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Assessment of Left Ventricular Diastolic Function with Three Dimensional Cardiac Magnetic Resonance Imaging

Carissa Grace Fonseca

A thesis submitted in partial fulfilment of the requirements for the degree of Doctor of Philosophy at the University of Auckland

THE UNIVERSITY OF AUCKLAND
NEW ZEALAND

Department of Anatomy with Radiology
Faculty of Medical and Health Sciences
The University of Auckland
New Zealand

2004
Primary Supervisor: Dr. Alistair A. Young
Department of Anatomy with Radiology
and The Bioengineering Institute
University of Auckland

Co-Supervisor: Dr. Ralph A. Stewart
Department of Cardiology
Auckland City Hospital
Auckland

Advisory Committee: Dr. Brett R. Cowan
(Department of Medicine, University of Auckland)

Associate Professor Bruce H. Smaill
(The Bioengineering Institute, University of Auckland)

Professor Colin R. Green
(Department of Anatomy with Radiology, University of Auckland)
I stand on the brink, on the edge of myself
and wonder at All that is beyond me
I am jealous of the Ocean and the Sky
    that do not seem to end;
    of the Universe itself
that holds so much Immensity.

I seek to comprehend all knowledge,
and I can't even know of all that has been written
    I am a finite creature
but I ever struggle to hold within my grasp
    the mystery of being
I want the power of knowing All,
    of seeing All,
    of having All

And I cannot even possess myself;
I have thoughts and fears and hopes
    that I cannot often understand,
    nor more frequently admit
I am not a comfortable creature
Even my most cherished dreams I cannot make come true
    My heart cries out to me to be God!
and my life shouts out that I am not!
and my faith is based on the hope that
    Someone else is!

I am left with the experience
    that I exist beyond myself
but cannot contain my source
I am a grain of sand wanting to possess the ocean
    and the miracle of Love is that I can
He has made me so small so that He can stretch me
to Immensity
He has made me so poor so He can fill me pressed down, and overflowing
    with his Richness
He has made me so limited so that He can make me
    Boundless
He has made me a creature
    so he can make me God.
He has entered my heart and he has called me,
    'Home'

~ Edward J Farrell
Abstract

Measurement of diastolic left ventricular (LV) function is vitally important in the assessment of cardiac disease. However, only limited information on tissue function can be obtained with current clinical techniques. This Thesis developed and investigated novel parameters of both global and regional myocardial function, using cardiac magnetic resonance imaging (MRI) with three-dimensional tissue tagging.

Multidirectional peak myocardial shortening strains and strain rates, as well as the peak systolic displacement and velocity of the mitral valve annulus plane (MVP), were considered as parameters of LV systolic function. The corresponding peak diastolic strain relaxation rates and peak diastolic MVP velocity were used to assess diastolic function. The effects of normal ageing were studied in people with no evidence of cardiac disease, and compared with the effects of disease in patients with type 2 diabetes mellitus (DM).

In normal healthy subjects, systolic strain parameters were preserved, while diastolic parameters were impaired, with age. DM patients showed impaired diastolic function on correction for age, and systolic functional parameters were also impaired, even though LV ejection fraction was normal. MVP systolic and diastolic motion were reduced both with age and in DM patients. Systolic LV torsion was increased with age and in DM, with no corresponding increase in torsional relaxation. Both systolic and diastolic function parameters were regionally heterogeneous. With normal ageing, diastolic function was impaired in a regionally non-uniform manner.

Thus, a complete assessment of LV function requires measurement of LV tissue mechanics as well as chamber haemodynamics. MRI provides valuable information regarding myocardial tissue behaviour, contributing to systolic and/or diastolic dysfunction, which cannot be obtained otherwise. Systolic tissue dysfunction may develop concomitantly in patients with diastolic dysfunction, even when global ejection fraction is preserved. Regional analyses provide important information on how local changes contribute to global function. The influence of age must be taken into account in studies of disease.
Acknowledgements

I have encountered some remarkable people, over the course of this doctoral degree, and have been fortunate to have friends, family, and colleagues who have offered encouragement and support throughout.

I am especially grateful to my supervisor, Alistair Young, for giving me the opportunity to undertake this study. Thank you, not only for your guidance, and the invaluable research skills you have taught me, but also for your trust and belief in me, which has given me confidence in my own abilities. It has been an honour to work with you.

Ralph Stewart, my co-supervisor, and the members of my advisory committee – Brett Cowan, Bruce Smaill, and Colin Green – have been nothing but supportive. Sincere thanks to each of you for sound advice, for always being so approachable, despite your other commitments, and for providing extremely helpful and constructive criticism of my work.

Many thanks to Brett and Dr. Chris Occleshaw (Department of Cardiology, Auckland City Hospital) who performed the MR scans for all of the subjects examined in this Thesis (after-hours, more often than not!). Chris also contributed to discussions on much of the work presented here.

A special note of thanks must go to Dr. Helen Oxenham (currently at the Department of Cardiology, Royal Infirmary of Edinburgh) who recruited the older normal, healthy people for the studies on the influence of age, whilst working in the Department of Medicine in 2001, and to Dr. Tom Gentles (Department of Cardiology, Auckland City Hospital) for recruiting the younger normal, healthy subjects. Thanks also to Prof. Garth Cooper and Dr. John Baker (School of Biological Sciences) and Dr. Ajith Dissanayake (Middlemore Hospital, South Auckland Health) who recruited the patients with type 2 diabetes, and provided access to the data from this group.

I would like to thank Gillian Whalley from the Department of Medicine who performed many of the echocardiographic examinations and, along with Greg Gamble and Assoc. Prof. Rob Doughty (also from the Department of Medicine), contributed to helpful and stimulating discussions on the data resulting from these studies.
The Auckland MRI Research Group, which I have been a part of, for the last four years, deserves special thanks. In particular I would like to thank Kevin Augenstein - my fellow PhD student, and John Baek - our head software programmer, who helped me learn to use the MR image analysis tools, which were so necessary for obtaining the data presented in this Thesis. It was their company that made life in the ‘dungeons’ (the basement of the Medical school) bearable.

Many thanks to all staff and postgraduate students in the Department of Anatomy with Radiology for creating such a great atmosphere to work in. The post-graduate experience would not have been the same without my peers, especially Robert Huang, Maurice Curtis and Adèle Pope; their support and friendship made all the difference. Lily Yang, Jacelyn Loh and Nimali Withana (the ‘dinner girls’) have been such wonderful friends all the way through university, and ensured that I visited some of Auckland’s best eating-places!

I have been blessed with two guardian angels – Prof. Colin Green and Assoc. Prof. Louise Nicholson! Colin and Louise introduced me to research and it was their infectious enthusiasm for science that led me to pursue this career. They are truly inspirational teachers, have been my mentors and, I am proud to say, have become two of my dearest friends. Thank you both for always being there for me, and for your constant encouragement.

I don’t know how I could ever repay Dr. Denis Loiselle (Department of Physiology) for proof-reading the final draft of my Thesis, and adding valuable input, in the incredibly short period of time that I allowed him. Many, many thanks for doing this for me; it is so deeply appreciated!

I am grateful to the National Heart Foundation of New Zealand, which provided generous support in the form of a postgraduate scholarship and an award for travel to an overseas conference. The Royal Society of New Zealand also provided an award for overseas travel.

Finally, I would like to pay tribute to Cecil and Coral Fonseca (my parents), Celia and Caraliza (my sisters), Lawrie Miranda (my grandfather), Abigail Fonseca (my cousin), and Ashika Akhil (my best friend). You are my world – this would not have been possible without you!
List of Publications

The following publications have arisen from work done as part of this Thesis:


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<tr>
<td>%s_C</td>
<td>percent circumferential shortening strain</td>
</tr>
<tr>
<td>%s_L</td>
<td>percent longitudinal shortening strain</td>
</tr>
<tr>
<td>α_CL</td>
<td>torsion angle (also ‘α’)</td>
</tr>
<tr>
<td>3D</td>
<td>three dimensional; in three dimensions</td>
</tr>
<tr>
<td>A</td>
<td>late diastolic transmitral flow velocity (due to atrial contraction) measured by Doppler echocardiography</td>
</tr>
<tr>
<td>A'</td>
<td>late diastolic mitral annular velocity measured by tissue Doppler imaging</td>
</tr>
<tr>
<td>AFP</td>
<td>echocardiographic abnormal filling pattern</td>
</tr>
<tr>
<td>ANCOVA</td>
<td>analysis of covariance (statistical)</td>
</tr>
<tr>
<td>ANOVA</td>
<td>analysis of variance (statistical)</td>
</tr>
<tr>
<td>ATP</td>
<td>adenosine triphosphate</td>
</tr>
<tr>
<td>B_0</td>
<td>magnetic field</td>
</tr>
<tr>
<td>BMI</td>
<td>body mass index</td>
</tr>
<tr>
<td>BP</td>
<td>blood pressure</td>
</tr>
<tr>
<td>BSA</td>
<td>body surface area</td>
</tr>
<tr>
<td>DBP</td>
<td>diastolic blood pressure</td>
</tr>
<tr>
<td>DENSE</td>
<td>displacement encoding with stimulated echoes (in cardiac magnetic resonance imaging)</td>
</tr>
<tr>
<td>DM</td>
<td>diabetes mellitus</td>
</tr>
<tr>
<td>E</td>
<td>early diastolic transmitral flow velocity measured by Doppler echocardiography</td>
</tr>
<tr>
<td>E</td>
<td>Lagrangian strain tensor</td>
</tr>
<tr>
<td>E'</td>
<td>early diastolic mitral annular velocity measured by tissue Doppler imaging</td>
</tr>
<tr>
<td>E:A</td>
<td>ratio of early to late transmitral flow velocity measured by Doppler echocardiography</td>
</tr>
<tr>
<td>ECG</td>
<td>electrocardiogram</td>
</tr>
<tr>
<td>ED</td>
<td>end-diastole</td>
</tr>
<tr>
<td>EDV</td>
<td>end-diastolic volume</td>
</tr>
<tr>
<td>EF</td>
<td>ejection fraction</td>
</tr>
<tr>
<td>e.g.</td>
<td>exempli gratia (Latin): for example</td>
</tr>
<tr>
<td>ES</td>
<td>end-systole</td>
</tr>
<tr>
<td>ESV</td>
<td>end-systolic volume</td>
</tr>
<tr>
<td>FEM</td>
<td>finite element model</td>
</tr>
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<td>FID</td>
<td>free induction decay</td>
</tr>
<tr>
<td>FLASH</td>
<td>fast low angle shot</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Description</td>
</tr>
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<td>--------------</td>
<td>-------------</td>
</tr>
<tr>
<td>HARP</td>
<td>harmonic phase</td>
</tr>
<tr>
<td>HbA1c</td>
<td>haemoglobin A1c;</td>
</tr>
<tr>
<td>HR</td>
<td>heart rate</td>
</tr>
<tr>
<td>i.e.</td>
<td><em>id est</em> (Latin): that is</td>
</tr>
<tr>
<td>LV</td>
<td>left ventricle; left ventricular</td>
</tr>
<tr>
<td>MANOVA</td>
<td>multivariate analysis of variance (statistical)</td>
</tr>
<tr>
<td>mm Hg</td>
<td>millimetres of mercury</td>
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<tr>
<td>MR</td>
<td>magnetic resonance</td>
</tr>
<tr>
<td>MRI</td>
<td>magnetic resonance imaging</td>
</tr>
<tr>
<td>MVP</td>
<td>mitral valve (annulus) plane</td>
</tr>
<tr>
<td>n</td>
<td>sample size (statistical)</td>
</tr>
<tr>
<td>NC</td>
<td>normal control</td>
</tr>
<tr>
<td>NMR</td>
<td>nuclear magnetic resonance</td>
</tr>
<tr>
<td>NS</td>
<td>non-significant (statistical)</td>
</tr>
<tr>
<td>P</td>
<td>P-value; probability (statistical)</td>
</tr>
<tr>
<td>PB</td>
<td>Bonferroni corrected P-value (statistical)</td>
</tr>
<tr>
<td>PFP</td>
<td>echocardiographic pseudonormal filling pattern</td>
</tr>
<tr>
<td>PWD</td>
<td>echocardiographic pulsed wave Doppler recording</td>
</tr>
<tr>
<td>r</td>
<td>correlation coefficient (statistical)</td>
</tr>
<tr>
<td>RAAS</td>
<td>renin-angiotensin-aldosterone system</td>
</tr>
<tr>
<td>RC</td>
<td>peak rate of relaxation of circumferential shortening strain</td>
</tr>
<tr>
<td>RF</td>
<td>radiofrequency</td>
</tr>
<tr>
<td>RL</td>
<td>peak rate of relaxation of longitudinal shortening strain</td>
</tr>
<tr>
<td>ROC</td>
<td>receiver operator curve analysis (statistical)</td>
</tr>
<tr>
<td>RP</td>
<td>peak rate of relaxation of principal shortening strain</td>
</tr>
<tr>
<td>RT</td>
<td>peak rate of relaxation of torsional shear strain</td>
</tr>
<tr>
<td>SBP</td>
<td>systolic blood pressure</td>
</tr>
<tr>
<td>SC</td>
<td>peak value of circumferential shortening strain</td>
</tr>
<tr>
<td>SL</td>
<td>peak value of longitudinal shortening strain</td>
</tr>
<tr>
<td>Sm</td>
<td>systolic mitral annular velocity measured by echocardiography</td>
</tr>
<tr>
<td>SP</td>
<td>peak value of principal shortening strain</td>
</tr>
<tr>
<td>SPAMM</td>
<td>spatial modulation of magnetization</td>
</tr>
<tr>
<td>SR</td>
<td>strain rate</td>
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<tr>
<td>SRI</td>
<td>strain rate imaging</td>
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<tr>
<td>SSR&lt;sub&gt;C&lt;/sub&gt;</td>
<td>peak systolic circumferential strain rate</td>
</tr>
<tr>
<td>SSR&lt;sub&gt;L&lt;/sub&gt;</td>
<td>peak systolic longitudinal strain rate</td>
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<tr>
<td>SSR&lt;sub&gt;p&lt;/sub&gt;</td>
<td>peak systolic principal strain rate</td>
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<tr>
<td>SSR&lt;sub&gt;T&lt;/sub&gt;</td>
<td>peak systolic torsional shear strain rate</td>
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<tr>
<td>ST</td>
<td>peak value of torsion</td>
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<tr>
<td>SV</td>
<td>stroke volume</td>
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<td>T</td>
<td>tesla</td>
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<tr>
<td>T&lt;sub&gt;1&lt;/sub&gt;</td>
<td>T&lt;sub&gt;1&lt;/sub&gt; Relaxation time</td>
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<td>T&lt;sub&gt;2&lt;/sub&gt;</td>
<td>T&lt;sub&gt;2&lt;/sub&gt; Relaxation time</td>
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<tr>
<td>TDI</td>
<td>tissue Doppler imaging</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Definition</td>
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<tr>
<td>TE</td>
<td>echo time</td>
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<td>TR</td>
<td>repetition time</td>
</tr>
<tr>
<td>tR&lt;sub&gt;C&lt;/sub&gt;</td>
<td>time from end-diastole to peak rate of relaxation of circumferential shortening strain</td>
</tr>
<tr>
<td>tR&lt;sub&gt;L&lt;/sub&gt;</td>
<td>time from end-diastole to peak rate of relaxation of longitudinal shortening strain</td>
</tr>
<tr>
<td>tR&lt;sub&gt;T&lt;/sub&gt;</td>
<td>time from end-diastole to peak rate of recovery of torsion</td>
</tr>
<tr>
<td>tS&lt;sub&gt;C&lt;/sub&gt;</td>
<td>time from end-diastole to peak circumferential shortening strain</td>
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<tr>
<td>tS&lt;sub&gt;L&lt;/sub&gt;</td>
<td>time from end-diastole to peak longitudinal shortening strain</td>
</tr>
<tr>
<td>tS&lt;sub&gt;T&lt;/sub&gt;</td>
<td>time from end-diastole to peak torsion</td>
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<tr>
<td><em>viz</em></td>
<td>videlicet; that is to say; namely</td>
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<td><em>vs.</em></td>
<td>versus; as opposed to</td>
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Chapter 1
Introduction and Background

1.1 Motivation

Qualitative and quantitative assessment of the function of the heart impacts heavily on clinical decision-making. Approximately 17 million people die of cardiovascular diseases, predominantly heart attacks and strokes, per year worldwide (World Health Organization, 2003). In New Zealand, cardiovascular disease is one of the leading causes of morbidity and mortality, accounting for 41% of total deaths in 2000 (Nicholl, 2004). This represents a significant burden with respect to quality of life and cost of treatment (New Zealand Ministry of Health, 2004). The risk for cardiovascular disease, particularly heart failure, increases significantly with age. Furthermore, cigarette smoking, obesity and an increasingly sedentary lifestyle have become more common due to industrialization and urbanization (especially in developing countries and also in lower socio-economic groups in developed countries). These factors, together with an ever-increasing elderly population, represent a greater risk of developing diabetes mellitus, dyslipidaemia and hypertension, with eventual cardiovascular consequences (Yusuf \textit{et al.}, 2001).

The purpose of the heart is to pump blood to the rest of the body, so it is interesting that a large proportion of patients with the signs and symptoms of heart failure are diagnosed with ‘diastolic heart failure’ – caused by impaired relaxation and/or filling of the left ventricular (LV) chamber of the heart – while systolic function – the ability to eject blood from the LV into the circulation – is often found to be clinically normal in these patients. It has even been suggested that diastolic function may be impaired earlier or more severely than systolic function in the progression to heart failure (Aroesty \textit{et al.}, 1985, Soufer \textit{et al.}, 1985, Raev, 1994).
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Accurate measurement of both systolic and diastolic LV function is important for making a precise diagnosis and selecting the most effective therapeutic strategy, thereby benefiting the patient and ultimately lightening the burden that cardiovascular disease represents to society and the economy. However, current clinical measures are often not sufficient to provide a complete picture of LV function. Magnetic Resonance Imaging (MRI) can provide a wealth of data on the three-dimensional geometry and mechanical function of the heart, and its use in measuring LV volumes and mass has been regarded as the in vivo gold standard in a research setting for over a decade. However the technology is still not widely used clinically. It is the aim of this Thesis to demonstrate how MR measurements of LV function can offer a useful alternative to, and/or complement, traditional clinical measures. New methods of assessment are investigated by focusing on two major processes that could lead to the development of diastolic dysfunction: normal ageing and type 2 diabetes mellitus.

An overview of the structure and function of the heart is presented below, together with a brief outline of the clinical problems considered in this Thesis. At the end of this Chapter, the major aims of the thesis are stated, and an outline of the studies that were undertaken is provided.

1.2 Structure and Function of the Heart

1.2.1 Gross Anatomy

The heart is a muscular organ that functions as a mechanical pump to ensure that oxygenated blood is efficiently distributed throughout the body.

The four chambers of the heart – the smaller left and right atria and the larger left and right ventricles – are illustrated in Figure 1.1. Considered in three dimensions, the shape of the left ventricle (LV) resembles that of a truncated ellipsoid, and the crescent-shaped right ventricle appears to wrap around it. The LV is thicker-walled than the right – a physiological adaptation to the greater pressure against which it must pump blood. Whereas the LV pumps blood to the greater systemic circulation, the right ventricle pumps the same volume of blood only to the lungs. The ventricles contract almost simultaneously and blood is ejected from them. When the ventricles have almost completely relaxed, they begin to fill again.

Blood is oxygenated in the lungs and is carried to the left atrium of the heart via the pulmonary veins. Oxygenated blood then enters the LV and during ventricular contraction it is ejected into the aorta and passed into the systemic circulation.
Figure 1.1 Cardiac anatomy: chambers, valves and great vessels in cross-section.

Blood flows from the two superior atrial chambers into the two inferior ventricles through the tricuspid valve (on the right side of the heart) and the mitral valve (left side of the heart). The great vessels transport blood between the heart, the lungs and the rest of the body. *Reprinted from Netter (1995).*
The myocardium itself is perfused by the coronary arteries, which have their origins at the base of the aorta, and course over the outer surface of the heart, branching into smaller vessels that penetrate the myocardium transmurally. Deoxygenated blood from the systemic circulation returns to the right atrium of the heart via the superior vena cava, the inferior vena cava and the coronary sinus. This deoxygenated blood then enters the right ventricle and is ejected, during contraction, into the left and right pulmonary arteries, which carry it to the lungs to be oxygenated.

Four valves control the direction of blood flow and its passage between the chambers, and into the great vessels leading out of the heart. The atrioventricular valves between the atria and the ventricles are the ‘inlet’ valves allowing blood to flow into the ventricles, and the semilunar valves are the ‘outlet’ valves, which control passage of blood out of the ventricles (Figure 1.2).

The mitral valve (often referred to as the bicuspid valve because it has 2 leaflets) allows unidirectional blood flow from the left atrium into the LV. Its three-leaved counterpart on the right side of the heart is the right atrioventricular tricuspid valve. Fibrous strands called ‘chordae tendineae’, which arise from the papillary muscles located on the inner surface of the ventricles, are attached to the tips and undersides of the atrioventricular valve leaflets. When the ventricles contract the pressure of blood forces the leaflets of the atrioventricular valves upwards until they meet, thus closing the valves. The simultaneous contraction of the papillary muscles tightens the chordae tendineae, restricting the leaflets from swinging into the atria and therefore preventing backward flow of blood. Meanwhile, the aortic and pulmonary semilunar valves direct blood from the left ventricle into the aorta and from the right ventricle to the pulmonary artery, respectively. Each of the semilunar valves has three crescent-shaped cusps - the crest of each cusp is attached to the wall of the encompassing blood vessel and the free edge curves upward and into the lumen of the vessel. Blood in the aorta and pulmonary artery flows backward towards the ventricles (during ventricular relaxation) and fills the cusps, which balloon out, tightly closing the valves. (Tortora and Grabowski, 1996)

Clinical indices of cardiac anatomy include heart mass, left ventricular volumes at the end of contraction (end-systolic volume) and relaxation (end-diastolic volume), wall thickness, and ventricular ellipticity index, whose departure from normal values can provide important information regarding the particular stress or disease process.
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1.2.2 Organization and Material Properties of Cardiac Myocytes

The function of the heart is influenced by myocardial architecture and is dependent on the capacity of individual cardiac myocytes (or muscle cells), acting in concert, to develop the forces and the dimensional changes that are necessary for ventricular filling and ejection of blood.

The myocardium, or heart muscle, lies between an outer epicardium and an inner endocardium and together these form the heart wall. Cardiac myocytes are shaped like...
flattened cylinders around 80 - 100 μm in length and up to 20 μm in dimension transverse to the long-axis. Each myocyte is composed of sarcomeres arranged in series and also in parallel with each other (Figure 1.3 A). The sarcomere is the fundamental unit of contraction in striated muscle cells and consists of interdigitating lattices of thick and thin filaments. The thin filament lattice – helical chains of actin molecules on which the regulatory proteins tropomyosin and troponin I, C and T are assembled – is cross-linked at the Z-line and slides with respect to the thick filament lattice, which is an ordered array of myosin molecules that are linked at the M-line. Sarcomere length – the distance between adjacent Z lines – therefore provides an index of the overlap between thick and thin filaments (Figure 1.3 B).

Myocytes lie parallel to each other, and each is connected electrically and mechanically to adjacent myocytes at the intercalated disks. In right and left ventricles, myocyte orientation varies in a consistent fashion through the heart wall. In the LV free wall, the transmural variation of myocyte orientation is approximately 120° (Figure 1.4), from around -60° near the epicardial surface, through 0° (circumferential) in the midwall region to +60° near the endocardium (Streeter, 1979, Nielsen et al., 1991). This variation occurs “as smoothly as the segments of an open Japanese fan” (Streeter, 1979). The ordered myocyte orientation is crucial for the effective development and release of the forces required for contraction and relaxation. It is possible to measure myocardial fibre orientation using diffusion tensor MRI (Hsu et al., 1998), but this is not used clinically at present.

Ventricular myocytes are arranged in layers, each about three to four cells thick. Adjacent layers are separated by cleavage planes, or interlaminar clefts, that can be relatively extensive in the midwall. The laminar organization of ventricular myocardium is generally consistent (LeGrice et al., 1995a, Young et al., 1998): myocyte layers are more or less transmurally directed, they branch and interconnect, but the cleavage planes between them allow for shearing, thereby facilitating wall thickening during systole (LeGrice et al., 1995b, Costa et al., 1999). A complex network of extracellular connective tissue, which extends from epicardium to endocardium, couples adjacent layers. Short radial collagen ‘struts’ (Robinson et al., 1983) couple adjacent myocytes within the layers.

Myofilament overlap is an important determinant of the interaction between contractile proteins and hence of the forces generated during muscle contraction. In cardiac muscle, however, force is developed over a much more restricted range of sarcomere lengths than is the case for skeletal muscle.
Figure 1.3 Cardiac myocyte microstructure and sarcomere arrangement.

A: Diagram of an electron micrograph of cardiac muscle showing sarcomere arrangement, sarcolemma (cell membrane), and the distribution of mitochondria, intercalated disks, and connective tissue. Within each myocyte, calcium is stored in the sarcoplasmic reticulum. *Reprinted from Berne and Levy (1993).*

B: Longitudinal (top) and cross-sectional (bottom) diagrams showing the relationship between thick (black) and thin (red) filaments of a sarcomere. *Reprinted from Murphy (1993).*
In the normal heart, ventricular sarcomere lengths are relatively uniform transmurally during passive filling and do not exceed 2.35 to 2.4 μm (Yoran et al., 1973, Weisman et al., 1988). The uniformity of sarcomere length has been explained by the transmural variation of myocyte orientation (Yoran et al., 1973), while the limitation on maximum sarcomere length reflects the material properties of the extracellular connective tissue matrix, and the role of the pericardium (which encloses the heart). The fact that sarcomere length can only marginally exceed optimal length (which corresponds to maximum myofilament overlap and force development) has important functional consequences. It is not possible to overfill the heart and drive it onto the descending limb of the force-sarcomere length relationship where increasing sarcomere length would reduce active force development. This ensures stable ventricular function (Berne and Levy, 1993).

Muscle contraction is triggered by the elevation of intracellular calcium and, in striated muscle, this process is initiated by depolarization of the cell membrane. Calcium is released from intracellular stores and binds to the protein troponin C causing conformational changes to occur in the thin filament that enables interaction between the contractile proteins to take place. The extent of this interaction depends on myofilament overlap, or sarcomere length. In cardiac myocytes, active force decreases to zero at sarcomere lengths of around 1.6 μm, whereas 80% of maximum force is generated at this sarcomere length in skeletal muscle. This phenomenon is due to the length-dependent calcium affinity of troponin C in
cardiac muscle (Allen and Kentish, 1985). In cardiac muscle, the affinity of the regulatory protein troponin C for calcium is greatest at a sarcomere length of 2.25 μm and reduces markedly as sarcomere length is reduced. This leads to much greater length-dependence of cardiac myofilament activation than would occur as a result of altered myofilament overlap alone and provides an explanation for the large changes in ventricular function that occur as a result of altered filling.

The greater the calcium influx into the myocyte from the extracellular space (and its release from stores in the sarcoplasmic reticulum within the cell), the greater the rate and the force of contraction. The process is quickly reversed to enable relaxation to occur: most of the cellular calcium is pumped back into the sarcoplasmic reticulum by calcium-ATPase pumps, and residual calcium is removed from the cell primarily via sodium-calcium exchange (Bers, 2000). Abnormalities in calcium flux and/or calcium interactions with contractile proteins often underlie the mechanical dysfunction in cardiac contraction and relaxation that may occur in disease.

1.2.3 Events of the Cardiac Cycle

The continuous beating of the heart is governed by an inherent electrical conduction system that ensures that cardiac chambers become excited to contract in a coordinated manner. Activation of the heart normally begins at the sinoatrial node, where autorhythmic (self-excitable) myocardial fibres repeatedly and rhythmically initiate electric impulses called action potentials that travel throughout the myocardium, from cell to cell via gap junctions, thus setting the basic pace for heart rate. First the right and left atria are activated and then the wave of electrical activation travels to the right and left ventricles via the ‘atrioventricular bundle’ (which bifurcates into the right and left bundle branches, respectively, at the top of the interventricular septum). Within the ventricles the atrioventricular bundle branches continue as a subendocardial network of specialized conducting fibres called ‘Purkinje fibres’, which transmit the electrical impulse throughout the ventricular myocardium (Berne and Levy, 1993, Katz, A. M., 2001). The electrical activity of the heart generates currents that can be detected at the surface of the body and recorded as an electrocardiogram (ECG), as shown near the bottom of Figure 1.5. Atrial contraction occurs about 0.1 s after onset of the P wave (which signals excitation of atrial myofibres). The R wave represents the end of ventricular relaxation.
Figure 1.5 The Cardiac Cycle.
Changes in LV pressure and volume over the phases of the cardiac cycle, with respect to the ECG recording, heart sounds (detected with a stethoscope), and left atrial and aortic pressures.
Modified from Katz, A. M (2001) to reflect the reversal of the ventricular-aortic pressure gradient during the reduced ejection phase; the original was slightly inaccurate in that it demonstrated a greater LV pressure than aortic pressure throughout ejection.
Shortly after the onset of the QRS complex, which represents excitation of ventricular myofibres, the ventricles contract. Ventricular relaxation occurs just after the T wave. The ECG is usually recorded in most clinical assessments of cardiac function, as it is easy to obtain and gives a quick indication of abnormalities. (Tortora and Grabowski, 1996)

The normal cardiac cycle consists of a phase of systole and a phase of diastole, where the events that occur in each phase are perfectly timed to ensure normal function. The Wiggers diagram (Figure 1.5) is extremely helpful in visualizing the timing of these events and their significance.

Systole is the phase during which the ventricles contract and during which blood is ejected from the heart. With respect to the left ventricle, this phase begins with the closure of the mitral valve. Cavity pressure rises sharply with no change in cavity volume during a period of 'isovolumetric' contraction (ventricular volume is constant as both the mitral and the aortic valve are closed). When left ventricular pressure becomes greater than aortic pressure, the aortic valve opens and blood is ejected into the aorta. The amount of blood ejected by the ventricle during contraction is known as the stroke volume. Cardiac output, the volume of blood ejected by the LV per minute, is calculated by multiplying stroke volume by heart rate and is a clinical measure of global performance. Another measure, the LV ejection fraction (EF), which is the fraction of the total ventricular filling volume that is ejected during each ventricular contraction, is widely considered to be one of the most important clinical indices of LV systolic function, because it is easily measured and can be used for prognosis. In normal healthy individuals, EF is usually above 55% (Katz, A. M., 2001).

LV cavity pressure slightly exceeds aortic pressure during early rapid ejection and the rate of outflow continues to increase. However in the latter two-thirds of ejection a reversal of the ventricular-aortic pressure gradient occurs due to storage of potential energy in the walls of the artery, and as a result the rate of blood flow from LV into the aorta decreases. At the end of the latter, slower phase of ejection, the direction of blood flow in the aorta reverses briefly towards the LV and fills the cusps of the aortic valve so that they extend outwards and shut the orifice, thus preventing blood from flowing back into the ventricle. This event is generally taken to signal the beginning of the next phase of the cardiac cycle – diastole.

During the first diastolic phase of 'isovolumetric' relaxation, left ventricular pressure falls sharply. When LV pressure falls below left atrial pressure the mitral valve opens, and the early, rapid filling phase of diastole begins. This phase comprises only 30% of diastole but accounts for up to 80% of LV volume. This is followed by a period of slower
filling. The final filling phase contributes 15 to 25% of LV volume and occurs as a result of left atrial contraction. When LV pressure rises above left atrial pressure, the mitral valve closes, and thus another cycle begins. Important clinical indices of LV filling include transmitral flow rates and the relative contributions of rapid early filling and atrial contraction components. The time to peak filling rate can also be measured. The isovolumetric relaxation time reflects the rate of relaxation prior to filling.

1.2.4 Left Ventricular Pressure-Volume Relationship

Each phase of the cardiac cycle, with respect to the LV, is clearly distinguished by changes in pressure and volume, as can be seen in Figure 1.6. The preload determines the stretch that ventricular myofibres undergo due to filling with blood and is generated during diastole by the venous return. Clinically, the preload is characterized by the left atrial pressure, the LV end-diastolic volume and the LV end-diastolic pressure, and is considered to be an important determinant of the nature of diastolic events. The preload determines the volume along the end-diastolic pressure-volume relationship at which systole begins. The ventricle begins to contract, but closure of the mitral valve means that this contraction – and the consequent rise in LV pressure – occurs without change in LV volume (i.e., isovolumetric contraction), until the aortic valve opens and the LV meets its afterload – aortic pressure. The afterload is therefore defined as the pressure against which the LV must eject blood. During ejection, the large decrease in ventricular volume is initially accompanied by an increase in pressure, which begins to drop towards the end of ejection. Aortic valve closure, which signals the end of systole, removes the afterload (aortic pressure) from the LV cavity and is followed by the phase of isovolumetric relaxation (Katz, A. M., 2001). The mean arterial pressure is a simple clinical measurement of afterload.

The Frank-Starling law of the heart reflects the relationship between end-diastolic volume and systolic pressure. Over the normal range of end-diastolic volumes, the heart’s ability to generate pressure increases with end-diastolic volume (i.e., a response to venous return or preload). However, the end-diastolic pressure-volume relationship in Figure 1.6 shows that only small increases in pressure occur with the increase in volume during diastole. As filling increases, the ventricle becomes less distensible.

Under normal conditions, an increase in venous return results in a larger end-diastolic volume (EDV) and, therefore, greater myofibre stretch. Consequently, systolic contraction occurs with greater force, which produces a larger stroke volume. Thus increased
filling results in increased cardiac output, and the opposite is also true. The non-linear compliance of cardiac muscle, along with the stiff pericardium, which encloses the heart, normally prevent the LV from dilating to non-physiological dimensions. The fibrous outer layer of the pericardium anchors the heart in the mediastinum while the inner visceral layer adheres to the surface of the heart. Pericardial fluid between these layers reduces friction between the membranes as the heart moves. (Tortora and Grabowski, 1996)

![Diagram](image)

Figure 1.6 LV pressure-volume loop.
A: isovolumetric contraction, B: ejection, C: isovolumetric relaxation, D: LV filling.

The end-systolic pressure-volume relationship corresponds to the active pressure-volume relationship of the LV, which reflects the active length-tension relationship for cardiac muscle. This represents the maximum possible tension that cardiac myocytes are able to generate for a given length, and therefore the maximum possible LV pressure for a given LV volume (at a specific contractile state). Since LV volume decreases with ejection, the LV pressure during this phase does not rise to the maximum level possible (i.e., it does not reach the end-systolic pressure-volume relation) until end-systole when the aortic valve closes and LV pressure is maximal in the face of a closed outlet. The end-diastolic pressure-volume relationship corresponds to the passive length-tension relationship for cardiac muscle. Passive stretching of the heart, which occurs during diastolic filling, increases passive wall tension and diastolic LV pressure.

*Modified from Katz, A. M. (2001) to include arrows showing the sequence of events, and to indicate preload and afterload on the 'pressure' axis, and ESV (end-systolic volume) and EDV (end-diastolic volume) on the 'volume' axis.*
Figure 1.7 Effects of altered preload, afterload and contractility on the myocyte length-tension relation and the LV pressure–volume loop.

A: Increased preload results in greater stretching of myocytes to enable the ventricle to accommodate a greater volume of blood during diastole. An increase in myofibre stretch (as illustrated by the schematic plot on the left) leads to a greater force of contraction, and therefore a greater volume of blood can be ejected.

