the 6 segments was calculated (Ts-SD).

Figure 2-7 Measurement of Ts-SD
Quantification of systolic dyssynchrony by Ts using TDI has previously been validated using velocity encoded MRI\textsuperscript{68, 123, 124}, and reference limits have been evaluated in relatively small samples of clinic-based populations\textsuperscript{69}. Using a 12 segment model, a normal cutoff value for Ts-SD of $<33$ms (2 standard deviations above "control" subjects), has been found, above which predicted a favourable response to CRT\textsuperscript{75}.

2.9 SEROLOGICAL TESTS

B-type natriuretic peptide

Amino-N-terminal pro-B-type natriuretic peptide (NT-proBNP) levels were measured using a commercially available and fully automated electrochemiluminescence sandwich immunoassay on an Elecys 1010 (proBNP, Roche Diagnostics, Basel, Switzerland). Venous blood was collected in serum tubes, centrifuged and stored at $-70^\circ$C until analysis. The immunoassay has a within-run coefficient of variability (CV) of 0.7\% to 1.6\% and a between-run coefficient of variability of 5.3\% to 6.7\%.

Cardiac troponin

A commercial high-sensitivity assay from Abbott Diagnostics was used to measure cTnI from blood samples collected during subject’s attendance for clinical assessment and echocardiography. Serum was stored at $-80^\circ$C and samples were only subjected to one freeze-thaw cycle. The long-term stability of cTnI with both the Beckman coulter high sensitivity (hs)-Tnl\textsuperscript{125} and the Abbott ARCHITECT STAT hs-cTnl\textsuperscript{126} assays has been demonstrated under these conditions.
Analytical studies of the ARCHITECT STAT hs-TnI assay from the Abbott Diagnostic, which was made available in a commercial form by the manufacturer (Abbott USA), showed that the limit of the blank (LoB) was 0.5ng/L, the limit of detection (LoD) was 1.0ng/L, the concentration corresponding to the 20% CV was 1.8ng/L, the concentration corresponding to the 10% CV was 3.9ng/L, and the concentrations corresponding to the 99th percentile values were 14ng/L in adult males and 11.1ng/L in adult females.\cite{footnote1, footnote2}
Chapter 3: MITRAL ANNULAR SYSTOLIC VELOCITY: CLINICAL DETERMINANTS IN POPULATION-BASED SUBJECTS

Submitted for publication in part in:

Jacobson BM, Abhayaratna WP. Mitral annular systolic velocity: clinical determinants and relationship to diastolic function in population-based subjects. Under review in American Journal of Cardiology
3.1 ABSTRACT

Objective: To assess the clinical determinants of s' measured by pulse-wave TDI in a population-based sample of older adults.

Design, setting and participants: A total of 821 participants of a longitudinal cohort study (mean age 75.3 ± 5.8yrs, 52% women) were examined by echocardiography. S' at the lateral (s'lat) and septal (s'sept) annulus was assessed by pulse-wave TDI.

Main outcome measures: To assess the clinical determinants of S’ and the relationship between s’ and diastolic dysfunction (DD).

Results: S’lat was higher than s’sept (7.4cm/s vs. 6.4cm/s, p<0.001) with a modest correlation between sites (p=0.49; p<0.001). S’lat was higher in men (7.7cm/s vs. 7.1cm/s, p=0.006) and lower in those with a history of myocardial infarction and atrial fibrillation (p<0.001 for both). There was weak correlation with age (p= -0.13;p=0.002); heart rate (p=0.11;p=0.006); and systolic BP (p=-0.16;p<0.001).

Conclusions: In an unselected population of older adults s' declines with age and is lower in women. S' velocities are reduced with adverse loadings conditions.
3.2 BACKGROUND

TDI is a robust and reproducible tool, which has permitted a quantitative assessment of both regional and global myocardial function. The acquisition of these parameters is rapid and readily available for use in routine clinical practice. Colour-coded TDI and pulsed wave TDI s' have been validated with established invasive indices of LV contractility in animal models, however in contrast to e' velocities, normal values for s' velocities and their clinical determinants are not well established.

Our objectives in this study were to characterise the relationship between LV systolic function as assessed by s'. There is limited data evaluating s' in unselected populations.

3.3 METHODS

Study sample

The methods for the Canberra Heart Study, a population-based prospective cohort study of adults of age 60 to 86 years, have been previously described. In this study, we report data from 821 subjects (mean age 75.3 ± 5.8yrs, 52% women) who attended the assessment clinic between February 2007 and June 2009. Subjects provided written and informed consent for the study. The study was approved by the Human Research Ethics Committees of the Australian National University and Australian Capital Territory Health.
Echocardiographic assessment

One of three experienced sonographers obtained images according to the guidelines of the American Society of Echocardiography (ASE) using transthoracic echocardiography (Vivid 7; Vingmed-General Electric) according to a standardised protocol\(^{29,121}\). LVEF was measured by the Simpson’s biplane disk summation method on two-dimensional echocardiographic images from the apical two- and four-chamber views. LV mass and LA volume were measured according to the ASE recommendations and indexed to BSA\(^{121}\). TDI recordings were measured online from the apical four-chamber view in the mitral annulus medial and lateral positions using a 2mm sample volume. S', peak early (e') and late diastolic (a') velocities were obtained for each patient. Diastolic function was graded according to the ASE guidelines\(^{29,121,122}\).

Assessment of clinical risk-factors

A self-administered questionnaire was used to gather data on a history of cardiac failure, myocardial infarction, angina, hypertension, diabetes, and alcohol consumption. Brachial artery systolic and diastolic BP were measured after 10 minutes of rest in a seated position and two recordings were averaged for each participant. Height and weight were measured while the subject was wearing light clothing without shoes. BSA was calculated.

Reproducibility of measurements

Intraobserver variability was assessed in 100 patients by repeating the measurements on two occasions ten days apart. Measurements were
performed offline by a second observer and variability was calculated as the mean percent error, derived as the difference between the two sets of measurements divided by the mean of the observations.

**Statistical analysis**

Continuous variables are presented as mean +/- standard deviation. Categorical variables are displayed as percentages. Differences between groups were assessed by likelihood ratio tests (categorical variables) or Kruskal-Wallis tests, and non-parametric tests for trend (continuous variables) as appropriate. Ordinal logistic regression was used to assess the association between the ordinal variable, s’ velocity, and clinical, anthropometric and echocardiographic factors in univariate and multivariate analyses. All hypothesis testing was two sided and significance was declared if p < 0.05. The assumptions for regression models were checked statistically.

**3.4 RESULTS**

**Participation rates**

A total of 821 randomly selected subjects, aged 60 to 86 years (mean age 75.3 ± 5.8yrs, 52% women), were examined. 46 had atrial fibrillation.

**Reproducibility of s’ measurement**

S’ measurement was reproducible with intra-rater correlation of 0.88 and inter-rater correlation of 0.82.
Effect of clinical parameters on s’ velocities at the lateral and septal annulus

The effect of clinical parameters on s’ velocities at the lateral and septal annulus was analysed. $s'_{\text{lat}}$ was higher than $s'_{\text{sept}}$ (7.3 cm/s vs. 6.3 cm/s, $p<0.0001$) with a modest correlation between sites ($p=0.55; p<0.0001$). There was a trend towards lower s’ in those with a history of diabetes. $s'_{\text{lat}}$ and $s'_{\text{sept}}$ were higher in men (7.5 cm/s vs. 7.1 cm/s, $p=0.005$, 6.5 cm/s vs. 6.0 cm/s, $p<0.0001$ respectively). S’ was significantly lower in subjects with a history of coronary artery disease ($s'_{\text{lat}}$ only, $p=0.047$), myocardial infarction ($p<0.0001$ for both), hyperlipidaemia ($s'_{\text{lat}}$ only, $p=0.023$) and atrial fibrillation ($p=0.0006$ for $s'_{\text{lat}}$ and $p<0.0001$ for $s'_{\text{sept}}$) (Table 3-1).

Table 3-1 Effect of clinical parameters on s’ velocities at the lateral and septal annulus

<table>
<thead>
<tr>
<th>Parameter</th>
<th>S’ lateral, cm/s</th>
<th>S’ septal, cm/s</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Parameter present</td>
<td></td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Women</td>
<td>7.5 (2)</td>
<td>7.1 (1.6)</td>
</tr>
<tr>
<td>Systemic hypertension</td>
<td>7.4 (1.9)</td>
<td>7.2 (1.8)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>7.3 (1.9)</td>
<td>7.1 (1.8)</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>7.3 (1.8)</td>
<td>7.0 (2.0)</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>7.4 (1.8)</td>
<td>6.4 (1.8)</td>
</tr>
<tr>
<td>Hyperlipidaemia</td>
<td>7.4 (1.9)</td>
<td>7.1 (1.8)</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>7.4 (1.9)</td>
<td>6.7 (1.8)</td>
</tr>
</tbody>
</table>
Anthropometric associations with s' velocities

There were differences between septal and lateral s’ velocities and their associations with anthropometric measurements (Table 3-2). Weak associations were observed at both sites with age, pulse pressure and weight. The s’lat was additionally associated with heart rate and systolic BP.

Table 3-2 Anthropometric associations with s’ velocities

<table>
<thead>
<tr>
<th>Parameter</th>
<th>S' lateral</th>
<th>S' septal</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>rho</td>
<td>p-value</td>
</tr>
<tr>
<td>Age</td>
<td>-0.12</td>
<td>0.0009</td>
</tr>
<tr>
<td>Heart rate</td>
<td>0.10</td>
<td>0.006</td>
</tr>
<tr>
<td>Systolic BP</td>
<td>-0.13</td>
<td>0.0003</td>
</tr>
<tr>
<td>Diastolic BP</td>
<td>-0.001</td>
<td>0.93</td>
</tr>
<tr>
<td>Pulse pressure</td>
<td>-0.14</td>
<td>0.0001</td>
</tr>
<tr>
<td>Body Mass Index</td>
<td>-0.002</td>
<td>0.96</td>
</tr>
<tr>
<td>Weight</td>
<td>0.08</td>
<td>0.02</td>
</tr>
</tbody>
</table>

3.5 DISCUSSION

Normal values for s’ velocities have been published, however are not well defined. Nikitin et al\textsuperscript{130} used offline TDI measurements, which are lower than those obtained online as in this study, and are not interchangeable\textsuperscript{131}. Previous studies have shown that clinical factors influence s’ velocities measured using TDI, however there is little data available and conflicting information. We found s’ to be significantly higher in men. In normal subjects
Nikitin et al\textsuperscript{130} found higher $s'$ velocities in men, whereas Sun et al\textsuperscript{132} found no effect of gender. Yip et al\textsuperscript{133} reported a good correlation of $s'$ with $e'$ and $a'$ velocities but that it was better after adjustment for age, sex and heart rate. In our study, age had a weak but significant negative correlation with $s'$, consistent with previous findings in healthy subjects\textsuperscript{130, 132, 134, 135}. Heart rate, systolic BP and pulse pressure had a weak correlation with $s'_{\text{lat}}$, whereas $s'_{\text{sept}}$ correlated with body weight in our study. Peverill et al\textsuperscript{136} also found the relationship of heart rate, body weight and BP was different at the lateral and medial sites. In another normal population, systolic velocities were not associated with age or heart rate whereas early and late diastolic velocities were\textsuperscript{137}. Pela et al\textsuperscript{138} and Mungala et al\textsuperscript{139} did not examine heart rate effects but found only $e'$ but not $s'$ to decline with age. In a study of obese subjects, regional TDI velocities were significantly lower than controls, correlating with BMI\textsuperscript{140} and diastolic velocities were lower in another study by Willens et al, although systolic velocities were not examined\textsuperscript{141}.

