Intra-left ventricular blood flow analysis to determine cardiac performance and dysfunction indices

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Intra-Left Ventricular Blood Flow Analysis to Determine Cardiac Performance and Dysfunction Indices

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ABSTRACT

Heart failure (HF) is one of the most common diseases in the developed world and is increasingly prevalent in developing countries, especially among the ageing population. It causes left ventricular (LV) dysfunction, involves high healthcare cost and has high mortality.

Traditionally, HF patients were grouped into diastolic HF and systolic HF. However, these terms are now abandoned due to the fact that diastolic dysfunction exists in all symptomatic HF patients and systolic dysfunction, to a lesser extent, has been observed in diastolic HF. HF patients are currently stratified based on their LV ejection fraction (EF), which is a measure of systolic performance, into HF with preserved EF (HFpEF) and reduced EF (HFrEF). Although HFpEF is becoming prevalent, due to its complex mixture of diastolic and systolic dysfunction, as well as various degrees of LV remodelling, it remains a challenge to diagnose and provide pharmacological therapies to HFpEF and thus, treatment and prognosis of HFpEF are mostly unaltered for the past 3 decades.

With the advancement of non-invasive cardiac imaging modalities in recent years, cardiac haemodynamic information, which is crucial to diagnosis and disease management, can now be directly measured or derived without the need for invasive catheterization. In this thesis, intra-left ventricular flow was derived from echocardiographic colour Doppler flow images using vector flow mapping (VFM) technique. In chapter 3, intra-LV flow patterns of HF patients with different extent of diastolic and systolic dysfunction, as well as normal controls were described in both diastole and systole. From the flow information obtained using VFM, quantitative assessment of LV diastolic and systolic performance was then developed and applied to small groups of HF patients in the following chapters.

In diastolic phase, most LV filling occurs during early diastolic and only about 20% of the LV stroke volume is filled by left atrial (LA) contraction. The LA contribution to LV filling

changes with ageing and progressive impairment of diastolic function. In chapter 4, to evaluate the change in LA haemodynamic and its contribution to LV diastolic performance, an intrinsic LA contractility index, termed maximum LA ejection force ($\text{LAEjF}_{\max}$), was formulated and compared in patients with HFrEF, HFpEF with different severity of diastolic dysfunction, versus ageing and young healthy controls. Load-adjusted $\text{LAEjF}_{\max}$ showed negative correlation with ageing and severity of diastolic dysfunction.

Next, in chapter 5, maximum LV ejection force ($\text{LVEjF}_{\max}$) was formulated and proposed as an index for LV contractile performance. Preload-adjusted $\text{LVEjF}_{\max}$ showed good correlations with conventional indices of systolic performance. It also had an exponential relationship with cardiac injury, assessed by blood biomarker Troponin T.

From the flow vectors, intra-LV pressure gradient distributions were also computed in chapter 6. Although comprehensive validation studies are required, this proposed method makes study of non-invasive intra-LV haemodynamic in large number of patients with various disease conditions possible in the clinical settings where high throughput is desired.

Lastly, in chapter 7, to gain insights into changes in LV stiffness in HF, extracellular volume fraction (ECV) measurement, which is believed to correlate with myocardial fibrosis, from magnetic resonance T1-mapping native- and post-contrast images. An algorithm to calculate pixel-wise ECV map of LV myocardium was developed and tested in a normal control and a diseased subject.

Conclusion and future directions are highlighted in Chapter 8.

In addition, clinical application of using contractility index for detection of early stage of siderotic cardiomyopathy is included in the Appendix.