B: Increased afterload (aortic pressure) opposes outflow of blood from the ventricle. Less myofibre shortening occurs and therefore stroke volume decreases.

C: An increase in contractility rotates the active tension curve anticlockwise. A greater degree of shortening is possible, and therefore a greater stroke volume is ejected, without any increase in preload.

Reprinted from Li and Nguyen (2002).
Changes in afterload and contractility, as well as changes in preload, significantly influence the shape of the pressure-volume loop (Figure 1.7). An increase in preload as described above would result in a greater EDV and, at a constant afterload, would give a greater stroke volume. Therefore the pressure-volume loop would be extended to the right due to a larger ‘D’ (filling volume) and ‘B’ (ejection volume). However, the end-systolic volume (ESV) would still be achieved at the same pressure, because the afterload is unchanged (Figure 1.7 A). An increase in afterload, at a constant preload, (Figure 1.7 B) means that LV contraction has to overcome a greater pressure (larger ‘A’) in order to eject blood. The opposing force of aortic pressure reduces myofibre shortening and therefore less blood is ejected in the time available for this phase of the cycle. A greater residual volume remains in the LV at the end of ejection (i.e., ESV is increased) and stroke volume (‘B’) decreases, as indicated by a narrower, taller LV pressure-volume loop. An enhancement of inotropic state (i.e., an increase in myocardial contractility), in the presence of unaltered preload and afterload (which can be achieved with cardiac sympathetic nerve stimulation or administration of catecholamines), widens the pressure-volume loop (Figure 1.7 C), as a greater volume of blood can be ejected and, therefore, ESV is reduced (Berne and Levy, 1993).

The LV pressure-volume relation is a direct reflection of the relationship between initial sarcomere length and the force that is developed by cardiac myocytes. As depicted in Figure 1.7, during contraction the reduction in LV volume can be equated with sarcomere shortening, and the increase in LV pressure can be equated with the developed force of contraction (or to be more precise, the developed ‘stress’, which is force per unit cross-sectional area of the muscle). Force and length are determined by the degree of myofilament overlap, the effects of length-dependent activation, and calcium homeostasis (described in Section 1.2.2). Under normal conditions, LV diastolic pressure is about 0 to 7 mm Hg and sarcomere length is about 2.2 μm. Peak force may be achieved at a filling pressure of 12 mm Hg, but in the intact heart sarcomere lengths do not increase, even at very high filling pressures, beyond 2.3 to 2.4 μm (Berne and Levy, 1993). Thus the Frank-Starling law also holds true for the force-length relationship of cardiac myocytes – the greater the sarcomere length prior to contraction, the greater the force that can be developed during contraction, within the normal range of sarcomere lengths.

The measurement of chamber pressure, blood flow rates, and chamber volumes are important in the clinical assessment of cardiac haemodynamics and are directly influenced by function at the level of the myocyte. It must be noted that the force-length relationship for
cardiac myocytes, described above, reflects one-dimensional changes, and the comparison with the LV pressure-volume relationship is qualitative. In reality, the changes observed in pressure and volume are the result of a complex three-dimensional deformation that changes the shape as well as the size of the LV over the cardiac cycle.

1.2.5 Three Dimensional Deformation of the Left Ventricle

Myocyte contraction and relaxation underlie marked changes in LV shape and dimension in the circumferential, longitudinal and radial directions. This complex deformation over the cardiac cycle can be described in terms of strain, which is simply a change in length, and therefore directly reflects the degree of contraction or relaxation. Strain can be considered in the direction of the muscle fibre axis (shortening or lengthening along the length of the myocyte), as well as in the direction of the LV axis (e.g., shortening in the circumferential or longitudinal directions with respect to the LV long-axis). Previous studies have shown that myocardial strain varies over the LV wall (Waldman et al., 1985, Bogaert and Rademakers, 2001). Furthermore, wall thickness is non-uniform – greater than 2 cm at the attachment of papillary muscles, while only a few millimetres at the LV apex (Brutsaert, 1987). The irregular geometry of the LV and the regional differences in fibre orientation add further complexity to the process of deformation (Hunter et al., 2003).

Circumferential strains are greater than longitudinal strains throughout the LV (Waldman et al., 1988, Costa et al., 1999, Takayama et al., 2002). In addition to these axial strains, the LV undergoes torsional shear during systole, with rapid reversal during diastole. The diastolic untwisting that the ventricle undergoes to reverse torsion is associated with the release of restoring forces that are stored in the wall during systole. The resulting suction that is developed in the LV cavity facilitates rapid filling in early diastole. Torsional deformation is greater at the endocardium than at the epicardium.

It has been observed in dogs, that during systole, more shortening (Waldman et al., 1985) and more wall thickening (Gallagher et al., 1985) occur in the inner than in the outer region of the ventricle. This transmural gradient in myocardial shortening has also been observed in human studies (Clark et al., 1991). Detailed analyses of this variation have shown that while strains in the fibre direction do not vary greatly across the LV wall (Waldman et al., 1985, McVeigh and Zerhouni, 1991, Costa et al., 1999), cross-fibre strains are markedly greater at the endocardium – reported to be nearly twice that of fibre strain – than at the epicardial surface, where they are less than fibre strains (Bogaert and Rademakers,
2001). However, myocytes at the endocardial surface are almost perpendicular to fibres at the epicardial surface (i.e., endocardial fibres are more longitudinally oriented than epicardial ones). It has been suggested that the large cross-fibre strains occurring in the endocardial layers are possible at least partly because of cross-fibre strain in myocytes in other layers of the wall (Rademakers et al., 1994).

Therefore, although changes in LV dimension are greater at the endocardial surface than at the epicardium, changes in sarcomere length (i.e., in the fibre direction) still occur within relatively narrow limits for normal function. The large changes in LV dimension are brought about not only by endocardial cross-fibre strain but also by a combination of radial strain (inward wall motion), and shearing which contributes to some degree of laminar rearrangement. It has been suggested that passive cardiac muscle may be more compliant in the cross-fibre direction than in the direction of the fibres (Guccione and McCulloch, 1991). The well organized laminar architecture of the myocardium and loose coupling perpendicular to layers in the midwall and subendocardium ensure uniform transmural fibre strains, and that the layers coincide with planes of maximum shear (LeGrice et al., 1995b, Costa et al., 1999, Arts et al., 2001). Furthermore, the ellipsoidal shape of the LV means that the systolic reduction in internal volume occurs with greater length changes along the minor axis than along the major axis. Thickening of the LV wall during systole is possible due to the incompressible nature of myocardium, and marked diastolic expansion of cavity dimensions can be achieved without overstretching of the myocytes.

Recently, Bogaert and Rademakers (2001) showed quantitatively that circumferential radius of curvature was greater at the base of the LV than at the apex, and vice-versa for longitudinal radius of curvature. Their study also showed that wall thickening was greater in the thinner anterior LV wall compared with the thicker posterior wall, and myocardial systolic strain was, in general, greater at the apex than at the base.

As described above, the normal left ventricle is non-uniform with respect to structure and function. It is therefore important to understand these variations and take them into account when considering the changes that occur in the LV, as part of a disease process, for example.

Many earlier studies have examined regional differences with respect to systolic parameters (Brutsaert, 1987, Kramer et al., 1994, Bogaert and Rademakers, 2001). In the context of diastolic dysfunction, the need for information on regional variations in LV myocardial relaxation is also important, because pathological changes could occur on a regional basis and may be the earliest indicators of disease when global function appears to be
normal. For example, in conditions such as myocardial ischaemia or infarction great structural and mechanical changes may occur in a localized portion of the myocardium without significantly affecting the global function. In addition, characterization of both systolic and diastolic regional myocardial mechanical function can provide important clues regarding the development of the changes observed in global performance.

1.3 The Left Ventricle: Development of Structural and Functional Changes

Changes in LV structure and function can occur for a number of reasons, not all of which are pathological. For example, long-term athletic training leads to an increase in left ventricular (LV) mass due to increases in LV diastolic cavity dimension, wall thickness, or both. However, while such differences between athlete and non-athlete populations are statistically significant, they are generally small (Maron, 2003). Another instance is normal pregnancy, which is accompanied by echocardiographic evidence of mild ventricular chamber enlargement, an increase in circulating blood volume of about 50% on average, and an increase in cardiac output (peaking between the midportion of the second and third trimesters) due to an increase in stroke volume with a smaller increase in heart rate (Bonow et al., 1998).

Under normal circumstances, however, the most significant changes in cardiac structure and function occur with ageing. Altered loading conditions in the ageing heart lead to significant LV remodelling. However, this also occurs in many disease conditions. The incidence of cardiovascular disease is generally increased in the elderly, so it is important to be able to distinguish between the normal physiological changes due to ageing and those caused by pathology, which are often very similar. The influence of age on LV myocardial function in normal healthy individuals is examined in Chapters 3 and 4. A study of patients with type 2 diabetes mellitus provides a focus to examine pathological changes in LV function (Chapters 5 and 6).

1.3.1 LV Dysfunction and Heart Failure

Heart failure is defined as "... a complex clinical syndrome that can result from any structural or functional cardiac disorder that impairs the ability of the ventricle to fill with or eject blood" (Hunt et al., 2001). It is associated with low cardiac output due to impairment of LV systolic (reduced ejection) or diastolic (reduced filling) function. In moderate heart failure, cardiac output may be maintained by increased central venous pressure (due to the
increase in blood volume, partly caused by renal retention of fluid). However, as function deteriorates, venous pressure increases further, but cardiac output decreases. Reduced cardiac output leads to diminished renal perfusion, which enhances fluid retention through activation of the renin-angiotensin system. Furthermore, increased systemic blood volume and elevated venous pressure raise capillary pressure, which forces fluid across the capillary endothelium and leads to the accumulation of salt and water in the interstitial spaces. As a result, oedema (swelling) develops in the lungs and in soft tissues and body cavities. The lungs become increasingly stiff and inelastic due to the congestion caused by pulmonary oedema, and the greater respiratory effort that is required is exhibited in the patient as dyspnoea (shortness of breath). Fatigue is a further symptom that accompanies dyspnoea and pulmonary and systemic oedema in patients with heart failure, and is thought to be caused by a molecular disorder in skeletal muscles (Katz, A. M., 2001).

While LV dysfunction (which refers to an impairment of mechanical function) is the underlying cause of symptoms in the majority of patients with heart failure, it can occur with or without the clinical syndrome of heart failure, and mechanical abnormalities may be either systolic or diastolic (or both).

LV systolic dysfunction is characterized by a reduced cardiac output due to impaired contractile function. Left ventricular pump function is depressed. Clinically, this is usually quantified as an abnormal reduction in LV ejection fraction (Gaasch, 1994, Matter et al., 1996). When patients become symptomatic the diagnosis of ‘systolic heart failure’ may be made (Gaasch, 1994).

LV diastolic dysfunction is characterized by a reduced cardiac output due to increased resistance to filling. Ejection fraction may be normal or reduced (Gaasch and Zile, 2004). Diastolic dysfunction reflects any or all of three major abnormalities: slowed or incomplete relaxation, abnormal left ventricular filling, and altered myocardial passive elastic properties (Matter et al., 1996). Clinical findings include elevated LV end-diastolic pressure, and abnormal transmitral filling patterns. Symptomatic patients who are suspected to have heart failure are diagnosed with ‘diastolic heart failure’, if their systolic function is clinically normal (preserved or only slightly reduced ejection fraction), and valvular abnormalities are absent (European Study Group on Diastolic Heart Failure, 1998). Therefore in current clinical practice diastolic heart failure appears to be largely a diagnosis of exclusion.

It is important to emphasize the distinction between ‘diastolic dysfunction’ and ‘diastolic heart failure’ not only in the context of this Thesis but also when interpreting the literature; the two terms should not be used interchangeably. Diastolic dysfunction refers to a
mechanical abnormality in LV function during diastole, while diastolic heart failure is a clinical syndrome that is characterized by the presence of diastolic dysfunction and a normal ejection fraction (Zile and Brutsaert, 2002a, Gaasch and Zile, 2004).

Gaasch (1994) has depicted the changes in the LV pressure-volume loop due to systolic or diastolic dysfunction (Figure 1.8). The difference is obvious: decreased contractility, which underlies systolic dysfunction, reduces the ventricle’s ability to increase pressure for ejection of blood and therefore the end-systolic pressure-volume relation is shifted downwards (lower pressure) and to the right (greater end-systolic volume) and ejection fraction is reduced. With diastolic dysfunction, the end-diastolic pressure-volume loop is shifted upwards (higher pressure) and to the left (lower end-diastolic volume), because filling is impeded by raised LV pressure. However ejection fraction may be maintained due to compensatory increase in preload (Gaasch, 1994).

**Figure 1.8** LV pressure-volume loops in systolic dysfunction and diastolic dysfunction. In systolic dysfunction, contractility is depressed, and the end-systolic pressure-volume line is rotated clockwise; there is diminished capacity to eject blood into a high-pressure aorta. In diastolic dysfunction, chamber stiffness is increased and the diastolic pressure-volume relation is rotated anticlockwise; there is diminished capacity to fill at low diastolic pressures. The LV ejection fraction is typically low in systolic dysfunction but can be normal in diastolic dysfunction. Reprinted from Gaasch and Zile (2004).
Many patients with diastolic dysfunction have clinically normal systolic function, whereas most patients with systolic dysfunction also have diastolic dysfunction. Thus there have been suggestions that abnormalities in left ventricular diastolic function may precede systolic dysfunction, in the progression to overt heart failure (de Simone et al., 2000, Mandinov et al., 2000).

In the earliest stages, diastolic dysfunction may be characterized by a mild impairment of relaxation with little or no change in LV filling at rest and patients may be asymptomatic. However, disease progression may lead to severely increased LV filling pressure and reduced LV filling at rest, accompanied by the signs and symptoms of heart failure.

LV filling pressures can be increased by a number of factors including myocardial ischaemia, LV hypertrophy and abnormal calcium flux. Obesity, tobacco smoking, coronary artery disease, hypertension, and diabetes mellitus result in major structural changes in the heart, often manifested by myocardial ischaemia and LV hypertrophy. Furthermore, diastolic dysfunction is reported to be highly prevalent in the elderly population (Tokushima et al., 2001).

The basic mechanisms underlying diastolic dysfunction are reviewed in detail by Zile and Brutsaert (2002b) and Mandinov et al. (2000). Very briefly, these processes include abnormal calcium homeostasis, modification of contractile protein interactions, changes in the composition of the extracellular matrix (particularly the amount, distribution and relative proportions of the various types of collagen), and activation of the renin-angiotensin-aldosterone system (RAAS), which has been shown to increase collagen and myocardial stiffness (Zile and Brutsaert, 2002b). These processes lead to the development of diastolic dysfunction in a number of cardiovascular disorders, particularly hypertension and LV hypertrophy, coronary artery disease and valvular heart disease. In hypertensive patients, diastolic dysfunction is associated most often with LV hypertrophy, however it can occur even in the absence of structural changes (e.g., the increased afterload associated with arterial hypertension impairs relaxation and filling). LV pressure overload stimulates cardiac growth, while stimulation of RAAS promotes cell growth and collagen production, thereby increasing myocardial stiffness. In hypertrophic cardiomyopathy, an additional factor leading to diastolic dysfunction is myocardial calcium overload, which may be due to impaired calcium sequestration by the sarcoplasmic reticulum. This results in delayed and prolonged myocardial relaxation. Diastolic dysfunction, represented by a decreased rate of LV pressure decline and a prolonged isovolumetric relaxation time, is associated with the earliest stages of
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ischaemia in patients with coronary artery disease. Impaired relaxation is a feature of both LV volume overload (eccentric) hypertrophy, which accompanies mitral or aortic regurgitation, and LV pressure overload (concentric) hypertrophy, which occurs in aortic stenosis.

1.3.2 Ageing

Many changes, both structural and functional, occur in the heart as part of the normal ageing process. In studies of the influence of age on the LV, the focus has long been on diastolic dysfunction, as the systolic parameters that have been examined appear to be unaffected (Iskandrian and Hakki, 1986, Bryg et al., 1987, Tresch and McGough, 1995, Tokushima et al., 2001, Tighe et al., 2003). Several studies have demonstrated, using echocardiography, that while LV ejection fraction, percentage of fractional shortening (difference between LV diastolic and systolic dimensions divided by LV diastolic dimension) and cardiac output are often preserved in older people, isovolumetric relaxation time (Lakatta, 1993), and time to peak early diastolic filling rate (Bonow et al., 1988) are prolonged, and the peak early diastolic filling rate itself is significantly reduced (Spirito and Maron, 1988). Alteration in diastolic filling velocities (usually a decrease in peak early filling velocity accompanied by an increase in the velocity of peak filling due to atrial contraction) is so common in the elderly that it has even been suggested that this is 'normal' for their age-group (Mantero et al., 1995).

Age-associated degenerative changes occurring in myocardial structure include increased collagen accumulation in the myocardium and the walls of the great vessels, an increase in connective tissue (Eghbali et al., 1989), a reduction in β-adrenergic tone (Gerstenblith et al., 1976, Lakatta, 1987), and increased overall vascular impedance. Furthermore, decreases in elastic tissue, together with the increased collagen content, reduce the compliance of the myocardium and vessel walls such as those of the aorta (Lakatta et al., 1987). Other changes in structure include a thickening of the aortic and mitral valve leaflets and a gradual increase in the circumference of all four cardiac valves. Animal studies have shown that the rate of calcium uptake by the sarcoplasmic reticulum decreases with age (Froehlich et al., 1978) leading to a prolonged contractile state. This, in turn, may result in a prolongation of isovolumetric relaxation time, as observed in the elderly (Lakatta and Sollott, 2002).
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The probability of tachycardia and ischaemia increases with age. In addition, the development of LV pressure overload hypertrophy (increased myocardial mass and LV wall thickness) and hypertension is extremely common in the elderly population (Gerstenblith et al., 1977, Villari et al., 1997, Lakatta and Sollott, 2002) and severely reduces the compliance of the heart, and thus its ability to contract and relax, eject and fill, effectively.

Studies on the influence of age on LV mass have yielded conflicting results. Gerstenblith et al. (1977) reported age-associated LV hypertrophy in normal healthy men. Kitzman et al. (1991) showed that LV mass was not different between two groups of older and young normal healthy men. Hees et al. (2002) found an age-related decrease in LV mass, measured with MRI, in normal men but no change in women. These differences may be explained, in part, by the different methodologies used in these studies – Gerstenblith et al. (1977) and Kitzman et al. (1991) employed echocardiography, which assumes a constant LV length (with ageing). However Hees et al. (2002) report that LV length is significantly reduced with age resulting in a more spherical shape of the LV.

The age-related structural changes described above can act alone or in combination to produce marked impairment in LV mechanical function.

1.3.3 Diabetes Mellitus

Heart disease is the leading cause of diabetes-related deaths, accounting for greater than 50% of the mortality in patients with Type 2 diabetes mellitus (DM) (Stamler et al., 1993). Type 2 DM, the most common form of diabetes mellitus, is often referred to as ‘maturity-onset diabetes’ due to its occurrence later in life. Its prevalence worldwide has reached epidemic proportions with 177 million people estimated to have the disease in 2000, and the figure projected to increase to almost 300 million by 2025 (World Health Organization, 2004).

The underlying cause of type 2 DM is insulin resistance, most probably due to the down-regulation of insulin receptors on target tissues, which results in impaired glucose uptake from the blood by these tissues. In addition, there is usually some impairment of insulin secretion by pancreatic β-cells. Obesity, physical inactivity and genetic makeup are the most important risk factors for this disease. Insulin secretion decreases with age, while insulin resistance is associated with a number of disorders including hypertension, dyslipidaemia, endothelial dysfunction, and accelerated cardiovascular disease (these insulin
resistance related abnormalities are often collectively referred to as the ‘metabolic syndrome’ due to their high frequency in the diabetic population) (Grundy et al., 1999).

The immense morbidity associated with type 2 DM is attributable to a variety of complications triggered by hyperglycaemia, which include coronary artery disease, stroke, nephropathy, retinopathy and neuropathy (Grundy et al., 1999). Hyperglycaemia is the initial trigger for these complications, possibly through the formation of advanced glycation end-products, which accelerate atherosclerosis, promote glomerular dysfunction (leading to renal disease), reduce nitric oxide synthesis, and induce endothelial dysfunction (Brownlee et al., 1988, Colucci and Price, 2003).

It was initially assumed that the increased cardiovascular morbidity and mortality in this patient population were entirely due to the vascular complications associated with diabetes mellitus such as hypertension, obstruction of the major coronary arteries, or valvular disease. In 1972, however, Rubier et al. (1972) showed that a specific cardiomyopathy related to diabetes might exist as a distinct clinical entity. Research since then has confirmed that this restrictive diabetic cardiomyopathy occurs even in the absence of atherosclerotic coronary artery disease, valvular or congenital disease, hypertension or alcohol (Regan et al., 1977, Bouchard et al., 1989, Fein and Sonnenblick, 1994). Diabetic cardiomyopathy is found in approximately 30% of patients with Type 2 DM and is characterized by abnormal myocardial relaxation and elevated left ventricular (LV) filling pressures. Histologically, patients have interstitial fibrosis with increased amounts of collagen, glycoprotein, triglycerides, and cholesterol in the myocardial interstitium, and, in some cases, intimal thickening, hyaline deposition, and inflammatory changes have been observed in small intramural arteries (Colucci and Price, 2003).

The assessment of the diabetic patient includes both physical examination and laboratory measurements (e.g., lipid profile, fasting plasma glucose and albumin/creatinine ratio). Impaired glucose tolerance is a risk factor not only for diabetes but also for cardiovascular disease (Grundy et al., 1999). Furthermore, it has been shown that poor glycaemic control as measured by haemoglobin A_{1c} (HbA_{1c}) levels, may be independently associated with an increased risk of heart failure, possibly through the development of atherosclerosis and coronary artery disease, and through direct myocardial damage (Iribarren et al., 2001). Albuminuria, which is characteristic of diabetic nephropathy, has been found to be related to abnormal midwall shortening and also to abnormal LV diastolic relaxation, independent of the duration of diabetes and confounding factors including LV mass, body mass index and coronary artery disease (Liu, J. E. et al., 2003b). It has been suggested that
the concentration of brain natriuretic peptide (BNP), which is elevated in LV dysfunction (Yamamoto et al., 1996), and in normotensive type 2 DM patients with microalbuminuria (Yano et al., 1999), could be used as a marker of LV function in diabetes (Chan and Hurel, 2001); this has yet to be investigated, however.

Clinically, diastolic dysfunction without the symptoms of heart disease is a common finding in patients with type 2 DM (Poirier et al., 2001, Boyer et al., 2004). Clinical indices of systolic function may not always be depressed, but prognosis tends to be better for patients with preserved versus reduced ejection fraction (Cohn and Johnson, 1990, Gustafsson and Hildebrandt, 2001). The limitations of current clinical techniques make it difficult to accurately assess myocardial diastolic function in patients suffering from Type 2 DM. Cardiac catheter studies are invasive, for example, and echocardiographic images are often difficult to interpret in obese patients, which is often the case in the diabetic population. Magnetic Resonance Imaging (MRI) may provide a useful alternative for non-invasively assessing alterations in myocardial structure and function.
1.4 Aims of the Thesis

The processes of systole and diastole are inextricably linked. Therefore, the methods developed in this Thesis are applied to indices of both systolic and diastolic function, in ageing and in type 2 diabetes mellitus. The major aims of the thesis were:

To develop kinematic parameters that quantify the temporal behaviour of regional systolic and diastolic function using 3D tagged MRI (e.g., systolic shortening velocity, diastolic lengthening velocity).

To determine the extent to which these temporal mechanical parameters are influenced by age and disease and to determine which parameters are the most sensitive indicators of remodelling processes.

To compare the MR parameters, examined in the course of this study, with traditional clinical measurement of LV systolic and diastolic function made with echocardiography.

1.5 Summary of Chapters

Chapter 2 provides a review of the various techniques for assessing LV function, along with a description of magnetic resonance imaging methods as they are used in this Thesis. The calculation of novel parameters of LV myocardial systolic and diastolic mechanical function is also detailed here.

Changes in LV myocardial function due to normal ageing must be characterized before pathological changes can be identified. Thus, the influence of age on the novel parameters described in this Thesis has been studied in detail. Previously, our research group had used MR tagging to show that ageing significantly alters global myocardial relaxation (Oxenham et al., 2003). That work has been extended in this Thesis to demonstrate age-related changes in regional myocardial relaxation patterns. A detailed description is given in Chapter 3.

Chapter 4 focuses on a simple measure of systolic and diastolic function – the motion of the mitral valve annulus plane (MVP). A method is developed to track the motion of the MVP in 3D, from MR anatomical long-axis images, and to recover kinematic indices. This is applied to younger and older adults to show the differences arising due to normal ageing. These indices are then compared with the more complex tissue strain parameters.
The relationship between systolic and diastolic MR myocardial mechanical parameters is also examined.

The MR parameters of LV function are applied to a group of patients with type 2 diabetes mellitus, in Chapter 5. These patients have diastolic dysfunction, by echocardiographic criteria, and a normal LV ejection fraction. LV myocardial strains and strain rates are measured in the diabetes group and compared with values from normal subjects. The motion of the mitral valve annulus plane is also tracked over the entire cardiac cycle and compared with normal values. Systolic as well as diastolic myocardial function is assessed and quantified.

The diastolic flow of blood across the mitral valve can be assessed with MRI as well as with echocardiography. Recently, echocardiographic tissue Doppler imaging studies have shown that the motion of the mitral valve annulus can provide useful information on myocardial function. MRI can be used analogously to track the displacement of the mitral valve annulus plane over the cardiac cycle. In Chapter 6, comparisons are made between the MR and echocardiographic values for transmitral flow and systolic and diastolic mitral annular velocities, which were obtained in the subjects studied in this Thesis.

Finally, the core findings of the studies described in this Thesis, their significance in terms of existing knowledge, and their practical applicability are discussed in Chapter 7.
Chapter 2

Assessment of LV Diastolic Function

2.1 Research and Experimental Methods

LV systolic function can be quantified easily and non-invasively, and routine clinical parameters that are measured include ejection fraction, fractional shortening and cardiac output. However, obtaining an accurate non-invasive index of LV diastolic function is more difficult. Left ventricular relaxation and filling are influenced by many factors including myocardial relaxation, LV suction, viscoelastic properties of the myocardium, ventricular compliance, left and right ventricular interaction, pericardial restraint and heart rate. The interaction of these factors may directly or indirectly determine diastolic function (Mandinov et al., 2000). A brief description of some experimental methods for assessing LV diastolic function is given below and currently used clinical methods are described in the next section.

The current gold standard index of LV diastolic function is the LV end-diastolic pressure, which can be directly measured by advancing a micromanometer-tipped catheter into the left ventricle. Although this gives the most accurate measure of diastolic function, cardiac catheterisation carries the risks of any invasive procedure, and is therefore indicated only for patients in whom the cause of symptoms cannot be elucidated with routine non-invasive studies, to identify the extent and severity of coronary artery disease, and in patients who are scheduled to undergo angioplasty.

Radionuclide ventriculography involves the administration of a radioactive agent into the patient’s blood supply. Monitoring the distribution of this ‘radionuclide’ within the left ventricle allows for measurement of peak filling rate and time to peak filling. Furthermore left ventricular volume and wall thickness can be estimated. However, direct visualization of cardiac chambers, walls, valves and the pericardium is not possible and
neither intracardiac pressures nor myocardial function can be evaluated with this technique. Another obvious disadvantage is the exposure of the patient to radiation.

The pattern of myocardial deformation can provide useful information about function. Until recently, it was possible to study this deformation only by using implanted markers (e.g., tantalum markers (Ingels et al., 1975, Yun et al., 1992)), or sonomicrometry crystals (Owen, C. H. et al., 1993), or by using strain gauges (length-transducers) (Semafuko and Bowie, 1975). Although these extremely invasive procedures have been performed in humans in the past (Yun et al., 1991), their use in recent years has been restricted to research in animal models (Mazhari et al., 1998, Rodriguez et al., 2004) with the advent of non-invasive and increasingly accurate cardiovascular imaging techniques.

Although of minor relevance to this Thesis, it must be mentioned that neurohumoral markers may have clinical value in the assessment of LV function as they provide complimentary diagnostic and prognostic information. Studies have shown elevated levels of serum atrial natriuretic peptide (ANP), brain natriuretic peptide (BNP), norepinephrine and other neurohormones in patients with heart disease (Nakamura and Hiramori, 2003). BNP, in particular, has been shown to be useful in detecting heart failure and in predicting prognosis (de Lemos et al., 2003). While these markers may be clinically useful in the detection of LV dysfunction and in predicting the development of heart failure, little is known about how they relate to myocardial mechanical function, and their ability to offer useful information regarding the nature of a particular myocardial impairment needs to be established.

2.2 Echocardiography

Echocardiography, which employs ultrasound to non-invasively image the heart and surrounding intrathoracic structures, is usually the first step in the clinical assessment of LV function. Ultrasound is an acoustic wave with a frequency higher than 20 kHz. However, for diagnostic purposes, the ultrasound used is typically in a higher frequency range of about 2 MHz, which allows improved accuracy with somewhat reduced penetration. As ultrasound penetrates through a non-homogeneous medium, it reflects from the boundaries of different regions with different acoustic impedance. An echocardiogram is a recording of the reflected ultrasonic beam.
Echocardiography, which is used to measure cardiac chamber size, wall thickness, and myocardial and valvular motion, provides useful information on the relationship between anatomy and function. It is a sensitive tool for identifying mass lesions within and adjacent to the heart, characterizing congenital cardiac defects, diagnosing valvular and myocardial pathology and also for detecting pericardial and pleural fluid accumulation. Simultaneous electrocardiography is usually performed during the echocardiographic examination ("Echocardiography Tutorial" 1999, Nishimura et al., 2004).

The three main types of echocardiography that are used clinically are M-mode, two-dimensional (2D, B-mode or real time), and Doppler echocardiography. In addition, tissue Doppler imaging of the mitral annulus is being used increasingly, and there have been several reports recently on the validity of the strain rate echocardiography technique for measuring myocardial tissue function.

2.2.1 Clinical Assessment

The M-mode echocardiogram yields a one-dimensional view (depth) of the cardiac structures moving over time. The echoes from various tissue interfaces along the axis of the beam are moving during the cardiac cycle and are swept across time, providing plots of distance vs. time. The lines on the recordings correspond to the position of the imaged structures in relation to the ultrasound transducer and other cardiac structures at any instant in time.

M-mode echocardiography has been used to assess the dimensional changes and its first derivatives during diastolic filling. For example, displacement of the atroventricular plane towards the apex directly reflects longitudinal fibre contraction. Thus, its measurement by M-mode echocardiography provides additional information regarding global and regional systolic and diastolic function (Mandinov et al., 2000). Two-dimensional echocardiography, which is performed from multiple acoustic windows with different transducer rotations, allows different planes of tissue (therefore, both depth and width) to be imaged in real time. Thus, the anatomic relationships between various structures are easier to appreciate than with M-mode echocardiographic images ("Echocardiography Tutorial" 1999, Nishimura et al., 2004).

Doppler echocardiography is based on the detection of frequency changes (the Doppler shift) occurring as ultrasound waves reflect off individual blood cells moving either away from or toward the transducer ("Echocardiography Tutorial" 1999) and therefore it is
extremely useful for the evaluation of blood flow direction and velocity. In this way abnormal blood flow patterns such as those associated with valvular insufficiency or stenosis and cardiac shunts, for example, can be detected and assessed. Furthermore, measurement of volume flow rates also allows calculation of stroke volume and cardiac output (Nishimura et al., 2004).

Perhaps the most useful application of Doppler echocardiography is the acquisition of the transmitral flow velocity pattern (Figure 2.1) which is used in the assessment of LV diastolic function to rapidly categorize patients with normal or abnormal diastolic function by E:A (the ratio of early to late peak filling velocity).

![Figure 2.1 Schematic representation of echocardiographic transmitral flow patterns.](image)

Age- and disease-related changes in early diastolic velocity (E), and filling velocity due to atrial contraction (A) are depicted. With increasing age the E:A ratio decreases, becoming less than 1 in elderly patients ('impaired relaxation' pattern). In subjects with impaired LV relaxation (e.g., myocardial hypertrophy, ischaemia) the filling pattern shows a further decrease in the E-wave, whereas with a decrease in LV compliance the filling pattern changes towards normal ('pseudo-normalization') and even shows enhanced early diastolic filling with an E:A ratio > 2 ('restrictive filling' pattern). Simplified reproduction from Mandinov et al. (2000).

In normal, healthy, young individuals, filling velocity is greatest in early diastole, therefore E:A > 1. In disease conditions, however, progressively impaired relaxation and decreased early diastolic filling are compensated for, by more vigorous atrial contraction. This reverses the E:A ratio (E:A < 1), and results in an increased deceleration time of the early transmitral flow. An increased isovolumetric relaxation time is also characteristic of individuals with this ‘abnormal relaxation’ pattern. A ‘pseudo-normalization’ pattern results when LV compliance decreases in the course of the disease: filling pressures become elevated and compensatory augmentation of left atrial pressure increases early filling, despite impaired relaxation, so that the filling pattern looks relatively normal (E:A > 1). This pattern is
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Assessment of LV Diastolic Function

distinguished from normal filling by a shortened early deceleration time. Finally, in patients with severely decreased LV compliance and impaired relaxation, left atrial pressure becomes markedly elevated and compensates with even more vigorous early diastolic filling, resulting in the 'restrictive' filling pattern (E:A >> 1) (Appleton et al., 1988, Mandinov et al., 2000).

2.2.2 Tissue Doppler Imaging

Tissue Doppler imaging (TDI) is used to measure myocardial velocities. It is especially useful in the assessment of LV diastolic function as the motion of the mitral valve annulus can be assessed. In normal persons the mitral annular velocity pattern produced by TDI is almost a mirror image of the transmitral flow pattern, with an early (E') to late (A') annular velocity ratio > 1, indicating normal diastolic function. While early transmitral flow velocity is increased in patients with pseudonormal or restrictive filling pattern (as described above), early annular velocity remains abnormally low (Figure 2.2), implying that it is not as influenced by the changes in preload that compensate for impaired relaxation (Sohn et al., 1997, Lindstrom and Wranne, 1999). Hence, TDI easily unmasks the pseudonormal transmitral flow pattern.

Research suggests that the early diastolic annular velocity (E') is a relatively preload-independent index of LV relaxation; interventions to alter preload such as saline or nitroglycerine infusion caused no alteration in E' (Sohn et al., 1997). The early transmitral flow velocity, E, is a function of preload as well as LV relaxation, however, and therefore may be combined with E' (i.e., the E/E' ratio) to correct for the influence of relaxation in order to estimate filling pressures. Studies have shown that the E/E' ratio can be used to discriminate between patients with normal and elevated filling pressure (Nagueh et al., 1997, Lindstrom and Wranne, 1999, Kim, Y. J. and Sohn, 2000, Ommen et al., 2000). Furthermore, E/E' has been shown to be independent of systolic function (Kim, Y. J. and Sohn, 2000, Ommen et al., 2000, Graham et al., 2003) and its relationship with LV filling pressures has been shown to be maintained even in patients with tachycardia (Nagueh et al., 1998) and atrial fibrillation (Sohn et al., 1999).
2.2.3 Strain Rate Imaging

Strain rate imaging (SRI) is a newer echocardiographic technique derived from TDI, to measure the velocity at which tissue deformation (i.e., strain; see Section 1.7.1) occurs. Velocities are colour-coded, allowing assessment of regional wall motion, and therefore, the ability to identify localized impairments (Miyatake et al., 1995). Local myocardial strain rate is estimated from the spatial velocity gradient, typically by dividing the difference in instantaneous myocardial velocity at two points in the same tissue by the distance between these points. Integration of strain rate over time gives an estimate of strain (Heimdal et al., 1998, Pislaru et al., 2002).