Overall, $s'$ measurements at the septal and lateral sites had similar echoclinical determinants. $s'_{\text{lat}}$ had correlations with heart rate, systolic BP and pulse pressure as well as RWT and LVEDV. $s'_{\text{lat}}$ velocities have been shown to correlate better than septal velocities to LV relaxation and pressure-volume loop analysis\textsuperscript{142}, and lateral E/e' has been found to correlate better with mean wedge pressure\textsuperscript{143}. $S'$ velocities have not been correlated with invasive measurements, however it is probable that systolic velocities measured at the septal and lateral mitral annulus are also influenced by slightly different factors. Septal measurements may be affected by right ventricular function and septal motion, which may explain some of the
differences we have observed, particularly in relation to dynamic factors, such as heart rate and BP.

S’ was lower in subjects with a previous myocardial infarct. This is consistent with other studies in patients with both acute\textsuperscript{144} and previous or chronic myocardial ischaemia\textsuperscript{50, 145, 146}. Most studies to date have excluded subjects with atrial fibrillation (AF) or examined only the prognostic value of TDI in this group. We found a significant reduction in s’ in subjects with AF. Oki et al\textsuperscript{147} examined 22 patients with AF and also found lower peak systolic velocities compared to controls. Although not reaching statistical significance, there was a trend towards lower s’ velocities in those with diabetes. Fang et al\textsuperscript{49} examined 53 diabetic subjects and found lower resting s’ values.

Longitudinal LV systolic function declines with age and within this older population of adults, s’ velocities were lower in females. Negative correlations were observed with clinical parameters associated with adverse LV loading conditions – systemic hypertension and increased pulse pressure.

**Limitations**

This is the largest cohort, and only population-based study that has reported on the clinical correlates of s’ velocities. An integrated medical record system available in this study provided the opportunity to confirm or exclude patient reported cardiovascular disease, however the presence of unrecognised cardiovascular conditions cannot be ruled out. The influence of medications was not specifically assessed. TDI has limitations including angle-dependency, the size and placement of sample volume and the assessment of complex myocardial motion in only one direction.
Implications

The clinical determinants of s' velocities have similarities to clinical factors associated with LV diastolic dysfunction. The subdivision of the cardiac cycle into systole and diastole has no physiological basis and many believe that they should be viewed as conceptual terms that are part of a continuous cardiac cycle. This subdivision has contributed to the ongoing controversy surrounding the classification of HF, and particularly HFNEF. In the next chapter we examine the relationship between s' velocities and LV diastolic function. Patients with low s' velocities are those we would expect to have impaired LV diastolic function. There is little data examining this relationship in population-based subjects.
Chapter 4: MITRAL ANNULAR SYSTOLIC VELOCITY: RELATIONSHIP TO DIASTOLIC FUNCTION IN POPULATION-BASED SUBJECTS

Submitted for publication in part in:

Jacobson BM, Abhayaratna WP. Mitral annular systolic velocity: clinical determinants and relationship to diastolic function in population-based subjects. Under review in American Journal of Cardiology
4.1 ABSTRACT

Objective: To assess the echocardiographic determinants of s' measured by pulsed wave TDI in a population-based sample of older adults.

Design, setting and participants: A total of 821 participants of a longitudinal cohort study (mean age 75.3 ± 5.8yrs, 52% women) were examined by echocardiography. s'lat and s'sep was measured by pulsed wave TDI.

Main outcome measures: To assess the echocardiographic determinants of s' and the relationship between s’ and diastolic dysfunction (DD).

Results: S’ had a modest correlation with markers of DD (for s'lat: e': p=0.35;p<0.001; E/e': p= -0.47;p<0.001) and was reduced according to DD severity. There was only weak correlation with left ventricular EF (p=0.12;p=0.003) and LV mass index (p= -0.19;p<0.001). In multivariable analysis, DD remained a strong independent predictor of s’ (p<0.001).

Conclusions: In an unselected population of older adults, the relationship between s’ and DD is independent of the effects of other echo-clinical factors. s’ is reduced according to the severity of DD.
4.2 BACKGROUND

The classification of HF currently includes those with “preserved LVEF”; diastolic HF or HFNEF. The division of systolic and diastolic HF into distinct disease entities has been debated for some time. There is no physiological basis for dividing HF patients into groups based on an arbitrary cut-off value for LVEF (e.g. above 50%), and this approach has led to significant controversy and misunderstanding about the pathophysiology and progression of HF, in particular HFNEF.

Over two decades ago Brutsaert illustrated that systole and diastole are conceptual terms rather than phenomenological, and represent two phases of a single transient event that should be considered as part of a continuous cycle. LVEF is a crude, non-specific measure, however it remains the mainstay for quantification of LV systolic function. It does not provide information on intrinsic muscle performance, involves many assumptions about LV cavity dimensions and complex physiological aspects of cardiac performance, including the interactions between load, heart rate and non-uniformity which continually regulate the systolic performance of the ventricle. There are multiple similarities between systolic and diastolic HF in regards to microscopic, neuroendocrine and echo – clinical features, with the principle difference being LV remodelling. Around 50% of patients with symptomatic HF have a normal ejection fraction, and the prognosis of HFNEF is similar to SHF, however there is still no general consensus on whether systolic HF and HFNEF are two distinct forms of HF, or that in fact, HFNEF represents a phenotype along a continuous spectrum of HF.
Our objectives in this study were to characterise the relationship between LV systolic function as assessed by s', and LV diastolic function. There is limited data to evaluate the echocardiographic determinants of s’ and independent effects of DD on s’ in unselected populations.

4.3 METHODS

Study population

The methods for the Canberra Heart Study, a population-based prospective cohort study of adults of age 60 to 86 years, have been previously described\(^6\). In this study, we report data from 821 subjects (mean age 75.3 ± 5.8yrs, 52% women) who attended the assessment clinic between February 2007 and June 2009. Subjects provided written and informed consent for the study. The study was approved by the Human Research Ethics Committees of the Australian National University and Australian Capital Territory Health.

Echocardiographic assessment

One of three experienced sonographers obtained images according to the guidelines of the American Society of Echocardiography (ASE) using transthoracic echocardiography (Vivid 7; Vingmed-General Electric) according to a standardised protocol. LVEF was measured by the Simpson’s biplane disk summation method on two-dimensional echocardiographic images from the apical two- and four-chamber views. LV mass and LA volume was measured according to the ASE recommendations and indexed to BSA (LAVI)\(^{121}\). TDI recordings were measured online from the apical four-chamber view in the mitral annulus medial and lateral positions using a 2mm
sample volume, s’, e’ and a’ velocities were obtained for each patient. Diastolic function was graded according to the ASE guidelines\textsuperscript{29,121,122}.

**Assessment of clinical risk-factors**

A self-administered questionnaire was used to gather data on a history of cardiac failure, myocardial infarction, angina, hypertension, diabetes, and alcohol consumption. Brachial artery systolic and diastolic BP were measured after 10 minutes of rest in a seated position and two recordings were averaged for each participant. Height and weight were measured while the subject was wearing light clothing without shoes. BSA was calculated.

**Reproducibility**

Intra-observer variability was assessed in 100 patients by repeating the measurements on two occasions ten days apart. Measurements were performed offline by a second observer and variability was calculated as the mean percent error, derived as the difference between the two sets of measurements divided by the mean of the observations. Inter-observer correlation was assessed in 50 subjects.

**Statistical analysis**

Continuous variables are presented as mean +/- standard deviation. Categorical variables are displayed as percentages. Differences between groups were assessed by likelihood ratio tests (categorical variables) or Kruskal-Wallis tests, and non-parametric tests for trend (continuous variables) as appropriate. Ordinal logistic regression was used to assess the association between the ordinal variable, s’, and clinical, anthropometric and
echocardiographic factors in univariate and multivariate analyses. All hypothesis testing was two sided and significance was declared if $p < 0.05$. The assumptions for regression models were checked statistically.

4.4 RESULTS

Participation rates

A total of 821 randomly selected subjects, aged 60 to 86 years (mean age $75.3 \pm 5.8$ yrs, 52% women), were examined. Of these, 46 had atrial fibrillation.

Reproducibility of s' measurement

S' measurement was reproducible with intra-rater correlation of 0.88 and inter-rater correlation of 0.82.

Prevalence rates of LV diastolic dysfunction

The prevalence of any diastolic dysfunction was 72%, and that of moderate or severe DD 30%. Rates of DD increased with decreasing LVEF and there were no subjects with a LVEF <40% and normal diastolic function.

Echocardiographic associations with LV diastolic dysfunction

Echocardiographic variables associated with DD included strong correlations with left ventricular mass index (LVMI) ($p<0.0001$), e' ($p<0.0001$), E/e' ($p<0.0001$), and LA volume index ($p=0.005$), each corresponding to the grade of diastolic dysfunction. Measures of systolic longitudinal left ventricular function, $s'_\text{lat}$ and $s'_\text{sept}$, had a modest correlation with markers of
DD (for $s^{' \text{lat}}$: e': $p=0.35$; $p<0.0001$; E/e': $p = -0.38$; $p<0.0001$) and were reduced according to the severity of DD (Table 4-1).