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GLOSSARY OF ABBREVIATIONS

AO	aorta
AV	aortic valve
CFD	computational fluid dynamics
CMR	cardiac magnetic resonance
DD	diastolic dysfunction
HF	heart failure
HFpEF	heart failure with preserved ejection fraction
HFrEF	heart failure with reduced ejection fraction
LA	left atrium
LGE	late gadolinium enhancement
LV	left ventricle
LVOT	left ventricular outflow tract
MOCO	motion correction
MV	mitral valve
PIV	particle imaging velocimetry
RV	right ventricle
RA	right atrium
VFM	vector flow mapping

GLOSSARY OF SYMBOLS

A	Doppler peak atrial contraction velocity [m/s]
A'	atrial contraction mitral annulus velocity [m/s]
CK	creatinine kinase [u/l]
CK-MB	creatinine kinase MB [μ g/l]
D	valve annulus diameter [cm]
dP/dt_{max}	maximal rate of ventricular pressure rise [mmHg/s]
$d\sigma^*/dt_{max}$	maximal rate-of-change of LV wall stress normalized to pressure [s^{-1}]
DT	early filling deceleration time [ms]
DBP	diastolic blood pressure [mmHg]
E	Doppler peak early filling velocity [m/s]
E'	early filling mitral annulus velocity [m/s]
Ea	effective arterial elastance [mmHg/ml]
Ees	end-systolic ventricular elastance [mmHg/ml]
ECV	extracellular volume fraction [%]
F	flow rate across the line [cm^2/s]
eFS	endocardial fractional shortening [%]
mFS	midwall fractional shortening [%]
cESS	circumferential end-systolic wall stress [kdynes/ cm^2]

IVRT	isovolumic relaxation time [ms]
LAEjF	left atrial ejection force [N]
LAaEF	left atrial active emptying fraction [%]
LApEF	left atrial passive emptying fraction [%]
LAV _{max}	end-systolic left atrial volume [ml]
LAV _{min}	end-diastolic left atrial volume [ml]
LAV _{pre-A}	left atrial volume before atrial contraction [ml]
LVEF	left ventricular ejection fraction [%]
LVEDVI	left ventricular end-diastolic volume index [ml/m ²]
LVEjF	left ventricular ejection force [N]
LVMI	left ventricular mass index [g/m ²]
NT-proBNP	N-terminal pro-brain natriuretic peptide [pg/ml]
PVs	systolic pulmonary vein velocity [m/s]
PVd	diastolic pulmonary vein velocity [m/s]
ρ	blood density [= 1.06 g/cm ³]
SBP	systolic blood pressure [mmHg]
SV	stroke volume [ml]
TnT	Troponin T [μ g/l]
Vp	flow propagation velocity [m/s]

CHAPTER 1. INTRODUCTION

1.1 Background

Heart failure (HF) , is one of the most common diseases in the developed world and is increasingly prevalent in developing countries, especially among the ageing population [1]. It involves high healthcare cost and high mortality.

HF patients are stratified into two groups, based on their LV ejection fraction (EF), which is a traditionally used LV contractility index. A patient who has signs and symptoms of HF, while LVEF is preserved, is characterized as HF with preserved ejection fraction (HFpEF), otherwise, classified as HF with reduced ejection fraction (HFrEF). Despite preserved EF, evidence of systolic dysfunction, to a lesser extent, has even been demonstrated in patients with HFPEF [2-4]. It is still debatable whether HFpEF and HFrEF exist as part of one HF spectrum with HFpEF preceding HFrEF or represent two distinct syndromes of HF: HFpEF has concentric remodelling with high LV mass/volume ratio and mainly diastolic dysfunction, while HFrEF has eccentric remodelling with low LV mass/volume ratio and a combination of systolic-diastolic dysfunction (HFrEF) [5]. The complex mixture of systolic and diastolic dysfunction and variable degrees of LV remodelling underlying HFpEF poses challenges to diagnose and provide pharmacological treatment for HFpEF. Further, other mechanisms underlying HFpEF include ventriculo-vascular coupling, chronotropic incompetence, left atrial (LA) dilatation, volume overload and pulmonary arterial hypertension have been identified and may all contribute to HF in HFpEF patients. All these concomitant structural and functional changes will affect the haemodynamic in the LV.