The high frame-rates that are available for SRI allow for real-time acquisition of myocardial velocities (D’Hooge et al., 2000), and for more meaningful assessment of regional asynchrony with respect to timing of mechanical events. Strain and strain rate measured using this technique can be taken as indices of LV myocardial function as they have been
shown to be influenced by changes in myocardial contractility (Weidemann et al., 2002). The ability to obtain local measures of myocardial deformation is especially useful in assessing myocardial ischaemia where regional asynchrony in the onset of contraction, for example, is easily detectable. The technique has also been applied in the examination of coronary artery disease, and in the detection of infarcted tissue which demonstrates lower systolic strain rates than non-infarcted regions (Heimdal et al., 1998). SRI has demonstrated superior sensitivity and specificity to 2D echocardiography and TDI in the discrimination between viable and nonviable myocardium (Hoffmann et al., 2002). With respect to diastolic function, SRI is able to detect reduced early diastolic strain rate and increased late diastolic strain rate in older people (Pislaru et al., 2002).

Several useful reviews, which document the principles and applications of strain and strain rate imaging in detail, are available (D’Hooge et al., 2000, Pislaru et al., 2002, Pellerin et al., 2003, Yip, G. et al., 2003).

2.2.4 Limitations

Echocardiography has several shortcomings due to the nature of the imaging process. Firstly, Doppler echocardiographic parameters are restricted to components toward and away from the transducer. Components of the motion transverse to the ultrasound beam are consequently ignored, and therefore components of deformation such as torsion cannot be measured. Secondly, good views of all regions of the heart are not always possible due to the lack of an acoustic window. In particular, the inferior wall of the LV, and right ventricular regions are often poorly imaged. Thirdly, echocardiographic assessment does not take into account the through-plane motion of the heart. The complex deformation of the ventricle results in tissue moving through and across the ultrasound beam during the cardiac cycle, thus leading to errors in velocity measurement.

Although SRI offers potential for rapid acquisition of myocardial strain information in the clinical setting, it is currently hindered by suboptimal signal-to-noise ratio. Furthermore, values obtained for strain rate are dependent on the Doppler angle since the directions of circumferential and longitudinal strain are mutually orthogonal to that of radial strain (Pislaru et al., 2002). Echocardiographic measurements of myocardial strain and strain rate provide uni-dimensional estimates of myocardial deformation, when in reality this deformation is a three-dimensional process (Pislaru et al., 2002). In addition, the direction of
the maximal shortening strain (known as the ‘principal’ strain) is oriented oblique to the ultrasound beam and therefore cannot be assessed with this technique.

These problems can be solved with another non-invasive imaging technique, MRI, in which superior spatial and contrast resolution can be obtained.

2.3 Cardiac Magnetic Resonance Imaging

2.3.1 MRI: Underlying Physics

The Magnetic Resonance Imaging technique is based on the principles of Nuclear Magnetic Resonance (NMR) spectroscopy. NMR is used to obtain chemical and physical information about molecules. MRI is used to obtain the NMR signal from molecules in the body, in a spatially encoded fashion, in order to create an image.

A ‘magnetic moment’ is associated with the ‘spin’ (angular momentum) of protons, neutrons and electrons. The magnetic moment of a nucleus is zero when protons, for example, are paired. Only nuclei with odd atomic number have a magnetic moment that can be used for NMR.

In the body, the hydrogen nucleus is the most abundant, and has the strongest magnetic moment. It has just one, unpaired proton and exists in both fat and water molecules, which are two major constituents of tissue. Thus, most clinical MRI relies on the NMR signal from hydrogen nuclei.

Normally, the spin axes of hydrogen nuclei are randomly orientated, such that the net magnetic moment of all of the spins is cancelled out. However, when the body is placed in an external magnetic field ($B_0$), such as inside the bore of an MR scanner ($B_0$ is typically 1.5 Tesla (T) for human MR imaging, although 3 T and higher scanners are now available for clinical use), the spin axes of the hydrogen nuclei align either parallel or anti-parallel to $B_0$. Thus, hydrogen nuclei are capable of two energy states - a low energy configuration where the spin axes are parallel with $B_0$, and a high-energy state where they are anti-parallel. At room temperature, the number of spins in the lower energy level slightly outnumber the number in the upper level (Hornak, 2004).

In order to transfer from the lower to the higher energy state, the hydrogen nucleus must absorb a photon whose energy must equal the energy difference between the two states. This energy difference is expressed by the equation:

$$\Delta E = h \gamma B_0$$
where $h$ is Planck’s constant ($6.6 \times 10^{-34}$ Js) and $\gamma$ is the gyromagnetic ratio of the hydrogen nucleus (42.6 MHz/T). Furthermore, the energy of the photon that must be absorbed is related to its frequency, $v$, measured in hertz (Hz), such that:

$$E = hv$$

Thus a hydrogen nucleus can transfer from a lower to higher energy state only by absorbing a photon whose frequency is given by:

$$v = \gamma B_0$$

This ($v$) is the Larmor frequency and it exists in the radiofrequency (RF) range for hydrogen imaging. RF pulses used in clinical 1.5 T MR scanners are typically around 65 MHz (i.e., $42.6 \text{ MHz/T} \times 1.5 \text{ T} = 63.9 \text{ MHz}$).

The presence of the external magnetic field causes the net magnetic moment of all the nuclear spins to rotate or ‘precess’ at a frequency equal to the frequency of the photon that induces a transition between the two energy levels of the hydrogen nucleus (i.e., $v = \gamma B_0$). Note that although the net spin is precessing at the Larmor frequency, the spins of the individual nuclei are affected by their molecular environment and therefore rotate at different speeds to each other so that they become randomly ‘out of phase’. When the appropriate RF pulse (at the Larmor frequency) is transmitted to the nuclei within $B_0$, not only do the hydrogen nuclei move from a lower to a higher energy state, but all of the individual spins precess ‘in phase’ (i.e., they rotate at the same phase angle relative to each other) and therefore the net magnetic moment moves out of alignment with $B_0$ by a certain angle (called the ‘flip angle’) from the longitudinal (y-z) to the transverse (x-y) plane. When the pulse is turned off, the spins begin to return to their equilibrium position within the magnet and start to precess out of phase. The precessing protons effectively produce a moving magnetic field, and thus, by Faraday’s law, induce a small electrical signal (a few millivolts) in a coil of wire that is designed to detect the resonating net magnetization. This is how the NMR signal is created. Newer MRI systems use multiple RF amplifiers to receive the different elements of the MR signal; this increases the signal to noise ratio and improves image resolution (Hornak, 2004).

In order to image the positions of the MR spins, gradient coils are used to produce a programmable variation in the magnetic field, such that the Larmor frequency varies as a function of position. The gradient can be oriented in any direction that is required and can be turned on or off during imaging. Three types of magnetic field gradients are temporarily created within the external magnetic field using gradient coils. The ‘slice-select’ gradient is
used to acquire the NMR signal from a particular location, or slice, in the body. The 'phase-' and 'frequency-encode' gradients are used to manipulate the in-slice spatial encoding. The encoded data – an array of numbers known as ‘k-space’ – is then subjected to a Fourier Transform, which results in the final appearance of the MR image (Hornak, 2004). Increasing gradient strength and/or switching reduces scan time, but care must be taken to prevent stimulation of skeletal muscle, which can occur if the rate of change of the magnetic field (dB/dt) is too great (Pohost et al., 2003).

After the application of the RF pulse, the time it takes for the magnetization to return to its equilibrium position in the magnet (called longitudinal, spin-lattice or $T_1$ relaxation time) is dependent on the molecular mobility of the protons. Protons in fats are relatively 'fixed' in place and take a short time (about 250 ms) to return to equilibrium, while the more mobile protons in free water take 1-2 s to recover their magnetization. The $T_1$ for myocardium is typically 800 ms (Evans, 2004, Hornak, 2004).

When tissue is excited by a 90° RF pulse, the magnetization is re-directed to 90 degrees from its original position, and the protons precess in phase in the transverse plane (as described above). When the RF pulse is turned off, the signal deteriorates because the protons quickly start to go out of phase (due to molecular interactions within the tissue and minute inhomogeneities in the external magnetic field increasing or decreasing the local magnetic field and, therefore, the resonant frequency). The time taken for the signal to decay is termed transverse, spin-spin, or $T_2$ relaxation time. Again due to the different molecular environment of protons, fat has a short $T_2$ relaxation time (about 20 ms) and water has a long $T_2$ relaxation time (about 60 ms) (Evans, 2004).

$T_2$ is always less than or equal to $T_1$. The net magnetization returns to zero in the transverse plane according to the $T_2$ time and then recovers its equilibrium value in the longitudinal plane according to the $T_1$ time. The differences in $T_1$, $T_2$ and proton density between various tissue types, fat, water and blood result in contrast in the MR images, and allow the distinction between different structures to be made (Hornak, 2004).

### 2.3.2 Cardiac MRI: Image Acquisition

MRI is non-invasive and provides natural high contrast between the blood pool and cardiovascular structures. MRI of the heart and great vessels can be acquired without contrast agents. Cardiac MRI offers an alternative to most existing imaging techniques, including Computerised Tomography (CT), because it does not use ionizing radiation and can
acquire high-resolution images in any plane. However, acceptance for routine use in the clinical domain is dependent on the availability of faster image acquisition times. Therefore, this has become one of the driving forces for research and development in cardiac MRI.

The appearance of the MR image is dependent on the type of pulse sequence used to excite protons in order to generate the NMR signal. Most pulse sequences used today are derived from one of two basic sequences – the spin-echo (SE) sequence or the gradient-recalled echo (GRE).

Spin-echo, which was used earliest for cardiac imaging, applies two RF pulses. The first 90° pulse is applied in conjunction with a slice-select gradient to selectively excite the protons in the required image slice. As the proton spins dephase (T2 relaxation) a ‘free induction decay’ signal (FID) is received (this signal is not used, however). After a brief interval during which a phase-encoding gradient is set, the second 180° RF pulse is applied – this causes the proton spins to rephase and to produce a signal, which is called the echo (Hornak, 2004). The time between the initial RF pulse and the maximum amplitude in the echo signal is called the echo time (TE). TE can be varied to control the appearance of the image. Spin-echo sequences can be used to produce ‘black-blood’ images. This is because blood leaves the image slice before being subjected to the second RF pulse and therefore does not produce an echo. High contrast is achieved between fat and the various myocardial structures that do produce a signal, due to differences in T2, thus enabling the identification of myocardial changes due to pathology, which can be identified by an abnormally longer or shorter T2. In addition, the presence of aneurysms or thrombi can sometimes be detected (blood flow is slower and therefore a signal is produced). In these ‘black-blood’ images, contrast due to differences in T1 is eliminated by using an interval between the successive applications of the pulse sequence (repetition time, TR) that is longer than T1 (Pettigrew et al., 1999).

Spin-echo imaging is limited by its temporal resolution and long acquisition times (due to relatively long TR). Although newer techniques that allow faster acquisition times are now available (e.g., single shot fast spin echo (SSFSE) (Stehling et al., 1996, Stemerman et al., 1999)), a trade-off is made with contrast in the resulting images. Other black blood-blood imaging sequences such as T2-weighted single-, double-, and triple-inversion recovery (Edelman et al., 1991, Simonetti et al., 1996), allow faster imaging and offer better contrast (Pettigrew et al., 1999, Earls et al., 2002).

Gradient-recalled echo imaging is used more often in studies of cardiac function because it affords shorter image acquisition times than spin-echo techniques. The basic
sequence requires the application of a single RF pulse (to excite the proton spins), followed by the application of a dephasing frequency encoding gradient (applied at the same time as the phase-encoding gradient). This disrupts the phases of the magnetic moments. The frequency-encoding gradient is then reversed after the phase-encoding gradient, which causes the spins to rephase and to produce what is called the 'gradient echo' signal (Hornak, 2004). In contrast to spin-echo, the gradient echo technique causes blood to generate a bright signal intensity (hence the term 'bright-blood' imaging) that is proportional to the rate of blood flow. This difference in the appearance of the images is due to two main reasons. First, in spin-echo imaging blood must remain in the image slice long enough to receive both RF pulses in order to generate a signal, but with GRE only one RF pulse is required to produce a signal. Second, GRE sequences have a shorter TE, which reduces signal loss due to spin dephasing (Pettigrew et al., 1999). The shorter TE allows for faster image acquisition. GRE can be used to quantify LV functional parameters including chamber volumes, ejection fraction and cardiac output, LV mass, and myocardial deformation.

The basic GRE sequence has given rise to many faster techniques, including fast gradient recalled echo (fGRE), fast low angle shot (FLASH), segmented k-space, and steady state free precession (SSFP). Although reduced TR (a feature of GRE sequences) decreases imaging time, it tends to compromise image quality as signal strength deteriorates due to decreased recovery of longitudinal magnetization. FLASH is based on the principle of using an RF excitation pulse with a small flip-angle, so that there is relatively little loss of longitudinal magnetization to begin with and therefore the time taken to recover is also reduced (Frahm et al., 1986).

Cine imaging is now performed fairly routinely with the segmented k-space technique, which employs short TEs (e.g., 2 ms) and TRs (< 10 ms) and allows multiple segments of k-space to be acquired during each cardiac cycle (Atkinson and Edelman, 1991, Epstein et al., 1999), rather than just one line per cycle for each phase, as with earlier GRE sequences. The marked improvement in imaging time is reflected in the choice of acronym, for these sequences – for example, turboFLASH, turboFFE (turbo fast field echo). The main limitation of the technique is that the short TR reduces inflow enhancement of the cardiac blood pool and, therefore, contrast with the myocardium (Earls et al., 2002). Figure 2.3 shows typical turboFLASH images of the heart.

With the SSFP technique, image contrast is governed by the T1/T2 ratio of the tissue rather than by flow. This represents an improvement over segmented k-space FLASH and older fGRE techniques, with respect to signal-to-noise (SNR) ratio, temporal resolution,
myocardial-blood contrast, and endocardial border definition through the cardiac cycle. Barkhausen et al. (2001) used the true-FISP (True Fast Imaging with Steady-State Precession) sequence, a variant of SSFP, with a very short TE (1.6 ms), and were able to halve the image acquisition time that was required for FLASH. For these reasons SSFP sequences have become the most widely employed in the assessment of cardiac function with MRI.

![Figure 2.3 MR images acquired with the turboFLASH pulse sequence.](image)

A short-axis image at the mid-ventricular level (A) in a normal volunteer, looking up from the apex of the heart through to the base, shows the thicker-walled LV on the right, and the crescent-shaped right ventricle on the left-hand-side. The dark spots that can be seen near the inner wall of the LV are papillary muscles. A long-axis image acquired in the same volunteer (B) shows all four chambers of the heart. Both images were obtained at end-diastole.

Temporal resolution can be further improved, while imaging time is conserved, by using a procedure known as ‘view-sharing’, where the data of adjacent temporal frames is shared, resulting in a data set that contains more time frames than were actually acquired. The temporal resolution of the measurement is improved, but that of the actual acquired images remains unchanged (Foo et al., 1995, Lotz et al., 2002); this is, therefore, an image processing technique rather than an image acquisition method.

Echo-planar imaging (EPI) is an ultra-fast technique where all of the lines of the k-space matrix can be acquired within a single TR, so that a complete snapshot image can be formed in 30 to 40 ms (Mansfield, 1984, Rzedzian and Pykett, 1987). The newer ‘multishot’ EPI techniques (Davis et al., 1995) that are now available further decrease acquisition time, and give better signal-to-noise ratio. However, at these increased speeds, image quality tends
to be inferior to both FLASH and SSFP techniques (Wiesmann et al., 1998, Krombach et al., 2004), especially with respect to image warping.

The marked reduction in image acquisition time, which most MR systems offer today, allows for acquisition at video rates so that an entire cardiac cycle can be imaged over a breath-hold of a few seconds, with consequent elimination of respiratory motion artifacts.

2.3.3 Phase Contrast Imaging and Flow Velocity Mapping

Quantitative assessment of blood flow can be performed with MR phase contrast imaging (van Dijk, 1984, O'Donnell, 1985, Nayler et al., 1986). The technique is based on the principle that nuclear spins that are moving (e.g., in flowing blood) will experience a shift in their phase with respect to stationary spins in the presence of a magnetic field gradient. This phase shift is proportional to the velocity of the moving spins, and is encoded in the detected MR signal.

Thus, in the resulting ‘phase image’ (Figure 2.4 B and D, for example) the signal intensity at any pixel is proportional to the velocity of protons which cross the corresponding volume element (voxel) in the image slice. The strength and duration of the magnetic field gradient can be varied in order to pre-define the amount of phase shift per unit velocity; the gradient is set to image the maximum flow velocity that can be expected (Pettigrew et al., 1999, Lotz et al., 2002).

MR flow imaging is not widely used in the clinical domain, mainly because of the greater accessibility of Doppler echocardiography, and the paucity of time-efficient MR image processing facilities. However, it offers a viable alternative when echocardiography is difficult or not possible, and unlike the latter, it is not limited by poor acoustic windows. Phase contrast imaging has been used to assess diastolic function in the past (Karwatowski et al., 1995), and measurements of peak E and A velocities, comparable to the Doppler E and A waves, could be obtained. It is also possible to measure the actual volume of flow across a valve (Hartiala et al., 1993).

In addition to measuring blood flow velocities, phase contrast imaging with velocity-encoding can be applied to the assessment of myocardial motion; tissue displacement may be measured by integrating velocity, thus enabling calculation of local strain (van Dijk, 1984). However the process of integration is relatively complicated.
The MR signal is processed into the standard anatomical (magnitude) images (A and C) and the corresponding phase contrast image (B and D) shown here for a normal volunteer at end-diastole (A and B) and during rapid filling (C and D). These images were acquired to record flow through the mitral valve. Grey pixels in the phase contrast images represent stationary tissue, white pixels represent flow (motion) into the image plane, and black pixels represent flow out of the image plane. Note the brighter pixel intensity within the LV in D, due to early diastolic filling and, therefore, blood flow into the image plane.

2.3.4 Myocardial Tissue Tagging

Studies of myocardial motion have primarily used MR myocardial tagging techniques, first described by Zerhouni et al. (1988). MRI myocardial tagging makes it possible to quantify the extent of regional heart wall motion abnormalities at rest and during stress. In the commonly used SPAMM (spatial modulation of magnetization) tagging method (Axel and Dougherty, 1989), a grid of "tag lines" is superimposed on the MR images.

This is achieved by pre-saturating planes of tissue, perpendicular to the subsequent imaging plane, with a short burst of radiofrequency pulses, thereby destroying the MR signal from these planes. The 'tag-planes' appear on the image as dark bands that move and deform along with the myocardium as it contracts during systole and expands during diastole (Figure 2.5). The image acquisition protocol for tagging uses the FLASH pulse.
sequence, rather than SSFP, so imaging is slower and contrast is lower than in standard ‘untagged’ images.

Figure 2.5 MR myocardial tagging.
Schematic showing placement of tags in the heart (top), and the appearance of the resultant short-axis images (bottom). Myocardial motion over the cardiac cycle results in deformation of the tags, which are straight at end-diastole (ED) and appear bent at end-systole (ES).

Tagged images can be used to track the 3D motion and deformation of the myocardium, by allowing exact mapping of the spatial wall motion (Young and Axel, 1992, Young et al., 1995). Analysis of this deformation then generates quantitative data on
circumferential and longitudinal shortening and lengthening through most of the cardiac cycle, on a global basis as well as for individual myocardial regions (Bogaert and Rademakers, 2001, Kuier et al., 2002, Young et al., 2002). It must be noted that myocardial motion is difficult to track in very late diastole because tag contrast and persistence is governed by $T_1$ relaxation.

2.4 MR Image Processing and Analysis

For MR imaging of the LV, images are typically acquired perpendicular to the long-axis of the LV, in several ‘slices’ from apex to base; these form the short-axis image series. A series of long-axis images is usually acquired in different orientations around the central axis of the LV (including images in the four-chamber and two-chamber views), such that the central long-axis is included in the plane of each image. Both short- and long-axis image series are acquired at uniform intervals over the cardiac cycle; each series typically contains 15 to 30 frames. Acquisition is usually gated to the R wave of the ECG, which is recorded while the patient lies in the scanner. This ensures that the images are acquired at the correct time and enables their identification with respect to the phase of the cardiac cycle.

2.4.1 Anatomical Imaging and Volumetrics

Once the images have been acquired, an efficient, accurate method of analysis is necessary for obtaining quantitative volumetric information. This usually involves the process of defining the boundaries of the LV wall on the images (either manually or automatically) in order to create a model of the LV that can be interrogated to automatically generate information regarding anatomy and function.

On standard cine anatomical MR images, the first step is to define the contours of the LV wall in order to obtain numerical values for parameters such as end-diastolic volume, end-systolic volume, wall thickness, LV mass and ejection fraction. Previous attempts at image analysis have estimated total LV wall and cavity volumes by adding up the volumes calculated through defining contours in each image (Singleton and Pohost, 1997). Due to the large number of images that are typically acquired, manual definition of the contours for each patient is extremely time-consuming and tedious. For this reason, computer software packages are being developed to automate the process. With most of these packages, the user defines contour points on the inner and outer surfaces of the LV walls in the image data set.
In an attempt to automate the process of defining contours, most methods have relied on variations in pixel intensity in the image, to detect the edges of different regions (Singleton and Pohost, 1997). Low temporal resolution, image artifacts, and insufficient contrast between the myocardium and blood pool have limited the accuracy of these techniques, and subsequent correction by the user is also time-consuming. A computerized model of the LV that allows interactive fitting of contour points by the user offers a better alternative.

Our group has developed custom software, employing the finite element modelling (FEM) method to describe LV geometry and myocardial deformation (Young et al., 1994, 1995, 2000). The LV wall is represented by a geometric model consisting of 16 discrete 3D regions i.e., finite elements – 4 longitudinally by 4 around the LV circumference, as illustrated in Figure 2.6. Each point within an element has properties with values that are weighted by the position of the point relative to the nodal points constraining the element. In order to ensure that the model is seamless, its elements are constrained so that adjacent edges have the same value for position and slope ('slope' being the tangent that the node makes to the curved ventricular surface).

Figure 2.6 Sixteen-element Finite Element Model of the LV.
The LV wall is represented by 16 discrete elements that make up the 3D model. The properties of each point within an element are weighted by the nodes constraining that element.
Figure 2.7 Guide-point modelling.
The user places guide-points on the epicardial (blue) and endocardial (green) contours of the LV, which represent the model-image intersections, on as many time frames and in as many slices as required. The images shown above are standard anatomical MR images in a short-axis (A and B) and a long-axis (C and D) slice at end-diastole (A and C) and end-systole (B and D), acquired in a normal volunteer.

Figure 2.8 Representation of Finite Element Model of the LV.
Long-axis MR image of LV with FEM superimposed. For clarity, the epicardium is depicted here as a wireframe representation of the model’s contours, while the endocardium is displayed as a solid 3D surface. The model representation of the LV base is also shown.
Chapter 2

The user first defines key contour points, such as the apex, the base and the intersection points of the right ventricle, on a few images in the data set in order to define a coordinate system within the LV of the patient. The patient’s images are then registered with the software’s ‘default’ 3D model, which was created from the manual contouring of nearly 100,000 images and is therefore reasonably representative of ‘average’ LV geometry. The intersections of this model with the patient’s image planes represent the endocardial and epicardial contours of the LV wall. These contours are displayed on all of the patient’s images, and the FEM is fitted interactively to guide-points placed by the user to make the model contours match those of the images (Figure 2.7). As the user places, modifies, or deletes guide-points, the model fit updates in 3D and in real time enabling fast reconstruction of LV geometry through the cycle (Figure 2.8).

In this way the user is able to guide the model-image intersections until an acceptable 3D representation of LV boundaries is achieved. Usually, guide-point fitting on the end-diastolic (ED) and end-systolic (ES) images only is sufficient to obtain values for LV mass and volume. The model contours from these two phases are input to the software and volumes at end-diastole and end-systole are calculated by multiplying the area defined by the endocardial contour in each image with the image slice thickness and the gap between slices. LV mass is calculated as the difference between the volume enclosed by the epicardial contour and the volume enclosed by the endocardial contour, multiplied by the specific gravity of muscle (i.e., (epicardial volume – endocardial volume) x 1.04 g/L). The LV mass eventually obtained represents the mean of ES and ED values.

2.4.2 Analysis of Phase Contrast Images

In the assessment of LV function, measurement of tissue and blood velocities is useful. With regard to LV diastolic function, it is helpful to analyse the nature of LV filling and transmitral flow can be calculated from velocity encoded MR phase contrast images. In typical short-axis phase contrast images (as shown in Figure 2.4), a region of interest can be defined and flow within this region can be calculated over all imaged frames. In this Thesis, a freely available software package – Scion Image (Rasband, 2000) – was used for the analysis of phase contrast images, in order to calculate the rate of blood flow across the mitral valve. The program automatically provides the mean pixel intensity within the selected region of interest in each time frame of the image data set. These pixel intensities, along with the knowledge of the specific velocity encoding that was used, can then be used to calculate the
velocity within the region of interest in each frame. Details of the procedure for analyzing phase contrast images, as used in this Thesis, are provided in the Appendix.

2.4.3 Analysis of Tagged Images

In order to reconstruct 3D motion and strain from tagged MR images, the tagging information in each image must be tracked to give displacement information in the plane of the image, and then the image displacement information must be integrated between image slices to give 3D displacement information. In this Thesis, a FEM based technique is used to integrate displacement information between images (Young and Axel, 1992, Young et al., 1995).

Firstly, tag stripes are located on the tagged images at each frame and tracked through the cycle using a semi-automated tracking procedure based on an active contour model (Young and Axel, 1992, 1994, 1995). The tag stripes are tracked through all the image frames, for each slice, to determine the exact position of several hundred points in the myocardium through most of the cardiac cycle (Figure 2.9). A FEM is constructed to model the geometry of the LV in each frame of the sequence (Young et al., 1995). Then, the FE model in each frame after ED is deformed to match the displacement of the tags back to ED. This is done because the displacement back to the ED tag planes is partially imaged by the deforming image stripe pattern, since tags are initially planar and orthogonal to the image plane (the displacement of points imaged at ED is not known due to through-plane motion and the deformation of the heart). This step reconstructs 3D displacement information. The model deforms smoothly to fit the displacement of the MR tags, as its 16 elements undergo cubic interpolation in the circumferential and longitudinal directions.

Through-plane motion and out-of-plane shears are accounted for, by fitting the model to long- and short-axis data simultaneously. The model interpolates displacement constraints between tag and image planes, resulting in a consistent 3D displacement field. Finally, a 3D FE model of the ED geometry is fitted to the reconstructed 3D motion in each subsequent frame. This allows the calculation of Lagrangian strain, which is referenced to the ED state.

Previous validation experiments using a silicone gel model have shown that the tag analysis method described here produces accurate, unbiased estimates of displacement and shortening (Young et al., 1995). The model can be interrogated to provide regional
circumferential and longitudinal shortening strains and torsional shear strain at each frame using standard continuum mechanics methods (Fung, 1965, Young et al., 1995).

![Figure 2.9 Tracking of MR myocardial tags.](image)

Tags are tracked semi-automatically, as in this short-axis slice, showing end-diastole (A), end-systole (B) and late diastole (C). A grid of stripes is placed on the LV at frame 1 (usually end-diastole). The green points represent 'active' (i.e., moving) myocardium and follow the motion of the MR tags over the cardiac cycle with minimal correction by the user.

Although reliable, the processes described above for the tracking of myocardial displacement are time-consuming. The recently developed Harmonic phase (HARP) MR image processing technique (Osman et al., 1999, Garot et al., 2000) allows fast processing of tagged images. HARP MRI incorporates Fourier filtering and special processing algorithms, to measure myocardial deformation in tagged MR images and to rapidly and automatically provide values for 2D Eulerian and Lagrangian strain. In addition, HARP can also be used in conjunction with special MR tagged image acquisition sequences for real-time acquisition and image processing, allowing for operator-independent strain measurement (Earls et al., 2002). Contrary to initial claims, however, the spatial resolution of HARP is the same as standard tagging analysis methods (i.e., on the order of the stripe spacing). The technique is still under development and its clinical applicability is being investigated.
2.5 Myocardial Mechanics

2.5.1 Myocardial Tissue Strain

Stress and strain measurements are of particular importance, because they give a direct description of myocardial mechanical and functional properties at each point in the ventricular wall. Strain is the relative change in shape or size of an object due to externally applied forces, and is, therefore, dimensionless (i.e., has no units). Stress is the internal force (per unit area) associated with a strain. Thus, strain can be defined as a measure of the extent to which a body is deformed when it is subjected to a stress. Myocardial strains can be positive (representing lengthening of myocardial segments) or negative (representing shortening). Direct measurement of myocardial stress is difficult as it is dependent on the complex interaction between the various forces acting on the tissue; indeed, its estimation relies on the use of mathematical models (Hu et al., 2003, Remme et al., 2004), which are based on, and can be validated with, measurements of myocardial strain.

The strain at each point in the myocardium can be described by the Lagrangian strain tensor. This is referenced to an undeformed state such as end-diastole (ED) and comprises six independent components: three ‘axial’ strains, which describe stretching or shortening along the mutually orthogonal circumferential, longitudinal and radial coordinate axes, and three ‘shear’ strains related to the angle change in each of the three coordinate planes (McCulloch and Omens, 1991).

The Lagrangian strain is the instantaneous strain (referenced to ED) defined for each moment of the deformation process. However, deformation can also be expressed with reference to the length at the current point in time. Thus the reference value is not constant over time but changes during the process of deformation. When expressed in this way, the deformation is known as the Eulerian strain. In effect, Eulerian strain refers strain to the deformed state, whereas Lagrangian strain refers strain to the undeformed state. When strain is small (about 5-10%), Lagrangian and Eulerian strains are approximately equal. However, with the much larger strains that occur during cardiac contraction and relaxation, the difference between Lagrangian and Eulerian strains becomes significant. This must be taken into account, therefore, when comparing echocardiographic data with that obtained from MRI, since strain derived from echocardiographic TDI is usually Eulerian, whereas strain derived from MR tagging is usually Lagrangian.

The state of 3D strain within the myocardium can be fully described only by using all components of either the 3D Lagrangian or the 3D Eulerian strain tensor (Fung, 1965).
TDI and strain rate echocardiography can provide only certain components of tissue velocity and strain rate (those in the direction of the ultrasound beam), and these may be converted to displacements and strains only under the assumption of zero transverse motion.

2.5.2 Measurement and Calculation of MR Strain Parameters

Processing of tagged MR images and analysis of the resulting FEM (as described in Section 1.6.5) yields values for myocardial tissue strain.

Circumferential and longitudinal strains can be defined as the percentage change in length of small line segments oriented in the circumferential and longitudinal directions, respectively, at end-diastole (ED). This is illustrated in Figure 2.10.

Torsional shear strain is a measure of LV 'twist' (i.e., rotation of the apex with respect to the base about the central LV axis), and is defined to be the change in the angle between small material line segments orientated longitudinally and circumferentially at ED, to the angle between the corresponding material line segments at a later time (Fung, 1965, Young et al., 2002). See Figure 2.10.

The 3D principal strain corresponds to the maximal shortening strain developed at any point in the LV myocardium. It is a single index of 3D strain, which combines circumferential and longitudinal axial strains and torsional shear strain and is independent of the coordinate system used to measure these individual components (Fung, 1965). Greater circumferential and longitudinal shortening strains, as well as greater LV torsion all lead to greater 3D principal shortening strain.

Circumferential and longitudinal strains (\(\%s_c\) and \(\%s_l\)) are calculated from the Lagrangian strain tensor \(E\) as follows (Fung, 1965):

\[
\%s_c = (\sqrt{1 + 2E_{CC}} - 1) \times 100\% \quad \text{and} \quad \%s_l = (\sqrt{1 + 2E_{LL}} - 1) \times 100\%
\]

The torsion angle (\(\alpha_{CL}\)) is calculated from the strain tensor \(E\) as follows (Fung, 1965):

\[
\sin \alpha_{CL} = \frac{2E_{CL}}{\sqrt{1 + 2E_{CC}} \sqrt{1 + 2E_{LL}}}
\]

\(E_{CC}\), \(E_{LL}\) and \(E_{CL}\) represent the circumferential, longitudinal and circumferential-longitudinal shear components, respectively, of the Lagrangian strain tensor.

The 3D principal shortening strain is calculated as the most negative Eigenvalue of the Lagrangian strain tensor (Fung, 1965).
Chapter 2
Assessment of LV Diastolic Function

Peak systolic strain rates and peak rate of diastolic relaxation of strain can be calculated using a central difference formula. The maximum systolic strain rate is given by the peak rate of change of strain measured during systole and the maximum diastolic strain relaxation rate is given by the peak rate of change of strain measured after peak strain.

Figure 2.10 Ventricular deformation and myocardial strains.
Small line segments in the LV, oriented in orthogonal circumferential (C) and longitudinal (L) directions, respectively, at end-diastole (ED) are shown on the left. During systole, the LV undergoes an anticlockwise rotation at the apex and a clockwise rotation at the base (viewed from the apex), with a reversal during diastole.

The systolic deformation of the LV is shown on the right. C' and L' represent the circumferential and longitudinal segments, and α the angle between them, at end-systole (ES). Thus circumferential strain $S_C = (C - C')/C \times 100\%$, longitudinal strain $S_L = (L - L')/L \times 100\%$, and torsional shear strain $S_T = 90° - \alpha$. Maximal shortening occurs in the direction of the line segment P at ED (deformed to $P'$ at ES) so that principal strain $S_p = (P - P')/P \times 100\%$.

2.5.3 Ventricular Twist and Torsion

The 3D motion of the heart is characterized by rotation (around the centre of gravity), radial displacement (towards or away from the centre of gravity) and translational motion (displacement relative to the long-axis of the heart). The non-invasive MR tagging technique has revealed the systolic ‘wringing’ motion of the LV, which is characterized by a clockwise rotation at the base with counter-clockwise rotation at the apex. During diastole, an ‘untwisting’ motion occurs in the opposite direction to the systolic ‘wringing’ motion, with a
counter-clockwise rotation at the base and a clockwise rotation at the apex (Maier et al., 1992).

In the normal, healthy heart torsional deformation of the left ventricle (systolic wringing motion) is built up during systole, while most of the untwisting occurs during isovolumetric relaxation before diastolic filling of the left ventricle can begin. It is thought that this may be the mechanism by which potential energy could be stored in the LV wall during ejection and then released during diastole to create suction and fast early filling. This could be achieved by straining the intercellular collagen matrix, which on relaxation would release its stored energy and restore the diastolic configuration of the ventricle. The resulting decrease in LV pressure causes suction and rapid early filling (Rademakers et al., 1992).

Rademakers et al. (1992) have used MRI myocardial tagging to show that untwisting and LV filling are temporally separated in the canine model. They expressed the dissociation of untwisting from filling as the percentage of untwisting that occurred before the onset of filling (the point of mitral valve opening – as measured by echo-Doppler). Their results showed that approximately 50% of untwisting occurred before mitral valve opening. Measurements were made at the apical- and mid-ventricular levels (with reference to the base level) in both the epicardium and the endocardium. Torsion of the apex was found to be larger than torsion of the mid level (as reported in humans (Hori et al., 1982)), and similarly the extent of untwisting before mitral valve opening was greater at the apex. The study concluded, “torsion reversal is an important mechanism for rapid early filling and may form the physiological basis of external restoring forces, generating suction at normal ventricular volumes and promoting both pressure decay and filling.”