**Table 4-1 Clinical and echocardiographic characteristics of the study population according to the grade of diastolic function (atrial fibrillation patients not included)**

<table>
<thead>
<tr>
<th></th>
<th>Normal (n=231)</th>
<th>Grade 1 (n=301)</th>
<th>Grade 2 (n=211)</th>
<th>Grade 3/4 (n=32)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female, n (%)</td>
<td>105 (45)</td>
<td>160 (53)</td>
<td>126 (60)</td>
<td>14 (44)</td>
<td>0.027</td>
</tr>
<tr>
<td>Systemic hypertension, n (%)</td>
<td>102 (44)</td>
<td>187 (66)</td>
<td>131 (62)</td>
<td>21 (66)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Diabetes mellitus, n (%)</td>
<td>18 (8)</td>
<td>41 (14)</td>
<td>29 (14)</td>
<td>7 (22)</td>
<td>0.046</td>
</tr>
<tr>
<td>Coronary artery disease, n (%)</td>
<td>27 (12)</td>
<td>42 (14)</td>
<td>23 (11)</td>
<td>8 (25)</td>
<td>0.14</td>
</tr>
<tr>
<td>Myocardial infarction, n (%)</td>
<td>16 (7)</td>
<td>29 (10)</td>
<td>17 (8)</td>
<td>8 (25)</td>
<td>0.009</td>
</tr>
<tr>
<td>Age, y (SD)</td>
<td>74 (5.1)</td>
<td>76 (6.0)</td>
<td>75 (5.6)</td>
<td>76 (5.9)</td>
<td>0.001</td>
</tr>
<tr>
<td>Heart rate, bpm (SD)</td>
<td>59 (9)</td>
<td>64 (10)</td>
<td>61 (9)</td>
<td>61 (12)</td>
<td>0.076</td>
</tr>
<tr>
<td>Systolic BP, mmHg (SD)</td>
<td>149 (18)</td>
<td>156 (21)</td>
<td>156 (21)</td>
<td>152 (19)</td>
<td>0.002</td>
</tr>
<tr>
<td>Diastolic BP, mmHg (SD)</td>
<td>82 (9)</td>
<td>83 (10)</td>
<td>81 (10)</td>
<td>79 (11)</td>
<td>0.058</td>
</tr>
<tr>
<td>Pulse pressure, mmHg (SD)</td>
<td>67 (16)</td>
<td>73 (19)</td>
<td>75 (18)</td>
<td>73 (19)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Body mass index, kg/h2 (SD)</td>
<td>26.5 (4.4)</td>
<td>27.6 (4.6)</td>
<td>27.9 (4.6)</td>
<td>27.6 (4.1)</td>
<td>0.001</td>
</tr>
<tr>
<td>LVEF, % (SD)</td>
<td>66 (6)</td>
<td>64 (9)</td>
<td>66 (8)</td>
<td>63 (9)</td>
<td>0.7</td>
</tr>
<tr>
<td>Cardiac Index, L/min/m2 (SD)</td>
<td>2.8 (0.7)</td>
<td>3.1 (0.8)</td>
<td>3.0 (0.8)</td>
<td>2.6 (0.7)</td>
<td>0.13</td>
</tr>
<tr>
<td>LV mass index, g/m2 (SD)</td>
<td>86 (24)</td>
<td>97 (29)</td>
<td>94 (28)</td>
<td>104 (30)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Relative wall thickness (SD)</td>
<td>0.47 (0.09)</td>
<td>0.50 (0.10)</td>
<td>0.50 (0.12)</td>
<td>0.47 (0.11)</td>
<td>0.27</td>
</tr>
<tr>
<td>Left atrial volume index, mL/m2</td>
<td>30 (9)</td>
<td>29 (8)</td>
<td>31 (9)</td>
<td>38 (15)</td>
<td>0.005</td>
</tr>
<tr>
<td>e' (lat), cm/s (SD)</td>
<td>8 (2)</td>
<td>6 (2)</td>
<td>6 (1)</td>
<td>7 (2)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>E/e'(lat) (SD)</td>
<td>7.7 (1.5)</td>
<td>10 (4.4)</td>
<td>14 (4.6)</td>
<td>15 (4.0)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>S' (lat), cm/s (SD)</td>
<td>8 (2)</td>
<td>7.4 (1.8)</td>
<td>6.8 (1.5)</td>
<td>6.3 (1.6)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>S' (med), cm/s (SD)</td>
<td>6.9 (1.4)</td>
<td>6.2 (1.4)</td>
<td>6.1 (1.3)</td>
<td>5.7 (1.2)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>
Association of s’ velocities with echocardiographic measures of LV function.

There were weak associations between s’ velocities and echocardiographic parameters of LV function; LVEF and cardiac index, LV diastolic function; e’lat, LV structure; LV mass index, LAVI, LV preload; E/e’ and LV afterload; LVESV. S’lat had additional correlations with RWT and LVEDV (Table 4-2).

Table 4-2 Associations of s’ velocities with echocardiographic measures of LV function

<table>
<thead>
<tr>
<th>Parameter</th>
<th>s’ lateral</th>
<th>s’ septal</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>rho</td>
<td>p-value</td>
</tr>
<tr>
<td>LV ejection fraction</td>
<td>0.15</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Cardiac index</td>
<td>0.18</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>LV mass index</td>
<td>-0.15</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Relative wall thickness</td>
<td>0.08</td>
<td>0.029</td>
</tr>
<tr>
<td>LV end-diastolic volume index</td>
<td>-0.13</td>
<td>0.0003</td>
</tr>
<tr>
<td>LV end-systolic volume index</td>
<td>-0.18</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>LA volume index</td>
<td>-0.14</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>e’ lateral</td>
<td>0.35</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>E/e’</td>
<td>-0.38</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

4.5 DISCUSSION

In an unselected population, mitral systolic annular velocities are impaired in subjects with diastolic dysfunction, and reduced in parallel with its severity.
This occurs independently after adjustment for multiple clinical and echocardiographic factors. LV systolic dysfunction can be identified in a predominantly "normal", asymptomatic population using s'. The clinical and echocardiographic determinants of s' velocities are primarily related to diastolic and systolic LV function, gender and preload.

It has been recognised since the 1990's from studies of M-mode long-axis excursion that LV long axis systolic function is impaired in patients with normal LV ejection fraction in various conditions, including diastolic dysfunction, valvular heart disease and ischaemia. Mitral annular velocities reflect the longitudinal function of the ventricle and their proven value emphasises the importance of long-axis, apex-to-base motion in overall LV function. Longitudinally directed myocardial fibres are found in the subendocardium, and during early systole, shortening of these fibres precedes shortening of circumferential fibres. Because of their subendocardial localisation, longitudinal fibres are particularly sensitive to fibrosis, hypertrophy and ischaemia, and impaired long-axis function can therefore provide a sensitive index for the assessment of systolic myocardial function. Tissue Doppler derived myocardial velocities are strongly dependent on both the number of myocytes and the myocardial Beta-adrenergic receptor density in patients with coronary disease. Down-regulation of Beta-adrenergic receptor density in cardiac failure occurs predominantly in the subendocardium. The prognostic value of s' has been documented in patients with HF, mitral regurgitation and ischaemic heart disease. S' correlates with BNP levels better than other standard
echocardiographic measurements including LVEF and mitral inflow patterns\textsuperscript{59}.

Abnormal left ventricular long axis systolic function assessed using s’ has been detected in those with normal LVEF, diastolic dysfunction or “isolated” diastolic HF\textsuperscript{25, 27, 28, 62, 63}, diabetic subjects\textsuperscript{64} and those with left ventricular hypertrophy\textsuperscript{65}. A number of studies have shown a graded association between s’ velocities and cardiac function, being highest in normal controls, followed by subjects with diastolic dysfunction, diastolic HF and lowest values in those with systolic HF\textsuperscript{25, 27, 28, 62, 63, 66}. However, these previous studies have been small, involved selected groups, and included limited adjustments for potential confounders.

This data from a large unselected population demonstrates a close correlation between LV diastolic function and LV systolic function (s’), providing further support to the concept that diastolic and systolic dysfunction represent a continuum of the same disease. Systolic function is not in fact “preserved” in subjects with diastolic dysfunction or HFNEF and the division of SHF and HFNEF based on LVEF is in many ways arbitrary. Systolic myocardial dysfunction can be demonstrated in those with “normal ejection fraction” using peak s’ velocities. The full utility of s’ velocities in the clinical setting requires correlation with invasive indices of cardiac function in humans, outcome data and the establishment of normal gender and age matched normal values.
Strengths and Limitations

This is the largest cohort, and only population-based study that has reported on the correlates of s’ velocities and their association with DD. An integrated medical record system available in this study provided the opportunity to confirm or exclude patient reported cardiovascular disease, however the presence of unrecognised cardiovascular conditions cannot be ruled out. The influence of medications was not specifically assessed. Although echocardiography is accepted as a safe and convenient method for the diagnosis and follow-up of patients with diastolic dysfunction, it is recognised that Doppler echocardiographic methods reflect integrative properties of diastolic function that lack specificity. TDI has limitations including angle-dependency, the size and placement of sample volume and the assessment of complex myocardial motion in only one direction.

Conclusion

In patients with left ventricular diastolic dysfunction, TDI measurements of s’ velocities can identify left ventricular systolic dysfunction that is graded according to the severity of diastolic dysfunction. This occurs independently of other echo-clinical factors. Left ventricular systolic and diastolic dysfunction in varying degrees, represent the same disease evolving along a similar pathophysiological path. The phenotype of the disease is likely to depend on patient specific factors or disease modifiers that influence the progression of LV remodeling and remain to be determined\textsuperscript{154}.
In the next chapter we examine the relationship of s’ velocities to LV ejection fraction and LV filling pressure. LVEF remains the main echocardiographic measure of LV systolic function, however it has significant limitations. It primarily assesses LV radial function, which remains compensated until late in the course of LV dysfunction. LV filling pressure is increased in patients with clinically significant LV dysfunction. We hypothesised that s’ may provide a more sensitive index than LVEF for assessing LV systolic function and illustrate a continuum of systolic function in this unselected population.
Chapter 5: THE CONTINUUM BETWEEN LONGITUDINAL AND RADIAL LEFT VENTRICULAR “SYSTOLIC” FUNCTION: RELATIONSHIP TO LEFT VENTRICULAR FILLING PRESSURE

Submitted for publication in part in:

Jacobson BM, Abhayaratna WP. The continuum between longitudinal and radial left ventricular “systolic” function: relationship to left ventricular filling pressure and circulating cardiac biomarkers. Under review in Heart
5.1 ABSTRACT

Objective: To assess the relationship between left ventricular (LV) long axis systolic function using s’ by TDI and its association with LVEF, a measure of global radial systolic function, and LV filling pressure in a population-based sample of older adults.

Design, setting and participants: A total of 821 participants of a longitudinal cohort study (mean age 75.3 ± 5.8yrs, 52% women) were examined by echocardiography. s’lat and s’sept was assessed by TDI and averaged (s’ave). LV filling pressure was estimated by the ratio of mitral inflow velocity and mitral annular velocity during early diastole (E/e’).

Main outcome measures: To assess the relationship of s’ with LVEF and left ventricular filling pressure.

Results: A continuum of systolic function, as assessed by s’ave was observed across the population. In subjects with an LVEF > 50%, s’ velocities gradually declined with LVEF. In those with normal LVEF but elevated LV filling pressure, s’ave velocities are lower but a similar rate of decline in LV function was observed in this group. When there is a reduction in radial systolic function, or LVEF <50 %, there was more rapid progression of systolic dysfunction. An s’ velocity > 8cm/s excluded the presence of LVEF < 50% or increased LV filling pressure (E/e’>10) in the majority of subjects.

Conclusions: In an unselected population of older adults, LV long axis systolic function relates strongly to LVEF and LV filling pressure. The continuum between longitudinal and radial systolic function in this predominantly asymptomatic population provides insights into the natural history of left ventricular dysfunction and cardiac failure.
5.2 BACKGROUND

There is still much controversy about the underlying pathophysiology of HF, and in particular, HFNEF. The simple separation of the cardiac cycle into systole and diastole is not well justified, and a number of studies have found that LV long axis systolic function is impaired in subjects with LV diastolic function. Using s' velocities in small, selected populations, a graded association with cardiac function has been found, being highest in normal controls, followed by those with diastolic dysfunction, diastolic HF and the lowest values in systolic HF. We have previously shown in this population based study that s' velocities are closely and independently associated with LV diastolic dysfunction. In this chapter we examine the correlation of s' with LVEF, and LV filling pressure. As a sensitive marker of longitudinal LV systolic function as well as providing information on LV diastolic function s' may be a useful measurement in clinical cardiology, providing a more accurate method for quantifying LV systolic function than LVEF.