Therefore, visualization of intra-LV flow patterns, which is the result of how the LV myocardium translates force to generate intra-LV pressure to direct blood in and out of the LV,

may provide additional dynamic information for understanding pathophysiological mechanisms in LV remodeling processes.

Cardiac magnetic resonance (CMR) imaging has been used for examining detailed blood flow patterns in the heart and great vessels for a range of clinical conditions [6-8]. In parallel to non-invasive imaging techniques, computational fluid dynamics (CFD) has been used for examining the global flow patterns and pressure distribution since the 1970s and 1980s [9, 10]. The early models were confined to one- or two-dimensions with simplified geometries. With the continuing development of high-performance computing, realistic geometries and fluid-ventricular wall interactions were subsequently incorporated into the CFD models to obtain velocity and pressure distributions in the LV, resulting from stress distributions within the wall [11-13].

The integration of current state-of-art real-time CMR flow data and CFD enables visualization of instantaneous three-dimensional flow field and at the same time, also eliminates the need for velocity scans of the whole heart, thus enabling subject-specific intra-LV flow simulations [14, 15]. However, CMR is relatively expensive and not readily available. Further, this phase contrast velocity mapping technique has limited spatio-temporal resolution, requires additional scans and is time consuming. It is thus not a routinely used technique in clinical settings.

Recent developments in echocardiography enable assessment of intra-LV blood flow patterns by tracking the patterns produced by contrast agent particles, called particle imaging velocimetry (echo-PIV) technique [16, 17]. However, this technique requires injection of contrast agent, which might lead to serious side effects and has limited velocity range due to tracking algorithm.

Vector flow mapping (VFM) technique has recently been developed to generate flow velocity vector fields by post-processing colour Doppler echocardiographic (echo) images [18, 19]. This technique has produced reasonable accuracy when validated with CFD and PIV.

1.2 Objectives and Scope

The work covered in this thesis involved biomechanics, mathematical formulation and image processing to:

- i. Determine the intra-LV blood flow distribution from echo Doppler flow images using VFM technique and demonstrated in representative cases of HF patients who had reduced and preserved ejection fraction, and exhibited different severity of diastolic dysfunction, versus young healthy as well as ageing controls.
- ii. Develop quantitative indices, load-adjusted maximum LA ejection force ($\text{LAEjF}_{\max}$), and preload-adjusted maximum LV ejection force ($\text{LVEjF}_{\max}$), derived from echo Doppler flow, assess diastolic function and systolic function, respectively and compare the indices in HF patients versus normal controls.
- iii. Compute the intra-LV pressure gradient distribution from LV blood flow velocities.
- iv. Develop an algorithm for post-processing of the CMR T1-weighted native and post-contrast images and computation of extracellular volume (ECV) fraction maps as well as ECV values, which have been shown to be histologically correlated to diffuse interstitial fibrosis of the myocardium.

1.3 Clinical Significance

LV pressure is the holy grail for HF diagnosis but it can only be obtained invasively by catheterisation. For the first time, intra-LV velocity and pressure gradient distributions can be obtained from echo Doppler images, without the need for contrast injection, computational simulation, or expensive CMR scans. Besides determining non-invasive LV haemodynamic

changes with HF disease process, attempt was made to estimate ECV, which has been associated with myocardial fibrosis, and thus, linked to myocardial stiffness.

The relationship between changes in myocardial stiffness and changes in intra-LV pressure gradient distributions would offer potentially significant insights into HF disease progression and would help to monitor response to pharmacological therapy.

1.4 Outline of the Thesis

The detailed works are explained in the following seven chapters.

Chapter 2 provides a thorough literature review of the cardiac anatomical structure and performance. It defines the clinical problems of HF, current approaches to diagnose HF and highlights the gap that need to be filled by this study.

Chapter 3 introduces the VFM algorithm and how it is applied to derive intra-LV flow velocity distribution in representative cases of HF with various extent of diastolic dysfunction, versus young and ageing controls.