2.5.4 Motion of the Mitral Valve Plane

A simple index of LV systolic and diastolic function, which is of current clinical interest, is the kinematics of the mitral valve annulus plane (MVP). This is often imaged with echocardiographic M-mode and TDI, and has been shown to be a sensitive indicator of both systolic and diastolic function (Yip, G. W. et al., 2002b). The base-to-apex motion of the MVP is an important component of longitudinal myocardial function. The base of the LV is more mobile than the apex, which moves very little (Rogers et al., 1991) and is assumed to be fixed in TDI studies of MVP motion.

The peak systolic displacement and velocity, and the peak diastolic velocity of the plane of the mitral valve annulus can also be studied with MRI, which offers superior spatial
resolution to echocardiography. Using the FEM-based software developed by our group, MVP motion can be tracked by placing guide-points at the site of attachment of the mitral valve leaflets to the wall (at the confluence of the left atrium and the LV), on standard MR anatomical images of the LV long-axis plane, in each frame. This is typically done for three different long-axis image planes, which are spaced at equal angular intervals around the central axis of the LV. The 3D positions of all mitral valve attachment points are averaged to give an estimate of the mitral valve centroid at each frame. The 3D displacement of this point is considered to be the MVP displacement, and peak systolic and diastolic MVP velocities are estimated using a two-point central difference formula.

Mitral valve plane displacement and velocity are different to longitudinal tissue strain and strain rate, in that the latter give information on local tissue deformation relative to the undeformed (i.e., ED) state at virtually any point in the myocardium, whereas the former parameters are absolute values (referenced to time – for example, ED – but not to initial/undeformed length), and are measured only at the base of the LV.

The influence of age and type 2 diabetes mellitus on MVP motion is examined as part of this Thesis. It is interesting to compare age- and disease-related changes that may occur in MVP motion (as measured with MRI) with those that may occur in the MR strain parameters described above.
Chapter 3

Influence of Age on Regional LV Myocardial Function

3.1 Introduction

Normal healthy older people have generally well preserved clinical indices of systolic function, but striking age-associated changes occur in diastolic function (Klein et al., 1994, Mantero et al., 1995, Fioranelli et al., 2001). These include a reduced early peak filling rate relative to the atrial component of filling (reduced E:A ratio) (Spirito and Maron, 1988, Kitzman et al., 1991, Cacciapuoti et al., 1992, Mandinov et al., 2000), a prolongation of isovolumetric relaxation time (Tokushima et al., 2001) and an increased time to peak filling rate (Bonow et al., 1988, Furutani et al., 1993).

Global LV function has been extensively studied, but little is known about regional myocardial function during diastole. It has been shown, however, that both normal (Brutsaert, 1987, Bogaert and Rademakers, 2001) and dysfunctional (Kramer et al., 1994, Garcia-Fernandez et al., 1999) left ventricles are regionally heterogeneous with respect to structure and function (Greenbaum and Gibson, 1981). Regional information can provide important clues on how structural and mechanical changes that occur in localized portions of the myocardium contribute to the changes observed in global function. Conversely, in pathological conditions such as myocardial ischaemia and infarcts, only localized mechanical changes may occur, without apparent change in global function (McCulloch and Omens, 1991). Importantly, changes due to normal ageing must be characterized before pathological changes in regional function can be identified.

Useful parameters of regional myocardial function include regional wall thickness, thickening, wall motion, and myocardial stress and strains. Non-invasive techniques such as radionuclide angiography (Bonow et al., 1988, Furutani et al., 1993) and
echocardiography (Wilkenshoff et al., 2001) have been used to show that age-related changes in diastolic function occur in a regionally heterogeneous way in normal healthy people. The increase in regional diastolic filling asynchrony and non-uniformity with age that these studies have demonstrated is thought to contribute to the age-related alterations observed in global left ventricular diastolic function (Spirito and Maron, 1988, Tokushima et al., 2001). However, radionuclide angiography requires the injection of radioactive isotopes, and measures of LV chamber dynamics do not directly quantify myocardial relaxation. Strain rate imaging, a technique derived from echocardiographic tissue Doppler imaging, can provide direct, non-invasive measures of myocardial relaxation on a regional basis (Wilkenshoff et al., 2001). However, the components of strain relaxation that can be quantified are limited to those in the direction of the ultrasound beam, and not all regions of the ventricle can typically be examined. Furthermore, the effect of through-plane motion on these measurements remains unknown.

The introduction of MRI with tagging has enabled the non-invasive assessment of true myocardial contraction and relaxation, both globally and on a regional basis (Zerhouni et al., 1988, Axel and Dougherty, 1989). The technique has been used to characterize the regional non-uniformity of systolic function in the normal LV (Young et al., 1994, Bogaert and Rademakers, 2001) and recently Kuijer et al. (2002) have quantified regional 3D diastolic strain evolution in 10 normal volunteers, demonstrating the feasibility of MR tissue tagging to measure regional strain relaxation parameters.

Global LV diastolic relaxation parameters have also been investigated (Paelinck et al., 2002). The rate of relaxation of LV torsion, for instance, has been shown to be relatively independent of preload and afterload (Dong et al., 2001), and to be reduced in disease (Stuber et al., 1999). Our research group has shown, using MR tissue tagging, that the peak rate and extent of global LV myocardial relaxation in older people is significantly delayed and reduced (Oxenham et al., 2003). Changes in the pattern of regional myocardial relaxation due to ageing, as assessed with MR tissue tagging, are presented in this Chapter.

Tagged MRI was used to quantify regional 3D diastolic strain and strain relaxation rates in old and young people. It was hypothesized that regional non-uniformities in myocardial strain relaxation are altered in a consistent pattern with normal ageing. The aims of this study were therefore: (i) to quantify the differences in myocardial relaxation in the different regions of the left ventricle, and (ii) to determine the effect of ageing on these regional non-uniformities.
3.2 Methods

3.2.1 Subjects

Subjects were recruited into the study after responding to advertisements within the University of Auckland. Approval for the study was obtained from Auckland Human Subject Ethics Committee, and written informed consent was obtained from all participants. Subjects were included only if the clinical examination, transthoracic echocardiogram and 12 lead ECG showed no evidence of pre-existing cardiac disease or other significant coexisting illness. Exclusion criteria included a history of hypertension, diabetes, ischaemic or valvular heart disease, regular use of medication for cardiovascular illness, or a resting blood pressure above 160/90. On the 12 lead ECG, atrial fibrillation, bundle branch block, pathological Q waves, left ventricular hypertrophy or changes consistent with myocardial ischaemia resulted in exclusion, as did any significant valvular abnormality, impaired systolic left ventricular function or left ventricular hypertrophy on the transthoracic echocardiogram. Transmitral Doppler echocardiography was performed successfully in all subjects, except for two in the younger group.

Of the 33 subjects screened, two from the older age-group were excluded – one due to coexisting cryptogenic fibrosing alveolitis, and the other on identification of an inferior wall motion abnormality by transthoracic echocardiography. Thus, a total of 31 subjects was scanned: 15 were classified as ‘younger’, (age 19-26 years, mean 23.2 years), and the remaining 16 subjects were classified as ‘older’ (age 60-74 years, mean 68.8 years). Approximately 75% of each group was male.

3.2.2 MRI Protocol

All of the MR tagging studies were performed in the supine position with the use of a Siemens 1.5 Tesla Vision MRI scanner and a phased array surface coil. A segmented k-space version of the spatial modulation of magnetization (SPAMM) tagging sequence was used to create a tag grid in the images with a spacing of 8 mm and width of approximately 1 mm. Tagged images were acquired in eight or nine short-axis slices, equally spaced from apex to base, and six long-axis slices at equal angular intervals around the central axis of the

---

1 MRI data from these subjects were previously examined to obtain information particularly on apical rotation. This study has been documented elsewhere Oxenham HC, Young AA, Cowan BR, Gentles TL, Occleshaw CJ, Fonseca CG, Doughty RN and Sharpe N (2003). Age-related changes in myocardial relaxation using three-dimensional tagged magnetic resonance imaging. *J Cardiovasc Magn Reson* 5(3):421-430.
LV. View-sharing was used to reconstruct 15-27 time frames per cardiac cycle with a breath-hold duration of 15-19 beats (scan parameters were: slice thickness 8 mm; in-plane resolution 1 mm/pixel; temporal resolution 35 or 45 ms, depending on subject’s heart rate; TE/TR = 4.0/8.9 ms; 128x256 image matrix). All images were prospectively gated, and therefore images could not be acquired during the last 10-15% of the cycle, to allow for detection of the R wave trigger. Tagged MR images from a typical subject in the older age-group are shown in Figure 3.1. Tags could be visualized and tracked throughout the imaged portion of the cardiac cycle.

![Tagged MR images](image)

**Figure 3.1 Tagged MR images for a typical subject in the older group.**

These short-axis images were acquired at the mid-ventricular level and show good tag persistence through the cardiac cycle. A: end-diastolic, 45 ms; B: end-systolic, 315 ms; and C: late diastolic, 675 ms).

### 3.2.3 Image Analysis

The images were stored digitally and analyzed ‘off-line’ with a custom computer software package that incorporates a finite element model (Young et al., 1994, 2000) to represent the geometry of the left ventricle (as described in 2.4.1).

The geometry of the LV was defined using guide-point modelling (Young et al., 2000) and tag stripes were located and tracked using a semi-automated tracking procedure based on an active contour model (Young et al., 1995). Finite element models were fitted to the tracked tag stripes using previously described methods (Young et al., 1995). Through-plane motion and out-of-plane shears were accounted for by fitting the model to long- and short-axis data simultaneously. Regional circumferential and longitudinal shortening strains and torsional shear strain at each frame were calculated from the model using standard continuum mechanics methods (Fung, 1965, Young et al., 1995).
3.2.4 Myocardial Strains

In each of the 16 standardized LV myocardial regions (Schiller et al., 1989), peak values were determined for circumferential and longitudinal strains and torsion, and the time (in ms) from end-diastole (ED) to peak value. Note that these regions are different to the 16 cubic elements of the FEM, described in Section 2.4.1, and are based on standard echocardiographic LV regions (Schiller et al., 1989). Therefore values for each of the 16 regions examined here may be derived from more than one element of the FEM. The mathematical calculation of strain is described in Section 2.5.2. By convention, ED was defined as the first image in the ECG triggered sequence (0 ms) and end-systole (ES) was the image with the smallest left ventricular cavity area. Each frame is taken at 35 or 45 ms intervals after ED, depending on temporal resolution.

For all three strain parameters (circumferential, longitudinal and torsional shear), peak systolic strain rates and peak rates of diastolic relaxation of strain were calculated using a central difference formula, as described in 2.5.2. The time from ED to peak relaxation rate was also measured.

Indices of regional asynchrony, with respect to time to peak strain and torsion and time to peak rate of relaxation, were obtained by calculating the absolute value of the difference between the global average and the value for each of the 16 regions, and then calculating the average of these 16 differences (Yamagishi et al., 1984, Bonow et al., 1988, Furutani et al., 1993). An increase in the index of regional asynchrony would indicate increased regional heterogeneity with respect to time to peak strain and time to peak relaxation.

3.2.5 Statistical Analysis

Data were analyzed using the SYSTAT software package (Version 10, copyright SPSS Inc., 2000, Standard Version). All data are presented as the mean ± SD. Statistical significance is defined as $P < 0.05$.

A two factor MANOVA was performed to examine the interaction between age and region. A significant interaction effect implies a significant difference in the pattern of regional heterogeneity due to age.

Strains at all tracked tag points were averaged into 16 standard LV myocardial regions (Schiller et al., 1989). To test for regional differences longitudinally from apex to base, the 16 regions were averaged into three longitudinal levels (apex, mid-ventricle and...
base, each averaged over all circumferential regions). Similarly, to test for circumferential differences, the 16 regions were averaged into four circumferential regions (septal, posterior, lateral and anterior, each averaged over all longitudinal regions). Thus, for each strain parameter, two MANOVAs were performed, one testing the longitudinal variation and the other testing the circumferential variation.

Where a significant interaction existed between age and region, the following pair-wise comparisons were performed. Between groups, each region in the older group was compared with the corresponding region in the younger group. Thus, for the three longitudinal levels or the four circumferential regions, the P-values were corrected in Bonferroni fashion for three or four tests, respectively. Within each age-group, comparisons between the three longitudinal regions were corrected for three tests, while comparisons between the four circumferential regions were corrected for six possible tests. In some cases the extent of the change due to age was compared between regions, and the resulting P-values were corrected for three tests for the longitudinal regions or six tests for the circumferential regions. Bonferroni corrected P-values are stated for each test where applicable; these are indicated with a superscript B.

An ANCOVA was performed in order to determine the influence of systolic blood pressure (SBP), diastolic blood pressure (DBP) and the ratio of LV mass to end-diastolic volume (EDV), on the rate of relaxation of each strain parameter.

### 3.3 Results

#### 3.3.1 Subjects

The baseline characteristics of each age-group are given in Table 3.1 and MRI volumetric data are presented in Table 3.2. SBP and DBP were both significantly higher in the older group. Body mass index (BMI) was greater in the older subjects, but there were no significant differences in body surface area (BSA), heart rate, ejection fraction, or left ventricular mass, between age-groups. EDV and stroke volume were significantly smaller in the older group. The ratio of LV mass to EDV was significantly greater in the older group. Taking both groups together, LV mass:EDV ratio correlated with both the SBP ($r = 0.610, P < 0.001$) and DBP ($r = 0.650, P < 0.001$). Transthoracic Doppler echocardiography showed a reduced diastolic peak E velocity and increased peak A velocity in older subjects. This resulted in a significantly decreased E:A in the older people.
### TABLE 3.1 Baseline characteristics of the normal healthy older and younger subjects.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Young</th>
<th>Old</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>15</td>
<td>16</td>
<td>-</td>
</tr>
<tr>
<td>Age, years</td>
<td>23.2 ± 2.6</td>
<td>68.8 ± 4.4</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Range</td>
<td>19-27</td>
<td>60-74</td>
<td></td>
</tr>
<tr>
<td>Female, n (%)</td>
<td>4 (26.7)</td>
<td>6 (37.5)</td>
<td>0.535</td>
</tr>
<tr>
<td>Height, m</td>
<td>1.7 ± 0.1</td>
<td>1.7 ± 0.1</td>
<td>0.146</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>70.2 ± 15.0</td>
<td>75.5 ± 17.4</td>
<td>0.388</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>23.1 ± 2.8</td>
<td>26.1 ± 4.6</td>
<td>0.047</td>
</tr>
<tr>
<td>Body surface area, m²</td>
<td>1.8 ± 0.2</td>
<td>1.8 ± 0.2</td>
<td>0.917</td>
</tr>
<tr>
<td>Heart rate, beats/minute</td>
<td>69.7 ± 9.8</td>
<td>70.3 ± 11.3</td>
<td>0.891</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>115.7 ± 14.5</td>
<td>144.9 ± 15.6</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Diastolic blood pressure, mm Hg</td>
<td>61.5 ± 5.5</td>
<td>83.8 ± 9.9</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>E, cm/s</td>
<td>74.2 ± 16.6</td>
<td>46.2 ± 10.0</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>A, cm/s</td>
<td>41.3 ± 8.1</td>
<td>57.9 ± 12.5</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>E:A</td>
<td>1.8 ± 0.3</td>
<td>0.8 ± 0.2</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

E = early and A = late peak transmitral flow velocities measured with pulsed wave Doppler echocardiography.

Values are mean ± SD, where applicable.

P-values were obtained from t tests between the two age-groups, for each parameter.

### TABLE 3.2 MRI volumetric data for the normal healthy older and younger subjects.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Young</th>
<th>Old</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ejection fraction, %</td>
<td>70.7 ± 3.0</td>
<td>69.3 ± 6.6</td>
<td>0.461</td>
</tr>
<tr>
<td>End-diastolic volume, ml</td>
<td>137.5 ± 26.5</td>
<td>115.7 ± 27.1</td>
<td>0.031</td>
</tr>
<tr>
<td>End-systolic volume, ml</td>
<td>40.4 ± 9.2</td>
<td>35.8 ± 12.7</td>
<td>0.259</td>
</tr>
<tr>
<td>Stroke volume, ml</td>
<td>97.1 ± 18.8</td>
<td>79.8 ± 19.5</td>
<td>0.018</td>
</tr>
<tr>
<td>LV mass, g</td>
<td>141.6 ± 33.8</td>
<td>144.6 ± 38.4</td>
<td>0.818</td>
</tr>
<tr>
<td>LV mass:end-diastolic volume, g/ml</td>
<td>1.0 ± 0.1</td>
<td>1.3 ± 0.3</td>
<td>0.005</td>
</tr>
<tr>
<td>LV mass:body surface area, g/m²</td>
<td>76.6 ± 11.0</td>
<td>81.8 ± 28.1</td>
<td>0.514</td>
</tr>
</tbody>
</table>

Values are mean ± SD.

P-values were obtained from t tests between the two age-groups, for each parameter.
3.3.2 Peak Systolic Shortening Strain

The peak value of circumferential percent shortening, $S_C$, was not significantly different between groups, on average ($20 \pm 2.9$ vs. $21.2 \pm 1.1 \%$, $P = 0.134$). (In the following, all average results were obtained by taking the average of the peak values, across regions.) $S_C$ was regionally heterogeneous, longitudinally as well as circumferentially ($P < 0.001$, in both directions), as shown in Figure 3.2 A and B. The longitudinal variation altered with age ($P = 0.005$, for interaction between region and age). While the apex showed greater peak shortening than the base in both age-groups ($P^B < 0.001$ for each group), $S_C$ was reduced only in the apex in the older subjects ($P^B = 0.009$).

Peak longitudinal strain, $S_L$, was not significantly different between groups on average, ($16.9 \pm 2.5$ vs. $18 \pm 1.2 \%$, $P = NS$, see Figure 3.2 C and D). $S_L$ was regionally heterogeneous, longitudinally as well as circumferentially ($P < 0.001$, in both directions). Ageing altered both the longitudinal variation ($P = 0.009$) and the circumferential variation ($P = 0.003$) in $S_L$. The apex showed a greater $S_L$ than the base in the younger group ($P^B = 0.018$) but this difference was abolished in the older group ($P = NS$). The lateral wall showed higher $S_L$ than the septum in the older subjects ($P^B < 0.001$); this difference was not observed in the younger group, however ($P = NS$). $S_L$ was reduced in the older subjects at the apex ($P^B = 0.01$), and the septum ($P^B = 0.01$), only.

Peak torsional shear strain, $S_T$, was increased in the older group, on average ($9.1 \pm 1.7$ vs. $7.8 \pm 0.9^\circ$, $P = 0.017$, see Figure 3.2 E and F), and was regionally heterogeneous longitudinally as well as circumferentially ($P < 0.001$, in both directions). The pattern of regional heterogeneity did not change significantly with age ($P = NS$).

The peak systolic circumferential strain rate was reduced in the older group, on average ($106.3 \pm 14.6$ vs. $114.8 \pm 6.7 \%/s$, $P = 0.047$) and was regionally heterogeneous both longitudinally and circumferentially ($P < 0.001$). The pattern of regional heterogeneity did not change significantly with age ($P = NS$).

Peak systolic longitudinal strain rate was reduced in the older group, on average ($94.5 \pm 11.7$ vs. $112.8 \pm 9.3\%/s$, $P < 0.001$) and was regionally heterogeneous both longitudinally and circumferentially ($P < 0.001$). However, the pattern of regional heterogeneity did not change significantly with age ($P = NS$).

The peak rate of change in torsion during systole was not significantly different between groups ($65.1 \pm 11.7$ vs. $74.3 \pm 17.9^\circ/s$, $P = NS$) and was regionally heterogeneous.
both longitudinally \( (P < 0.001) \) and circumferentially \( (P = 0.021) \). The pattern of regional heterogeneity did not change significantly with age \( (P = \text{NS}) \).

![Graphs showing regional variation in peak systolic shortening strain and the influence of age](image)

**Figure 3.2 Regional variation in peak systolic shortening strain, and the influence of age**

Peak strain is compared between older and younger subjects (mean ± SD, for each group), across the three longitudinal LV regions (in A, C and E) and across the four circumferential regions (in B, D and F). A and B show peak circumferential strain \( (S_c) \), C and D show peak longitudinal strain \( (S_l) \), and E and F show peak torsion. Changes due to age that are significant after Bonferroni correction \( (P^B < 0.05) \) are indicated, for each region, with an asterisk, *.
3.3.3 Peak Rate of Relaxation

Peak rate of relaxation of circumferential strain, $R_C$, was reduced in the older group, on average (104.5 ± 27.7 vs. 162.7 ± 18.2 %/s, $P < 0.001$), and was regionally heterogeneous, longitudinally ($P = 0.001$) as well as circumferentially ($P < 0.001$). Ageing altered both the longitudinal variation ($P < 0.001$) and the circumferential variation ($P = 0.001$) in $R_C$. A greater $R_C$ was observed in the apex than in the base in younger subjects ($P^B < 0.001$); this difference was not observed in the older subjects, however ($P = \text{NS}$). In both age-groups a greater $R_C$ was observed in the lateral wall than in the septum ($P^B < 0.001$ for each). Significant decreases in $R_C$, due to age, were observed in all regions ($P^B < 0.05$, for each). This decrease in $R_C$ was greater in the apex than in the base ($P^B < 0.001$; see Figure 3.3 A), and greater in the lateral wall than in the septum ($P^B = 0.016$; see Figure 3.3 B).

Peak rate of relaxation of longitudinal strain, $R_L$, was reduced in the older compared to the young group, on average (93.7±26.9 vs. 154.5±18 %/s, $P < 0.001$; see Figure 3.3 C and D), and was regionally heterogeneous circumferentially ($P = 0.008$) but not longitudinally ($P = \text{NS}$). The interaction effect of age and regional strains on $R_L$, was significant both longitudinally ($P < 0.001$) and circumferentially ($P = 0.020$). In the younger group, $R_L$ was greater in the apex than the base ($P^B < 0.001$). In the older group, however, $R_L$ was greater in the base than in the apex ($P^B = 0.024$). In the older group, $R_L$ was significantly greater in the lateral wall than in the septum ($P^B < 0.001$); there was no difference in $R_L$ between septal and lateral regions in the younger group ($P = \text{NS}$), however. $R_L$ was significantly reduced, in the older subjects, in all regions ($P^B < 0.001$ for each). This reduction was greater in the apex than in the base ($P^B < 0.001$).

Peak rate of relaxation of torsion, $R_T$, was reduced in the older group, on average (74.5±16 vs. 91.1±15.5 %/s, $P = 0.006$; see Figure 3.3 E and F), and was regionally heterogeneous both longitudinally and circumferentially ($P < 0.001$). Ageing altered the longitudinal variation ($P = 0.017$). The base of the ventricle showed a greater $R_T$ of torsion than the apex in both age-groups ($P^B < 0.001$, for both groups). However, the reduction in $R_T$ due to age was significant in the base only ($P^B = 0.015$, leading to a greater reduction in the base than in the apex, $P^B = 0.035$).

Taking both groups together, peak values of $R_C$, $R_L$ and $R_T$ (averaged over all regions) were inversely correlated with the LV mass:EDV ratio (for $R_C$: $r = 0.758$, $P < 0.001$; for $R_L$: $r = 0.742$, $P < 0.001$ and for $R_T$: $r = 0.500$, $P < 0.001$). In addition, $R_C$, $R_L$ and $R_T$ were also inversely correlated with SBP (for $R_C$: $r = 0.627$, $P < 0.001$; for $R_L$: $r = 0.588$, $P < 0.001$).
and for $R_T$: $r = 0.383, P < 0.05$) and with DBP (for $R_C$: $r = 0.737, P < 0.001$; for $R_L$: $r = 0.723, P < 0.001$ and for $R_T$: $r = 0.382, P < 0.05$). However, ANCOVA showed that the effect of age (after correction for LV mass:EDV ratio, SBP and DBP as covariates) was still significant on $R_C$ and $R_L$ ($P < 0.001$ for each) and $R_T$ ($P = 0.046$).

Figure 3.3 Regional variation in peak rates of strain relaxation, and the influence of age.
Peak rates of strain recovery are compared between older and younger subjects (mean ± SD, for each group), across the three longitudinal LV regions (in A, C and E) and across the four circumferential regions (in B, D and F). A and B show peak rates of circumferential strain relaxation ($R_C$), C and D show peak rates of longitudinal strain relaxation ($R_L$), and E and F show peak rates of recovery of torsion ($R_T$). Changes due to age that are significant after Bonferroni correction ($P_{B} < 0.05$) are indicated, for each region, with an asterisk, *.
3.3.4 Time from ED to Peak Strain

The time to $S_C$ was prolonged with age, on average (381.3 ± 21.7 vs. 348 ± 17.4 ms, $P < 0.001$; see Figure 3.4 A and B), and was regionally heterogeneous both longitudinally and circumferentially ($P < 0.001$). Ageing altered both the longitudinal variation ($P < 0.001$) and the circumferential variation ($P = 0.003$) in time to $S_C$. In the younger group, $S_C$ occurred later in the apex than in the base ($P_B < 0.001$); however, in the older group, the peak value was achieved later in the base than the apex ($P_B = 0.009$). $S_C$ in the lateral wall occurred later than in the septum in younger subjects ($P_B < 0.001$), but not in the old ($P = NS$). The increase in time to $S_C$ due to age was significant in all regions except the apex and the posterior wall ($P_B < 0.05$ for each).

Similarly, the time to $S_L$ was prolonged with age, on average (393.8 ± 36.8 vs. 362.3 ± 23.2 ms, $P = 0.008$; see Figure 3.4 C and D), and was regionally heterogeneous both longitudinally ($P = 0.001$) and circumferentially ($P = 0.042$). The longitudinal variation altered with age ($P = 0.002$). $S_L$ was achieved later in the base than in the apex in the older group ($P_B < 0.001$). This difference was not observed in the younger group ($P = NS$). The increase in time to $S_L$ due to age was significant in the mid-ventricular region ($P_B = 0.023$) and the base ($P_B = 0.004$) only.

Time to peak torsion was unchanged between age-groups (432.7 ± 62.6 older vs. 425.1 ± 57.7 ms younger, on average, $P = NS$; see Figure 3.4 E and F), and was regionally heterogeneous longitudinally ($P < 0.001$), but not circumferentially ($P = NS$). The pattern of regional heterogeneity in time to peak torsion did not alter significantly, with age ($P = NS$).

3.3.5 Time from ED to Peak Rate of Relaxation

Time to peak rate of circumferential strain relaxation was greater in the older group, on average (522.7 ± 51.9 vs. 482.8 ± 23.9 ms, $P = 0.011$). No significant regional heterogeneity in time to $R_C$ was observed, either along the length of the LV or around the circumference ($P = NS$ for both directions). The interaction effect of age and regional strains on time to $R_C$, was also non-significant both longitudinally and circumferentially.

Time to peak rate of longitudinal strain relaxation was not different between the two age-groups, on average (525.1 ± 66.5 vs. 497.7 ± 33.7 ms, $P = NS$). Time to $R_L$ was regionally heterogeneous circumferentially ($P = 0.012$) but not longitudinally ($P = NS$). Ageing did not alter the pattern of regional heterogeneity in time to $R_L$.
Figure 3.4 Regional differences in the time from ED to peak shortening strain, and the influence of age.
The time taken to achieve peak strain is compared between older and younger subjects (mean ± SD, for each group), across the three longitudinal regions (in A, C and E) and the four circumferential regions (in B, D and F). The plots show time to peak circumferential (A and B), longitudinal (C and D) and torsional shear (E and F) strain. Changes due to age that are significant after Bonferroni correction ($P^B < 0.05$) are indicated, for each region, with an asterisk, *.

Similarly, no significant difference in time to peak rate of relaxation of torsion was observed between old and young individuals (478.5 ± 43.8 vs. 471.7 ± 24.8 ms, $P = NS$). Time to $R_T$ was regionally heterogeneous circumferentially ($P = 0.031$) but not longitudinally ($P = NS$). Ageing did not alter the pattern of regional heterogeneity in time to $R_T$ ($P = NS$).
Peak rate of relaxation of torsion, over all subjects, was achieved earlier than the peak rate of relaxation of both circumferential ($P^b < 0.001$) and longitudinal ($P^b < 0.001$) strains.

### 3.3.6 Asynchrony of Contraction and Relaxation

In the older subjects, increased regional asynchrony was observed in time to peak circumferential (46.8 ± 11.5 vs. 37.5 ± 7 ms, $P = 0.011$) and longitudinal (60.1 ± 19 vs. 45.7 ± 10.7 ms, $P = 0.015$) shortening strains. Regional asynchrony in time to peak torsion was not different between the two age-groups (105 ± 42.3 vs. 96.4 ± 49.2 ms, $P = \text{NS}$). The time to $R_C$ was more asynchronous in the older than in the younger group (39.7 ± 12.1 vs. 21.6 ± 4.9 ms, $P < 0.001$). Similarly, increased regional asynchrony in time to $R_L$ was observed in the older group (46.4 ± 15.6 vs. 26.1 ± 7.7 ms, $P < 0.001$). Regional asynchrony in time to peak rate of relaxation of torsion was not different between old and young groups, however (59 ± 25.3 vs. 51 ± 15.8 ms, $P = \text{NS}$).

Scatterplots showing individual subject datapoints revealed no consistent outliers in the MR strain results described above.

### 3.4 Discussion

It is well established that cardiac structure and function alter with age (Gerstenblith et al., 1977, Miller et al., 1986, Patel and Sonnenblick, 1998). Recent studies have shown that the earliest manifestation of these age-related changes is abnormal LV diastolic filling and that diastolic dysfunction is highly prevalent in the elderly population (Mandinov et al., 2000, Tokushima et al., 2001). LV filling is influenced by a number of interrelated factors including myocardial relaxation, heart rate, myocardial compliance, atrial function, and filling pressure. The process of LV filling has been studied extensively and parameters such as the E:A ratio, peak filling rate, filling pressure, and EDV are used routinely in the assessment of diastolic function (Appleton et al., 1988, Little and Downes, 1990, Sohn et al., 1997, Nagueh et al., 1999). However, these parameters are more reflective of chamber haemodynamics and blood flow than of myocardial relaxation itself. In the absence of systolic dysfunction, abnormal diastolic function is usually attributed to abnormal
relaxation and/or changes in the passive LV characteristics. Therefore an understanding of normal relaxation patterns is important in the clinical assessment of diastolic function.

Recently our group has shown that ageing causes significant alterations in global LV myocardial relaxation (Oxenham et al., 2003). In particular, circumferential and longitudinal shortening persists into diastole in older people, who also experience increased torsion and reduced strain relaxation rates. Since it is likely that impairment in localized portions of the myocardium may underlie the changes observed in global function, and that changes in regional function may be masked by global measures, a study of the influence of age on regional myocardial function is necessary.

Thus, the present study aimed to non-invasively assess the normal changes in regional myocardial relaxation that occur with age and, in support of the work done by Kuijer et al. (2002), demonstrates the potential utility of 3D MR tagging for the quantification of regional LV diastolic function. The data show that not only are peak LV systolic shortening strain and torsion regionally heterogeneous, as others have shown (Hansen et al., 1988, Bogaert and Rademakers, 2001), but peak myocardial relaxation rates are also markedly heterogeneous, and the impairment that occurs with age is similarly non-uniform.

Table 3.3 summarises the major differences that were detected between the older and younger subjects with respect to regional non-uniformity in tissue strain and relaxation.

### 3.4.1 Global Function

LV ejection fraction was preserved in the older subjects, as was LV mass, in agreement with other studies (Kitzman et al., 1988, Sandstede et al., 2000). Stroke volume was found to be significantly smaller in older subjects. The ratio of LV mass to EDV was increased, indicating a mild concentric hypertrophy consistent with the decrease in EDV that was observed in the older group. Both SBP and DBP were higher in the older age-group, as reported by others (Gerstenblith et al., 1977, Bonow et al., 1988), and correlated with the LV mass:EDV ratio, consistent with increasing concentric hypertrophy as blood pressure increases. Echocardiography produced results in accordance with previous studies of diastolic function in the elderly (Spirito and Maron, 1988, Kitzman et al., 1991, Mantero et al., 1995, Tokushima et al., 2001) with a reduced E:A value observed in the older subjects.
TABLE 3.3 Summary of LV regional non-uniformity and differences between normal healthy older and younger subjects.

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Check marks (✓) denote: i) a difference between age groups with respect to average peak value of each parameter (over all regions), ii) a regional variation in the LV in the circumferential and/or longitudinal directions, respectively, in each parameter, and iii) an age-related difference in the circumferential and/or longitudinal variation in each parameter.

SC, SL and ST = peak circumferential and longitudinal strains and torsion, respectively; SSR<sub>C</sub>, SSR<sub>L</sub> and SSR<sub>T</sub> = peak systolic strain rates with respect to circumferential and longitudinal strains and torsion; tSC, tSL and tST = time from end-diastole to peak circumferential and longitudinal strains and torsion; RC, RL and RT = peak rate of relaxation of circumferential and longitudinal strains and peak rate of recovery of torsion; tRC, tRL and tRT = time from end-diastole to peak rates of relaxation of circumferential and longitudinal strains and time to peak rate of recovery of torsion.

3.4.2 Peak Systolic Shortening and Torsion

The observed regional heterogeneity in systolic function agrees with previous findings (Bogaert and Rademakers, 2001). On average, peak circumferential and longitudinal shortening in the older group was similar to that observed in younger subjects, in agreement
with other studies that have shown that ageing causes little change in LV systolic function at rest (Gerstenblith et al., 1977, Bonow et al., 1988, Furutani et al., 1993). However, the interaction of age with region was significant and, on examination of regional differences (after Bonferroni correction), apical shortening was impaired in both circumferential and longitudinal directions and longitudinal shortening was impaired in the septum. Thus, regional function parameters may be more sensitive than global parameters for evaluating systolic function.

Peak torsional shear strain was found to be greater in the older group overall, possibly due to an increase in concentric hypertrophy (mass:volume ratio), since LV torsion is known to be increased with hypertrophy (Young et al., 1994, Stuber et al., 1999). While peak torsion was non-uniform along the length of the LV as well as around the circumference, ageing did not have any effect on the pattern of this regional heterogeneity.

During systole, the rates of change of both circumferential and longitudinal strains were reduced overall in the older group and were regionally heterogeneous in both the longitudinal and the circumferential directions. While the systolic rate of change in torsion was, on average, similar in old and young individuals, it was also regionally heterogeneous. However, ageing did not influence the pattern of regional non-uniformity in any of the three systolic strain rate parameters.