A time-dependant progression paradigm of chronic HF has been proposed, depicting cardiac performance along a time trajectory. Three pathophysiological stages have been suggested. In the first, pre-disease stage, under stress, the heart has the capacity to delay the onset of ventricular relaxation, modulating the systolic time duration it has to deliver a given amount of stroke work. The second stage ("mild systolic dysfunction"), involves these adaptive physiological mechanisms becoming maladaptive with progressive loss of the ability to regulate the timing of onset of relaxation. This leads to abnormally slow ventricular relaxation in the
presence of preserved haemodynamic pump performance (normal LV ejection fraction). This stage can be detected with echocardiographic findings of diastolic dysfunction and systolic abnormalities can be objectified by TDI. The third stage (“pump failure”) involves deterioration in haemodynamic pump performance with reduced LVEF. A similar conceptual approach to HF has been adopted by the American Heart Association guidelines.

Ventricular long-axis motion is a sensitive marker of myocardial dysfunction, and studies have consistently revealed that systolic function is abnormal in patients with diastolic dysfunction. S’ velocities should provide a more sensitive and specific marker of LV systolic function than LVEF, but no data exist using s’ velocity to analyse the spectrum of LV systolic function in community based subjects. The ratio of early mitral valve flow velocity divided by the early mitral annular velocity (E/e’) is closely correlated with LV filling pressures. An elevated ratio is considered diagnostic evidence of LV diastolic dysfunction. We examine the relationship of s’ velocities with estimates of LV filling pressure and hypothesise that a continuum of LV systolic function can be illustrated in a population-based sample of older adults.

5.3 METHODS

Study population

The methods for the Canberra Heart Study, a population-based prospective cohort study of adults of age 60 to 86 years, have been previously described. In this study, we report data from 821 subjects (mean age 75.3 ± 5.8yrs, 52% women) who attended the assessment clinic between February
2007 and June 2009. All participants provided written and informed consent for the study. The study was approved by the Human Research Ethics Committees of the Australian National University and Australian Capital Territory Health.

**Echocardiographic assessment**

One of three experienced sonographers obtained images according to the guidelines of the American Society of Echocardiography (ASE) using transthoracic echocardiography (Vivid 7; Vingmed-General Electric) and a standardised protocol. LVEF was measured by the Simpson’s biplane disk summation method on two-dimensional echocardiographic images from the apical two- and four-chamber views. LV mass and LA volume was measured according to the ASE recommendations and indexed to BSA. TDI recordings were measured online from the apical four-chamber view in the mitral annulus medial and lateral positions using a 2mm sample volume. S' and e' velocities were obtained for each patient. Diastolic function was graded according to the ASE guidelines and left ventricular filling pressure was estimated using the lateral E/e’ with a value >10 signifying elevated pressures.

**Statistical analysis**

Continuous variables are presented as mean +/- standard deviation. Categorical variables are displayed as percentages. Differences between groups were assessed by likelihood ratio tests (categorical variables) or Kruskal-Wallis tests, and non-parametric tests for trend (continuous variables) as appropriate. Subjects were categorised into three groups based
on LVEF and the presence of clinically significant LV dysfunction (elevated LV filling pressure); a) LVEF>50% and E/e’<10 b) LVEF>50% and E/e’>10, and c) LVEF<50%. Linear regression analysis was used within these groups to assess the association between s’, LVEF and filling pressure. All hypothesis testing was two sided and significance was declared if p < 0.05. The assumptions for regression models were checked statistically.

5.4 RESULTS

Characteristics of the study population

The study population was classified according to LV ejection fraction and estimated LV filling pressure (Table 5-1). Patients with an LVEF>50% were defined according to whether they had clinically significant LV diastolic dysfunction (high estimated LV filling pressures, E/e’>10).

The prevalence of “normal” subjects with LVEF>50% and E/e’<10 was 413 (50.2%). There were 370 subjects (45.0%) with LVEF>50% and E/e’>10, and 40 (4.9%) with LVEF<50%. The prevalence of any DD was 72%, and that of moderate or severe DD 30%.

Echocardiographic associations with LV systolic and diastolic function

Table 5-1 summarises the main echocardiographic variables in the population with subjects classified into 1) LVEF>50% and E/e’ <10, 2) LVEF>50% and E/e’>10 or 3) LVEF <50%. Strong correlations were observed with LVEF, LVMI, LAVI, e’(lat), E/e’ and s’ave. (all p<0.0001). Cardiac index (p=0.0002), and RWT (p=0.003) had weaker, but significant associations.
Table 5-1 Clinical and echocardiographic characteristics according to left ventricular ejection fraction and estimated filling pressure

<table>
<thead>
<tr>
<th></th>
<th>LVEF≥ 50% +</th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>E/e’&lt;10</td>
<td>E/e’&gt;10</td>
<td>LVEF≤ 50%</td>
<td>p value</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(n=413)</td>
<td>(n=370)</td>
<td>(n=40)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Women, n (%)</td>
<td>196 (47)</td>
<td>224 (61)</td>
<td>7 (18)</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>Systemic hypertension, n (%)</td>
<td>179 (51)</td>
<td>212 (67)</td>
<td>16 (52)</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus, n (%)</td>
<td>31 (9)</td>
<td>53 (17)</td>
<td>8 (26)</td>
<td>0.001</td>
<td></td>
</tr>
<tr>
<td>Coronary artery disease, n (%)</td>
<td>39 (11)</td>
<td>40 (13)</td>
<td>11 (35)</td>
<td>0.001</td>
<td></td>
</tr>
<tr>
<td>Atrial fibrillation, n (%)</td>
<td>37 (11)</td>
<td>36 (11)</td>
<td>3 (10)</td>
<td>0.93</td>
<td></td>
</tr>
<tr>
<td>Heart Failure, n (%)</td>
<td>10 (3)</td>
<td>23 (7)</td>
<td>9 (30)</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>Age, y (SD)</td>
<td>74 (5.5)</td>
<td>76 (6.0)</td>
<td>77 (5.9)</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>Heart rate, bpm (SD)</td>
<td>62 (9.8)</td>
<td>63 (10.5)</td>
<td>64 (12)</td>
<td>0.24</td>
<td></td>
</tr>
<tr>
<td>Systolic BP, mmHg (SD)</td>
<td>151 (19.2)</td>
<td>157 (20.7)</td>
<td>149 (21.4)</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>Diastolic BP, mmHg (SD)</td>
<td>83 (9.4)</td>
<td>82 (10.4)</td>
<td>80 (10.7)</td>
<td>0.28</td>
<td></td>
</tr>
<tr>
<td>Pulse pressure, mmHg (SD)</td>
<td>68 (17.6)</td>
<td>75 (18.1)</td>
<td>68 (19.2)</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>Body mass index, kg/m2 (SD)</td>
<td>26.8 (4.5)</td>
<td>27.9 (4.5)</td>
<td>28.0 (5.2)</td>
<td>0.003</td>
<td></td>
</tr>
<tr>
<td>LVEF, % (SD)</td>
<td>66 (6.2)</td>
<td>66 (6.4)</td>
<td>42 (5.8)</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>Cardiac Index, L/min/m2 (SD)</td>
<td>2.9 (0.7)</td>
<td>3.0 (0.9)</td>
<td>2.5 (0.5)</td>
<td>0.0002</td>
<td></td>
</tr>
<tr>
<td>LV mass index, g/m2 (SD)</td>
<td>90 (25)</td>
<td>94 (27)</td>
<td>133 (33)</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>Relative wall thickness, (SD)</td>
<td>0.49 (0.10)</td>
<td>0.51 (0.12)</td>
<td>0.46 (0.12)</td>
<td>0.003</td>
<td></td>
</tr>
<tr>
<td>Left atrial volume index, mL/m2</td>
<td>29.8 (9.4)</td>
<td>32 (10.3)</td>
<td>37.3 (12.5)</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>e’ (lat), cm/s (SD)</td>
<td>8 (2)</td>
<td>6 (2)</td>
<td>5 (2)</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>E/e’(lat) (SD)</td>
<td>7.6 (1.7)</td>
<td>14.0 (4.4)</td>
<td>13.8 (7.3)</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>S’ Ave, cm/s (SD)</td>
<td>7(2)</td>
<td>6 (1)</td>
<td>5 (1)</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
</tbody>
</table>

Figure 5-1 illustrates the association between s’ave and LVEF, separating subjects into the three groups: 1) LVEF > 50% and E/e’ <10, 2) LVEF >50% and E/e’>10 and 3) LVEF <50%. Linear regression lines illustrate the
association between s’ and LVEF in each of the groups. A continuum of systolic function, as assessed by s’ is observed. In subjects with an LVEF > 50% and E/e’ <10 there is a gradual decline in s’ velocities, with lower velocities but a similar rate of decline in LV function observed in those with LVEF>50% and E/e’ >10. When there is a reduction in radial systolic function, or LVEF < 50%, there is more rapid progression of systolic dysfunction. In this cohort, a cutoff value for s’ velocity > 8 cm/s, could exclude the presence of any significant systolic or diastolic dysfunction in the majority of people, however there remains a significant “grey zone” in those with reduced s' velocities but no elevation in LV filling pressures.

Figure 5-1 Distribution of subjects according to s’, LVEF and estimated LV filling pressure
Clinical correlates of LV systolic and diastolic function

More females had diastolic dysfunction with preserved LVEF, and more males had a LVEF <50% (p<0.0001). In those with elevated LV filling pressures and preserved LVEF there were more females, an increased prevalence of systemic hypertension, higher systolic BP and pulse pressure (all p<0.0001). Subjects with LVEF<50% were older, with a history of HF (both p<0.0001) and had more coronary artery disease and diabetes (both p=0.001). There were no significant differences across groups with regard to heart rate, diastolic BP or the presence of atrial fibrillation (Table 5-1).

In a multivariate linear regression analysis (Table 5-2), the relationship between s' velocities and measures of LV systolic and diastolic function remained independent of the effects of other echocardiographic and clinical factors.

Table 5-2 Multivariate model looking at the clinical and echocardiographic determinants of s'_{ave}

<table>
<thead>
<tr>
<th></th>
<th>β- Coefficient</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Women</td>
<td>-0.006</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>e'</td>
<td>0.1</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Cardiac output</td>
<td>0.002</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>CRP</td>
<td>0.0002</td>
<td>0.001</td>
</tr>
<tr>
<td>E/e'</td>
<td>-0.0009</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>LV ejection fraction</td>
<td>0.0002</td>
<td>0.006</td>
</tr>
</tbody>
</table>
5.5 DISCUSSION

A continuum of systolic function is observed across this community-based population using s' velocities. This provides support to the time-dependent progression paradigm of HF whereby chronic HF incorporates HFNEF and systolic HF within the same pathophysiological time trajectory.

Reduced s' velocities illustrate impaired LV systolic function despite a normal LVEF. LV systolic dysfunction can be identified in a predominantly "normal", asymptomatic population using s'. Across the community there exists varying degrees of cardiac dysfunction. Through mechanisms such as cardiac remodeling, myocyte loss and inflammation, adaptive, physiologic mechanisms become maladaptive leading to increased LV filling pressures, symptoms of congestion and subsequently failure of the haemodynamic muscular pump manifest by a reduction in LVEF.