Chapter 4 formulates an intrinsic LA contractility index, load-adjusted $LAejF_{max}$, and compares it in patients with HFrEF, HFpEF with different severity of diastolic dysfunction, versus ageing and young healthy controls.

Chapter 5 proposes an LV contractile performance index, preload-adjusted $LVEjF_{max}$, and also compares it in the same groups of patients and volunteers as mentioned in Chapter 4.

In Chapter 6, by using the same representative cases as those presented in Chapter 2, intra-LV pressure gradient distribution will be computed from LV blood flow velocities.

Chapter 7 details the algorithm for post-processing of the CMR T1-weighted native and post-contrast images and computation of extracellular volume fraction (ECV) maps as well as ECV values in 2 representative cases of normal and diseased myocardium.

Chapter 8 summarizes the work done and proposes the future directions for this work.

Lastly, the Appendix details another clinical application of contractility index in patients with siderotic cardiomyopathy.

CHAPTER 2. LITERATURE REVIEW

2.1 Overview of Cardiac Anatomy and Physiology

2.1.1 Gross Anatomy of the Heart

The heart is composed of cardiac muscle (myocardium) and connective tissues, enclosed in a double-walled sac called pericardium. It is divided into right and left sides by the septum and has four chambers: two superior atria and two inferior ventricles (Figure 2-1).

Deoxygenated blood enters through the superior vena cava into right atrium (RA) then through tricuspid valve (TV) into the right ventricle (RV) before being pumped through the pulmonary valve (PV) to the pulmonary arteries (PA) and eventually into the lungs. Oxygenated blood returns from the lungs through the pulmonary veins to the left atrium (LA), then enters the left ventricle (LV) through the mitral valve (MV) and pumped out to the aorta (AO) through the aortic valve (AV).

Figure 2-1 Structure of the heart (adopted from www.nhlbi.nih.gov)

The myocardium is comprised of myocardial muscle cells, called myocytes. The main function of these cells is to execute the cardiac contraction-relaxation cycle. Each myocyte is bounded

by a complex cell membrane, called sarcolemma, and is filled with rod-like bundles of contractile elements, called myofibrils. The myofibrils have distinct fundamental contractile units, called sarcomere. Each sarcomere is composed of the thick myosin and the thin actin filaments. During contraction, the filaments slide over each other without actual shortening of the individual molecules of actin or myosin. As they slide, they pull together the two ends of the sarcomere, which is limited on the side where actin filament is attached by the Z line (Figure 2-2). The interaction between actin and myosin serves as the basis for the sliding filament theory of muscle contraction.

Figure 2-2 The microarchitecture of contractile cells and proteins (Figure adopted from Harrison's Principles of Internal Medicine, 17th edition)

2.1.2 Cardiac Cycle

A cardiac cycle consists of three major events: LV contraction, LV relaxation and LV filling (Figure 2-3).

At the start of LV *contraction*, electrical cells of the sinoatrial (SA) node are activated. Voltage-gated calcium channels on the cell membrane open and allow calcium ions to pass through the muscle cell. The arrival of these ions at the contractile proteins starts to trigger actin-myosin interaction. LV pressure starts to build up and eventually exceeds that in the LA, followed by MV closure. LV volume is fixed during this phase (isovolumic contraction) due to closure of both AV and MV.

As the electrical excitation wave travels along the spirally oriented myofibers, it induces contraction of these fibers, resulting in torsion. As more and more fibers enter the contracted state, LV twists and releases myocardial energy that is stored as myocardial contractile elastic energy [20]. This causes increase in LV pressure and torque generation. Concurrently, actin-myosin interaction and cross-bridge cycling continue to increase. AV eventually opens when the LV pressure exceeds that in the AO and marks the start of rapid ejection phase.