3.4.3 Peak Rate of Relaxation

The peak rate of relaxation of circumferential and longitudinal strains and the peak rate of recovery of torsion were, on average, reduced in older subjects. Age-related decrease in calcium uptake by the sarcoplasmic reticulum (Pugh and Wei, 2001) and an increase in myocardial stiffness (Villari et al., 1997) may explain, in part, why myocardial relaxation is slower in these individuals. It is suggested that a reduced relaxation rate is directly related to the diastolic dysfunction observed in the elderly. The results of this study demonstrate that the process of myocardial relaxation is regionally heterogeneous at all ages. The most dramatic reductions in regional relaxation rate occurred in the apex for circumferential and longitudinal relaxation. This region is also associated with a reduction in peak systolic strain, although not to as great an extent. Peak systolic strain rates were also slightly reduced overall, but showed no change in the pattern of heterogeneity with age. This suggests that regional diastolic relaxation parameters may be more sensitive than regional systolic parameters for the detection of impaired function.
Currently, tissue Doppler imaging is commonly used to assess diastolic function (Sohn et al., 1997, Nagueh et al., 1999, Mandinov et al., 2000), giving measures of longitudinal motion and strain rate at the mitral annulus region. The present study shows that longitudinal relaxation is more severely reduced in the apex than in the base, and that the lateral wall undergoes greater longitudinal relaxation than the septum in the older group only. An awareness of regional non-uniformity in myocardial strain rate in the longitudinal direction is therefore important in the interpretation of echocardiographic data.

The peak rates of relaxation of both circumferential and longitudinal strains were inversely correlated with the ratio of LV mass to EDV and with systolic blood pressure and diastolic blood pressure, suggesting that relaxation rates are influenced by concentric hypertrophy and, possibly, by hypertension. Nevertheless, the ANCOVA (in which the covariate effects of the LV mass:EDV ratio, the systolic blood pressure and the diastolic blood pressure were accounted for) showed that hypertrophy or hypertension alone do not explain impairment of global rates of relaxation.

### 3.4.4 Time from ED to Peak Shortening and Torsion

Time from ED to both peak circumferential and peak longitudinal shortening strain was prolonged in the older individuals. This result was unexpected, as others have reported no change in peak ejection rate and time to end-systole at rest (Kitzman et al., 1991, Fioranelli et al., 2001). However animal studies (Lakatta et al., 1975, Templeton et al., 1979) have shown an age-associated prolongation of the duration of contraction.

### 3.4.5 Time from ED to Peak Rate of Relaxation

The time from ED to peak rate of relaxation of circumferential strain was prolonged with age. This was expected since time to peak filling rate, and the time constant of LV pressure decay (τ), both increase with age (Lakatta et al., 1987, Bonow et al., 1988, Villari et al., 1997). However time to peak rate of relaxation of longitudinal strain and time to peak rate of recovery of torsion were not different between the two age-groups. In support of the findings of Kuijer et al. (2002), all subjects in the present study achieved peak rate of recovery of torsion earlier than peak rate of relaxation of both circumferential and longitudinal strains. This finding supports the hypothesis that torsion recovery in early diastole may be dependent on the release of stored elastic energy in the myocardium, as well as on LV filling (Dong et al., 2001, Kuijer et al., 2002).
3.4.6 Asynchrony

The results suggest that regional asynchrony in time to peak circumferential and longitudinal shortening strains, as well as in time to peak relaxation rates, increase with age in a fashion that is inconsistent between individuals. Bonow et al. (1988) and Furutani et al. (1993) both reported a significant increase in indices of regional diastolic asynchrony with age, particularly with respect to time to peak filling rate, and showed that this increased asynchrony was inversely correlated with both the rate and extent of global rapid filling.

3.4.7 Study Limitations

The temporal resolution that is currently possible with MRI is limited and this may influence the accuracy of the measurement of peak rate of relaxation and time to peak relaxation. Although better temporal resolution is possible with strain rate echocardiography (Heimdal et al., 1998), this technique does not allow measurement of all components of myocardial strain and relaxation and cannot account for through-plane motion effects, as is possible with MRI. It is expected that with the development of faster MR imaging techniques, approaching echocardiographic frame rates, it will be possible to obtain more reliable estimates of the extent and temporal evolution of myocardial strains.

The presence of coronary artery disease in these subjects cannot be ruled out with absolute certainty because coronary angiography or stress tests were not performed. Thus, it is possible that some of the impairment observed in older subjects may be due to undetected cardiovascular disease.

The older subjects that were examined in this study would be classified as having Stage 1 hypertension (SBP: 140-159 or DBP: 90-99 mm Hg) according to the latest clinical guidelines (Chobanian et al., 2003). It is indeed possible that increased systolic blood pressure may have influenced the results obtained for strain and relaxation in the older subjects. However the ANCOVA that was performed suggests that the differences observed between the older and younger groups cannot be accounted for by increased blood pressure alone. A study assessing the MR strain parameters, described in this Chapter, in older people with blood pressure lower than 140/90 mm Hg would be useful to determine the influence of hypertension (the new clinical guidelines consider individuals with a blood pressure measurement of 120/80 mm Hg or less to be normotensive (Chobanian et al., 2003)).
Offline analysis of cardiac images is still quite labour-intensive, however recent improvements in the field are making the process increasingly automated (Aletras et al., 1999, Osman et al., 1999, Garot et al., 2000, Kuijer et al., 2001).

3.4.8 Conclusions

MR tagging is a highly effective tool for the description and quantification of local as well as global changes in myocardial function. The results of this study have shown that marked regional non-uniformities in myocardial relaxation exist in both old and young people. Furthermore, the pattern of regional non-uniformity in myocardial contraction and relaxation alters significantly with age in normal healthy people. This has important implications for the assessment of cardiovascular disease and highlights the necessity of taking into account the normal age-related changes in myocardial function in studies of disease.
4.1 Introduction

The current therapeutic strategy for patients with heart failure depends on whether clinical markers of systolic dysfunction or diastolic dysfunction, or both, are present (Zile and Brutsaert, 2002b, a). Angiotensin-converting enzyme inhibitors, digoxin, diuretics and beta-blockers are prescribed in heart failure patients with impaired systolic function (Packer et al., 1999), while treatment of diastolic dysfunction targets the underlying pathophysiology. For example, beta-blockers and calcium channel blockers are generally used when diastolic dysfunction occurs due to hypertension or ischaemia, but calcium channel blockers would not normally be used in the treatment of systolic heart failure (Shamsham and Mitchell, 2000, Zile and Brutsaert, 2002b). In order to distinguish between heart failure with impairment in systolic function and that with impairment primarily in diastolic function, reliable indices of each are necessary.

Diastolic dysfunction has been defined by Zile and Brutsaert (2002a) as “a condition in which abnormalities in mechanical function are present during diastole” and in which systolic function can be normal or abnormal. However the majority of studies on diastolic dysfunction, and on patients diagnosed with ‘diastolic heart failure’, by definition (European Study Group on Diastolic Heart Failure, 1998), describe the finding of clinically normal systolic function (Mandinov et al., 2000). These include studies of diastolic function in the aged (Spirito and Maron, 1988, Cacciapuoti et al., 1992, Kitzman, 2002) and also in disease conditions – for example, congestive heart failure, diabetes mellitus, and aortic stenosis (Soufer et al., 1985, Shapiro and Gibson, 1988, Bonow and Udelson, 1992, Hess et al., 1993, Schannwell et al., 2002).
The definition of what constitutes normal systolic function has always been somewhat contentious, however, and the validity of traditional parameters such as the most commonly used LV ejection fraction is now being questioned. The cut-off value used to define ‘normal’ ejection fraction seems to vary between studies; the European Study Group on Diastolic Heart Failure (1998) recommends taking a value of \( \geq 45\% \) as normal, while others propose this be raised to \( > 50\% \) (Vasan and Levy, 2000). Nevertheless, ejection fraction can be maintained in the presence of diastolic abnormalities, and related systolic measurements such as LV fractional shortening are also found to be similar to normal control values (Gerstenblith et al., 1977, Villari et al., 1997). Furthermore, ejection fraction can be elevated or normal in the presence of reduced myocardial shortening, due to concentric hypertrophy, for example (Maron et al., 1981, Young et al., 1994), and recent investigations show reduced indices of tissue shortening (‘subclinical systolic dysfunction’ (Fang et al., 2004)) in the presence of diastolic dysfunction and normal ejection fraction (Bolognesi et al., 2001, Poulsen et al., 2003). The sensitivity of ejection fraction as an index of systolic function is therefore quite poor (Brutsaert, 2000, Zile and Brutsaert, 2002a).

Cardiac catheterization, the gold standard for measuring LV pressure and volume at rest and during exercise, is obviously not feasible in the routine clinical setting. Currently, echocardiography and other non-invasive imaging modalities such as MRI and radionuclide imaging allow calculation of LV mass and volumes (end-diastolic, end-systolic, and stroke volumes) and diastolic filling rates (Lee et al., 1989, Young et al., 2000, Grothues et al., 2002). Doppler echocardiography has established a classification system for the evaluation of diastolic dysfunction, based on the ratio of the early (E) to late (A) transmitral filling velocities (Appleton et al., 1988, Giannuzzi et al., 1996). Other investigations include measuring the levels of the natriuretic peptides which have been shown to correlate with impaired LV function (Sayama et al., 2000, Struthers, 2002, Hall et al., 2003), and the calculation of the myocardial performance index (the sum of isovolumetric relaxation and contraction times divided by ejection time) which can give an indication of combined LV systolic and diastolic function (Tei et al., 1996, Spencer et al., 2004). However, LV filling rates are load-dependent and mass and volume measurements do not reliably indicate myocardial function. Time intervals for the calculation of the ‘myocardial performance index’ are difficult to measure and interobserver reliability is poor (Massel et al., 2003). Although a sensitive marker for identifying systolic dysfunction, BNP levels can also be elevated in patients with clinically normal systolic function, and therefore its specificity is low (Struthers, 2002).
Echocardiographic tissue Doppler imaging (TDI) and MRI are the two best-equipped modalities for providing reliable global as well as regional measures of myocardial mechanical function. The accessibility and ease of use of echocardiography make it the more widely used clinical technique, but MRI has long been the gold-standard for measuring 3D myocardial tissue motion and, unlike the former, imaging is possible in all regions of the LV.

Recent TDI studies have shown that LV long-axis systolic function is often impaired in patients with presumed isolated diastolic dysfunction, although ejection fraction is preserved (Petrie et al., 2002, Yip, G. et al., 2002a, Yu et al., 2002, Andersen et al., 2003). Shortening of longitudinally oriented fibres plays an important role in wall thickening and in the normal reduction of LV cavity dimensions during systole; the decrease in the LV minor axis is too great to be explained by circumferential fibre shortening alone (Henein, M. Y. and Gibson, 1999b). During the cardiac cycle the base of the ventricle moves down towards the apex in systole and away from the apex in diastole. There is less motion at the mid ventricle level, and the apex itself moves very little (Rogers et al., 1991). Thus, the motion of the plane of the mitral valve annulus (situated at the base of the ventricle and easily measured with TDI) is thought to give a good approximation of longitudinal function.

Our investigations (Fonseca et al., 2003, Oxenham et al., 2003) and the work of others (Mandinov et al., 2000, Tokushima et al., 2001) have shown that both haemodynamic and myocardial markers of LV diastolic function are significantly altered in the elderly. As described in Chapter 3, 3D MRI with tissue tagging showed that the onset of myocardial relaxation is delayed in older people and that their myocardial strain relaxation rates are markedly reduced in nearly all regions of the LV. This was accompanied by a significant reduction in echocardiographic E:A ratio (one of the most widely used clinical indices of LV diastolic function) (Mandinov et al., 2000). Although providing accurate information on tissue mechanical function, measurement of myocardial strain is time consuming. This Chapter seeks to evaluate the use of the motion of the mitral valve annulus (measured with MRI) as a simple index of global systolic and diastolic function.

It was hypothesized that 3D MR measures of both systolic and diastolic mitral valve annulus plane motion are altered with age. The purpose of this study was to determine whether the alterations (if any) in diastolic mitral valve plane motion occurred independently of the hypothesized ‘long-axis systolic changes’. Furthermore, the extent to which age influences LV global peak values of circumferential, longitudinal, torsional shear and principal shortening strains and strain rates throughout the cardiac cycle was assessed. MR
measurements of peak early and peak late transmitral filling velocity are also presented for comparison with Doppler values.

4.2 Methods

4.2.1 Imaging

Data were generated from the same MR images that were acquired to study the influence of ageing on regional LV myocardial function (Chapter 3). Subject recruitment and inclusion criteria are described in 3.2.1.

In addition to the acquisition of tagged MR images (described in 3.2.2), eight or nine short-axis and three long-axis standard turboFLASH cine MR images, without tagging, were also acquired (15 to 19 time frames per slice; slice thickness 8 mm; in plane resolution 1 mm/pixel; temporal resolution of 40 or 50 ms depending on heart rate; TE/TR = 4.0/9.0 ms). As before, subjects undertook approximately 15-second breath-holds during the scans to eliminate respiratory motion artifacts, and images were prospectively gated on the R-wave.

Phase contrast images of a short-axis slice of the LV at the level of the mitral valve plane had been obtained without breath-hold with scan parameters as follows: slice thickness 8 mm; in-plane resolution approximately 1 mm/pixel; temporal resolution 40 to 50 ms depending on heart rate; TE/TR = 4.0/9.0 ms, velocity encoding 150 cm/s.

4.2.2 Image Analysis

The standard cine MR images were stored digitally and analyzed offline, using interactive 3D guide-point modelling to define the LV geometry (Young et al., 2000). The motion of the mitral valve plane (MVP) was tracked by placing guide-points at the site of attachment of the mitral valve leaflets to the wall (at the confluence of the left atrium and the LV), on the three long-axis images, in each frame (see Figure 4.1).

The 3D positions of all mitral valve attachment points were calculated using the image slice location information (encoded in the DICOM header), and averaged to give an estimate of the mitral valve centroid at each frame. The 3D displacement of this point was used as the MVP displacement and the peak systolic value was recorded. Peak systolic and diastolic MVP velocities were estimated using a two-point central difference formula.
Figure 4.1 Tracking the plane of the mitral valve annulus (MVP) through the cardiac cycle, in a typical subject from the older age-group.

Guide-points (pink) are placed by the user at the site of attachment of the mitral leaflets to the LV wall, on each of 3 long-axis images, which were spaced 60° apart. Images for this particular subject were acquired at 40 ms intervals (based on the subject’s heart rate). The top row shows images acquired in the four-chamber view, the middle row shows images between four-chamber and two-chamber views, and the bottom row shows images in a two-chamber view. A: end-diastole (0 ms); B: end-systole (280 ms); C: late diastole (560 ms). Yellow dotted line: MVP; yellow arrows: mitral valve leaflet tips.

Values were also obtained for circumferential, longitudinal, and torsional shear strains and strains rates, and the principal shortening strain and strain rates in both systole and
diastole, from the tagged images. These values were calculated as the average around the LV for each frame. Peak values were obtained from the time series of average strain.

MR phase contrast images were analyzed offline using Scion Image for Windows (version Beta 4.0.2) on a standard desktop computer with Windows 2000 operating system (see Appendix A.1 for details).

4.2.3 Statistics

Data are presented as mean ± SD. MVP motion data was compared between old and young groups using the Student’s two-tailed t test. A linear regression analysis was performed to examine the relationship between peak systolic MVP displacement and peak diastolic MVP velocity. An analysis of variance (ANOVA) was performed to check for any interaction effect of age and peak systolic MVP displacement on peak diastolic MVP velocity. If no significant interaction existed, an analysis of covariance (ANCOVA) would be performed to examine the effect of age, corrected for the effect of systolic MVP displacement, on diastolic MVP velocity. Linear regression was used to determine the correlations (if any) between the LV mass:end-diastolic volume ratio (an index of concentric hypertrophy) and each of peak systolic MVP displacement and peak diastolic MVP velocity. With respect to peak E and A diastolic filling velocities, and the E:A ratio, the Student’s two-tailed t test was first used to test for differences in the MR measurements between old and young groups, and then taking both groups together, to compare MR measurements with the corresponding echocardiographic values. Statistical significance was defined as \( P < 0.05 \).

4.3 Results

Clinical characteristics of subjects in each group are detailed in Table 3.1. To summarize, both systolic and diastolic blood pressure measurements were significantly higher in the older group; heart rate, LV ejection fraction, LV mass and body surface area (BSA) were comparable between age-groups; and end-diastolic volume and stroke volume were significantly smaller in the older group. The ratio of LV mass to EDV was also greater in the older group. When indexed to BSA, neither LV mass nor EDV differed between the two age-groups (LV mass/BSA: 81.8 ± 28.1 vs. 76.6 ± 11.0, \( P = 0.514 \); EDV/BSA: 65.1 ± 21.5 vs. 74.8 ± 8.7, \( P = 0.121 \)). The motion of the mitral valve plane, as a function of time, is compared between the old and young groups in Figure 4.2.
Figure 4.2 Temporal evolution of mean mitral valve plane (MVP) displacement. MVP displacement in each subject was normalized to end-systolic (ES) time (i.e., the time at which LV volume is calculated to be the smallest, in the MR images). Data points represent the mean displacement for each age-group at each time point relative to ES. Vertical bars represent ± 1 SD.

4.3.1 Systolic Myocardial Function

Peak average systolic circumferential and longitudinal shortening strains in the older subjects were found to be comparable to the values obtained in the younger group ($S_C$: $18.7 \pm 3.1$ older vs. $20.2 \pm 1.1$ % younger, $P = 0.085$; $S_L$: $15.5 \pm 2.5$ vs. $16.9 \pm 1.3$ %, $P = 0.054$). However, peak torsion was greater in the older group ($S_T$: $6.5 \pm 1.0$ vs. $5.1 \pm 1.1 \degree$, $P < 0.001$). The peak principal shortening strain was not different between old and young groups ($S_P$: $27.1 \pm 3.0$ vs. $26.9 \pm 1.3$ %, $P = 0.764$). However, peak systolic mitral valve plane displacement was significantly smaller in the older subjects ($1.0 \pm 0.2$ vs. $1.4 \pm 0.2$ cm, $P < 0.001$).

Peak systolic circumferential strain rate, peak systolic rate of change of torsion and peak systolic principal shortening strain rate were not different between groups ($SSR_C$: $94.6 \pm 14.0$ vs. $101.4 \pm 6.5$ %/s, $P = 0.096$; $SSR_T$: $30.3 \pm 4.4$ vs. $29.4 \pm 6.3$ %/s, $P = 0.655$; $SSR_P$: $126.0 \pm 24.2$ vs. $132.1 \pm 19.6$ %/s, $P = 0.447$). However, peak systolic MVP velocity and peak systolic longitudinal strain rate were lower in the older group (MVP systolic velocity: $4.8 \pm 1.1$ vs. $5.8 \pm 1.2$ cm/s, $P = 0.019$; SSR$_L$: $75.3 \pm 10.1$ vs. $86.5 \pm 8.0$ %/s, $P = 0.002$).
4.3.2 Diastolic Myocardial Function

Peak diastolic rate of relaxation of circumferential, longitudinal and principal strains were all found to be lower in the older age-group (R_C: 76.2 ± 28.5 vs. 142.5 ± 16.6 %/s, \( P < 0.001 \); R_L: 62.7 ± 21.3 vs. 122.5 ± 19.6 %/s, \( P < 0.001 \); R_P: 66.4 ± 21.5 vs. 125.7 ± 15.6 %/s, \( P < 0.001 \)). Peak diastolic MVP velocity was also lower in the older group (MVP diastolic velocity: 4.3 ± 1.3 vs. 7.7 ± 1.2 cm/s, \( P < 0.001 \)). Peak diastolic rate of change of torsion did not differ between the two groups (R_T: 36.4 ± 8.1 vs. 31.8 ± 10.1 °/s, \( P = 0.169 \)).

4.3.3 Relationship between MVP Peak Systolic Displacement and Peak Diastolic Velocity

Linear regression of both groups together revealed a significant relationship between peak systolic MVP displacement and peak diastolic MVP velocity (\( r = 0.801, P < 0.001 \)). See Figure 4.3. A general linear model ANOVA showed no significant interaction effect of peak systolic displacement and age on peak diastolic MVP velocity. ANCOVA showed that age still had a significant influence on peak diastolic MVP velocity (\( P < 0.001 \)), independent of the covariate effect of peak systolic MVP displacement.

![Figure 4.3 Relationship between MVP peak diastolic velocity and peak systolic displacement.](image)

Examination of all subjects, old and young together, revealed a significant relationship between these systolic and diastolic parameters.
4.3.4 Relationship between MVP Motion and LV Mass:EDV ratio

An inverse relationship was found between peak MVP displacement and the LV mass:EDV ratio (Figure 4.4 A, linear regression over all subjects, young and old, together: $r = -0.523$, $P = 0.003$), but ANCOVA showed that age still has a significant effect ($P = 0.002$). Peak diastolic MVP velocity was also inversely and significantly related to the LV mass:EDV ratio (Figure 4.4 B, $r = -0.653$, $P < 0.001$), but ANCOVA showed that age still has a significant effect ($P < 0.001$).

Figure 4.4 Relationship between MVP motion and LV mass:EDV.

Pooling of old and young subjects showed that both peak systolic MVP displacement (A) and peak diastolic MVP velocity (B) correlated inversely with LV mass:EDV, an index of LV hypertrophy.
4.3.5 MR Measurement of Transmitral Flow Velocity

MR measurements of diastolic filling velocities (Figure 4.5) yielded similar patterns to those obtainable with echocardiography.

![Blood flow velocity over time](image)

**Figure 4.5** LV filling velocity pattern obtained with MR phase contrast imaging. The graph shows filling velocity over time in a typical subject from each age-group. The peaks observed are analogous to those that may be obtained with echocardiography. In the younger subject, the early peak filling velocity (E) is greater than the late peak filling velocity (A). In the older subject, however, this pattern is reversed.
Peak E velocity, as measured with MR velocity mapping, was lower in the older group compared with the younger subjects (43.3±14.2 vs. 68.8±12.1 cm/s, \(P < 0.001\)). Peak A velocity, measured with MRI was greater in the older subjects (39.3±11.8 vs. 24.0±6.3 cm/s, \(P < 0.001\)), and the resulting E:A ratio was found to be lower in this group compared with the young (1.2±0.5 vs. 3.0±0.7, \(P < 0.001\)). Measurement of E velocity with MRI was comparable to values obtained with echocardiography in all subjects (55.7±18.4 MRI vs. 58.7±19.3 echocardiography, \(P = \text{NS}\)). However, MRI significantly underestimated the peak A velocity in all subjects (31.9±12.2 vs. 50.5±13.5, \(P < 0.001\)). Therefore, E:A values obtained with MRI were found to be much greater than the E:A values obtained with echocardiography (averaged over all subjects, 2.1±1.1 vs. 1.3±0.6, \(P = 0.001\)).

No consistent outliers could be detected when the influence of individual subject datapoints on the mean result was examined in scatterplots.

### 4.4 Discussion

Not surprisingly, the MR measures of global LV myocardial function during diastole were found to be depressed with age. In support of the findings of Owen, A. (1999), peak diastolic MVP velocity was significantly reduced in older people. Peak circumferential, longitudinal and principal shortening strain relaxation rates were also lower in the older group. However, the rate of relaxation of torsion was not different between the two groups and this may be a reflection of the increased systolic torsion observed in the older subjects. These findings support our study of the influence of age on regional diastolic function (Chapter 3, (Fonseca et al., 2003)).

3D MR assessment of systolic myocardial function showed that peak systolic mitral valve plane displacement and velocity, and peak systolic longitudinal velocity were significantly reduced in older people, while peak systolic circumferential and principal shortening strains and strain rates, and peak systolic longitudinal strain remained unchanged. Peak systolic torsion was increased in the older group.

The values of global LV strain used here differ from those in Chapter 3. In this Chapter, strain was automatically averaged across all regions of the heart at each time frame and the highest of these average values, over all time frames, was taken as the global peak strain achieved by the LV during the imaged portion of that cardiac cycle. In Chapter 3,
however, a regional analysis of strain was performed and for this reason, global LV values were presented as an average, over regions, of the peak strain values achieved in each of the 16 regions. Thus, Chapter 3 indices of global function represent ‘average peak strain’, whereas indices in this Chapter represent ‘peak average strain’. The reason for the difference in values obtained is that peak strain occurs in each region of the LV at different times in the cycle, so an average of the peaks will lead to higher values than the peak of the averages.

4.4.1 Transmitral Flow Velocity

MR phase contrast imaging was used to assess blood flow across the mitral valve. The results show that MR measurements of transmitral flow velocity follow the same trend as Doppler echocardiography, and indeed the same E and A wave patterns can be generated (for instance, E:A reversal with age due to decreasing diastolic function). Previous studies also have shown that diastolic function (with respect to haemodynamics) can be assessed with MRI (Karwatowski et al., 1995, Paelinck et al., 2002). This could provide a ‘one-stop-shop’ alternative for patients that cannot be studied with echocardiography – for example, due to lack of an acoustic window. However, as with echocardiography, measurement of filling rates is load-dependent.

4.4.2 LV Longitudinal Function

The results of this Chapter indicate that longitudinal myocardial tissue parameters may provide more sensitive measures of systolic function, as has been shown by others (Petrie et al., 2002, Yu et al., 2002). Indeed, the longitudinally oriented and longer fibres at the subendocardium undergo greater strain than fibres at the midwall and subepicardium (Bogaert and Rademakers, 2001), thus making the major contribution to systolic contraction. The predominantly subendocardial situation of longitudinally oriented fibres brings them into close proximity with the conduction system which runs through this portion of the myocardium (Henein, M., 1999, Pennisi et al., 2002). Furthermore the subendocardial layer is more sensitive to ischaemia. Therefore longitudinal shortening, which plays a major role in the maintenance of LV ejection fraction and in determining atrioventricular interactions, is easily influenced by cardiac disease, including coronary artery disease, activation abnormalities, LV hypertrophy and atrial dysfunction (Henein, M. Y. and Gibson, 1999a). This could explain, in part, why functional changes – due to ageing or disease – may be apparent earliest in the LV long-axis direction.
Although peak systolic MVP displacement was reduced in the older age-group, peak systolic longitudinal strain did not appear to be influenced by age. In a recent study of long-axis LV function in sheep using implanted radiopaque markers, Rodriguez et al. (2004) suggested that while mitral annular descent accounts for the greater part of long-axis shortening (approximately 5 mm in sheep), apical motion also makes a significant contribution to LV longitudinal strain (apical displacement was 1 mm, contributing ~20% of the longitudinal shortening). However, they found that mitral annular descent (which does not take into account apical motion) correlated as well as long-axis shortening to preload-recruitable stroke work and, in fact, the ROC (receiver operator curve) analysis showed that mitral annular descent was a better predictor of LV systolic function than long-axis shortening. Strain estimation accentuates noise in the data, whereas tracking the centroid of the MVP is more robust to noise and therefore may provide a more sensitive marker of global LV function.

4.4.3 Relationship between MVP Motion and LV Mass:EDV ratio

Both peak systolic MVP displacement and peak diastolic MVP velocity correlated inversely and significantly with LV mass:EDV over both age-groups. The LV mass:EDV ratio was greater in the older subjects than in the younger. It should be noted that although LV mass:EDV was increased, this is a reflection of the reduced EDV observed in the older group; LV mass itself was not influenced by age. There have been conflicting reports on the effect of age on LV mass, with some reporting the development of LV hypertrophy (Gerstenblith et al., 1977, Salmasi et al., 2003), and others finding no change (Kitzman et al., 1991, Deague et al., 2000, Sandstede et al., 2000). When indexed to body surface area (BSA), however, neither LV mass nor EDV differed between the two age-groups.

4.4.4 Relationship between MVP Peak Systolic Displacement and Peak Diastolic Velocity

The changes due to age in the measures of longitudinal function presented here appear to be more pronounced in diastole than systole. That diastolic dysfunction may precede systolic impairment in the progression of LV dysfunction to heart failure, has been suggested in a number of scenarios including ageing (Tokushima et al., 2001) and disease conditions such as hypertension (de Simone et al., 2000) and diabetes (Raev, 1994), for example. However, it now appears that such an assumption is dependent on both the method of measurement and the parameters being measured in both systole and diastole.
Of greater importance is the association between peak systolic MVP displacement and peak diastolic MVP velocity. It seems reasonable to expect that some alteration in systolic function might occur when diastolic function is impaired, as the processes that occur during systole in one way or another influence diastole, and vice versa. For example, the development of LV suction to enable rapid ventricular filling in early diastole is a consequence of the release of restoring forces stored in the LV wall during systolic ejection. In addition, it has been demonstrated that early diastolic filling correlates significantly with end-systolic volume and also with measures of LV contractility and afterload (Courtois et al., 1992). An important consideration is that the mechanics of the mitral valve itself are influenced by LV systolic function. A study by Dent et al. (1995) suggests that impairment in LV systolic function – for example, reduced contractility (systolic +dP/dt) – results in a decreased rate of elastic recoil and therefore a reduction in the rate of increase of the diastolic atrioventricular pressure gradient. Consequently, the degree of mitral leaflet excursion into the LV during diastole is reduced. Accordingly, a decrease in LV contractile function and, therefore, a reduced rate of increase in the left ventricular-left atrial pressure gradient during systole may impair closure of the mitral valve, and, in extreme conditions, could lead to mitral regurgitation (Dent et al., 1995).

Thus, in addition to providing useful information on diastolic function, tracking of the mitral valve plane may provide a more sensitive index of global LV systolic function than parameters that are commonly used clinically.

4.4.5 Study Limitations

This study would have been strengthened by the inclusion of subjects from all age-groups. However, the literature suggests that most age-associated changes in myocardial structure and function parameters occur linearly over the decades, vis à vis decrease in mitral inflow E velocity, increase in mitral inflow A velocity, reduction in echocardiographic mitral valve annulus displacement and velocities, reduction in LV volumes and impairment of LV relaxation (Gerstenblith et al., 1977, Cacciapuoti et al., 1992, Mantero et al., 1995, Owen, A., 1999, Sun et al., 2004).

With respect to the measurement of diastolic filling rates, it is acknowledged that MRI consistently underestimated the peak A wave velocity in comparison with echocardiography. Karwatowski et al. (1995) reported similar findings. Therefore, absolute
MR measurements of late transmitral flow velocity would be meaningful only with improved temporal resolution.

Although MRI is limited with respect to temporal resolution, it offers an advantage over the more commonly used imaging modalities, in that tissue motion can be tracked in all dimensions and therefore estimates of strain can be obtained both globally and in any individual region. Furthermore, MR tagging allows direct measurement of tissue strain; the major difficulty with echocardiographic tissue Doppler Imaging, which is being used increasingly to measure LV tissue velocities and strain, is that the calculation of either a spatial or temporal gradient and/or an integral is required, thereby introducing noise in the resultant data.

It is acknowledged that some degree of operator error may have occurred when aligning the MR image acquisition plane with the LV long-axis. However, it is unlikely that this would have had more than a negligible influence on the resultant data.

In most echocardiographic TDI studies the peak early (E’) and peak late (A’) velocities of the mitral valve annulus are often presented with the aim of distinguishing between the classes of diastolic dysfunction (Sohn et al., 1997, Ommen et al., 2000). However, this was not the aim of the work presented here, and, therefore, instead of providing values for diastolic peak early and peak atrial systolic MVP velocities, only the overall peak diastolic velocity has been presented (i.e., this could be E’ or A’ depending on functional status).

4.4.6 Conclusions

The work described here confirms and extends recent echocardiographic studies that have shown a reduction in LV systolic longitudinal function in the presence of preserved ejection fraction. Both systolic and diastolic motion of the mitral valve plane is impaired in normal healthy older people. The motion of the mitral valve plane can be easily assessed with MRI, gives a good indication of global LV myocardial performance, and is more sensitive than currently used clinical parameters to alterations in systolic as well as diastolic LV function.
Chapter 5

LV Myocardial Strain in Patients with Type 2 Diabetes Mellitus, Diastolic Dysfunction and Normal Ejection Fraction

5.1 Introduction

Although coronary artery disease is a common co-morbidity in patients with type 2 diabetes mellitus (DM), many patients develop impairments in myocardial relaxation and exhibit elevated filling pressures independent of vessel disease, valvular or congenital heart disease, regional wall motion defects, hypertension or alcohol-induced cardiomyopathy (Rubler et al., 1972, Bouchard et al., 1989, Colucci and Price, 2003). It has been suggested that LV diastolic dysfunction, prevalent in the type 2 DM population, may precede the development of abnormalities in systolic function (Raev, 1994, Grundy et al., 1999, Poirier et al., 2001, Schannwell et al., 2002) and therefore diastolic parameters such as the pattern of LV filling and the rate of relaxation may be more sensitive markers of disease progression, and may provide an earlier indication of dysfunction than systolic indices, such as ejection fraction, that are currently used in clinical practice. However, traditional diastolic parameters such as the echocardiographic E and A wave pattern use haemodynamic measurements as surrogates for myocardial mechanics, rather than directly measuring tissue function (Xie et al., 1994, Giannuzzi et al., 1996, Nagueh et al., 1999). Similarly, ejection fraction and LV cavity dimensions during systole (widely used as indices of systolic function) may not be reflective of myocardial behaviour.

Recent investigations have questioned the existence of ‘isolated’ diastolic dysfunction and have reported the concomitant presence of some degree of systolic dysfunction that is not detectable by routine clinical methods (Yu et al., 2002, Andersen et al., 2003). Echocardiographic tissue Doppler imaging (TDI) studies have demonstrated
reductions in mitral annular velocity, peak systolic strain and peak strain rate (measured in the LV long-axis) in patients with diastolic abnormalities in the presence of normal ejection fraction and normal LV regional function (Bolognesi et al., 2001, Yip, G. et al., 2002a, Fang et al., 2003, Vinereanu et al., 2003).

Although effective at identifying global LV dysfunction, TDI provides estimates of tissue motion and strain in only a limited number of directions and regions. In addition, the complex nature of the ventricular deformation, which includes ventricular torsion and transmural shear, ensures that tissue will move through and across the ultrasound beam during systole and diastole, with resultant error in the strain estimate.

MRI with tissue tagging is a useful alternative as it can provide estimates of three-dimensional (3D) strain and strain-rate in all directions and in all regions of the left and right ventricles, and accounts for the effect of through-plane motion (Axel and Dougherty, 1989, Fonseca et al., 2003). MR tagging has previously been used as a gold standard to validate tissue Doppler imaging measures of strain and strain rate (Edvardsen et al., 2002). Recently, the MR tagging technique has been used to investigate diastolic myocardial relaxation parameters including torsion, apical rotation, and longitudinal motion, as well as strain and strain-rate (Paelinck et al., 2002, Fonseca et al., 2003, Oxenham et al., 2003).

The present study aimed to assess both systolic and diastolic 3D myocardial function in patients with Type 2 DM, identified by echocardiographic criteria as having a normal ejection fraction and diastolic dysfunction. It was hypothesized that MRI-derived systolic as well as diastolic 3D strain parameters, including circumferential, longitudinal and torsional components of the deformation (and the 3D principal strain, which is a combination of these components), would be depressed in these patients. In addition, the motion of the mitral valve annulus plane (MVP) was tracked in three dimensions. Since MVP displacement and velocity are commonly estimated in TDI and other echocardiographic examinations, and are thought to be sensitive indicators of systolic as well as diastolic function (Mandinov et al., 2000), it was hypothesized that MRI-derived 3D MVP motion would also be depressed in systole and diastole.
5.2 Methods

5.2.1 Subjects

Patients with Type 2 DM were recruited from the register of patients attending the South Auckland Diabetes Service at Middlemore Hospital, Auckland, to take part in a randomized, double-blind, placebo-controlled clinical trial of a new therapy targeting diabetic cardiomyopathy. This trial was approved by the North Health Ethics committee and the clinical board of Middlemore hospital, and was performed in accordance with their guidelines for research involving human subjects, after obtaining written informed consent from all participants. The end-points of the trial included changes in MR parameters of myocardial relaxation, and, as such, provided the opportunity to examine alterations in myocardial tissue behaviour in a disease model, with standard MRI and also with MR tissue tagging techniques. This Chapter deals with only the baseline data from the trial and therefore all patients were considered to belong to the same group (DM), regardless of whether they were to be assigned to therapy or to placebo.