The clinical and echocardiographic determinants of s' velocities are primarily related to systolic and diastolic LV function, gender and preload. In this cohort, a cutoff value for s' velocity > 8cm/s, could exclude the presence of any significant systolic or diastolic dysfunction in the majority of people, however there remains a significant "grey zone" in those with reduced s' velocities but no elevation in LV filling pressures. In this study s' velocity measurements were at cm/sec and more detailed increments would be likely to increase its discriminating power.
Previous studies have examined selected populations and found a graded association between s' velocities and cardiac function, being highest in normal controls, followed by subjects with diastolic dysfunction, diastolic HF and lowest values in those with systolic HF\textsuperscript{25, 27, 28, 62, 63, 66}. However, these studies were performed on small numbers of patients, involved selected groups, and included limited adjustments for potential confounders. This is the first study examining s' velocities in an unselected cohort. Prospective analysis with outcome data in this study sample will provide further information about the natural history of LV dysfunction.

To support these findings, the next chapter assesses the relationship of cardiac biomarkers to increasing levels of LV dysfunction.
Chapter 6: THE CONTINUUM BETWEEN LONGITUDINAL AND RADIAL LEFT VENTRICULAR “SYSTOLIC” DYSFUNCTION: RELATIONSHIP TO CIRCULATING CARDIAC BIOMARKERS

Submitted for publication in part in:

Jacobson BM, Abhayaratna WP. The continuum between longitudinal and radial left ventricular “systolic” function: relationship to left ventricular filling pressure and circulating cardiac biomarkers. Under review in Heart
6.1 ABSTRACT

Objective: To assess the relationship between left ventricular long axis systolic function using s' measured by TDI and cardiac biomarkers (NT-proBNP and hs-cTn) with LVEF and LV filling pressure in a population-based sample of older adults.

Design, setting and participants: A total of 821 participants of a longitudinal cohort study (mean age 75.3 ± 5.8yrs, 52% women) were examined by echocardiography. S'lat and s'sepf was assessed by TDI and averaged (s'ave). NT-proBNP and hs-cTn were measured.

Main outcome measures: To assess the relationship NT-proBNP and hs-cTnT and s' with other echocardiographic measures of LV systolic and diastolic function,

Results: Cardiac biomarkers NT-proBNP and hs-cTnT increased significantly (p<0.0001 and p=0.002 respectively), and s' declined (p<0.0001) with increasing grades of LV dysfunction, supporting the concept that adverse loading conditions and remodeling processes leading to myocyte loss are important mechanisms in the progression of cardiac failure.

Conclusions: In an unselected population of older adults, cardiac biomarkers NT-proBNP and hs-cTn relate to progressive stages of LV dysfunction and provide further support into the pathophysiology of cardiac dysfunction as markers of progressive myocyte loss, cardiac remodelling and myocyte stretch. These findings add support to findings in the previous chapter that systolic and diastolic HF are not separate diseases, but rather, cardiac dysfunction evolves along a similar time trajectory with similar pathophysiological mechanisms.
6.2 BACKGROUND

There is increasing interest in using cardiac biomarkers for categorising HF\textsuperscript{156}. The use of data on BNP together with troponin has been shown to provide better risk stratification than that obtained with either biomarker alone\textsuperscript{104, 117}. Cardiac biomarkers may provide insight into mechanisms of transition from compensated to decompensated HF. Amino-N-Terminal pro-BNP (NT-pro-BNP) is primarily secreted by a myocyte stretch-mediated mechanism as a result of increased ventricular or atrial wall stress, reflecting volume or pressure overload. Plasma levels increase with the severity of LV diastolic and systolic dysfunction and it provides a sensitive marker of elevated LV filling pressures.

High sensitivity cardiac troponin has enabled the detection of low plasma levels with high accuracy. A number of potential mechanisms leading to its release have been proposed, including subendocardial ischaemia and myocyte necrosis, cardiomyocyte damage from inflammatory cytokines or oxidative stress, hibernating myocardium or apoptosis\textsuperscript{105-109}. Multiple studies have documented an association between elevated circulating cTn and adverse clinical outcomes in various HF populations\textsuperscript{114}. A large observational study in Europe has shown associations between low levels of cTn and the future development of HF in asymptomatic subjects, similar to observations with BNP\textsuperscript{115}. Both cTnT and cTnl are prognostic indicators in patients with acute and chronic HF. In addition, when added to other biomarker considerations may provide insight into mechanisms of transition from compensated to decompensated HF. Persistently increased cTn
concentrations during compensated phases of HF suggest ongoing myocyte injury and cardiac remodeling resulting in further deterioration in ventricular function and worse clinical outcomes\textsuperscript{116, 117}. In a study comparing BNP, cTn and markers of ventricular remodelling in patients with acute HF, stable HF and control subjects, acute HF patients had significantly higher cTn, markers of collagen biosynthesis and markers of extracellular matrix remodeling\textsuperscript{118}. In patients post myocardial infarct, a strategy of combining BNP and LV ejection fraction improved risk stratification beyond using either alone\textsuperscript{189}.

Findings in the previous chapter illustrated diastolic and systolic HF within the same pathophysiological time trajectory. Correlation of these findings with cardiac biomarkers, as indices of cardiac remodeling and adverse loading conditions may support these findings.

6.3 METHODS

Study population

The methods for the Canberra Heart Study, a population-based prospective cohort study of adults of age 60 to 86 years, have been previously described\textsuperscript{67}. In this study, we report data from 821 subjects (mean age 75.3 ± 5.8yrs, 52% women) who attended the assessment clinic between February 2007 and June 2009. All participants provided written and informed consent for the study. The study was approved by the Human Research Ethics Committees of the Australian National University and Australian Capital Territory Health.
Echocardiographic assessment

One of three experienced sonographers obtained images according to the guidelines of the American Society of Echocardiography (ASE) using transthoracic echocardiography (Vivid 7; Vingmed-General Electric) and a standardised protocol. LVEF was measured by the Simpson's biplane disk summation method on two-dimensional echocardiographic images from the apical two- and four-chamber views. LV mass and LA volume was measured according to the ASE recommendations and indexed to BSA (LAVI)\(^{121}\). TDI recordings were measured online from the apical four-chamber view in the mitral annulus medial and lateral positions using a 2mm sample volume. S' and e’ velocities were obtained for each patient. Diastolic function was graded according to the ASE guidelines\(^{29,122}\) and left ventricular filling pressure was estimated using the lateral E/e’ with a value \(>10\) signifying elevated pressures.

B-Natriuretic Peptide

NT-proBNP levels were measured using a commercially available and fully automated electrochemiluminescence sandwich immunoassay on an Elecsys 1010 (proBNP, Roche Diagnostics, Basel, Switzerland). Venous blood was collected in serum tubes, centrifuged and stored at -70C until analysis. The immunoassay has a within-run coefficient of variability (CV) of 0.7% to 1.6% and a between-run coefficient of variability of 5.3% to 6.7%.
High sensitivity cardiac troponin T

A commercial high-sensitivity assay from Abbott Diagnostics was used to measure cardiac troponin I (cTnl) from blood samples collected during subject’s attendance for clinical assessment and echocardiography. Serum was stored at -80°C and samples were only subjected to one freeze-thaw cycle. The long term stability of cTnl with both the Beckman Coulter high sensitivity (hs)-Tnl and the Abbott ARCHITECT STAT hs-cTnl assays has been demonstrated under these conditions.

Analytical studies of the ARCHITECT STAT hs-Tnl assay from Abbott Diagnostics, which was made available in a commercial form by the manufacturer (Abbott USA) showed that the limit of blank (LoB) was 0.5ng/L, the limit of detection (LoD) was 1.0ng/L, the concentration corresponding to the 20% CV was 1.8ng/L, the concentration corresponding to the 10% CV was 3.9ng/L, and the concentrations corresponding to the 99th percentile values were 14.0ng/L in adult males and 11.1ng/L in adult females.

**Statistical analysis**

Continuous variables are presented as mean +/- standard deviation. Categorical variables are displayed as percentages. Differences between groups were assessed by likelihood ratio tests (categorical variables) or Kruskal-Wallis tests, and non-parametric tests for trend (continuous variables) as appropriate. Subjects were categorised into three groups based on LVEF and the presence of clinically significant LV diastolic dysfunction; a) “normal” LVEF > 50% and E/e’<10, b) “normal” LVEF > 50% and E/e’>10 or c) reduced LVEF < 50%. Linear regression analysis was used within these
groups to assess the association between s’ and LVEF. All hypothesis testing was two sided and significance was declared if p < 0.05. The assumptions for regression models were checked statistically.

NT-proBNP levels were positively skewed and natural log transformation was required to satisfy statistical modeling assumptions for regression analyses. For the entire cohort the associations with NT-proBNP were assessed for their univariate correlation within the three groups of patients.

6.4 RESULTS

Characteristics of study population

The study population was classified according to LVEF and estimated LV filling pressure (Table 6-1). Patients with an LVEF >50% were defined according to whether they had clinically significant LV diastolic dysfunction (high estimated LV filling pressures, E/e’ >10).

Amino-terminal pro-B-type natriuretic peptide and high sensitivity cardiac troponin T association with LV function