As the concentration of calcium ions starts to decline, more myofibers enter the *relaxation* phase. The AV closes when the pressure in the AO exceeds the falling pressure in the LV. Thereafter, the ventricle continues to relax until its pressure falls to below that in the LA, the MV opens. The phase when both AV and MV close is called isovolumic relaxation. During this phase, LV untwists rapidly, enables low filling pressure [21]. Hence, torsion acts as a critical functional link between systole and diastole.

Just after MV opening, early *filling* phase occurs to account for most of ventricular filling. As pressures in the LA and LV equalize, LV filling stops. During atrial filling, pressure gradient from the LA to the LV increases, thus, filling renews. As LV continues to relax during filling (diastole) phase, it further untwists.

Figure 2-3 The mechanical events in the cardiac cycle (Figure adopted from Braunwald's Heart Disease – A Textbook of Cardiovascular Medicine)

2.1.3 *Cardiac Performance and Left Ventricular Contractility Indices*¹

2.1.3.1 Cardiac Performance

Preload refers to the stretching of myocardial fibers at the end of diastole, prior to contraction. According to Frank-Starling's law, the greater the stretch, the greater the force of contraction of the myocardium which will increase cardiac output.

Afterload is the load that LV has to overcome during contraction. It is related to LV contractile wall stress generated by myocardial fibers during systole and consists of three components: the peripheral resistance, the arterial compliance and the intra-ventricular pressure.

LV contractility is assessed by the capacity of the myocardium to contract independently of changes in the preload and afterload. The complex interactions of preload, afterload and contractility to cardiac output are shown in Figure 2-4. Cardiac output is determined by stroke volume and heart rate, and when combined with peripheral resistance, it determines arterial pressure. The interaction of arterial system and carotid and aortic arch baroreceptors provides a feedback mechanism to medullary vasomotor and cardiac centres, and to higher nervous centres to modulate heart rate, peripheral resistance, venous return and contractility. Arterial pressure, on the other hand, also contributes to afterload. Therefore, when interference occurs in one of these factors that affects cardiac output, compensatory mechanisms will be activated, by modulating other factors, to maintain adequate cardiac output. If the causative factor of the reduced cardiac performance persists, the heart will eventually fail.

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¹ The content of this section is published in Dhanjoo N Ghista, Liang Zhong, Thu-Thao Le, and Ru-San Tan, "Chapter 5 – Cardiac contractility measures for left ventricular functional assessment in normal and diseased hearts", in *Cardiology Science and Technology* by Dhanjoo N Ghista (CRC Press, 2016), 134-151. Permission to use as part of the thesis has been obtained from co-authors.

Figure 2-4 Interactions of preload, afterload and contractility to cardiac output (Figure reproduced from Harrison's Principles of Internal Medicine, 17th edition)

An ideal index of contractility should be responsive to inotropic manipulation, independent of preload and afterload, simple to apply and relevant in the clinical settings. In this section, we shall discuss various LV contractility indices in the literature.

2.1.3.2 Contractility Indices Based on Experimental Data

One of the first contractility indices was proposed by Sonnenblick [22, 23] based on the Hill's theory on activated muscle. A characteristic hyperbolic relation between the velocity of shortening of the contractile element (V) and the force developed was demonstrated. The maximal velocity of shortening (V_{max}) was also shown to be independent of initial muscle length or preload. Figure 2-5 shows flattened force-velocity curves with increase in preload (A) while V_{max} remains unchanged, and a right shift in the curve with an increase in both V_{max} and the maximal force of contraction with injection of strophanthidin to alter the contractile state.

However, the disadvantage of this index is the need to extrapolate V_{max} from the peak rates of force development in unloaded muscle and hence, the application of this index in vivo is limited. Further, based on a later review of force-velocity analyses derived from animal experiments and the development of indices for the assessment of heart muscle function, Mirsky and Ghista [24] have concluded that V_{max} is indeed sensitive to the relatively high preloads and may not be a reliable contractility index.