Patients were eligible for inclusion if they had: Type 2 diabetes mellitus and HbA1c > 7%, evidence of diastolic dysfunction with normal systolic function (cardiac ejection fraction \( \geq 45\% \), with no regional wall motion anomalies), normal electrocardiogram (sinus rhythm, normal PR interval, normal T wave and QRS morphology, and an isoelectric ST segment), evidence of diabetic retinopathy and/or evidence of diabetic nephropathy (urine albumin > 300 mg/l and serum creatinine > 150 \( \mu \text{M} \)). Patients were ineligible if they were pregnant, morbidly obese (body mass index \( \geq 45 \text{kg/m}^2 \)), had evidence of autonomic neuropathy, or standard contraindications to MRI scanning.

For the purposes of this Chapter, the control group (NC) consisted of the same normal healthy old and young subjects (collectively), as those presented in Chapters 3 and 4. As stated before, these volunteers were included only if they had no evidence or history of cardiac disease and were not on regular medication for cardiovascular or other significant coexisting illness. Details of the exclusion criteria used for this group are given in Section 3.2.1.

5.2.2 Echocardiography

All echocardiographic examinations were performed using an ATL HDI 5000 echo machine (Bothell, Washington, USA). Images were obtained by a research cardiac
sonographer according to a standard protocol, recorded onto videotape and acquired digitally for offline analysis. For each parameter, three measurements were taken and the average value was recorded.

Mitral valve pulsed wave Doppler (PWD) recordings were obtained from the apical four-chamber view. A 5-mm PWD sample volume was placed distal to the mitral annulus, between the mitral leaflets, and measurements were made at the end of the expiratory phase of normal respiration, with the interrogation beam aligned with mitral flow (Gardin et al., 1986). Peak early transmitral inflow velocity (E), peak transmitral flow velocity in late diastole (A), the E:A ratio, and the early filling deceleration time (DT) were determined from these recordings.

Diastolic filling was classified as ‘normal’ if E:A was 1.0-2.0 and the DT was 0.14-0.23 s (Xie et al., 1994, Giannuzzi et al., 1996). The classification of diastolic dysfunction was based on the finding of ‘abnormal relaxation’ (E:A < 1; DT > 0.23 s), ‘pseudonormal relaxation’ (E:A = 1.0-2.0, but reversing to E:A < 1.0 and DT > 0.23 s with the Valsalva manoeuvre (Dumesnil et al., 1991)), or ‘restrictive filling’ (E:A > 2.0; DT < 0.14 s) (Xie et al., 1994, Giannuzzi et al., 1996). The Valsalva manoeuvre was used whenever a normal E:A value was obtained, in order to unmask a possible pseudonormal filling pattern (Dumesnil et al., 1991).

5.2.3 MRI

All of the MR studies were performed in the supine position with the use of a Siemens 1.5T Vision MRI scanner and a phased array surface coil. MR image acquisition parameters for the normal subjects are described in Sections 3.2.2 (tagged images) and 4.2.1 (standard cine turboFLASH anatomical images). For the DM group, three scout scans were performed in order to define the long- and short-axes of the left ventricle. Cine turboFLASH MR images were obtained without tagging in eight or nine short-axis slices, equally spaced from apex to base, and three long-axis slices at equal angular intervals around the central axis of the LV (scan parameters were: slice thickness 8 mm; in-plane resolution ~1 mm/pixel; temporal resolution of 40 to 50 ms depending on heart rate; TE/TR = 4.0/9.0 ms). Subjects and patients undertook approximately 15-second breath-holds during the scans to eliminate respiratory motion artifacts. View-sharing was used to reconstruct 15-27 time frames per cardiac cycle, depending on the heart rate.
Tagged images were acquired at the same locations as the untagged images, plus in three more long-axis slices spaced at equal angular intervals around the LV (scan parameters were: slice thickness 8 mm; in-plane resolution ~1 mm/pixel; temporal resolution of 35 or 45 ms depending on heart rate; TE/TR = 4.0/8.9 ms). A segmented k-space version of the spatial modulation of magnetization (SPAMM) tagging sequence was used to create a tag grid in the images with a spacing of 8 mm and width of approximately 1 mm, immediately after the R-wave trigger. View-sharing was used to reconstruct 11-23 time frames per cardiac cycle, depending on the heart rate.

All images were prospectively gated and, therefore, could not be acquired during the final 10-15% of the cycle, to allow for detection of the next R wave trigger. Tags could be visualized and tracked throughout the imaged portion of the cardiac cycle. Tagged MR images from a typical patient in the DM group are shown in Figure 5.1.

Figure 5.1 Tagged MR images for a typical patient with type 2 diabetes mellitus.
Short-axis images at the mid-ventricular level. Good tag persistence was observed through the cardiac cycle. A: end-diastolic, 35 ms; B: end-systolic, 315 ms; C: late diastolic, 525 ms.

5.2.4 Image Analysis

The images were stored digitally and analyzed offline. Interactive 3D guide-point modelling was used to define LV geometry on the untagged images to produce values for mass and volumes by numerical integration (Young et al., 2000). As described in Section 4.2.2 for the normal subjects, the motion of the mitral valve plane (MVP) was tracked on the three untagged long-axis images for each patient in the DM group.
The displacement of tagged myocardial points were reconstructed in 3D from the tagged MR images by deforming a 3D finite element mathematical model of the LV to match the tracked displacements of the tag stripes (Young et al., 1995). The model was then interrogated, using standard continuum mechanics methods (Fung, 1965, Young et al., 1995), to provide average measures of circumferential and longitudinal shortening strains and torsional shear strain, as well as the 3D principal (i.e., maximal shortening) strain, at each time frame. By convention, end-diastole (ED) is 0 ms, and each frame was taken at 35 or 45 ms intervals after ED, depending on heart rate.

5.2.5 Myocardial Strain Parameters

Peak systolic displacement and peak systolic and diastolic velocities of the mitral valve plane were calculated as before (Section 4.2.2). Peak global values of circumferential and longitudinal shortening strains, torsional shear strain, and 3D principal shortening strain, and the corresponding peak global systolic strain rates and peak global diastolic strain relaxation rates were also obtained (calculations described in Chapter 2, Section 2.5.2). The reported peak global strain measures represent average values taken over the entire ventricle and are intrinsically corrected for the effects of through-plane motion.

A regional analysis of the deformation was also performed, and values were obtained for circumferential and longitudinal shortening strains and torsional shear strain at each frame (and the corresponding peak systolic and diastolic strain rates), in each of the 16 standardized LV myocardial regions (Schiller et al., 1989), as described in Chapter 3 (Section 3.2.4).

Finally, the time (in ms) from ED to peak strain and from ED to peak rate of relaxation was also measured.

5.2.6 Statistics

Data were analyzed using the SYSTAT software package (Version 10.2, copyright SYSTAT software Inc., 2002, Standard Version). All data are presented as the mean ± SD. Statistical significance was defined as $P < 0.05$.

Subject characteristics, echocardiography measurements and MRI volumetrics were compared between the NC and the DM groups using the Student’s two-tailed $t$ test. Strain and strain rate are known to be age-dependent (Fonseca et al., 2003), so comparisons of MRI strains and displacements between DM patients and normal subjects were performed.
using an ANCOVA with age as covariate. A linear regression analysis was performed to examine the relationship between peak global MR systolic and diastolic strain parameters. Finally, the correlations of LV mass:end-diastolic volume ratio (LV mass:EDV is an index of concentric hypertrophy) with peak global systolic strain and with peak global strain relaxation were examined by linear regression.

Analysis of regional strain data was performed as in Chapter 3 (Section 3.2.5). For peak circumferential and longitudinal strain and torsion and for their respective peak rates of relaxation, two MANOVAs were performed, one testing the longitudinal variation and the other testing the circumferential variation, in order to examine the interaction effect, if any, of group (i.e., DM or NC) and region. A significant interaction effect implies a significant difference in the pattern of regional heterogeneity due to DM. Between groups, each region in the DM group was compared with the corresponding region in the NC group using an ANCOVA in order to correct for age. Thus, for the three longitudinal levels or the four circumferential regions, the P-values were corrected in Bonferroni fashion for three or four tests, respectively. Bonferroni adjusted P-values are stated for each test where applicable; these are indicated with a superscript B.

5.3 Results

5.3.1 Study Population

Of 35 DM patients who were eligible for MRI, seven had either unacceptable image quality or were intolerant of the imaging (e.g., claustrophobia). Acceptable MR images had been obtained from all 31 subjects in the normal control group. Characteristics of both groups are summarized in Table 5.1, and the clinical details of the type 2 DM group are given in Table 5.2.

The DM patients had a long history of disease and many had poor metabolic control of their disease. They had higher body mass index (BMI), heart rate and diastolic blood pressure (DBP), in comparison with the NC group. No difference in systolic blood pressure (SBP) was detected between DM and NC groups.
### TABLE 5.1 Characteristics of normal healthy control subjects (NC) and type 2 diabetes mellitus patients (DM).

<table>
<thead>
<tr>
<th>Parameters</th>
<th>NC</th>
<th>DM</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>31</td>
<td>28</td>
<td>-</td>
</tr>
<tr>
<td>Age, years</td>
<td>46.7 ± 23.5</td>
<td>52.6 ± 7.7</td>
<td>0.214</td>
</tr>
<tr>
<td>Range</td>
<td>19-74</td>
<td>33-70</td>
<td></td>
</tr>
<tr>
<td>Female, n (%)</td>
<td>10 (32%)</td>
<td>9 (32%)</td>
<td>0.993</td>
</tr>
<tr>
<td>Height, m</td>
<td>1.7 ± 0.1</td>
<td>1.7 ± 0.1</td>
<td>0.336</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>72.7 ± 16.1</td>
<td>93.3 ± 19.3</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>24.5 ± 4.0</td>
<td>32.8 ± 4.9</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Body surface area, m²</td>
<td>1.8 ± 0.2</td>
<td>2.0 ± 0.2</td>
<td>0.003</td>
</tr>
<tr>
<td>Heart rate, beats/minute</td>
<td>70.0 ± 10.4</td>
<td>75.3 ± 8.6</td>
<td>0.040</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>130.8 ± 21.0</td>
<td>134.1 ± 15.7</td>
<td>0.499</td>
</tr>
<tr>
<td>Diastolic blood pressure, mm Hg</td>
<td>73.0 ± 13.9</td>
<td>84.0 ± 7.8</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

Values are mean ± SD, where applicable.

P-values were obtained from t tests between NC and DM groups, for each parameter.

---

5.3.2 Echocardiography

Early diastolic filling velocity (E) was similar between DM and NC groups (58.6 ± 15.2 vs. 58.7 ± 19.3 cm/s, P = NS), however the late filling velocity (A) was greater in DM (67.8 ± 11.7 vs. 50.5 ± 13.5 cm/s, P < 0.001). The E:A ratio was lower, in the DM group (0.9 ± 0.2 vs. 1.3 ± 0.6 P = 0.002).

The normal transmitral diastolic filling pattern (Xie et al., 1994, Giannuzzi et al., 1996) was observed in the NC group. However, none of the DM patients exhibited normal filling: 17 had abnormal relaxation and the remaining 11 patients showed a pseudonormal filling pattern (Xie et al., 1994, Giannuzzi et al., 1996).

5.3.3 MRI Volumetrics

MRI measurements of LV ejection fraction, end-diastolic volume, end-systolic volume and stroke volume were comparable between the DM and NC groups (see Table 5.3). Both LV mass and the LV mass:EDV ratio were greater in the DM group, compared with NC.
### TABLE 5.2 Clinical details of the type 2 diabetes mellitus patient group (n = 28).

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smokers</td>
<td>6 (21%)</td>
</tr>
<tr>
<td>Being treated for hypertension</td>
<td>19 (68%)</td>
</tr>
<tr>
<td>Diabetes duration, years</td>
<td>10.5 ± 6.8</td>
</tr>
<tr>
<td>Poor glycaemic control (haemoglobin A1c ≥ 8)</td>
<td>24 (86%)</td>
</tr>
<tr>
<td>Haemoglobin A1c, %</td>
<td>9.3 ± 1.7</td>
</tr>
<tr>
<td>Glucose, mmol/L</td>
<td>11.0 ± 4.0</td>
</tr>
<tr>
<td>Cholesterol, mmol/L</td>
<td>5.5 ± 0.9</td>
</tr>
<tr>
<td>On medication: Insulin</td>
<td>16 (57%)</td>
</tr>
<tr>
<td>Beta-blockers</td>
<td>3 (11%)</td>
</tr>
<tr>
<td>Calcium antagonists</td>
<td>3 (11%)</td>
</tr>
<tr>
<td>Angiotensin converting enzyme inhibitors</td>
<td>18 (64%)</td>
</tr>
<tr>
<td>Diuretics</td>
<td>4 (14%)</td>
</tr>
<tr>
<td>Cholesterol lowering drugs</td>
<td>11 (39%)</td>
</tr>
<tr>
<td>Antiplatelet agents</td>
<td>6 (21%)</td>
</tr>
</tbody>
</table>

Values are mean ± SD, where applicable.

### TABLE 5.3 MRI volumetric data of normal healthy control subjects (NC) and type 2 diabetes mellitus patients (DM).

<table>
<thead>
<tr>
<th>Parameters</th>
<th>NC</th>
<th>DM</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ejection fraction, %</td>
<td>69.9 ± 5.2</td>
<td>69.1 ± 6.6</td>
<td>0.608</td>
</tr>
<tr>
<td>End-diastolic volume, ml</td>
<td>126.2 ± 28.6</td>
<td>121.4 ± 33.4</td>
<td>0.553</td>
</tr>
<tr>
<td>End-systolic volume, ml</td>
<td>38.1 ± 11.2</td>
<td>38.1 ± 15.5</td>
<td>0.989</td>
</tr>
<tr>
<td>Stroke volume, ml</td>
<td>88.2 ± 20.8</td>
<td>83.3 ± 22.1</td>
<td>0.387</td>
</tr>
<tr>
<td>LV mass, g</td>
<td>143.2 ± 35.6</td>
<td>199.5 ± 46.4</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>LV mass:end-diastolic volume, g/ml</td>
<td>1.2 ± 0.3</td>
<td>1.7 ± 0.3</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>LV mass:body surface area, g/m²</td>
<td>79.0 ± 20.5</td>
<td>98.2 ± 17.5</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

Values are mean ± SD.

P-values were obtained from t tests between NC and DM groups, for each parameter.
5.3.4 Mitral Valve Plane Motion

MVP displacement during the cardiac cycle is compared between a typical DM patient and a typical normal control subject in Figure 5.2A. The DM group had a 12% lower peak MVP displacement (1.1 ± 0.2 vs. 1.2 ± 0.3 cm, \( P = 0.040 \)), compared with normal subjects (with age as covariate). Peak systolic MVP velocity was not significantly different between the DM group and NC (4.9 ± 1.3 vs. 5.3 ± 1.2, \( P = \text{NS} \)). However, peak diastolic MVP velocity was 21% lower in DM (4.7 ± 1.3 vs. 5.9 ± 2.1 cm/s, \( P = 0.008 \)).

![Figure 5.2](image)

**Figure 5.2** Temporal evolution of mitral valve plane (MVP) displacement (A) and myocardial principal shortening strain (B).

The graphs show data for a typical patient from the type 2 DM group compared with a typical normal control subject (NC). Values were obtained with intervals of 40 ms for MVP motion and 35 ms for principal shortening strain, in these individuals.
5.3.5 MRI Strain

Peak systolic strain:

Peak circumferential strain (Sc) was 14% smaller in the DM group (16.7 ± 2.0 vs. 19.5 ± 2.4 %, \( P < 0.001 \)), and peak longitudinal strain (SL) was 22% smaller (12.5 ± 2.2 vs. 16.2 ± 2.1 %, \( P < 0.001 \)), compared with normal subjects. However, peak torsional shear strain (ST) was 17% greater in the diabetic patients (6.8 ± 1.4 vs. 5.8 ± 1.3 °, \( P = 0.025 \)). The peak principal strain (Sp) was 10% smaller in the DM group (24.2 ± 2.4 vs. 27.0 ± 2.3 %, \( P < 0.001 \)). Temporal evolution of the principal shortening strain, during the cardiac cycle, is compared between a typical DM patient and a typical normal control subject in Figure 5.2 B.

Regional analysis: The pattern of regional non-uniformity in Sc was similar in DM and normal subjects (\( P = \text{NS} \), for interaction between region and group, with respect to both the longitudinal and the circumferential variation). However, Sc was reduced in the DM patients (corrected for age and compared with the normal group), in all regions (\( P^B < 0.01 \) for each) except for the lateral wall. The longitudinal variation in SL was different between DM and NC (\( P = 0.005 \)), but the circumferential variation was similar (\( P = \text{NS} \)). On correction for age, SL was reduced in the DM patients in all regions along the length and around the circumference of the LV, in comparison with the normal group (\( P^B < 0.01 \) for each). The pattern of regional non-uniformity in ST was not different between DM and normal people (\( P = \text{NS} \), for both the longitudinal and the circumferential variation). In all regions, ST was similar in DM patients (on correction for age) and normal subjects (\( P^B = \text{NS} \)). See Figure 5.3.

Time from ED to Peak Systolic Shortening Strain and Torsion

In patients with type 2 DM, tSc (with correction for age) was similar to that in the normal subjects (333.9 ± 46.2 vs. 343.4 ± 26.2 ms, \( P = 0.222 \)). In the DM patients, tSc in the apex and lateral wall was reduced, on correction for age, when compared with these same regions in normal subjects (\( P^B < 0.01 \) for each).

In DM patients, tSL, on correction for age, was not different to that recorded in the normal group (351.8 ± 53.6 vs. 350.3 ± 43.5 ms, \( P = 0.478 \)). Apical SL occurs earlier in DM patients than in the NC group (\( P^B = 0.027 \)), but in other regions tSL is not different between DM and NC groups.

The time taken to achieve peak global torsion (tST) was not influenced by DM, on correction for age (350.9 ± 35.1 vs. 341.9 ± 36.0 ms, \( P = 0.730 \)). Regional analyses also
showed that, on correction for age, DM patients achieved $S_T$ earlier than the NC group in all regions ($P^B < 0.05$ for each), except for the lateral and anterior walls.

Figure 5.3 Regional variation in peak systolic shortening strain, and the influence of type 2 DM.

Peak strain is compared between patients with type 2 diabetes mellitus (DM) and normal control subjects (NC) (mean ± SD, for each group), across the three longitudinal LV regions (in A, C and E) and across the four circumferential regions (in B, D and F). A and B show peak circumferential strain ($S_C$), C and D show peak longitudinal strain ($S_L$), and E and F show peak torsion. Changes due to DM (on correction for age) that are significant after Bonferroni correction ($P^B < 0.05$) are indicated, for each region, with an asterisk, *.
Peak systolic strain rate (SSR)

During systole, peak circumferential strain rate (SSRc) was 10% lower (88.2 ± 12.4 vs. 97.9 ± 11.4 %/s, \( P = 0.008 \)), and peak longitudinal strain rate (SSRL) was 14% lower (69.1 ± 14.4 vs. 80.7 ± 10.6 %/s, \( P = 0.003 \)) in the DM group. In contrast, peak rate of change of torsion (SSRT) was 21% higher in DM (36.0 ± 7.5 vs. 29.9 ± 5.4 °/s, \( P = 0.002 \)). The peak principal strain rate (SSRP) was not significantly different between DM and NC (116.8 ± 23.3 vs. 128.9 ± 22.0 %/s, \( P = 0.082 \)).

**Regional analysis:** In DM patients, SSRc, examined on a regional basis and corrected for age, was impaired compared with normal only in the septal and anterior walls (\( P^B < 0.05 \) for each). In DM patients, regional analysis of SSRL showed reductions (corrected for age) only in the base, and in the lateral and anterior walls compared with NC (\( P^B < 0.05 \) for each). In all regions, SSRT was similar in DM patients (on correction for age) and normal subjects (\( P^B = \text{NS} \) for each region).

Peak diastolic strain relaxation rate

Peak rate of circumferential strain relaxation (RC) was 35% lower (70.8 ± 19.8 vs. 108.3 ± 40.9 %/s, \( P < 0.001 \)), and peak rate of longitudinal strain relaxation (RL) was 32% lower (62.5 ± 21.1 vs. 91.7 ± 36.5 %/s, \( P < 0.001 \)) in the DM group. Peak rate of relaxation of torsion (RT) was not different between DM and NC (34.1 ± 10.6 vs. 34.2 ± 9.3 °/s, \( P = 0.886 \)). Peak rate of relaxation of the principal strain (RP) was 33% lower in the DM group (64.3 ± 17.4 vs. 96.0 ± 35.4 %/s, \( P < 0.001 \)).

**Regional analysis:** The longitudinal variation in RC was not different between DM and NC (\( P = \text{NS} \)), although a significant interaction effect of group and region was found for the circumferential variation (\( P = 0.012 \)). In the DM patients, regional analysis showed that RC was reduced in all regions, compared with normal, on correction for age (\( P^B < 0.001 \) for each). The longitudinal variation in RL was similar (\( P = \text{NS} \)) but the circumferential variation differed (\( P = 0.044 \)) between DM and NC. On correction for age, RL was reduced in the DM patients in all regions (\( P^B < 0.05 \) for each), in comparison with the normal group. Both the circumferential and the long variations in RT differed between DM and normal subjects (\( P = 0.004 \) and 0.007, respectively). In DM patients, regional analysis showed that RT was reduced only in the base, compared with normal, on correction for age (\( P^B = 0.009 \)). See Figure 5.4.
Figure 5.4 Regional variation in peak rates of strain relaxation, and the influence of type 2 DM.

Peak rates of strain recovery are compared between patients with type 2 diabetes mellitus (DM) and normal control subjects (NC), (mean ± SD, for each group), across the three longitudinal LV regions (in A, C and E) and across the four circumferential regions (in B, D and F). A and B show peak rates of circumferential strain relaxation ($R_c$), C and D show peak rates of longitudinal strain relaxation ($R_l$), and E and F show peak rates of recovery of torsion ($R_t$). Changes due to DM (on correction for age) that are significant after Bonferroni correction ($P^B < 0.05$) are indicated, for each region, with an asterisk, *.

**Time from ED to Peak Diastolic Rate of Relaxation**

The time taken to achieve global peak rate of circumferential relaxation ($t_{R_c}$) was not influenced by DM, on correction for age (500.9 ± 54.8 vs. 503.3 ± 52.3, $P = 0.486$).
Regional analysis showed significant reductions in $tR_C$ in DM patients (corrected for age and compared with normal) in all regions ($P^B < 0.05$ for each) except the apex and lateral wall.

On correction for age, $R_L$ was achieved earlier in the DM patients than in the normal subjects ($485.6 \pm 53.9$ vs. $524 \pm 48.6$ ms, $P = 0.001$). Significant reductions in the time taken to achieve global $R_L$ ($tR_L$) were observed in DM patients (corrected for age and compared with normal) in all regions ($P^B < 0.05$) compared with NC, except for the apex and lateral wall.

The time taken to achieve global peak rate of relaxation of torsion ($tR_T$) was not significantly different in DM, on correction for age ($428.1 \pm 74.4$ vs. $453.2 \pm 40.7$ ms, $P = 0.076$). Regional analysis showed significant reductions in $tR_T$ in DM patients (corrected for age and compared with normal) in all regions ($P^B < 0.05$ for each) except the posterior wall.

### 5.3.6 Relationship between Systolic and Diastolic Myocardial Function

A significant correlation was found between peak systolic MVP displacement and peak diastolic MVP velocity in both groups (see Table 5.4 and Figure 5.5). In both DM and NC, significant correlations were observed between the peak rate of relaxation and the peak systolic value of the circumferential, longitudinal, and torsional shear strains. Peak principal shortening strain correlated with its peak diastolic relaxation rate in the DM subjects but not in the normal controls, although a significant correlation was found for this parameter when the two groups were considered together.

### TABLE 5.4 Relationship between systolic and diastolic myocardial function.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>NC</th>
<th>P</th>
<th>DM</th>
<th>P</th>
<th>NC+DM</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>MVP</td>
<td>0.801</td>
<td>&lt;0.001</td>
<td>0.776</td>
<td>&lt;0.001</td>
<td>0.798</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Circumferential</td>
<td>0.606</td>
<td>&lt;0.001</td>
<td>0.572</td>
<td>0.005</td>
<td>0.691</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Longitudinal</td>
<td>0.508</td>
<td>0.004</td>
<td>0.575</td>
<td>0.003</td>
<td>0.630</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Torsion</td>
<td>0.623</td>
<td>&lt;0.001</td>
<td>0.532</td>
<td>0.005</td>
<td>0.544</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Principal</td>
<td>0.248</td>
<td>0.186</td>
<td>0.579</td>
<td>0.004</td>
<td>0.496</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

*Results of linear regression analyses, which examined the relationship between the peak systolic value and the peak diastolic rate of each strain parameter, and between peak systolic displacement and peak diastolic velocity of the mitral valve plane (MVP).*

$r = \text{correlation coefficient, } P = \text{P-value}$
Figure 5.5 Relationship between systolic and diastolic myocardial function.
Peak diastolic velocity of the MVP correlated significantly with peak systolic MVP displacement in both patients with type 2 diabetes mellitus (DM) and the normal control group (NC). Similar relationships were also observed for the tissue strain parameters.

A general linear model ANOVA showed no significant interaction effect of peak systolic displacement and disease on peak diastolic MVP velocity (P = 0.157), indicating that an ANCOVA analysis is feasible. ANCOVA (to test influence of DM on peak diastolic MVP velocity, with peak systolic MVP displacement as a covariate) showed that the effect due to group became non-significant (Table 5.5). Thus, the reduced peak diastolic MVP velocity observed in the DM group might be due to the covariate effect of peak systolic MVP displacement rather than the direct influence of diabetes alone.

For each parameter $R_C$, $R_L$, $R_T$, and $R_p$, a general linear model ANOVA showed no significant effect of the interaction of group (i.e., DM or NC) and $S_C$, $S_L$, $S_T$, or $S_p$, respectively. Therefore an ANCOVA was performed, and demonstrated, for $R_C$, $R_L$, and $R_T$, that the effect due to group was no longer significant, indicating that the reductions in $R_C$, $R_L$, and $R_T$, respectively, in the DM group may be due to the covariate effect of the corresponding peak systolic strain values rather than the direct influence of diabetes (Table 5.5). The effect of disease was still significant on $R_p$, however, independent of the effect of $S_p$. 
Chapter 5  Myocardial Strain: Effects of Diastolic Dysfunction in Type 2 Diabetes Mellitus

**TABLE 5.5** ANCOVA to account for the influence of systolic function on diastolic parameters.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Group effect P-value</th>
<th>Covariate effect P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>MVP velocity</td>
<td>0.073</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>$R_C$</td>
<td>0.123</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>$R_L$</td>
<td>0.661</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>$R_T$</td>
<td>0.090</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>$R_P$</td>
<td>0.031</td>
<td>0.020</td>
</tr>
</tbody>
</table>

MVP velocity = peak diastolic mitral valve plane velocity; $R_C$ = peak rate of circumferential relaxation; $R_L$ = peak rate of longitudinal relaxation; $R_T$ = peak rate of torsion reversal; $R_P$ = peak rate of relaxation of principal shortening strain.

The effect of DM (group effect) on diastolic function parameters was examined with the corresponding peak systolic values considered as covariates.

**TABLE 5.6** Relationship between myocardial function and LV mass:EDV ratio.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>NC</th>
<th></th>
<th>DM</th>
<th></th>
<th>NC+DM</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$r$</td>
<td>$P$</td>
<td>$r$</td>
<td>$P$</td>
<td>$r$</td>
<td>$P$</td>
</tr>
<tr>
<td>MVP (systolic)</td>
<td>-0.523</td>
<td>0.003</td>
<td>-0.455</td>
<td>0.015</td>
<td>-0.528</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>$S_C$</td>
<td>-0.626</td>
<td>&lt;0.001</td>
<td>-0.519</td>
<td>0.005</td>
<td>-0.712</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>$S_L$</td>
<td>-0.730</td>
<td>&lt;0.001</td>
<td>-0.615</td>
<td>&lt;0.001</td>
<td>-0.813</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>$S_T$</td>
<td>0.334</td>
<td>0.066</td>
<td>0.122</td>
<td>0.535</td>
<td>0.383</td>
<td>0.003</td>
</tr>
<tr>
<td>$S_P$</td>
<td>-0.410</td>
<td>0.022</td>
<td>-0.234</td>
<td>0.230</td>
<td>-0.553</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>MVP (diastolic)</td>
<td>-0.653</td>
<td>&lt;0.001</td>
<td>-0.372</td>
<td>0.080</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>$R_C$</td>
<td>-0.746</td>
<td>&lt;0.001</td>
<td>-0.377</td>
<td>0.084</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>$R_L$</td>
<td>-0.653</td>
<td>&lt;0.001</td>
<td>-0.247</td>
<td>0.233</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>$R_T$</td>
<td>0.226</td>
<td>0.222</td>
<td>0.179</td>
<td>0.382</td>
<td>0.142</td>
<td>0.293</td>
</tr>
<tr>
<td>$R_P$</td>
<td>-0.585</td>
<td>0.001</td>
<td>-0.139</td>
<td>0.526</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

Results of linear regression analyses, which examined the relationship between LV mass:EDV ratio and each of the systolic and diastolic parameters studied here. Analysis for both groups together (NC+DM) was performed only if the preceding ANOVA showed 'homogeneity of slopes' (i.e., the interaction effect of group and LV mass:EDV on the myocardial function parameter was non-significant).

$r$ = correlation coefficient, $P$ = P-value
5.3.7 Relationship between Myocardial Function and the LV Mass:EDV Ratio

A significant inverse relationship was observed between the LV mass:EDV ratio and peak MVP displacement (Table 5.6 and Figure 5.6). While LV mass:EDV ratio was related to peak diastolic MVP velocity in the normal subjects, no such relationship was found in the DM patients.

In both DM and normal groups, significant inverse relationships were found between the LV mass:EDV ratio and each of peak systolic circumferential strain and peak systolic longitudinal strain (Table 5.6). LV mass:EDV did not correlate with peak torsion in either group. LV mass:EDV correlated with peak principal shortening strain in the NC subjects but not in DM.

LV mass:EDV ratio was related to each of $R_C$, $R_L$, and $R_P$ in the normal subjects, but no such relationship was found in the DM patients. LV mass:EDV ratio was not related to $R_T$ in either DM or NC groups.

\[ \text{Figure 5.6 Relationship between myocardial function and LV mass:EDV.} \]

Peak systolic MVP displacement correlated inversely with LV mass:EDV, an index of LV hypertrophy, in both patients with type 2 diabetes mellitus (DM) and the normal control group (NC). While most systolic and diastolic tissue strain parameters correlated with LV mass:EDV in the normal subjects, none of the MR diastolic parameters were related to LV mass:EDV in DM.
5.3.8 Myocardial Function in DM Patients vs. Older Normal Subjects

The peak systolic displacement of the MVP was not different between DM and the older normal group \((P = 0.732)\). \(S_C\) \((P = 0.010)\) and \(S_L\) \((P < 0.001)\) were reduced in the DM group, while \(S_T\) was similar in DM patients and the normal older people \((P = 0.455)\). \(S_P\) was also reduced in DM compared with the normal older group alone \((P < 0.001)\). The DM group showed reduced \(S_C\) in the base and mid-ventricular levels, and in the septum and posterior walls \((P^B < 0.05\) for each). All regions, except the apex and septum, showed reduced \(S_L\) in the DM patients \((P^B < 0.01\) for each). Furthermore, values for \(S_T\) in each LV region in the DM patients were not different to the corresponding regions in the older normal group \((P^B = NS)\).

No difference was observed in \(tS_C\) between the DM and older normal group \((333.9 \pm 46.2\) vs. \(352.2 \pm 24.8\) ms, \(P = 0.152)\). \(tS_C\) was less in DM patients in the apex and lateral wall \((P^B < 0.01)\), but similar to older normal subjects in other regions. \(tS_L\) was similar in DM and the older normal group \((351.8 \pm 53.6\) vs. \(371.3 \pm 48.0\) ms, \(P = 0.731)\). Regional analysis showed that \(tS_L\) in DM was very similar in all regions \((P^B = NS)\) to values in the normal older subjects. Furthermore, no difference was observed in \(tS_T\) between the DM and older normal group \((350.9 \pm 35.1\) vs. \(357.2 \pm 37.9\) ms, \(P = 0.649)\). \(tS_T\) in the DM patients was reduced in all regions \((P^B < 0.05\) for each), except the apex and the lateral and anterior walls.

The peak systolic velocity of the MVP was not different between DM patients and the older normal subjects \((P = 0.903)\). Similar values for both groups were observed for SSR\(_C\) \((P = 0.124)\) and SSR\(_L\) \((0.134)\), but SSR\(_T\) was greater in the DM group \((0.008)\). SSR\(_P\) was not different between older normal subjects and the DM patients \((P = 0.220)\). DM values of SSR\(_C\), SSR\(_L\) and SSR\(_T\) were similar to those in the normal older group in all regions \((P^B = NS\) for each).

The peak diastolic velocity of the MVP was not different between DM and the older normal group \((P = 0.444)\). Similar values were observed in DM patients and the older normal group for global \(R_C\) \((P = 0.499)\), \(R_L\) \((P = 0.974)\), \(R_T\) \((P = 0.458)\) and \(R_P\) \((P = 0.751)\). \(R_C\), compared with the normal older group on a regional basis, was reduced only in the posterior and anterior walls in the DM patients \((P^B < 0.05\) for each), while values for other regions were comparable \((P^B = NS)\). For each region, values for \(R_L\) and \(R_T\) obtained in DM were similar to those in the normal older subjects \((P^B = NS\) for each).

\(tR_C\) was similar in DM and the older normal group \((500.9 \pm 54.8\) vs. \(527.1 \pm 62.0\), \(P = 0.192)\). Regional analysis showed that \(R_C\) occurred earlier in DM compared with only the
Chapter 5  Myocardial Strain: Effects of Diastolic Dysfunction in Type 2 Diabetes Mellitus

older normal group, in all regions ($P^B < 0.05$ for each) except the apex. At the global level $R_L$ was achieved earlier in DM, when compared with the older normal group alone ($485.6 \pm 53.9$ vs. $551.8 \pm 47.1$ ms, $P < 0.001$). Regionally, DM patients showed reduced $tR_L$ only in the base, and the posterior and anterior walls ($P^B < 0.05$). $tR_T$, at the global level, was not significantly different between DM and the older normal group ($428.1 \pm 74.4$ vs. $467.2 \pm 39.3$ ms, $P = 0.060$). $R_T$ also occurred earlier in DM in all regions ($P^B < 0.01$ for each) except the apex and the septal and posterior walls.

5.3.9 Abnormal vs. Pseudonormal Filling Pattern

The DM group was divided into patients with abnormal filling pattern (AFP) and those with pseudonormal filling pattern (PFP), by echocardiographic E:A ratio. The peak systolic value and peak rate of relaxation of circumferential, longitudinal and principal strains were lower compared with NC, in both patients with PFP and patients with AFP ($P < 0.05$ for all). There were no significant differences between the PFP and AFP subgroups with respect to peak value, peak systolic rate, and peak rate of relaxation of any of the strains (circumferential, longitudinal, torsional shear and principal; $P = NS$ for all). Note that the Valsalva manoeuvre was not performed during MR scanning.