Consistent with the principal mechanism of BNP secretion from myocyte stretch there was a clear increase in peptide levels with increased LV filling pressure (E/e’>10), and further increase in those with LVEF <50% (p<0.0001). hs-cTn was also significantly correlated with higher levels in those with progressively lower LV systolic function (p=0.002). This relationship is illustrated in Figure 6-1 and Figure 6-2.
<table>
<thead>
<tr>
<th></th>
<th>LVEF= 50% +</th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>E/e'&lt;10</td>
<td>E/e'&gt;10</td>
<td>LVEF&lt; 50%</td>
<td></td>
<td>p value</td>
</tr>
<tr>
<td>Women, n (%)</td>
<td>196 (47)</td>
<td>224 (61)</td>
<td>7 (18)</td>
<td></td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Systemic hypertension, n (%)</td>
<td>179 (51)</td>
<td>212 (67)</td>
<td>16 (52)</td>
<td></td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Diabetes mellitus, n (%)</td>
<td>31 (9)</td>
<td>53 (17)</td>
<td>8 (26)</td>
<td></td>
<td>0.001</td>
</tr>
<tr>
<td>Coronary artery disease, n (%)</td>
<td>39 (11)</td>
<td>40 (13)</td>
<td>11 (35)</td>
<td></td>
<td>0.001</td>
</tr>
<tr>
<td>Atrial fibrillation, n (%)</td>
<td>37 (11)</td>
<td>36 (11)</td>
<td>3 (10)</td>
<td></td>
<td>0.93</td>
</tr>
<tr>
<td>Heart Failure, n (%)</td>
<td>10 (3)</td>
<td>23 (7)</td>
<td>9 (30)</td>
<td></td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Age, y (SD)</td>
<td>74 (5.5)</td>
<td>76 (6.0)</td>
<td>77 (5.9)</td>
<td></td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Heart rate, bpm (SD)</td>
<td>62 (9.8)</td>
<td>63 (10.5)</td>
<td>64 (12)</td>
<td></td>
<td>0.24</td>
</tr>
<tr>
<td>Systolic BP, mmHg (SD)</td>
<td>151 (19.2)</td>
<td>157 (20.7)</td>
<td>149 (21.4)</td>
<td></td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Diastolic BP, mmHg (SD)</td>
<td>83 (9.4)</td>
<td>82 (10.4)</td>
<td>80 (10.7)</td>
<td></td>
<td>0.28</td>
</tr>
<tr>
<td>Pulse pressure, mmHg (SD)</td>
<td>68 (17.6)</td>
<td>75 (18.1)</td>
<td>68 (19.2)</td>
<td></td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Body mass index, kg/m2 (SD)</td>
<td>26.8 (4.5)</td>
<td>27.9 (4.5)</td>
<td>28.0 (5.2)</td>
<td></td>
<td>0.003</td>
</tr>
<tr>
<td>LVEF, % (SD)</td>
<td>66 (6.2)</td>
<td>66 (6.4)</td>
<td>42 (5.8)</td>
<td></td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Cardiac Index, L/min/m2 (SD)</td>
<td>2.9 (0.7)</td>
<td>3.0 (0.9)</td>
<td>2.5 (0.5)</td>
<td></td>
<td>0.0002</td>
</tr>
<tr>
<td>LV mass index, g/m2 (SD)</td>
<td>90 (25)</td>
<td>94 (27)</td>
<td>133 (33)</td>
<td></td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Relative wall thickness, (SD)</td>
<td>0.49 (0.10)</td>
<td>0.51 (0.12)</td>
<td>0.46 (0.12)</td>
<td></td>
<td>0.003</td>
</tr>
<tr>
<td>Left atrial volume index, mL/m2</td>
<td>29.8 (9.4)</td>
<td>32 (10.3)</td>
<td>37.3 (12.5)</td>
<td></td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>e' (lat), cm/s (SD)</td>
<td>8 (2)</td>
<td>6 (2)</td>
<td>5 (2)</td>
<td></td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>E/e'(lat) (SD)</td>
<td>7.6 (1.7)</td>
<td>14.0 (4.4)</td>
<td>13.8 (7.3)</td>
<td></td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>hs-cTnT, ng/L (SD)</td>
<td>9.2 (7.4)</td>
<td>11.7 (11.0)</td>
<td>17.5 (13.3)</td>
<td></td>
<td>0.002</td>
</tr>
<tr>
<td>NT-proBNP, ng/L (SD)</td>
<td>206 (300)</td>
<td>326 (667)</td>
<td>646 (661)</td>
<td></td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>S' ave, cm/s (SD)</td>
<td>7(2)</td>
<td>6 (1)</td>
<td>5 (1)</td>
<td></td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>
Figure 6-1 Distribution of NT-proBNP based on LVEF and LV filling pressures

Figure 6-2 Distribution of hs-cTnT based on LVEF and LV filling pressures
6.5 DISCUSSION

Pathological remodelling of the heart involves structural and functional abnormalities of cardiac myocytes and the extracellular matrix that are mediated by several factors including mechanical strain, neurohormones and inflammatory cytokines.

Persistently increased cTn concentrations during compensated phases of HF suggest ongoing myocyte injury and cardiac remodelling resulting in further deterioration in ventricular function and worse clinical outcomes\textsuperscript{116, 117}. In a study comparing BNP, cTn and markers of ventricular remodeling in patients with acute HF, stable HF and control subjects, acute HF patients had significantly higher cTn, markers of collagen biosynthesis and markers of extracellular matrix remodeling\textsuperscript{118}.

Plasma levels of BNP are positively correlated with LV dimensions, volumes and mass, and inversely with LV ejection fraction. In subjects with LV hypertrophy and clinical HF, levels are further elevated\textsuperscript{94-98}. BNP levels increase with greater severity of diastolic dysfunction independently of LVEF, age, sex, BMI and renal function. The highest levels are present in those with restrictive filling patterns. Levels reflect indices of filling pressure, including transmitral early filling velocity (E) and its ratio to early diastolic annular velocity (E/e’). Positive correlations have been found with LA volume in the general population and in patients with HF and normal ejection fraction\textsuperscript{93, 99}. 

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There is a modest relationship between BNP levels and LV filling pressures that reflects the complexity of factors influencing secretion and clearance. Aside from the effects of age, gender, renal function and neurohormonal or cytokine status, the right ventricle and LA contribute to peptide levels. Dilated ventricles secrete more peptide for a given filling pressure due to greater wall stress and mass. Low BNP levels however have a high negative predictive value for an elevated filling pressure in most settings.

Doppler echocardiography is a widely validated method to accurately assess LV filling pressures. These indices have been validated with BNP for detection of PCWP>15mmHg in patients admitted to the intensive care unit. In patients with cardiac disease, BNP levels >400pg/ml had similar sensitivity (91%) but poorer specificity (51% vs. 91%) and overall accuracy than Doppler indices such as E/e' for detecting a PWCP >15mmHg.

Pathologic changes in cardiac myocytes are an important cause of cardiac remodelling. Troponin is a three-unit complex located in the actin filament, comprising troponin I, T and C. Along with tropomyosin it is essential for the regulation of calcium-mediated contraction of the skeletal and cardiac muscles. Cardiac troponin (cTn) T and I are highly sensitive and specific markers of myocardial injury and have replaced the MB fraction of creatinine kinase as the gold standard for the diagnosis of AMI.

Detectable circulating cTnI is rare in the general population using currently available assays. The high-sensitivity (hs) assay allows the measurement of low concentrations of cTn with high precision. In the Val-HeFT study of over
4000 patients, hs-cTn was detectable in 92% of patients compared to only 10.4% using the standard cTnT assay.

Troponin release occurs in patients with and without obstructive coronary disease. Potential contributing mechanisms have been proposed including subendocardial ischaemia leading to myocyte necrosis, cardiomyocyte damage from inflammatory cytokines or oxidative stress, hibernating myocardium or apoptosis\textsuperscript{105-108}. cTn can be released from injured but viable myocardium as a result of increased membrane permeability or by a stretch-related mechanism mediated by integrins\textsuperscript{110-112}. Altered calcium handling resulting from increased preload has been found to activate intracellular proteolytic enzymes that degrade cTn, releasing cTn fragments into the circulation which may have epitopes with an affinity for the cTnl immunoassays\textsuperscript{113}.

Multiple studies have documented an association between elevated circulating cTn and adverse clinical outcomes in various HF populations\textsuperscript{114}. A large observational study in Europe has shown associations between low levels of cTn and the future development of heart failure in asymptomatic subjects, similar to observations with BNP\textsuperscript{115}. Both cTnT and cTnl are prognostic indicators in patients with acute and chronic HF. In addition, when added to other biomarker considerations may provide insight into mechanisms of transition from compensated to decompensated HF. Patients with chronic heart failure frequently experience episodes of acute HF characterised by interstitial fluid overload, elevated cardiac filling pressure, and decreased cardiac output. Persistently increased cTn concentrations
during compensated phases of HF suggest ongoing myocyte injury and cardiac remodelling resulting in further deterioration in ventricular function and worse clinical outcomes\textsuperscript{116, 117}. In a study comparing BNP, cTn and markers of ventricular remodeling in patients with acute HF, stable HF and control subjects, acute HF patients had significantly higher cTn, markers of collagen biosynthesis and markers of extracellular matrix remodelling illustrating that processes central to pathological myocardial remodelling are activated by episodes of decompensation\textsuperscript{118}. Increased mechanical strain on the heart with activation of neurohormonal systems and increased inflammation and oxidative stress are known stimuli that mediate myocardial injury\textsuperscript{157, 158}.

Prospective follow-up in this cohort may provide incremental prognostic information using s’ and biomarkers.
Chapter 7: LEFT VENTRICULAR SYSTOLIC DYSSYNCHRONY: PREVALENCE AND DETERMINANTS IN A POPULATION-BASED COHORT

Submitted for publication in part in:

Jacobson BM, Abhayaratna WP. Left ventricular systolic dyssynchrony; prevalence and determinants in a population-based cohort. Under review in JACC imaging
7.1 ABSTRACT

**Background:** Assessment of the prevalence and determinants of LV dyssynchrony, quantified by Ts-SD, in an unselected population may provide insights as to why this measure is a suboptimal marker for the selection of HF patients who benefit from cardiac resynchronisation therapy (CRT).

**Objectives:** To assess the prevalence and clinical/echocardiographic determinants of LV systolic dyssynchrony in older adults.

**Methods:** Eight hundred and twenty-one participants (75.3 ± 5.8yrs; 52% women) of a prospective population-based study were examined by echocardiography. LV systolic synchrony was quantitated as Ts-SD, and measured as the time from QRS onset to peak systolic velocity at 6 basal segments from the apical views. Effective arterial elastance (Ea) was calculated from stroke volume and systolic BP. Ventricular systolic elastance (Ees) was estimated non-invasively by a modified single-beat method.

**Results:** Of the 821 subjects (mean Ts-SD: 44 ± 26ms), 481 (67%) had LV systolic dyssynchrony, defined previously as Ts-SD>33ms. Ts-SD was higher in women (48 ± 22ms vs. 40 ± 23; p<0.0001). Clinical correlates of Ts-SD included a history of systemic hypertension; systolic BP and pulse pressure; heart rate and BMI. Whereas Ts-SD was negatively associated with indices of increased aortic pulsatile load including Ea (ρ = -0.10; p=0.03) and the vascular-ventricular coupling ratio (Ea/Ees) (ρ = -0.13; p=0.0005); it was positively associated with measures of LV preload including increased LA pressure (E/e': ρ = 0.21; p<0.0001) and increased indexed LV end-diastolic volume (ρ = 0.10; p=0.02). Ts-SD increased with stroke volume index, LV total systolic period and ejection time, LV mass index and LA...
volume index. In multivariable analysis, independent predictors of Ts-SD included sex, heart rate, pulse pressure, and LV filling pressure (all p<0.05).

**Conclusions:** In an unselected population of older adults, LV systolic dyssynchrony, as assessed by Ts-SD, is highly prevalent and characterised by intrinsic properties of LV structure. The opposing influences of aortic pulsatile load and ventricular preload. Future studies are required to identify the mechanisms that result in inappropriate dyssynchrony in disease states.
7.2 BACKGROUND

Left ventricular (LV) dyssynchrony is a significant contributor to LV systolic dysfunction and has been linked to increased morbidity, mortality and arrhythmia susceptibility in patients with HF\textsuperscript{159-161}. Dyssynchrony exacerbates HF through a number of mechanisms, generating myocardial inefficiency and changes at the tissue, cellular and molecular levels\textsuperscript{162}. Quantification of systolic dyssynchrony by Ts-SD using TDI has previously been validated\textsuperscript{68} and reference limits have been evaluated in relatively small samples of clinic-based populations\textsuperscript{69}. Extensive research has emerged in relation to CRT in selected HF patients, with proven benefits of therapy on functional status, LVEF, reverse LV remodelling, hospitalisation and mortality\textsuperscript{163-165}. However, selection of patients for CRT based on the current guidelines\textsuperscript{76} results in approximately 30\% not responding to therapy despite the use of TDI to predict response to CRT\textsuperscript{77}. Multiple reasons have been postulated to explain the negative findings using echocardiography to select patients for CRT, including the definition of a “non-response”, technical factors related to data acquisition, and pathophysiological issues such as lead placement and the extent of scar tissue\textsuperscript{166}.