Figure 2-5 Effects of (A) increasing initial length (preload) and (B) changing contractile state by injection of strophanthidin on the force-velocity relation (Figure adopted from Sonnenblick et al. [23])

Gleason and Braunwald [25] performed catheterization studies on 40 patients and proposed the maximal rate of ventricular pressure rise dP/dt_{max} as an index of myocardial contractility. This dP/dt_{max} has been proved to be the most sensitive to inotropic changes [26, 27] and is considered as a “gold standard” for assessing myocardial contractility. Even so, it is not entirely heart rate and load independent [27]. It is minimally dependent on afterload in physiological and high resistance ranges, but highly dependent on preload. Due to its preload dependence,

the relationship between ventricular end-diastolic volume and dP/dt was suggested to be a more accurate index of contractility [26]. However, precise quantification of the rate of ventricular pressure rise requires invasive measurement of LV intracavitary pressure, which limits its clinical applicability.

From experimental data of canine models, Suga [28, 29] observed that the instantaneous ratio of ventricular pressure to absolute volume, $P(t)/V(t)$, was almost independent of end-diastolic volume and arterial blood pressure, yet varied markedly with inotropic interventions [30]. He then defined the pressure-volume ratio at any time point during one cycle, $E(t) = P(t)/(V(t) - V_d)$, where V_d is the fixed correction volume, and related $E(t)$ to time-varying elastance [31]. The end-systolic pressure-volume relationship (ESPVR), which comprises the loci of pressure and volume points at end-systole on a pressure-volume graph, has also been established (Figure 2-6). This relationship is usually linear, with its slope denoted as end-systolic ventricular elastance, E_{es} , as shown in Figure 2-5. E_{es} has been designated as a load independent standard of intrinsic LV contractile function [28, 31]. However, its load dependence has been challenged [32-35]. ESPVR becomes curvilinear and concave towards the volume axis [36, 37] if LV pressure and volume vary over a wide range. Other problems of ESPVR include measurement variability [35] and dependence on LV cavity size [38, 39]. Further, despite recent advances in ESPVR analysis [40], quantifying E_{es} requires monitoring of LV pressures under varying induced loading conditions, without altering the contractile state, in order to obtain multiple LV pressure-volume data points, which is virtually impossible in the clinical setting. Chen et al. [41] has developed a method to quantify single-beat E_{es} from non-invasive echocardiographic parameters to be used in clinical setting.

Figure 2-6 Pressure-volume loops obtained at different loading conditions A, B, C. ESPVR is the line through end-systolic pressure-volume points, of which slope is E_{es} , a measure of LV contractility under physiological conditions.

Later, based on hydraulic system concepts, expressions of LV work and power generation can be formulated. The “power index” of preload-adjusted maximal power (PAMP), which is the ratio of maximal LV power and the square of LV end-diastolic volume, was proposed by Kass et al. [42]. This index appears to be an attractive alternative index of contractility as its calculation does not require assessment over a wide range of pressure and volume values. However, its independence on loading conditions is debatable [42-44]. Besides, power inherently is not a parameter describing the heart or arterial system alone. Hence, changes observed in this index may not pertain to the cardiac changes exclusively.

Recently, with the advent of new imaging technology, myocardial strain and strain rate can be measured non-invasively and have been proposed to assess contractile performance. Myocardial strain reflects tissue deformation in response to myocardial wall stress, and strain rate is the rate of deformation. Tagged MRI provides accurate “gold-standard” for non-invasive measurements of strain but is constrained by high cost and lack of availability. Echocardiographic tissue Doppler imaging (TDI) for measurement of strain and strain rate has

been validated and enjoys good correlation with sonomicrometry and dP/dt_{max} values [45-47]. Caveats to this technique include inaccuracies introduced by non-alignment between the Doppler beam and LV axis, degraded spatial resolution at high temporal resolution, sensitivity to signal-noise. Two-dimensional (2D) speckle tracking is a newer echocardiographic technique which tracks frame-to-frame displacement of speckles. Free from insonation angle restriction, 2D speckle tracking strain can potentially provide comprehensive multi-directional assessment of LV myocardial deformation. It has demonstrated good correlation and agreement with strain measurements using invasive sonomicrometry, tagged-MRI [48] and TDI [49].