Scatterplots of individual subject/patient datapoints revealed no consistent outliers with respect to the mean results presented above.

5.4 Discussion

5.4.1 Global Function

The results presented here corroborate recent tissue Doppler imaging (TDI) studies which have shown systolic tissue dysfunction, measured as a decrease in LV longitudinal shortening, in patients with normal ejection fraction who were assumed to have ‘isolated’ diastolic dysfunction (Petrie et al., 2002, Yip, G. et al., 2002a, Andersen et al., 2003). Peak systolic displacement of the mitral valve plane (MVP) was found to be impaired in the DM group. Furthermore, peak LV systolic circumferential and longitudinal shortening were lower in the DM subjects; however peak LV torsional shear strain during systole was greater. Thus, peak principal shortening strain, while smaller in the DM group, was not
reduced by as great an extent as the circumferential and longitudinal shortening strains, because these reductions were partly compensated for, by the increase in peak torsion.

Studies using TDI have shown a decrease in longitudinal shortening in type 2 DM patients with diastolic dysfunction (Andersen et al., 2003, Fang et al., 2003, Vinereanu et al., 2003). Longitudinal impairment has been reported even when global LV function is observed to be normal (Garcia et al., 1996, Cardim et al., 2002). Andersen et al. (2003) observed a decrease in LV longitudinal contraction using TDI in patients with type 2 diabetes mellitus who had normal ejection fraction, normal diastolic function and no symptoms or history of heart disease; this decrease was exacerbated when diastolic dysfunction was also present. Similar findings have also been reported by Vinereanu et al. (2003) and Fang et al. (2003).

The diastolic relaxation rates of circumferential, longitudinal, and principal strains, and diastolic MVP velocity were also lower in the type 2 DM patients. It is perhaps not surprising that both systolic and diastolic indices of tissue function were impaired, or that diastolic relaxation velocity and peak systolic strain were significantly related, as the processes of systole and diastole are interdependent. These results are consistent with those of Yu et al. (2002) who found that systolic and diastolic dysfunction can occur concomitantly with a range of severity in the progression to heart failure. In the present study, ANCOVA results showed that the effect due to group (i.e., diabetic or normal) was not significant when systolic function was considered as a covariate. This suggests that systolic function is an important determinant of diastolic function in these patients.

The time taken to achieve peak values of circumferential and longitudinal strains and torsion was similar in DM patients and normal subjects. While the time taken to achieve the peak rates of relaxation of circumferential strain and torsion were not different in DM and NC groups, the peak rate of relaxation of longitudinal strain was achieved earlier in the DM patients than in normal subjects.

5.4.2 Regional Function

Regional analysis of strain parameters has shown that the diabetic patients have a similar pattern of non-uniformity to normal subjects. In comparison with the normal older subjects alone, both the systolic peak value and the diastolic rate of relaxation of circumferential and longitudinal strain were either similar or reduced in many regions of the LV in the DM patients who were in fact younger, on average, than the normal older group.
This suggests that changes associated with ageing may occur at an accelerated rate in patients with type 2 DM.

5.4.3 Influence of LV Hypertrophy

LV hypertrophy and hypertension commonly coexist in patients with type 2 DM. A large proportion of the DM group, in the present study, was being treated for hypertension, and it is possible that increased blood pressure and LV mass:EDV ratio may have influenced the systolic and diastolic strains measured here. Furthermore, a significant inverse relationship was found between the LV mass:EDV ratio and each of peak systolic MVP displacement, circumferential and longitudinal shortening strain, in both patients and controls. However, LV mass:EDV was not considered as a possible covariate as it is unclear whether mass:EDV should be regarded as an independent determinant of systolic function. Fang et al. (2003) used tissue Doppler imaging to show that myocardial changes due to diabetes are similar to changes caused by LV hypertrophy, but are independent and incremental to the effects of LV hypertrophy (Fang et al., 2003).

5.4.4 MR Myocardial Parameters in relation to Echocardiographic Filling Patterns

Within the DM group, patients with pseudonormal transmitral filling pattern appeared no different to patients with an abnormal filling pattern, by MRI measures of LV function, although both systolic and diastolic impairments were observed when each group was compared separately with normal subjects. Thus, 3D MR tissue tagging identified both groups as having abnormal LV function under resting conditions, without the application of an ‘unmasking’ technique such as the Valsalva manoeuvre, which is commonly used in echocardiography (Dumesnil et al., 1991, Mandinov et al., 2000). However, these stages in the progression of diastolic dysfunction have important prognostic value (Whalley et al., 2002) and therefore methods which can show this progression are extremely useful.

The results show that the relative diastolic impairment of LV myocardial function was greater than systolic impairment in the DM group. The diagnostic and prognostic significance of this observation is unknown. It is possible that indices of diastolic function may be more sensitive to pathological change, but this does not necessarily indicate that diastolic function is impaired earlier than systolic function, as has been suggested by others.
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(Raev, 1994, Poirier et al., 2001, Schannwell et al., 2002). Therefore, the question of which measures of strain and strain rate are clinically meaningful must be addressed.

This study implies that the limited tissue strain information obtainable by tissue Doppler imaging in isolated regions of the heart extends to multidimensional strain measures averaged over the entire LV.

5.4.5 Study Limitations

It is acknowledged that the small sample size limits the statistical power of this study. The possibility of subclinical coronary artery disease in any subject or patient cannot be excluded because coronary angiography was not performed. Therefore the contribution of undetected cardiovascular disease to the impairment of myocardial function in these patients remains unknown.

The extent to which hypertension may have influenced the results for strain and relaxation in the diabetic patients (and also in the older subgroup of the control subjects) is unknown. According to the latest clinical guidelines (Chobanian et al., 2003) individuals with a blood pressure measurement lower than 120/80 mm Hg would be considered normotensive. These guidelines recommend that in diabetic patients management should be targeted towards achieving a blood pressure measurement of 130/80 mm Hg or less. In the present study, the use of ANCOVA to adjust for the influence of hypertension was deemed inappropriate due to the large number of confounding factors and the relatively small sample size.

MR tissue tagging has lower temporal resolution than tissue Doppler imaging and strain rate echocardiography. However, unlike tissue Doppler imaging, MR tagging can provide true estimates of tissue displacement, strain and strain rate in three dimensions. Faster acquisition and analysis methods may eventually allow this technique to be used routinely in clinical practice (Aletras et al., 1999).

5.4.6 Conclusion

Systolic as well as diastolic myocardial function, as measured by 3D MR tissue tagging, is impaired in patients with type 2 DM who have preserved ejection fraction. The data presented here lend support to recent studies that question the existence of diastolic dysfunction as an isolated entity, and highlight the need to take into account both tissue behaviour and LV haemodynamics when measuring LV function.
Chapter 6

Assessment of LV Function by MRI compared with Echocardiography

6.1 Introduction

The wide accessibility and ease of use of echocardiography have made it the technique of choice for the examination of cardiac function. However, as the previous chapters have shown, MRI is capable of providing data on additional parameters of myocardial function as well as on parameters that are currently measured with echocardiography (e.g., the calculation of LV mass and volume). Although MR measures of cardiac mass and volumes are already considered to be the gold standard (Katz, J. et al., 1988, Stewart et al., 1999, Young et al., 2000), parameters of myocardial mechanical function, as described in Chapters 3 to 5, are not yet employed clinically.

In this Chapter, measures of LV function that can be obtained with both echocardiography and MRI are tested for statistical agreement between the two methods. It was hypothesised that MR and echocardiographic measures of the transmitral filling velocities and the systolic and diastolic velocities of the mitral valve annulus plane would be well correlated. A further aim of the study was to test for agreement between MRI and echocardiography with respect to the values obtained for these parameters, although no attempt is made to evaluate the clinical benefit of one method over the other. Both echocardiography and MRI were employed in the preceding chapters; Chapter 6 is therefore included to highlight the differences between these imaging modalities, and to suggest improvements.
6.2 Methods

Comparisons were made between the MR and echocardiographic data used in Chapters 3 to 5, for both normal subjects and patients with type 2 diabetes mellitus (DM). The parameters that were studied were: peak early diastolic transmitral velocity (E), peak transmitral velocity due to atrial contraction (A), the E:A ratio, peak early diastolic mitral annulus velocity, the ratio of peak early transmitral inflow to peak early diastolic mitral annulus velocity, and the peak systolic mitral annulus velocity.

Data from all normal subjects (n = 31) and DM patients (n = 28) were pooled into one group (n = 59) for statistical analysis of E, A and E:A. However, TDI data on mitral valve annulus motion were not obtained in the normal subjects, and therefore comparisons between echocardiographic and MR values of peak early mitral annular velocity, the ratio of peak early transmitral inflow to early mitral annulus velocity, and peak systolic mitral annular velocity could be performed only in the type 2 DM patients (n = 28). Data are presented as mean ± SD and are compared between MRI and echocardiography using the Student’s two-tailed t test. Linear regression analyses were performed to examine the relationships between MR and echocardiographic measures of each parameter. The method proposed by Bland and Altman (1986) was used to test the agreement in values obtained between the two methods. Statistical significance was defined as P < 0.05.

6.3 Results

Echocardiographic and MR values obtained for each parameter are given in Table 6.1. Values obtained for the E velocity were similar between MRI and echocardiography (mean difference between modalities was 5.7 ± 13.6 cm/s, P = 0.072). However, MRI significantly underestimated the A velocity (mean difference of 16.9 ± 12.5 cm/s, P < 0.001). Consequently the MR value for E:A was significantly greater than that obtained with echocardiography (mean difference of -0.5 ± 0.6, P = 0.001).

The MR value of peak early diastolic mitral annular velocity was lower than the value obtained with echocardiographic TDI (mean difference of 2.0 ± 1.6 cm/s, P < 0.001), and the ratio of E to peak early diastolic mitral annular velocity was greater with MRI (mean difference of -2.7 ± 4.1, P = 0.009). MRI also underestimated the peak systolic mitral annular velocity (mean difference of 3.0 ± 1.9 cm/s, P < 0.001).
Significant correlations were observed between MR and echocardiographic measurements of E, A, E:A, and the ratio of E to peak early mitral annular velocity (see Table 6.2 and Figure 6.1).

### TABLE 6.1  Echocardiographic and MR values obtained for parameters of LV function.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>MRI</th>
<th>Echocardiography</th>
</tr>
</thead>
<tbody>
<tr>
<td>E (cm/s)</td>
<td>52.9 ± 16.3</td>
<td>58.6 ± 17.3</td>
</tr>
<tr>
<td>A (cm/s)</td>
<td>41.1 ± 15.9</td>
<td>58.7 ± 15.3</td>
</tr>
<tr>
<td>E:A</td>
<td>1.6 ± 1.0</td>
<td>1.1 ± 0.5</td>
</tr>
<tr>
<td>Peak early diastolic mitral annular velocity (cm/s)</td>
<td>4.7 ± 1.3</td>
<td>6.7 ± 1.2</td>
</tr>
<tr>
<td>Ratio of E to peak early diastolic mitral annular velocity</td>
<td>11.6 ± 4.6</td>
<td>8.9 ± 2.0</td>
</tr>
<tr>
<td>Peak systolic mitral annular velocity (cm/s)</td>
<td>4.9 ± 1.3</td>
<td>7.8 ± 1.6</td>
</tr>
</tbody>
</table>

E = early and A = late peak transmitral inflow velocities.
Values are mean ± SD.

### TABLE 6.2  Relationship between echocardiographic and MR measures of LV function.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>( r )</th>
<th>( P \text{-value} )</th>
</tr>
</thead>
<tbody>
<tr>
<td>E</td>
<td>0.675</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>A</td>
<td>0.681</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>E:A</td>
<td>0.861</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Peak early mitral annular velocity</td>
<td>0.256</td>
<td>0.251</td>
</tr>
<tr>
<td>Ratio of E to peak early mitral annular velocity</td>
<td>0.431</td>
<td>0.045</td>
</tr>
<tr>
<td>Peak systolic mitral annular velocity</td>
<td>0.209</td>
<td>0.317</td>
</tr>
</tbody>
</table>

E = early and A = late peak transmitral inflow velocities.
Results of linear regression analyses, which examined the relationship between echocardiographic and MR values, for each parameter.
\( r \) = correlation coefficient.
Comparison of echocardiographic and MRI data for early (E - top panels), and late (A - middle panels) diastolic transmitral filling velocities, and the E:A ratio (bottom panels), in all normal control subjects (NC) and patients with type 2 diabetes mellitus (DM); n = 59. The plots on the left show linear regression lines, which represent the relationship between echocardiographic and MR measurements of each parameter. The panels on the right show Bland-Altman plots of the difference in measurement between the two imaging modalities vs. the average of the two methods (horizontal broken lines indicate mean difference ± two standard deviations of the differences).

Figure 6.1 Linear regression and Bland-Altman analyses for transmitral filling velocities.
Chapter 6  Assessment of LV Function by MRI compared with Echocardiography

**Figure 6.2 Linear regression and Bland-Altman analyses for mitral valve motion.**

Echocardiographic and MRI data are compared for peak early mitral annular velocity (echocardiographic E’ and MR peak diastolic mitral valve plane (MVP) velocity – top panels), the ratio of peak early transmitral inflow to early mitral annular velocity (echocardiographic E/E’ and MR E/peak diastolic MVP velocity – middle panels), and the peak systolic mitral annular velocity (echocardiographic S_m and MR peak systolic MVP velocity – bottom panels) in patients with type 2 diabetes mellitus; n = 28. The plots on the left show linear regression lines, which represent the relationship between echocardiographic and MR measurements of each parameter. The panels on the right show Bland-Altman plots of the difference in measurement between the two imaging modalities vs. the average of the two methods (horizontal broken lines indicate mean difference ± two standard deviations of the differences).
Bland-Altman plots are shown in Figure 6.1 for E, A and E:A, and in Figure 6.2 for peak early mitral annular velocity, the ratio of peak early transmural inflow to early mitral annular velocity, and the peak systolic mitral annular velocity. While the mean bias of E was not significant, the limits of agreement were wide. Greater bias and wide limits of agreement were observed for each of the other parameters.

MR measurements could be used to identify differences due to age and diabetes. Table 6.3 shows the P-values that were obtained for echocardiography as well as for MRI when t-test comparisons were made between normal healthy older and younger people and between the entire normal group and patients with type 2 DM. Comparisons could be performed only for mitral flow parameters (i.e., E, A and E:A), but not for mitral annulus motion, because no echocardiographic TDI data were obtained in the normal subjects. Table 6.3 shows that age- and diabetes-related differences in transmural filling velocities, detected by echocardiography, could also be identified with MR phase contrast imaging: E is reduced with age but not affected by diabetes, A is increased with age as well as with diabetes, and E:A is reduced due to age as well as due to diabetes.

**TABLE 6.3 Age- and type 2 diabetes-related differences by echocardiography and MRI.**

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Normal (Y)</th>
<th>Normal (O)</th>
<th>Normal (mean)</th>
<th>DM</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Echocardiography</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>E (cm/s)</td>
<td>74.2 ± 16.6</td>
<td>46.2 ± 10.0</td>
<td>58.7 ± 19.3</td>
<td>58.6 ± 15.2</td>
</tr>
<tr>
<td>A (cm/s)</td>
<td>41.3 ± 8.1</td>
<td>57.9 ± 12.5</td>
<td>50.5 ± 13.5</td>
<td>67.8 ± 11.7 t</td>
</tr>
<tr>
<td>E:A</td>
<td>1.8 ± 0.3</td>
<td>0.8 ± 0.2</td>
<td>1.3 ± 0.6</td>
<td>0.9 ± 0.2 §</td>
</tr>
<tr>
<td><strong>MRI</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>E (cm/s)</td>
<td>68.8 ± 12.1</td>
<td>43.3 ± 14.2</td>
<td>55.7 ± 18.4</td>
<td>49.7 ± 13.2</td>
</tr>
<tr>
<td>A (cm/s)</td>
<td>24.0 ± 6.3</td>
<td>39.3 ± 11.8</td>
<td>31.9 ± 12.2</td>
<td>51.6 ± 12.9 t</td>
</tr>
<tr>
<td>E:A</td>
<td>3.0 ± 0.7</td>
<td>1.2 ± 0.5</td>
<td>2.1 ± 1.1</td>
<td>1.0 ± 0.3 t</td>
</tr>
</tbody>
</table>

E = early and A = late peak transmural inflow velocities; Y = younger and O = older normal healthy subjects; DM = patients with type 2 diabetes mellitus.

Values are mean ± SD for each group.

* P < 0.001 (normal older vs. younger subjects; t test analysis).
† P < 0.001 and § P < 0.05 (DM vs. normal; t test analysis).
6.4 Discussion

Although MR measures of diastolic filling correlated significantly with echocardiographic values, MR significantly underestimated transmitral flow in late diastole and consequently overestimated E:A. MR measurement of mitral valve plane motion also underestimated echocardiographic measurement of systolic and diastolic mitral annular velocities. Bland-Altman analysis has shown little agreement between the MR and echocardiographic measures of LV function obtained here in either type 2 DM patients or normal subjects.

The temporal resolution of MRI ranged from 30 to 50 ms for these subjects and patients (depending on their breath-hold during imaging). In contrast the temporal resolution of echocardiography is considerably greater at approximately 10 ms (and better). It is believed that this difference in temporal resolution is an important contributor to the lack of agreement between echocardiographic and MR measurements of blood and tissue velocities, observed in this study.

The method that was used to analyze the MR phase contrast images for E and A velocities may also have influenced the results. A small region of interest – 5x5 pixels, was selected for each image time-series, based on the frame showing the E-wave (see Appendix A.1 for details). Therefore, pixels with maximum intensity in the frame showing the A-wave may not necessarily have been captured in this same region of interest. This may explain why the MR results underestimated transmitral flow in late diastole, compared with echocardiographic values. Choosing a larger region of interest has given good agreement with echocardiography (Paelinck et al., 2005).

MR was able to identify differences in transmitral flow due to age, as well as due to the presence of type 2 DM, similar to the differences observed with echocardiographic measurements. In Chapter 4 it is shown that equivalent filling patterns can be obtained with echocardiographic and MR measurements of transmitral filling velocities.

MRI offers a reasonable alternative when echocardiography is not possible, as the general trend in the parameters studied here (mitral valve motion and diastolic filling velocities) is similar with the two techniques. However, the current temporal resolution of standard MRI requires considerable improvement before it can be used to obtain meaningful measures of diastolic filling and tissue velocities.
Chapter 7

Discussion and Conclusions

7.1 Overview

The primary aim of this Thesis was to develop and investigate novel parameters for the clinical assessment of LV diastolic function in a non-invasive setting. Three-dimensional Magnetic Resonance Imaging (3D MRI) with tissue tagging has proved to be an extremely valuable tool in this endeavour. MR measures of myocardial behaviour can complement traditional clinical measures of LV function and can also provide valuable information that is not obtainable by routine methods. Although the emphasis has been on the development of new parameters to quantify diastolic function, parameters of systolic function were also studied to investigate the links between systole and diastole.

The methods used in this Thesis allow the direct measurement of tissue strain over the cardiac cycle in the circumferential and longitudinal directions, as well as the measurement of LV torsion. The rate of strain development during systole, together with the peak strain achieved, quantify systolic function of the LV myocardium. The peak rate of reversal of tissue strain – i.e., the peak rate of tissue relaxation – quantifies diastolic function of the LV myocardium. Myocardial strain parameters, as described in the preceding chapters, are representative of the 3D mechanical behaviour of LV tissue and provide a direct indication of LV contractile and relaxation status.

Circumferential strain refers to myocardial dimension changes in the plane that is tangential to the LV wall and in the direction that is parallel to the LV circumference. Circumferential shortening strain is considered to make the major contribution to the systolic reduction in LV volume, and is brought about by shortening of circumferentially-oriented myofibres in the midwall, as well as by cross-fibre shortening of the almost longitudinally-oriented fibres in the endocardium due to systolic LV shape change (Waldman et al., 1988).
Cross-fibre shortening in the LV endocardium far exceeds fibre shortening in this region due to the interplay between fibre shortening, wall thickening, and LV geometry (Rademakers et al., 1994).

Longitudinal shortening of the LV myocardium also plays an important role in systolic ejection of blood from the ventricular cavity through shortening of longitudinally oriented fibres (as at the endocardium) along their fibre axis. Since myocardial tissue is considered to be incompressible, shortening of myofibres in two dimensions necessitates lengthening in the third dimension in order to preserve volume. This is manifested as radial thickening towards the central meridional axis of the LV (i.e., perpendicular to both the circumferential and longitudinal shortening directions) (Rademakers et al., 1994).

LV torsion, as described in this Thesis, refers to tissue shear in the circumferential-longitudinal direction and is brought about as a result of the transmural coupling (imparted by the connective tissue matrix) between circumferentially, longitudinally, and obliquely oriented myofibres which are, of course, shortening at the same time. During contraction, a clockwise rotation of the ventricle is observed at the base, together with an anticlockwise rotation at the apex (Maier et al., 1992). This ventricular twist can be quantified by measuring circumferential-longitudinal torsional shear. During diastole the LV untwists, resulting in release of torsional shear as the muscle relaxes. The consequent pressure decline creates suction and rapid early filling (Rademakers et al., 1992).

The principal shortening strain refers to strain measured in the direction of maximal shortening within the tissue. In the LV it is found that the direction of global maximal shortening corresponds to the local myofibre direction of the epicardial surface. Given the transmural variation in fibre orientation, the direction of maximal shortening in the sub-endocardium is nearly perpendicular to the local myofibre direction in this region (Waldman et al., 1988). The principal strain is influenced by strain in the circumferential and longitudinal directions as well as by torsional shear.

The MR measures of strain that are described in this Thesis therefore reflect the combined effect of local fibre and cross-fibre strains, which result in: (i) myocardial deformation in the circumferential direction of the LV, (ii) deformation in the direction of the LV long-axis (longitudinal strain), (iii) torsional shear in the circumferential-longitudinal plane, and (iv) deformation in the direction associated with maximum shortening (principal strain).

The motion of the mitral valve annulus, which is readily measured by echocardiography, has been proposed as an index of LV myocardial tissue function (both
systolic and diastolic) (Lindstrom and Wranne, 1999, Sohn et al., 2001). Mitral valve annular motion is influenced by tissue strain, most directly the longitudinal strain. Therefore the systolic descent, and diastolic ascent, of the mitral valve annulus plane (MVP) was examined in this Thesis, using untagged cine MR images. Peak systolic MVP displacement and peak systolic and diastolic MVP velocities were quantified in a similar fashion to the strain and strain-rate measures.

The differences due to age and disease in MR parameters of global LV myocardial function are summarised in Figures 7.1 to 7.4, for easy visualization. The data points on these graphs represent global, averaged values of strain (and displacement, with respect to the MVP) throughout the imaged portion of the cardiac cycle and are indexed to the end-systolic (ES) time (e.g., 200%ES signifies twice the time to end-systole).

These MR parameters successfully identified and quantified diastolic myocardial impairment in normal healthy older people who were compared with normal younger subjects. It is well documented that diastolic function is depressed with age, and the findings of this Thesis concur with reported impairments including echocardiographic E:A reversal (Spirito and Maron, 1988, Cacciapuoti et al., 1992, Mandinov et al., 2000) and reduced mitral annular velocities (Owen, A., 1999, Yamada et al., 1999, Sun et al., 2004), mild concentric hypertrophy (Gerstenblith et al., 1977), and elevated blood pressure in older people (Kitzman, 2002). LV ejection fraction, a widely used clinical index of systolic function, was found to be preserved with age, and MR measures of tissue shortening strain were also similar in older and younger individuals. However, LV torsion was increased with age while the peak systolic displacement and velocity of the MVP were reduced. This was unexpected, as systolic function is reported to be generally uninfluenced by normal ageing. These subtle changes in myocardial deformation may be the earliest features of a developing systolic dysfunction.

The parameters were also employed to examine myocardial differences between patients with type 2 diabetes mellitus (DM) and normal healthy people. The DM patients were known, by echocardiography, to have diastolic dysfunction, and their mean ejection fraction was comparable with that of the normal subjects. DM-related impairment in myocardial relaxation could be quantified by measuring the rates of tissue relaxation with MR tagging. Normal ejection fraction in the diabetic patients implies that the disease did not affect systolic function. However, not only was peak systolic displacement of the MVP reduced, as has been reported in recent studies (Andersen et al., 2003, Fang et al., 2003, Vinereanu et al., 2003), but peak systolic tissue shortening strain in all directions was also
markedly impaired in the DM group. These findings have important implications, as they contradict the clinical indication of normal LV systolic function in these patients. The reliability of the LV ejection fraction as a measure of systolic function in asymptomatic patients seems questionable. MR parameters of diastolic function were similar in DM patients and the older normal subjects although the two groups were separated by an age-gap of about two decades. In addition, MR parameters of systolic function were reduced in the DM patients compared with the older normal group alone.

Circumferential, longitudinal and principal strains do not show significant systolic differences between older and younger normal people, but the DM group have markedly reduced peak strain values compared with NC. In diastole, the rates of relaxation of circumferential, longitudinal, and principal strain are reduced with age as well as with disease. In addition, an interesting feature of Figures 7.1 (circumferential strain), 7.2 A (longitudinal strain) and 7.4 (principal strain) is that the curves for the older normal people and the diabetic patients reach a plateau in mid-diastole after an initial rapid rate of relaxation. Furthermore, this plateau appears at a greater level of shortening strain for the older normal and the DM groups than the younger normal subjects; a phenomenon that is also visible for torsion (Figure 7.3). This means that a greater degree of strain and torsion persists in mid to late diastole, in the older normal people and the DM patients, because the rate and consequently, the extent, of strain recovery are reduced. In order for the LV, in these individuals, to return to the end-diastolic state, a greater component of strain recovery would have to occur in the late phase of diastole. Atrial contraction must therefore make a substantially greater contribution to end-diastolic filling in these groups than in normal younger people. This has important implications for the assessment of LV diastolic function, since the rate and extent of LV myocardial strain relaxation at a given time in mid-diastole (e.g., 200%ES) can indicate the extent of atrial contribution to end-diastolic LV filling.

Regional analysis of LV function showed non-uniformity of tissue strain and strain relaxation in all subjects and patients. This supports earlier studies (Brutsaert, 1987, Bogaert and Rademakers, 2001, Kuijer et al., 2002), which have shown that significant regional differences in systolic shortening are a feature of the normal LV. This Thesis also shows that age-related impairment in myocardial relaxation occurs in a non-uniform manner. The fact that regional function is non-uniform along the length of the LV as well as around its circumference is especially important in light of echocardiographic TDI where diastolic mitral annular velocities are considered to be indicative of (global) tissue relaxation. In Chapter 3 it is shown that longitudinal strain relaxation is reduced with age to a greater degree in the apex.
than in the base, and in older people longitudinal strain relaxation along the septum is lower than along the lateral wall. All diastolic parameters were sensitive to differences in relaxation rate between different LV regions, and to the inhomogeneous change in this pattern with age. Regional asynchrony in time to peak circumferential and longitudinal diastolic strain rates is increased in older people, possibly further hindering relaxation and filling. Although DM caused impairment in tissue strain and strain relaxation in most LV regions, the pattern of regional non-uniformity generally did not differ significantly between patients and normal subjects.

Finally, the MR parameters developed were compared with currently used echocardiographic measures of function. Correlations were observed between MR and echocardiographic measurements of transmtral filling and mitral annular velocities, but the limits of agreement between the two methods were wide. MR measures of these parameters could be used to identify differences between older and younger normal subjects and between diabetic patients and the normal subjects; however, absolute values for blood flow and tissue velocities measured with this technique would be meaningful only when the temporal resolution is improved.

In addition to the realization of the goals set out for this Thesis, the characterization of functional changes in both global and regional LV myocardial function aid the understanding of the processes of ageing and disease that either directly or indirectly result in these changes. The major findings of the studies described in the preceding chapters and their implications are discussed in detail below.
Figure 7.1 Temporal evolution of peak global circumferential shortening strain.

The peak systolic strain rate did not differ between young and old normal control (NC) subjects, but was lower in patients with type 2 diabetes mellitus (DM). Peak value for shortening strain was lower in older, compared with younger normal people, although not significantly. In DM patients this reduction (in relation to all the normal subjects) was significant, even on correction for age. Peak diastolic rate of relaxation of circumferential strain was significantly reduced in normal older people compared with normal younger subjects, and also in DM patients (on correction for age) compared with all of the normal subjects. The DM patients showed similar diastolic strain rate to the older normal subjects.

Time is indexed to the end-systolic time. Therefore, 100%ES represents the total time from end-diastole to end-systole.
Figure 7.2 Temporal evolution of peak global longitudinal shortening strain and mitral valve annulus plane motion.

A: The peak systolic longitudinal strain rate was significantly lower in older compared with younger normal control (NC) subjects, and in patients with type 2 diabetes mellitus (DM) compared with the entire NC group. Peak value for shortening strain in the normal subjects was not significantly influenced by age, but was reduced in DM patients (on correction for age) compared with the entire NC group. Peak diastolic rate of relaxation of longitudinal strain was significantly reduced in older compared with younger NC subjects, and also in DM patients (on correction for age) compared with all of the NC group. The DM patients showed similar diastolic strain rate to the older normal subjects.

B: Mitral valve annulus plane (MVP) motion was impaired by both age and diabetes, and DM patients followed a similar trend to the older normal subjects. Both peak MVP displacement and peak diastolic MVP velocity were reduced in older compared with younger NC, and in DM (on correction for age), compared with all NC.
Figure 7.3 Temporal evolution of peak global torsional shear strain.

The temporal pattern of torsion was altered with both age and diabetes. Increased peak torsion was observed in older compared with younger normal control (NC) subjects, and also in patients with type 2 diabetes mellitus (DM) corrected for age and compared with the entire NC group. Neither age nor diabetes appeared to influence the peak diastolic rate of reversal of torsion. However, it can be seen here that the extent of torsion reversal during diastole was reduced in older compared with younger NC subjects, and in DM patients compared with normal.
Figure 7.4 Temporal evolution of peak global principal shortening strain.
The peak systolic strain rate did not differ between young and old normal control (NC) subjects, but a reduction (albeit non-significant) was observed in patients with type 2 diabetes mellitus (DM). The peak principal shortening strain achieved was not influenced by age in the NC subjects, but was significantly lower in DM patients compared with the entire NC group, on correction for age. Peak diastolic rate of relaxation of principal strain was significantly reduced in normal older people compared with normal younger subjects, and also in DM patients (on correction for age) compared with normal values. The DM patients showed similar diastolic strain rate to the older normal subjects.
7.2 Systolic Function Parameters

Current clinical assessment of systolic function is based predominantly on the measurement of LV ejection fraction (EF) with echocardiography. Clinical trials often use a cut-off value to define reduced EF but this varies greatly among studies (Vasan et al., 1995) and also among guidelines for diagnosis and therapy (European Study Group on Diastolic Heart Failure, 1998, Chavey et al., 2001, Zile and Brutsaert, 2002a). It has been shown recently that EF may be maintained in the presence of subclinical changes in systolic myocardial behaviour (Petrie et al., 2002, Tongue et al., 2003, Mottram et al., 2004). Thus, although systolic performance may be normal, subtle systolic abnormalities may exist. EF reflects global LV performance and cannot be used to identify regional abnormalities in tissue function. Furthermore, EF is also influenced by LV geometry, in that reduced shortening in the presence of LV hypertrophy may actually result in normal EF (Young et al., 1994).

The peak value of circumferential, longitudinal, torsional shear, and principal shortening strains and the peak displacement of the mitral valve annulus plane are presented in this Thesis as parameters of LV systolic function. The peak systolic strain rates and mitral valve plane velocity are also considered. Measurements of tissue strain and strain rate were obtained from the analysis of tagged MR images, and the motion of the mitral valve annulus plane was examined in the anatomical MR images.

7.2.1 Circumferential Function

Peak global systolic values of circumferential shortening strain \(S_C\) and strain rate \(SSR_C\) were not influenced by age; this is in keeping with previous reports of preserved systolic function in older people (Gerstenblith et al., 1977, Fioranelli et al., 2001, Spencer et al., 2003). In patients with type 2 DM, however, \(S_C\) and \(SSR_C\) were significantly lower in patients than in normal subjects, after correction for age. This finding was unexpected as the patients had a mean EF that was comparable to that of the normal subjects - 70%, on average, which traditionally implies normal systolic function. Furthermore, peak systolic circumferential shortening was reduced in the DM group in comparison with normal older people alone, and peak global value of \(SSR_C\) observed in DM was similar to that in the older normal group. Thus, systolic function was impaired in the DM patients more than any possible effect due to normal ageing. These findings are displayed in Figure 7.1.
As reported by others (Bogaert and Rademakers, 2001, Kuijer et al., 2002), $S_C$ was non-uniform over LV regions in the normal subjects, reaching a greater value in the apex than in the base, for example. An age-related decrease in this parameter was found only in the apical region. Thus, regional function parameters may be more sensitive to impairment than global measures. The pattern of regional non-uniformity in $S_C$ was similar in DM and normal subjects. Corrected for age, $S_C$ was reduced in the DM patients in all regions with respect to normal values (except for the lateral wall). These regional impairments are reflected in the reduction of global $S_C$ in the DM patients.

The global value for time to $S_C$ does not appear to be influenced by age or by type 2 DM. A regional analysis of this parameter showed that not only is $S_C$ achieved at different times in different LV regions in normal individuals, but this regional asynchrony also increases with age.

A decrease in circumferential shortening in the presence of normal EF has been observed before, in studies of patients with hypertension (Shimizu et al., 1991), and also in patients with hypertensive LV hypertrophy (Palmon et al., 1994). LV hypertrophy results in marked changes in wall and chamber geometry and it has been suggested that this is the mechanism by which ejection fraction may be preserved in the presence of depressed myocardial shortening – an increase in the ratio of LV end-diastolic wall thickness to cavity volume implies that the thicker-walled LV would have to undergo less systolic thickening in order to achieve the same end-systolic cavity volume (Palmon et al., 1994). Indeed, LV hypertrophy was a common feature in the DM group studied here.

### 7.2.2 Longitudinal Function

Two parameters of longitudinal function were considered – longitudinal tissue shortening strain and the motion of the mitral valve annulus plane.

Global longitudinal tissue shortening strain ($S_L$) is summarised in Figure 7.2 A. Of the shortening strain parameters studied, only global LV longitudinal strain rate ($SSR_L$) was reduced in older people. As with the reduction in circumferential tissue shortening, the finding of reduced $S_L$ and $SSR_L$ in the DM patients was unexpected in light of their preserved LV ejection fraction.

$S_L$ is greater in the apex than in the base in the normal younger subjects, but is not different between these regions in the normal older group due to an age-related decrease only in the apex. A reduction in $S_L$ also occurred in the septum in the older normal group; it is
unknown whether or not right-ventricular interaction could have played a role in septal impairment. On correction for age, $S_L$ was reduced in the DM patients not only in the apex but also in all regions along the length and around the circumference of the LV in comparison with the normal group, providing further evidence of impaired systolic function in these patients.

The time taken to achieve $S_L$ (globally) was prolonged with age in normal healthy people. This may be explained by the lower SSR$_L$ in the older normal group. Furthermore, regional asynchrony in time to $S_L$ is also greater in older than in younger normal people. These findings reflect the development of subtle systolic impairments in normal healthy older people, although $S_L$, on a global basis, does not differ significantly to that in younger normal subjects. In contrast to the data presented here, previous studies have reported that the peak LV ejection rate and the time to end-systole, at rest, do not change with age (Kitzman et al., 1991, Fioranelli et al., 2001). Earlier work in animals, however, has shown that the duration of contraction may increase with age (Lakatta et al., 1975, Templeton et al., 1979).