LV systolic dyssynchrony reflects in part the concept of ventricular non-uniformity in the mechanical performance of the heart providing temporal and spatial information about mechanical performance of the ventricle\textsuperscript{167}. It may be affected by loading conditions and activation-inactivation sequences and has been shown to be prevalent in various clinical and subclinical cardiac diseases including left ventricular hypertrophy\textsuperscript{70}, ischemia\textsuperscript{71}, infarction\textsuperscript{72},
HF\textsuperscript{73}, and with right ventricular pacing\textsuperscript{74}. In combination with load and activation-inactivation, non-uniformity is a principle determinant of ventricular performance and can become imbalanced and increased in diseased states\textsuperscript{80}. Systolic time intervals reflect a dimension of LV function that is unique compared with other measures of ventricular performance, offering a temporal description of the sequential phases of the cardiac cycle\textsuperscript{168}. In this study, we sought to assess the prevalence and clinical and echocardiographic determinants of LV systolic dyssynchrony in a population-based cohort of older adults. Identification of the determinants of Ts-SD should facilitate a better understanding of the pathophysiology and natural history of LV dysfunction, and may provide insights to why this measure is a suboptimal marker for the selection of HF patients who benefit from CRT.

7.3 METHODS

Study population

The methods for the Canberra Heart Study, a population-based prospective cohort study of adults of age 60 to 86 years, have been previously described\textsuperscript{169}. Patients examined in the initial assessment were not suitable for analysis of TDI due to the echocardiographic analysis at the time. In this study, we report data from 821 subjects (mean age; 75.3 ± 5.8yrs, 52% women) who attended the assessment clinic between February 2007 and June 2009 for follow up examination. Subjects provided written and informed consent for the study. The study was approved by the Human Research Ethics Committees of the Australian National University and Australian Capital Territory Health.
Assessment of clinical risk factors

A self-administered questionnaire was used to gather data on a history of cardiac failure, coronary artery disease, myocardial infarction, angina, hypertension, and diabetes. Brachial artery systolic and diastolic BP were measured after 10 minutes of rest in a seated position and two recordings were averaged for each participant. BSA was calculated.

Echocardiography

One of three experienced sonographers obtained images according to the guidelines of the American Society of Echocardiography (ASE)\textsuperscript{121} using transthoracic echocardiography (Vivid 7; General Electric) according to a standardised protocol. LV ejection fraction and LV volumes were measured by the Simpson's biplane disk summation method on two-dimensional echocardiographic images from the apical two- and four-chamber views. LV mass, LV diastolic function and LA volume was measured according to the ASE recommendations. Colour TDI was recorded from the apical four-chamber, two-chamber and long-axis views with the images optimised to achieve a frame rate >150Hz. At least three consecutive beats were stored and the images analysed offline using customised software (EchoPac-PC, version 6.1.0; Vingmed General Electric). Myocardial velocity curves were reconstructed offline using a six basal segment model (septal, lateral, anteroseptal, posterior, anterior and inferior segments) of the LV. Investigators performing the measurements were blinded to the clinical information. The basal segments were sampled one centimetre above the annulus. Ts (time to peak myocardial systolic velocity during the ejection
period) was measured from the beginning of the QRS complex to peak velocity and the Ts-SD between the 6 segments was calculated. Intraobserver variability was assessed in 50 patients by repeating the measurements on two occasions at least ten days apart. A second observer performed measurements and variability was calculated as the mean percent error, derived as the difference between the two sets of measurements divided by the mean of the observations.

**Non-invasive assessment of aortic pulsatile load**

Pulse wave velocity was measured at the brachial artery using arterial applanation tonometry to derive the augmentation pressure (AP). Effective arterial elastance (Ea) was calculated from stroke volume and systolic BP. Ventricular systolic elastance (Ees) was estimated non-invasively by a modified single-beat method and the vascular-ventricular coupling ratio (Ea/Ees) was calculated.

**Statistical analysis**

Continuous variables are presented as mean ± standard deviation (SD). Categorical variables are displayed as percentages. Differences between groups were assessed by likelihood ratio tests (categorical variables); Kruskal-Wallis tests or non-parametric tests for trend (continuous variables) as appropriate. Multiple regression analysis was used to assess the association between Ts-SD and clinical, anthropometric and echocardiographic factors. All hypothesis testing was two sided and significance was declared if p < 0.05. The assumptions for regression models were checked statistically.
7.4 RESULTS

Clinical characteristics

Of the 821 subjects, 723 (mean age 75.3 ± 5.8yrs, 52% women) had measurements of Ts in all 6 basal LV segments. In those in whom Ts could not be measured in all segments, there was a lower proportion of women and slightly lower mean BMI and LV ejection fraction (Table 7-1).

The mean Ts-SD was 44 ± 26ms and 481 (67%) had LV systolic dyssynchrony using a previously defined cut-off of Ts-SD > 33 ms (+ 2 SD of normal controls) for LV systolic dyssynchrony. Ts-SD was higher in women (48 ± 22ms vs. 40 ± 23ms in men; p<0.0001) and those with a history of systemic hypertension (46 ± 23ms vs. 41 ± 22ms; p=0.005) but was not different in those with a history of diabetes mellitus (46 ± 23ms vs. 45 ± 23ms; p=0.49) or myocardial infarction (43 ± 22ms vs. 44 ± 23ms; p=0.69).
<table>
<thead>
<tr>
<th>Parameter</th>
<th>Ts-SD measured (n = 723)</th>
<th>Ts-SD not measured (n = 99)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yrs (SD)</td>
<td>75.2 (5.8)</td>
<td>75.9 (6.2)</td>
<td>0.23</td>
</tr>
<tr>
<td>Women, n (%)</td>
<td>388 (54)</td>
<td>38 (38)</td>
<td>0.004</td>
</tr>
<tr>
<td>Body mass index, kg/m² (SD)</td>
<td>27.5 (4.6)</td>
<td>26.5 (4.4)</td>
<td>0.047</td>
</tr>
<tr>
<td>Heart rate, bpm (SD)</td>
<td>62 (10)</td>
<td>63 (11)</td>
<td>0.52</td>
</tr>
<tr>
<td>Systolic BP, mmHg (SD)</td>
<td>153 (20)</td>
<td>155 (21)</td>
<td>0.37</td>
</tr>
<tr>
<td>Diastolic BP, mmHg (SD)</td>
<td>82 (10)</td>
<td>82 (10)</td>
<td>0.74</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>418 (58)</td>
<td>56 (57)</td>
<td>0.80</td>
</tr>
<tr>
<td>Diabetes mellitus, n (%)</td>
<td>90 (12)</td>
<td>12 (12)</td>
<td>0.92</td>
</tr>
<tr>
<td>Coronary artery disease, n (%)</td>
<td>100 (14)</td>
<td>13 (13)</td>
<td>0.85</td>
</tr>
<tr>
<td>Myocardial infarction, n (%)</td>
<td>72 (10)</td>
<td>8 (8)</td>
<td>0.55</td>
</tr>
<tr>
<td>LV ejection fraction, % (SD)</td>
<td>65 (8)</td>
<td>63 (10)</td>
<td>0.02</td>
</tr>
<tr>
<td>Indexed LV mass, g/m² (SD)</td>
<td>94 (27)</td>
<td>96 (29)</td>
<td>0.42</td>
</tr>
<tr>
<td>E/e' ratio, (SD)</td>
<td>11 (5)</td>
<td>11 (4)</td>
<td>0.62</td>
</tr>
</tbody>
</table>
Influence of gender on Ts-SD

Figure 7-1 illustrates the distribution of Ts-SD according to gender. The plot for women is clearly skewed to the right, reflecting the fact that women had a higher Ts-deviation. Figure 7-1 also illustrates that for both sexes that there is a bimodal distribution, with an initial peak in the normal range and another at around 50ms. Our statistical analyses were performed to reflect the non-normal distribution of Ts-SD.

Figure 7-1 Distribution plots of Ts-SD by sex

Clinical and echocardiographic variables and Ts-SD

Ts-SD was positively correlated with indices of LV remodelling including LVEDD and LVMI, and negatively correlated with RWT. Measures of LV function including LV ejection time and total systolic period, stroke volume
index, and e’ and s’ velocities correlated significantly with Ts-SD. Cardiac loading conditions influence Ts-SD with correlation to systolic BP, pulse pressure. Whereas Ts-SD was negatively associated with indices of increased aortic pulsatile load including Ea ($\rho = -0.10; p=0.03$) and the vascular-ventricular coupling ratio (Ea/Ees) ($\rho = -0.13; p=0.0005$); it was positively associated with measures of LV preload including increased LA pressure ($E/e': \rho = 0.21; p<0.0001$) and increased indexed LV end-diastolic volume ($\rho = 0.10; p=0.02$) (Table 7-2). There was no correlation between Ts-SD and age, LVEF, QRS duration or PR interval.

In multivariable analysis, independent predictors of increased Ts-SD included female sex ($p<0.0001$); increased pulse pressure ($p=0.03$), LV filling pressure ($p<0.0001$) and decreased heart rate ($p<0.0001$).
Table 7-2 Ts-SD correlation with clinical and echocardiographic parameters

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Ts-SD (ms)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>rho</td>
</tr>
<tr>
<td>Age</td>
<td>0.01</td>
</tr>
<tr>
<td>Heart rate</td>
<td>-0.22</td>
</tr>
<tr>
<td>Body mass index</td>
<td>0.14</td>
</tr>
<tr>
<td>Systolic BP</td>
<td>0.12</td>
</tr>
<tr>
<td>Diastolic BP</td>
<td>-0.08</td>
</tr>
<tr>
<td>Pulse pressure</td>
<td>0.17</td>
</tr>
<tr>
<td>LV ejection fraction</td>
<td>0.07</td>
</tr>
<tr>
<td>Indexed stroke volume</td>
<td>0.17</td>
</tr>
<tr>
<td>Indexed cardiac output</td>
<td>0.03</td>
</tr>
<tr>
<td>LV mass index</td>
<td>0.10</td>
</tr>
<tr>
<td>LV RWT</td>
<td>-0.12</td>
</tr>
<tr>
<td>LV end-diastolic diameter</td>
<td>0.14</td>
</tr>
<tr>
<td>LV end-systolic diameter</td>
<td>0.03</td>
</tr>
<tr>
<td>Indexed left atrial volume</td>
<td>0.1</td>
</tr>
<tr>
<td>Mitral valve deceleration time</td>
<td>-0.04</td>
</tr>
<tr>
<td>Mitral valve early diastolic velocity (E)</td>
<td>0.1</td>
</tr>
<tr>
<td>Lateral early diastolic annular velocity</td>
<td>-0.16</td>
</tr>
<tr>
<td>Lateral systolic annular velocity</td>
<td>-0.28</td>
</tr>
<tr>
<td>Septal early diastolic annular velocity</td>
<td>-0.11</td>
</tr>
<tr>
<td>Septal systolic annular velocity</td>
<td>-0.1</td>
</tr>
<tr>
<td>E/e' ratio</td>
<td>0.21</td>
</tr>
<tr>
<td>LV total systolic period</td>
<td>0.26</td>
</tr>
<tr>
<td>LV pre-ejection period (PEP)</td>
<td>-0.06</td>
</tr>
<tr>
<td>LV ejection time (LVET)</td>
<td>0.31</td>
</tr>
<tr>
<td>PEP/LVET ratio</td>
<td>-0.15</td>
</tr>
<tr>
<td>QRS duration</td>
<td>-0.06</td>
</tr>
<tr>
<td>PR interval</td>
<td>0.02</td>
</tr>
</tbody>
</table>
7.5 DISCUSSION

This study is the first to examine LV systolic dyssynchrony using Ts-SD in a largely asymptomatic, unselected population of older adults. We have shown that Ts-SD is closely related to parameters associated with cardiac load and our findings are consistent with the physiological effects of load on systolic time intervals, and earlier studies of echocardiography and systolic time intervals. The total systolic period (pre-ejection period and LV ejection time) is directly related to the contractile state of the myocardium. A history of systemic hypertension, systolic (not diastolic) BP, widened pulse pressure, arterial elastance, the vascular-ventricular coupling ratio and LV filling pressures as estimated by E/e’ were found to be important determinants of Ts-SD.

Previous studies examining Ts-SD have involved selected patients in a much younger age group than this study. Using a 12 segment model, a normal cutoff value for Ts-SD of <33ms (2 standard deviations above "control" subjects), has been found, above which predicted a favourable response to CRT. In our study a 6 basal segment model was used. To maintain high frame rates (>150Hz) the sample volume was reduced and an adequate sampling area in the mid ventricular segments was not present in a significant proportion of studies. We found only a minimal difference with 12-versus 6-segment Ts-SD with overall slightly lower values, which did not reach statistical significance. Systolic dyssynchrony using Ts-SD>33ms was observed in 67% of our subjects, in a population with predominantly normal LV ejection fraction and no symptoms of HF. Importantly this age group has
the highest burden of HF. Among normal controls and healthy volunteers previous studies have reported similar values of Ts-SD and prevalence of dyssynchrony on the basis of Ts-SD >33ms\textsuperscript{171-173}, in contrast to much lower values reported in others\textsuperscript{137, 174}.

The concept of non-uniformity in the mechanical performance of the heart has existed for a long time\textsuperscript{79} and in combination with load and activation-inactivation is a principle determinant of ventricular performance. The non-uniform behaviour of load (volume and/or pressure) and activation-inactivation in time and space regulates the function of the normal ventricle, and may become imbalanced and increased in diseased states\textsuperscript{80}.

**Figure 7-2 Concept of Non-Uniformity**

Increased non-uniformity prolongs the overall duration of inactivation, delaying mitral valve opening and reducing rapid ventricular filling. Mitral annular systolic and diastolic velocities (s’ and e’) are sensitive indices of longitudinal cardiac function, and reflect cardiac activation and inactivation\textsuperscript{48}, both of which had significant negative correlations with Ts-SD. The modulating role played by non-uniformity can become imbalanced because of abnormal cavity size or shape or because of regional dysfunction. We
found correlations between Ts-SD and LV characteristics including increased end-diastolic diameter, indexed mass and RWT; all of which reflect adverse remodelling that can result from unfavourable chronic loading conditions. Consistent with previous data, LV ejection fraction and QRS duration was not correlated with Ts-SD\textsuperscript{175, 176}.

Brutsaert established in isolated cardiac muscle and the in vivo heart that increasing loads delay the onset of relaxation of isotonic Twitches and introduced the concept of “load dependence of relaxation”\textsuperscript{148}. This is a key feature of systolic activation and provides the normal heart with the capacity to modulate the time of onset of ventricular relaxation and therefore adjust the “systolic time window” during which the ventricle delivers its stroke work. Dysfunction of the capacity to modulate systolic function by adapting the time of onset of relaxation may be an early sign of ventricular systolic dysfunction and can progress into impaired relaxation (impaired rate or extent of pressure decline and rapid filling), resulting in an upward shift in the pressure-volume relation, increased PCWP, and over time, ventricular remodelling and hypertrophy. Impaired relaxation can result from impaired load dependence (cellular function: calcium handling and contractile protein function), excessive changes in load and inappropriate non-uniformity\textsuperscript{148, 177}.

The interaction between the heart and the arterial system, “vascular-ventricular coupling” is a key determinant of cardiovascular performance and is becoming an area of increasing interest with relevant clinical implication\textsuperscript{178}. Changes in arterial wave reflection may induce change in regional stress distribution leading to LV non-uniformity\textsuperscript{179}. Increased non-uniformity
produces an imbalance in the process of LV relaxation, which reduces the mechanical efficiency of ventricular ejection and slows the rate of LV pressure fall\textsuperscript{180-182}. LV systolic dyssynchrony has recently been examined using echocardiography strain imaging and changes in LV load resulted in dynamic changes in measures of dyssynchrony\textsuperscript{183}.

Our findings support the hypothesis that inappropriate loading conditions, with imbalances of the ventricular-arterial load (ventricular-arterial coupling), affect the timing of LV relaxation and can eventually result in inappropriate dyssynchrony and myocardial inefficiency. Understanding the determinants of LV systolic dyssynchrony contributes to a better understanding of the pathophysiology of HF, and may, in combination with other parameters help identify early LV dysfunction.

Women had significantly higher Ts-SD. This was found in a study of healthy adults with a mean age of 30\textsuperscript{171}. Previous reports suggest that women have inappropriately high vascular loading conditions compared with men, with disproportionately higher rates of hypertensive heart disease, and greater age-related incremental LV hypertrophy compared to men\textsuperscript{184}. BMI, known to be closely associated with hypertension\textsuperscript{185} was related to LV systolic dyssynchrony, however this correlation most likely reflects the influence of gender on BMI. Ts-SD was not correlated with age as previously documented\textsuperscript{69,186}. This finding is interesting given the known age-related increases in LV pulsatile afterload due to increased vascular stiffening. Our data illustrates that pathophysiological changes in cardiac function and structure principally determine LV systolic dyssynchrony.
7.6 STRENGTHS AND LIMITATIONS

This is the largest cohort, and only population-based study that has been reported on the correlates of Ts-SD. An integrated medical record system available in this population-based study provided the opportunity to confirm or exclude patient reported cardiovascular disease, however the presence of unrecognised cardiovascular conditions cannot be ruled out. The effect of medications was not specifically analysed, however is unlikely to have altered our findings. TDI has limitations including angle-dependency, the size and placement of sample volume and the assessment of complex myocardial motion in only one direction. It is readily available with a large body of literature in validation and outcome studies. Whilst the reproducibility of our measures was high as in other single centre studies, multicentre trials such as the PROSPECT reported higher inter- and intra-observer variability. Strain based imaging using speckle-tracking has advantages of less angle dependency and allows the analysis of radial and longitudinal dyssynchrony, but requires high image quality and analysis software is variable between vendors.\(^{187}\)

7.7 CONCLUSIONS

In an unselected population of older adults, LV systolic dyssynchrony, as assessed by Ts-SD, is highly prevalent and is determined by the opposing influences of aortic pulsatile load and ventricular preload, total systolic time, and intrinsnic properties of LV structure and diastolic function. Although the high prevalence of LV systolic dyssynchrony and complex determinants may limit the positive predictive value of the measure for the selection of patients
for CRT, future studies are required to assess the value of Ts-SD as an integrative marker of non-uniformity that could be used to characterise cardiovascular risk and the benefits of medical therapy.
Chapter 8: CONCLUSIONS AND FUTURE DIRECTIONS
8.1 CONCLUSIONS

Results of this thesis have advanced the knowledge of echocardiography and cardiovascular epidemiology. Using novel indices to assess cardiac function through TDI and cardiac biomarkers, valuable information about the natural history of HF and HFNEF has been acquired.

TDI derived s’ velocities have large potential for clinical use in the assessment of LV systolic function, however its clinical determinants are not well defined. We evaluated s’ in a population-based study for the first time, and determined that longitudinal LV systolic function declined with age and that ‘s velocities were lower in females. Negative correlations were observed with clinical parameters associated with adverse LV loading conditions – systemic hypertension and increased pulse pressure.

The widespread use of LVEF has led to misunderstandings and controversy about the pathophysiology and natural history of HF. We assessed the relationship between LV systolic function using s’ and LV-DD and found the association to be independent of the effects of other echo-clinical factors. S’ is reduced according to the severity of DD, providing further support to the concept that diastolic and systolic dysfunction represent a continuum of the same disease. We hypothesised that s’ may provide a more sensitive index than LVEF for assessing LV systolic function and that a continuum of systolic function could be observed in this unselected population. We examined the relationship between s’, LVEF, and LV filling pressure and illustrated a continuum between longitudinal and radial systolic function, in a predominantly asymptomatic population. Reduced s’ velocities illustrate
impaired LV systolic function despite a normal LVEF. This information has international significance, and will play a significant role in advancing its potential for use in routine clinical echocardiographic measurements to assess LV function.

These findings were supported by our assessment of the relationship between s’ and its association with cardiac biomarkers (NT-proBNP and hs-cTn), LVEF and LV filling pressures. Cardiac biomarkers increased significantly with increasing grades of LV dysfunction, supporting the concept that adverse loading conditions and remodelling processes leading to myocyte loss are important mechanisms in the progression of HF.

LV dyssynchrony is a significant determinant of cardiac function, linked to increased morbidity, mortality and arrhythmia susceptibility in patients with HF. Quantification of systolic dyssynchrony by Ts-SD using TDI has previously been validated and reference limits have been evaluated in relatively small samples of clinic-based populations. Understanding the determinants of Ts-SD may facilitate a better understanding of the pathophysiology and natural history of LV dysfunction. We evaluated the clinical and echocardiographic determinants of Ts-SD for the first time, in a large, population-based cohort. LV systolic dyssynchrony, as assessed by Ts-SD, was highly prevalent and determined by the opposing influences of aortic pulsatile load and ventricular preload, total systolic time, and intrinsic properties of LV structure and diastolic function. These findings are of national and international significance, providing insights as to why this
measure is a suboptimal marker for the selection of HF patients who benefit from CRT.

8.2 FUTURE DIRECTIONS

The HF epidemic in the aging population requires identification of at risk patients in the pre-symptomatic phases of the disease (Stage B). Pharmacotherapy to change the natural history of the disease and improve prognosis will reduce the increased burden posed on a limited healthcare system. The results emanating from this thesis, and the database of information provided by the Canberra Heart Study offer multiple opportunities for future research. Prospective analysis with outcome data in this study sample will provide valuable information about the natural history of LV dysfunction.

Further refinement of TDI data may increase its sensitivity and specificity to diagnose early LV dysfunction. Increasing the accuracy of s’ velocity measurements with higher velocity increments may increase its sensitivity and specificity to differentiate patients in the “grey zone” with normal LVEF and estimated LV filling pressures but reduced s’. Further refinement of normal age and gender matched cutoff values for s’ may enable it to become used as a standard measurement in clinical echocardiography and provide additional and potentially superior information than LVEF about LV function. Because of its widespread availability, ease of acquisition and measurement, it could serve as a useful tool in monitoring response to medical therapy in clinical trials.
Ts-SD appears to be an integrative marker of non-uniformity with complex determinants that has potential uses in characterising cardiovascular risk and monitoring the response to therapy.

The use of s', Ts-SD and other echocardiographic indices potentially in conjunction with cardiac biomarkers and other measures of CV loading conditions has great potential in identifying at risk patients and for monitoring response to medical therapy.
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