Diabetes did not alter the time taken to achieve $S_L$ although patients had lower SSR$_L$ than normal, since the value of $S_L$ that could be achieved in the DM group was reduced.

Recently, TDI studies have shown that LV longitudinal function during systole may be impaired even when EF is normal (Petrie et al., 2002, Yip, G. et al., 2002a). As described in Chapter 4, older people were found to have a significant reduction in the peak systolic displacement and velocity of the mitral valve plane (MVP), in the presence of a normal ejection fraction (Figure 7.2 B). In type 2 DM, peak systolic MVP displacement was reduced in comparison with normal individuals, in support of recent studies (Andersen et al., 2003, Fang et al., 2003, Vinereanu et al., 2003). Values obtained for peak systolic MVP displacement in DM patients were similar to those observed in normal older subjects.

It is interesting that global peak systolic longitudinal shortening strain does not appear to be influenced by age, while peak systolic mitral valve plane displacement is impaired in older people. Recently Rodriguez et al. (2004) showed, using implanted radiopaque markers in sheep, that mitral annular descent (which does not take into account apical motion) is a better predictor of LV systolic function than long-axis shortening (which does include an apical component), by ROC analysis. Their study and ours suggest that MVP motion may be a more sensitive indicator of global LV systolic function than averaged strain.

The regional analysis described in Chapter 3 has shown that both circumferential and longitudinal strains are reduced in the older subjects, in the apex, but not in the mid-ventricular and basal regions. This has a number of implications. First, the decrease in apical
shortening strain may be the primary cause of the decrease in MVP motion. Second, MVP motion, which is considered to be indicative of global LV myocardial function, is sensitive to changes in regional function. Third, regional longitudinal tissue strain may be a more specific measure of tissue function than globally averaged values.

Longitudinal tissue strain and MVP motion are distinctly different parameters. Longitudinal tissue strain, which represents tissue mechanical/contractile function at the global as well as regional level, appears to influence MVP motion, which represents tissue displacement at the base of the LV. An important factor to consider, and especially so in valvular heart disease, is the structural and functional status of the mitral valve itself in order to determine whether the changes observed in LV longitudinal function are due in part to a mitral valve abnormality (e.g., stiffer annulus due to calcification), or whether impaired LV myocardial contractility is the major underlying cause. Measurement of local tissue strain with 3D MR tissue tagging can play an important role here.

7.2.3 Torsion

Although peak global systolic values of circumferential and longitudinal shortening strain were not influenced by age, peak torsional shear strain (ST) was significantly greater in normal older people. An increase in ST was also observed in the DM patients compared with normal values. Figure 7.3 summarises the findings for global torsion.

ST and SSR_T differ between LV regions in both old and young people, but the patterns of non-uniformity observed in each systolic parameter do not appear to change with age. The patterns of regional non-uniformity in ST and SSR_T are also not different between DM and normal people. When examined on a regional basis, values for ST and SSR_T were similar in DM patients and older normal people in all LV regions.

Time to ST (globally) was greater in older than in younger normal subjects, although no age-related differences were observed when individual regions were examined. As with the prolonged time to SL, this finding was unexpected because it is well known that no significant age-related changes in systolic function occur in normal healthy older people (Schulman, 1999). Studies of rat myocardium have shown age-related prolongation of the action potential duration (Capasso et al., 1983) and reduction in the rate of calcium uptake by the sarcoplasmic reticulum, which may result in prolonged contraction; however, this has not been reported in humans.
Compared with normal subjects, diabetes did not significantly alter the time taken to achieve $S_T$ (globally), but regional analysis showed that in DM patients, $S_T$ was achieved earlier than in normal control subjects in almost all regions.

LV torsion ensures homogeneous systolic shortening of myofibres across the wall (Arts et al., 1984, Ingels et al., 1989, MacGowan et al., 1997). This allows for energy-efficient generation of high-intracavitary pressure with minimal shortening of myofibres, facilitating LV ejection. If the transmural homogeneity in myofibre shortening is perturbed – for example, due to impaired subendocardial function, as occurs in aortic stenosis – then it is possible that torsion would increase (Stuber et al., 1999, Nagel et al., 2000, Van Der Toorn et al., 2002). Recently, Van Der Toorn et al. (2002) studied the relationship between torsional shear and circumferential shortening strain. They showed increased transmural differences in epicardial and endocardial fibre shortening, in association with increased ratio of torsion to shortening (of the LV short-axis), in patients with severe aortic stenosis. These findings were attributed to impairment of endocardial contractile function.

Increased torsion is also associated with other forms of LV concentric hypertrophy, including hypertrophic cardiomyopathy (Young et al., 1994). Stuber et al. (1999) showed that peak torsion increased in patients with aortic stenosis who had pressure overload hypertrophy, characterized by an increased ratio of wall thickness to chamber radius. They suggested that changes in LV geometry and myofibre orientation would increase transmural inhomogeneities in systolic shortening thereby leading to an increase in LV torsion. Therefore, an increase in the ratio of LV mass to end-diastolic volume could well explain, in part, the finding of increased peak systolic torsion in the normal older subjects and the diabetic patients studied in this Thesis.

Studies of the influence of preload and afterload on torsion provide conflicting information. Hansen et al. (1988) found that torsion did not change with volume-loading, but MacGowan et al. (1996) observed a decrease in torsion when afterload was increased. Dong et al. (1999) found that greater torsion was associated with an increase in end-diastolic volume, due to increased preload (at a constant afterload), while increased afterload independently decreased torsion. Furthermore they found that inotropic stimulation led to an increase in torsion, independent of changes in volume. In the subject and patient groups considered in this Thesis, the only difference in volume observed between groups was a lower end-diastolic volume in the older normal subjects compared with the younger normal group. It is therefore interesting that these older subjects showed an increase in peak torsion, a
finding also observed in the diabetic patients who had comparable end-diastolic volume and end-systolic volume (indicative of afterload) to normal values.

### 7.2.4 Principal Shortening Strain

Principal shortening strain was not influenced by age; however, significant differences were found in the DM patients (Figure 7.4). Peak $S_P$ was reduced in DM patients compared with normal subjects, but not to the same extent as $S_C$ and $S_L$, possibly due to the increased $S_T$ observed in the patients. SSR$_P$ in DM patients was not significantly different to normal values, however.

Of the MR systolic function parameters studied here, the principal shortening strain shows the least difference between older and younger normal groups. In fact, the systolic strain evolution of these groups neatly overlaps, as can be seen in Figure 7.4. In contrast, small non-significant decreases were observed in peak circumferential and longitudinal shortening strains in the older normal subjects (Figure 7.1 and 7.2 A), and the peak systolic longitudinal strain rate was significantly reduced in the older compared with the younger normal group. Meanwhile, both LV torsion and MVP displacement identified differences between the old and young normal group. These differences are not reflected in the principal shortening strain in the normal subjects. In the DM group however, impairments in systolic function are more marked and affect all the MR parameters studied. Consequently, impaired function could be identified in the DM group by the reduction in peak principal shortening strain.

The principal shortening strain is therefore a useful single measure of myocardial function and indicates overall performance. Detailed information, however, can be obtained only by examining the individual components characterizing 3D myocardial deformation, i.e., axial circumferential and longitudinal tissue strains and torsional shear. The results of this Thesis show, for example, that parameters of LV longitudinal function are more sensitive to impairment than principal strain. However, principal shortening strain is also strongly influenced by changes in torsion. Increased torsion in the presence of decreased circumferential and longitudinal strains possibly leads to some normalization of the principal shortening strain.

In a study of patients with hypertrophic cardiomyopathy, Young et al. (1994) showed that the magnitude of the principal shortening strain was preserved in patients, although circumferential and longitudinal strains were reduced. Furthermore an increase in
torsion was observed in the patients. It was suggested that “more of the mechanical work is contributing to wall shearing and not cavity volume reduction” in these patients. Thus, a change in the mode of deformation had occurred.

### 7.3 Novel Parameters of Diastolic Function

The hallmarks of diastolic dysfunction are impaired filling, elevated LV pressures and abnormal relaxation. These processes are interrelated – for example, myocardial relaxation abnormalities may impede the rate of LV pressure decay and consequently diminish rapid early diastolic filling. In addition, increased LV pressure may itself modify relaxation properties. One obvious, albeit non-specific, symptom of diastolic dysfunction is shortness of breath on exertion, suggestive of raised filling pressure, without LV dilation on chest x-ray. Not surprisingly, the development of methods for quantifying LV filling pressures as well as myocardial relaxation is the focus of much study in the area of diastolic dysfunction. Currently used clinical measurements include: the rate of LV pressure decline (-dP/dt) during isovolumetric relaxation, the duration of the isovolumetric relaxation period, peak filling velocity, echocardiographic transmitral flow and mitral annular velocities, pulmonary capillary wedge pressure, and myocardial stiffness (which is reported to be inversely related to Doppler early filling deceleration time (Little et al., 1995, Marino et al., 2002)).

LV filling properties are readily quantified with Doppler echocardiography (Appleton et al., 1988). Preload-dependent echocardiographic transmitral filling velocities are influenced by a number of confounding factors, including rate and extent of LV relaxation, atrial and ventricular compliance, and LV suction. Therefore E:A cannot give a true indication of LV myocardial tissue relaxation in the presence of increased filling pressures and its usefulness in determining LV diastolic function is limited. Tissue Doppler imaging is used to measure the early diastolic mitral annular velocity, E’, which has relatively less preload-dependence than blood flow (Sohn et al., 1997) and is considered to be a useful echocardiographic index of LV tissue relaxation. However, mitral annular velocity reflects tissue relaxation in the LV long-axis dimension only, without taking into account the combined effects of translational and rotational myocardial motion. With regard to LV pressure, -dP/dt can be measured directly where catheterisation is indicated. As this procedure is invasive and cannot be performed in all patients, methods of estimating LV
pressure with echocardiography, such as $E/E'$, have been proposed (Nagueh et al., 1997, Ommen et al., 2000). Direct measurement of the material properties of myocardium is not available clinically, at present.

In this Thesis the rates of relaxation of myocardial tissue shortening strains are proposed as parameters of diastolic function. The peak diastolic velocities of circumferential, longitudinal, torsional shear, and principal shortening strains were obtained from the analysis of tagged MR images, and the diastolic velocity of the mitral valve annulus plane was measured from the anatomical MR images.

7.3.1 Circumferential Relaxation

In Chapters 3 and 4 it is shown that global peak rate of relaxation of circumferential shortening strain ($R_C$) was markedly reduced in older people, free from cardiovascular disease, compared with younger individuals. Diastolic dysfunction is known to be prevalent in the elderly (Tokushima et al., 2001); decreases in echocardiographic $E:A$ ratio, prolonged isovolumetric relaxation time, and increased time to peak filling rates have been recorded in older people in studies of ageing (Mantero et al., 1995, Tokushima et al., 2001). However, the rate of relaxation of tissue strain gives a direct measure of LV myocardial impairment in these older people. In a study of senescent mouse hearts, decreased lusitropy was shown to correlate with decreased uptake of calcium by the sarcoplasmic reticulum (Lim et al., 1999), although contractile function was preserved. Furthermore, an increase in collagen and decrease in elastin content of the extracellular connective tissue matrix is a feature of the ageing myocardium and leads to fibrosis and decreased diastolic distensibility, independent of disease (Lakatta, 1993, Burgess et al., 2001).

Patients with Type 2 DM also showed reduced global $R_C$ compared with normal healthy people. Furthermore, global $R_C$ was similar in older normal subjects and patients with DM (see Figure 7.1). The decrease in global $R_C$ in the DM patients correlated with the reduced peak systolic circumferential shortening strain observed in this group, and it appears that this systolic impairment may be a major underlying cause of the reduced diastolic circumferential function. Increased myocardial collagen (specifically, types I and III, which are the most abundant myocardial types) is also a feature of the diabetic heart (Liu, J. et al., 2003a). In addition, the accumulation of advanced glycation end products plays an important role by modifying collagen structure and adversely affecting its interaction with myocytes and
other matrix proteins, thereby impairing cardiac function (Liu, J. et al., 2003a). The increase in collagen also contributes to the LV hypertrophy commonly observed in these patients.

Localized measurements of $R_c$ show significant differences in this parameter over LV regions in normal subjects and a change in the pattern of non-uniformity with age. A greater $R_c$ was observed in the apex than in the base in normal young people but not in older normal healthy people; this difference was also observed in peak systolic strain. In the DM patients, regional analysis showed that $R_c$ was reduced in all regions, compared with normal, on correction for age. $R_c$, compared with the normal older group on a regional basis, was reduced only in the posterior and anterior walls in the DM patients.

The time to achieve global $R_c$ was increased with age but was not influenced by DM. Regional analysis also showed an age-related prolongation in almost all regions. However in DM patients most regions achieved $R_c$ earlier than normal. Regional asynchrony in time to $R_c$ also increased with age.

There is little information available regarding diastolic tissue behaviour in the circumferential direction, specifically. Measurement of circumferential strain and strain relaxation is relatively difficult with echocardiography due to the requirement for suitable acoustic windows. Therefore this component of myocardial deformation is not assessed clinically at present.

7.3.2 Longitudinal Relaxation

The peak global rate of relaxation of longitudinal tissue shortening strain ($R_L$) is lower in normal older people than in normal young people, unlike peak longitudinal shortening which was not significantly different between these groups. In the DM patients, peak global $R_L$ was lower than normal, on correction for age, as was $S_L$. Furthermore, $R_L$ in the DM group was similar to that observed in the older normal group alone (Figure 7.2 A). As with circumferential relaxation, the impairments observed in longitudinal diastolic function are most likely related to the decrease in myocardial compliance due to changes in extracellular matrix composition.

The pattern of regional non-uniformity in $R_L$ was influenced by age. In the older people, $R_L$ was reduced in the apex to a greater extent than in other regions, for example. On correction for age, $R_L$ was reduced in the DM patients in all regions, in comparison with the normal group. For each region, $R_L$ values obtained in DM were similar to those in the normal older subjects.
Chapter 7
Discussion and Conclusions

Peak diastolic MVP velocity is reduced with age, as well as with DM (on correction for age). When compared with the older normal subjects alone, the DM patients showed comparable values for peak diastolic MVP velocity.

In the DM patients, it is likely that the reductions in both global $R_L$ and peak diastolic MVP velocity may be due, at least in part, to the impairment observed in systolic peak longitudinal shortening and peak MVP displacement.

The time to achieve global $R_L$ was prolonged with age but was reduced in DM patients. Regional analysis showed no difference between normal old and young subjects in any individual region. However in DM patients almost all regions achieved $R_L$ earlier than normal. The regional asynchrony in time to $R_L$ was found to be greater in older than in younger normal people.

Parameters of longitudinal function appear to be extremely sensitive to impairment in that they revealed both systolic and diastolic abnormalities in the older normal subjects. This sensitivity may be due to the predominantly subendocardial location of longitudinally oriented myocardial fibres (Henein, M., 1999, Pennisi et al., 2002), which may be more susceptible to the changes caused by age and disease. Animal studies have shown an association between ageing and decreased maximal subendocardial perfusion relative to the subepicardium (Hachamovitch et al., 1989, Tomanek et al., 1993). Furthermore, a reduction in the endo/epicardial perfusion gradient has also been reported in disease conditions (Choudhury et al., 1999, Muehling et al., 2003, Muehling et al., 2004).

7.3.3 Relaxation of Torsional Shear Strain

Several studies have described alterations in cardiac torsion and diastolic relaxation in pathologically hypertrophied hearts (Hansen et al., 1987, Maier et al., 1992, Stuber et al., 1999, Nagel et al., 2000). Earlier, Rademakers et al. (1992) had demonstrated a distinct separation between untwisting and filling in the healthy heart. In a study of aortic stenosis, by Stuber et al. (1999), a significant increase in apical peak rotation was observed in aortic stenosis patients with LV hypertrophy compared with control subjects. It was expected that the velocity of untwisting would be greater than normal in order to compensate for the increased systolic torsion, or that there would at least be a prolongation of the untwisting time. Indeed, a tendency toward an increased untwisting velocity, as well as a significant prolongation of untwisting duration into the filling phase of the LV was observed in these patients. This delayed relaxation may well impede normal filling and is most probably
responsible for the occurrence of diastolic dysfunction (characterised by an echocardiographic E:A pattern which deviates from the normal) in patients with LV hypertrophy. In addition, that study investigated the effects of physiological LV hypertrophy on diastolic function. It was demonstrated that in the hearts of athletes, where the ratio of LV wall thickness to cavity volume was maintained, torsion and untwisting remained unchanged compared with the control subjects. Patients with aortic stenosis, on the other hand, showed signs of concentric hypertrophy and clearly showed diastolic dysfunction (Stuber et al., 1999). In another study, Nagel et al. (2000) used MR tagging to show that during systole, basal (clockwise) rotation is reduced but apical (counter-clockwise) rotation is increased in patients with aortic stenosis resulting in an enhanced torsion of the LV. However, in these patients diastolic untwisting occurred with reduced velocity and was delayed and prolonged, resulting in the overlap of relaxation and early diastolic filling. This is, perhaps, also the case for the older normal subjects and the DM patients studied in this Thesis who had increased peak systolic torsion, while global peak torsion reversal rate ($R_T$) remained similar with age and in type 2 DM. Thus, the increase in $S_T$ is not offset by a corresponding increase in $R_T$, and this leads to greater torsion persisting in late diastole in the older normal people and in the DM patients (Figure 7.3).

Normal $R_T$ is greater in the base than in the apex in both young and old subjects. Examined on a regional basis, $R_T$ was lower only in the base in normal older subjects compared with the normal younger group. In DM patients, regional analysis showed that $R_T$ was reduced only in the base, compared with normal, on correction for age. Furthermore, when compared with the normal older group alone, DM patients showed similar values for $R_T$ in every LV region.

The time to achieve global $R_T$ was prolonged with age but not influenced by DM. Regional analysis also showed no difference between normal old and young subjects in any individual region. However, in DM patients almost all regions achieved $R_T$ earlier than normal.

The rate of relaxation of torsion reaches it peak earlier than the circumferential and longitudinal strain relaxation rates in the normal subjects as well as in DM patients, in support of the theory that the major portion of untwisting occurs before filling and LV expansion begins (Rademakers et al., 1992). A recent MR tagging study in normal human subjects has shown that reversal of LV shear strains (including circumferential-longitudinal shear) actually begins in late systole, just before the aortic valve closes, and is then followed closely by radial thinning, whereas the onset of circumferential and longitudinal axial strain
occurs nearer the time of onset of the increase in ventricular volume (Rosen et al., 2004). These investigators therefore propose that it is the restoring forces associated with shear and torsion that induce rapid LV pressure decline, facilitating early diastolic filling.

### 7.3.4 Relaxation of Principal Shortening Strain

Despite the increased torsion and similar peak systolic principal shortening strain in older compared with younger normal people the peak rate of relaxation of principal shortening strain is reduced with age. However, both $S_p$ and $R_p$ were reduced in DM patients. This reduction in principal strain relaxation rate reflects the combined effect of reduced rates of relaxation of the circumferential and longitudinal strains in both older normal people and in DM patients, without any change in the rate of recovery of torsion. Figure 7.4 shows a distinct separation between the older normal and DM groups, and the younger normal subjects, during diastole. It appears that less recovery of principal shortening strain has occurred in the older normal and DM groups than in younger individuals, by equivalent phases of the cardiac cycle in mid to late diastole. This reflects the greater contribution of atrial contraction to LV filling in late diastole, in individuals with diastolic dysfunction.

### 7.4 Interdependence of Systolic and Diastolic parameters

In both normal healthy subjects and in DM patients, significant relationships were found between systolic and diastolic function, with respect to almost all of the MR parameters that were studied. An interesting question is whether the age- and disease-related impairments in systolic and diastolic function occur independently. In Chapter 4 it is shown that although the peak diastolic MVP velocity correlates significantly with the peak systolic MVP displacement, to some extent ageing influences each parameter independently (impaired systolic function alone does not explain differences in diastolic relaxation between the age-groups). In Chapter 5, however, the impairments in peak diastolic MVP velocity, $R_C$, $R_L$, and $R_T$ in the DM patients appears to be explained by the impairment in peak systolic MVP displacement, $S_C$, $S_L$, and $S_T$, respectively. This deserves further study because some P-values (for the influence of diabetes) approached significance (Table 5.5), and the effect of disease on principal strain relaxation rate was still present after correction for systolic shortening values.
Increased systolic torsion does not seem to be compensated for, by relaxation velocity in diastole (which is unchanged between younger and older healthy individuals, and between healthy individuals and DM patients). Therefore, in older people and in patients with type 2 DM the LV must remain in a greater state of twist for a longer period of time during diastole, than in younger healthy individuals. As a result of this impaired relaxation, the rate of LV pressure decay during early diastole may be reduced, creating a greater resistance to filling.

Diastolic impairment may not necessarily occur earlier than systolic dysfunction, in the progression to heart failure, for example. Diastole and systole are two phases of a continuously cycling process; therefore, a functional abnormality in one invariably affects the other. However, the relative size of the reduction in peak rates of strain relaxation appears larger than the decreases observed in systolic strain and strain rates, thus making diastolic indices more sensitive to disease processes or to normal ageing.

7.5 LV Haemodynamics: MR Measures of Mass and Volumes

LV mass, EDV, ESV and SV were calculated through analysis of MR cine anatomical images in all subjects. MR measures of mass and volumes are known to have superior precision and accuracy to other non-invasive methods (Stewart et al., 1999, Young et al., 2000, Darasz et al., 2002).

The ratio of LV mass to end-diastolic volume (LV mass:EDV) is useful for detecting LV hypertrophy, and is greater in older healthy subjects than younger ones, and greater in DM patients versus normal healthy individuals. In the normal healthy subjects, LV mass:EDV correlated significantly with diastolic strain relaxation parameters; however, ANCOVA (detailed in Chapter 3) showed that the influence of concentric hypertrophy cannot be held solely accountable for these impairments. In the DM patients, however, no relationship was found between diastolic rates of relaxation and the LV mass:EDV, although the latter was found to be related to systolic shortening strains. An ANCOVA was not performed here due to the presence of a variety of confounding factors including age and increased heart rate, and the presence of hypertension and obesity in many of the patients. Therefore it may not be appropriate to test the effects of increased LV mass:EDV as an independent determinant of function.
7.6 Comparison of MR and Echocardiographic Measures of Function

MRI can offer a more comprehensive assessment of systolic function than is currently available with other techniques as it provides information on local as well as global tissue strain, in addition to measurements of mass and volumes. The analyses performed in Chapter 6 show that there are strong relationships between echocardiographic and MR measurements of LV diastolic filling velocities. For systolic and early diastolic mitral annular velocities, modest relationships were found between the echocardiographic and MR measures. However, the statistical limits of agreement between the two imaging modalities were wide for each parameter, due to the low temporal resolution of MRI.

Although conventionally used echocardiography offers superior temporal resolution to that which is currently possible with MRI, the latter shows similar trends for measurement of blood and tissue velocities that can be used, albeit only qualitatively, to detect abnormal function.

7.7 Study Limitations

The contribution of occult cardiovascular disease (if any) to the impairment of myocardial function observed in these studies remains unknown, because coronary angiography and stress tests were not performed in any subject or patient. The degree to which hypertension (a characteristic of both the older normal group and the patients with Type 2 diabetes) influenced the data obtained for tissue strain and relaxation is not known.

The small number of subjects in each of the old and young normal groups and the similarly small diabetic patient group limits the statistical power of the analyses performed here. Future studies with an appropriately large sample size are very necessary for examining the influence of various confounding factors on these parameters.

The inclusion of subjects from all age-groups would have strengthened this Thesis. It is widely accepted, and indeed the studies presented here show, that diastolic function changes substantially with age. The mean age for the older normal subjects was 69 years, 22 years for the younger normal group, and 53 years for the DM patients – all statistically different to each other. Thus, the normal control data are not continuous with respect to age, and taking these two distinct age-groups together to provide a control for the DM group whose mean age falls between them, is a limitation of this work. However, all studies to date have found that age-related changes in cardiovascular function generally occur
in an approximately linear fashion over the decades (Gerstenblith et al., 1977, Owen, A., 1999, Sun et al., 2004). If this is indeed the case, then ANCOVA procedures that correct for the influence of age are entirely justified.

Radial strain, i.e., myocardial deformation perpendicular to the circumferential-longitudinal plane and in the direction of systolic wall thickening and diastolic wall thinning, was not examined in this study, since the tag spacing of 8 mm and width of 1 mm were too great in proportion to wall thickness.

It is unfortunate that echocardiographic TDI data were not available for the normal subjects, as this would have enabled comparison with MR measures of longitudinal function. TDI was available for the DM patients, however, and these data were compared with the appropriate MR parameters.

An important limitation of this work is that scan-rescan reproducibility tests were not performed. Studies using the MR methods employed for this thesis should include a protocol for quantifying reproducibility in order to estimate the degree of variation in the results obtained from independent scans within individual patients.

The temporal resolution currently possible with MRI (approximately 35-50 ms for the studies presented in this Thesis, depending on the subjects’ heart rates) is not as good as that possible with echocardiography (about 10 ms, and better). However, ongoing developments in MR technology will improve on this. Indeed, a recent study describes measurement of global and regional LV strain, using an MR tagging protocol with a temporal resolution of 14 ms (Zwanenburg et al., 2004), and even more recently a temporal resolution of 1.5 ms has been reported for cardiac imaging (Pai et al., 2005).

An MR examination, typical of those described in the preceding chapters, takes about 1 hour per person to acquire the entire image dataset. If standardized for routine clinical examinations, it is likely that this time would be reduced. In comparison, a clinical echocardiographic examination takes about 30 minutes and analysis of images is easily performed on widely available commercial software. Analysis of the MRI dataset, however, is substantially more time-consuming, and, depending on the availability of appropriate image analysis software, tends to be quite tedious. This, combined with the high cost associated with MR examinations and the wider availability of ultrasound, makes it less desirable to use MRI routinely. As with image acquisition, post-processing of MR images is also an area of intense research, which seeks to decrease analysis time and improve the accuracy of measurements, thereby improving the feasibility of the tool for routine clinical use.
Claustrophobia is reported to occur in approximately 2% of people when placed inside an MR scanner (Task Force of the European Society of Cardiology, 1998), prohibiting image acquisition in these individuals. The bore of a typical scanner is about 60 cm in diameter. In addition to the possibility of claustrophobia, morbid obesity may preclude MR imaging, as individuals with an abnormally large girth cannot fit into the scanner.

Metallic implants, such as cardiac pacemakers and stents, and aneurysm clips are standard contraindications to MRI, making it impossible to study patients who have these. However, newer, implanted devices that are composed of non-ferromagnetic materials (e.g., titanium) have been shown to be safe for patients in 1.5 T (and lower) MR scanners (Shellock and Crues, 2004).

7.8 Potential Applications and Future Research

In the assessment of LV diastolic function, it is important to consider the information derived from all available sources, rather than utilizing any single parameter. The MR parameters developed in this Thesis provide valuable information regarding mechanical function of LV myocardial tissue. Three-dimensional shortening strain measurements can be obtained in any plane and in any region of the LV, which is not possible with current clinical techniques such as echocardiography. It may be important to consider these parameters in the assessment of LV function, as they: appear to be influenced by age and disease in a different manner to the existing clinical parameters, may be more sensitive to structural and functional changes, and may indicate these changes earlier than currently used indices. Accurate measurement of LV mass and volumes is already possible with MRI and with the ability to measure blood flow velocities and tissue strain, as demonstrated in this Thesis, the technique may prove to be a ‘one-stop shop’ in the assessment of LV function.

However, further work must be done in order to understand the combined influence of the factors contributing to diastolic function, and to separate their effects.

In addition to the effects of filling pressure, diastolic pre-stretch, and afterload, the functional status of the right ventricle and the left and right atria will no doubt ultimately influence LV performance. Therefore, there is a need for more information on the mechanical and haemodynamic function of these chambers and the relationship with LV function.

With the recent focus on longitudinal LV function, predominantly measured by TDI, it seems important to consider the properties of the mitral valve itself. Changes in valve
architecture and geometry can affect measurements of mitral annular velocities separately from the effects of LV myocardial abnormalities, for example, and it would be interesting to examine the relationship between mitral valve and LV myocardial behaviour.

The timing of diastolic and systolic events with respect to myocardial tissue behaviour requires further study. This is especially important for the study of pathological asynchrony, but relies on the improvement of MR temporal resolution.

The parameters that were examined in this Thesis are by no means exhaustive of those that could be studied. In particular, it is interesting to note that the strain persisting after rapid filling, but before atrial ejection, provides a potentially useful index of the atrial contribution to LV diastole. Figures 7.1 to 7.4 suggest that this atrial component varies considerably with age and disease. Not only does this support echocardiographic transmural filling patterns that are currently used to characterize diastolic dysfunction, but it also highlights the importance of examining these MR strain parameters in late diastole as they could provide useful information on LV compliance as well as atrial function. With regard to the studies presented in this Thesis, MR tag fading during late diastole and atrial contraction made it difficult to examine tissue deformation during these phases. Others have proposed methods for MR strain data acquisition throughout the cardiac cycle. Indeed, Ennis et al. (2003) have shown decreased early relaxation rates of midwall circumferential strain, in patients with familial hypertrophic cardiomyopathy, with increased mid-diastolic strain relaxation rate and increased percent lengthening during atrial contraction, compared with normal values.

Long-term follow-up studies are required to investigate the diagnostic and prognostic value of the MR parameters presented in this Thesis, to determine outcome in clinical trials and in individual patients. Similar studies in other disease conditions should also be performed, including the examination of myocardial function in ischaemic heart disease.

Current research and development of image-processing software is focused on the reduction of analysis time to clinically feasible periods, and to provide user-friendly analysis methods for clinicians. DENSE is a promising technique for measuring tissue strain at high resolution (Aletras et al., 1999, Kim, D. et al., 2004). Harmonic Phase (HARP) MRI, a technique still under development, may allow strain data to be calculated almost as rapidly as the images are acquired (Osman et al., 1999, Earls et al., 2002).

The ultimate goal is to reduce the morbidity and mortality associated with cardiovascular disease, through improved therapy. As the pathological processes underlying
changes in function are elucidated, it is anticipated that more specific and efficient therapies will be developed – for example, to improve myocardial function/contractility. Naturally, this is dependent on optimising currently used tools for functional assessment as well as on recognizing the value of newer ones.

The findings of this Thesis emphasize the ability of MRI and MR myocardial tissue tagging to identify and quantify the changes that occur with age and disease, and underscore the value of the technique in providing independent reliable markers of myocardial function.
Conclusions

MR can offer valuable information, which cannot be obtained by routine clinical methods, regarding left ventricular myocardial tissue behaviour during both systole and diastole.

Calculating the rate of myocardial tissue relaxation gives a real index of diastolic function. The rates of tissue strain relaxation are reduced, both with age and in type 2 diabetes mellitus, providing specific and quantifiable evidence of diastolic dysfunction in the normal healthy older people and in the diabetic patients studied here.

Although a normal ejection fraction is observed in all subjects and patients, systolic abnormalities can be detected. In older people, this is represented by a decrease in peak systolic MVP motion and an increase in peak torsion. Diabetic patients have additional systolic impairments to those seen with ageing, exhibiting reduced circumferential, longitudinal, and principal shortening strains. These findings suggest that diastolic dysfunction may often be accompanied by clinically undetectable systolic changes.

MR tagging is especially useful for measuring regional tissue function, which can provide important clues on how localized structural and mechanical changes contribute to impairments observed in global function. Conversely, local impairment may be masked by normal global function. In all subjects and patients, values for both systolic and diastolic function parameters are non-uniform over LV regions. Furthermore, the pattern of regional non-uniformity changes significantly with age.

Finally, a complete assessment of LV function must precisely measure both left ventricular wall mechanics and the nature of blood flow into and out of the left ventricular cavity, and the influence of age on these measurements must be accounted for in studies of disease.
Appendix

A.1 Scion Image

MR velocity-encoded phase contrast images in a short-axis plane of the LV at the level of the mitral valve were analyzed with Scion Image for Windows (version Beta 4.0.2). Scion Image is a port of the public domain image acquisition and analysis program, NIH Image, developed by Wayne Rasband at the National Institutes of Health, Maryland, USA. It is freely available for downloading from the internet website, www.scioncorp.com.

1. The series of phase contrast images for a particular patient should all be stored in a single directory. In Scion image, choose ‘Import’ from the ‘File’ menu, locate the image directory, select DICOM, select ‘Open All’, highlight the first image in the directory and then click ‘Open’.
2. When all the images have opened, select ‘Windows to Stack’ from the ‘Stacks’ menu.
3. Use the magnifying glass tool to zoom in on the area of interest (i.e., the LV cavity). Choose a 5x5 pixel region of interest (ROI), using the rectangle select tool. Ideally this should cover the area that appears the brightest at the onset of filling, in order to ‘capture’ mitral inflow. Therefore, it may be better to choose the ROI by scrolling through the image stack (using the < and > keys) to the image that shows LV cavity area with the brightest pixel intensity. Once the ROI has been chosen scroll through the entire stack to see the area selected in each image.
4. Select ‘Options’ from the ‘Analyze’ menu. Choose ‘Mean’ (this gives the mean pixel value in the selected ROI).
5. Save the stack as a TIFF file (with the ROI selection still active), and close it.
6. Select ‘reset’ from the ‘Analyze’ menu.
7. ‘Import’ the patient’s flow images once more (as described in step 1).
8. Without converting the open image windows into a stack, select ‘restore selection’ from the ‘Analyze’ menu.

9. From the ‘Special’ menu, choose ‘Load Macro’ and select the ‘measure’ macro from the ‘Macros’ folder that accompanies the Scion Image software. Now click on the ‘Special’ menu and select ‘Measure All’.

10. Click on ‘Show Results’ from the ‘Analyze’ menu.

11. Choose ‘Export’ from the ‘File’ menu, and save the results as a ‘measurements’ file. This can then be opened in Microsoft Excel for further analysis.

12. In Excel the actual flow velocity can be calculated in cm/s by using the formula:

   \[ \text{Velocity} = \frac{(\text{mean} \times \text{velocity encoding})}{4095} \]

This formula applies only if Scion Image reads the images in as ‘signed’. The scale of pixel intensity values for signed images is \(-4095\) to \(+4095\). Therefore the maximum velocity achievable, which corresponds to the velocity encoding value, would be \(+4095\). However, if the images are read in as ‘unsigned’, then the resulting mean pixel values have to be scaled to ‘signed’ values in Excel. This is because the scale of pixel intensity values for unsigned images is \(0\) to \(4095\). This means that if the same velocity encoding as for signed images is used, then \(4095\) in an unsigned image must correspond to \(2 \times \text{velocity encoding value}\). Therefore, the formula to be used for unsigned images is:

   \[ \text{Velocity} = \left(\frac{(\text{mean} \times 2 \times \text{velocity encoding})}{4095}\right) - \text{velocity encoding} \]

Velocity encoding is subtracted at the end of the formula in order to scale the unsigned velocities to signed values.

Although Scion Image gives the option of importing images in specific file formats (e.g., TIFF or DICOM) or as a custom format such as signed or unsigned, it was possible to import images only as ‘DICOM’ in this study, and therefore scaling unsigned results to signed values could be done only in Excel. The unsigned pixel values were easily recognizable as they tended to be much larger (usually \(>1500\)) compared with the signed values (usually \(<1000\) and including negative values).
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