Experimental studies have shown that regional systolic strain is mainly related to stroke volume, whereas regional systolic strain rate is closely related to the changes in contractility. The peak systolic strain rate determines the rapidity of force development during early ejection, and is proposed as an index of contractility [50]. In this regard, it is germane to note that strain and strain rate are measures of deformation, and not of contractility (which should reflect both myocardial stress and strain), and therefore load sensitive [51].

2.1.3.3 Contractility Indices Based on Left Ventricular Modeling

The LV can be described as a blood pressure pump and its biomechanical behavior is expressed by the time-varying relationship between intra-ventricular blood volume and pressure. This relationship has been used as a measure of cardiac function, based on the form of time-varying elastance or its inverse, known as compliance [52-54]. However, the mechanisms which regulate LV pressure and filling through changes of these elastance were not explained in these models. Zhong et al. [55] has introduced a novel concept of passive (volume-dependent) elastance, $E_{passive}$, and active (time-dependent) elastance, E_{active} , operating in tandem throughout the cardiac cycle. Passive elastance $E_{passive}$ represents the LV pressure response to LV volume changes during LV filling phase and ejection phase and is a measure of LV

stiffness. Active elastance E_{active} represents LV contraction and relaxation, both of which can be traced to LV sarcomeric units activation and of the actin-myosin units disengagement, respectively [56]. From this new concept, he then determined the temporal relationship of elastance to the generated LV pressure and thus, showed how this active-elastance profile can explain the increase in LV pressure during isovolumic contraction and the LV suction effect during rapid filling.

In order to determine these passive and active elastances, the author adopted a spherically-shaped LV model with radius R and wall thickness h . The governing differential equation, relating LV pressure and volume, is:

$$M\ddot{V} + d(EV) = M\dot{V} + VdE + EdV = dP \quad (\text{Eq. 2.1})$$

where V represents LV volume, P represents LV pressure, M represents the inertia coefficient ($= \rho h / 4\pi R^2$) and E is the LV elastance ($= E_{passive} + E_{active}$).

The first term of (Eq. 2.1) is of a much smaller order of magnitude relative to the other terms, and can hence be safely omitted. (Eq. 2.1) becomes:

$$VdE + EdV = dP \quad (\text{Eq. 2.2})$$

Based on the exponential relation of filling pressure-volume data reported by Mirsky et al. [57] and the classical definition of elastance as ratio of change in pressure to change in distending volume, the passive elastance can be adopted as:

$$E_{passive} = \frac{dP}{dV} = E_{p0} e^{z_p V} \quad (\text{Eq. 2.3})$$

where E_{p0} is the passive elastance coefficient, z_p is the passive elastance exponent.

The active elastance shapes the LV pressure curve and hence could be presented by an analogous under-damped function:

$$E_{active} = E_{a0}e^{-z_a t} \sin(\omega_a t) \quad (\text{Eq. 2.4})$$

where $\omega_a = \pi/T$, T is the period of the cardiac cycle, and z_a is the active elastance exponent.

During isovolumic contraction phase, equation is modified to:

$$VdE = dP \quad (\text{Eq. 2.5})$$

(Eq. 2.5) is discretized to correspond to time instants i and $(i - 1)$ as:

$$E_{a,i} = \frac{P_i - P_{i-1}}{V_i} + E_{a,i-1} \quad (\text{Eq. 2.6})$$

(Eq. 2.6) can be used to evaluate $E_{a,i}$ during isovolumic contraction phase. These values are then substituted into (Eq. 2.4) to obtain the values of z_a and the average value of E_{a0} . Similarly, $E_{a,i}$ values during isovolumic relaxation phase can be obtained. Upon determining these instantaneous values of active elastance during isovolumic contraction and relaxation, the cyclic variation of E_{active} can be represented by a double exponential function, as:

$$E_{active} = E_{a0} \left(1 - e^{-\left(\frac{t}{\tau_c}\right)^{z_c}} \right) \left(e^{-\left(\frac{t-d}{\tau_r}\right)^{z_r}} \right) \quad (\text{Eq. 2.7})$$

where t is measured from the start of isovolumic contraction, time coefficient τ_c describes the rate of elastance rise during contraction phase, τ_r describes the rate of elastance fall during relaxation phase, z_c and z_r are parameters of the E_{active} curve during isovolumic contraction and relaxation, respectively, and d is a time constant ($t - d = 0$ when $t < d$). These parameters are determined by fitting (Eq. 2.7) to the computed instantaneous values of E_a during a cardiac cycle.

The active elastance vs normalized time plot shown in Figure 2-7 reveals the development and decrease of E_a during systole, which in turn governs the generation of LV pressure.

Maximum active elastance, $E_{a,max}$, was proposed to be a contractility index. The author has depicted good correlation with the traditional dP/dt_{max} index ($E_{a,max} = 0.006 dP/dt_{max} - 5$, $r = 0.93$, $p < 0.0001$) in a group of 30 patients with different tertiles of LV ejection, as shown in Figure 2-8.

Figure 2-7 Active elastance versus normalized time for subjects HEL, with myocardial infarct, and DDM with double vessel disease and hypertension. (Figure adopted from Zhong et al. [55])

Figure 2-8 Correlation between $E_{a,max}$ and dP/dt_{max} (correlation coefficient 0.8792). (Figure adopted from Zhong et al. [55])

The study showed that while E_a develops at the start of isovolumic contraction and maximizes during late ejection, it becomes zero only during diastolic filling. The retention of E_a during diastolic phase, therefore, explains the phenomenon of LV suction before the onset of LV atrial contraction [58]. However, this index is based on invasive measurement of instantaneous pressure and volume data, and thus, is limited in clinical settings.

Zhong et al. [59] has also proposed a novel LV contractility index based on LV wall stress, defined as the maximal rate-of-change during systole of LV wall stress normalized to LV intracavitary pressure, $d\sigma^*/dt_{max}$ where $\sigma^* = \sigma_\theta/P$. The author employed a thick-walled spherical LV model with radius r and expressed LV pressure-normalized wall stress, σ^* , as:

$$\sigma^*(r) = \frac{\sigma_\theta}{P} = \frac{r_i^3}{r_o^3 - r_i^3} \left(1 + \frac{r_o^3}{2r^3} \right)$$

(Eq. 2.8)

where σ_θ is the wall stress, P is LV intra-cavitary pressure, r_i and r_o are inner and outer radii of the LV, respectively.

$$\sigma^*(r = r_i) = \frac{\frac{V}{V_m + V} + \frac{1}{2}}{1 - \frac{V}{V_m + V}} = \frac{3V + V_m}{2V_m} = \frac{3V}{V_m} + \frac{1}{2}$$

(Eq. 2.9)

where $V = \frac{4\pi r_i^3}{3}$ denotes LV volume, $V_m = \frac{4\pi(r_o^3 - r_i^3)}{3}$ denotes LV myocardial volume.

Differentiating with respect to time, the stress-based contractility index can be obtained as:

$$\left(\frac{d\sigma^*}{dt}\right)_{max} = \left|\frac{d\left(\frac{\sigma}{P}\right)}{dt}\right|_{max} = \frac{3}{2V_m} \left|\frac{dV}{dt}\right|_{max}$$

(Eq. 2.10)

This contractility index has shown good correlation with dP/dt_{max} , E_{es} and $E_{a,max}$, as demonstrated in Figure 2-8. Both V_m and $\left|\frac{dV}{dt}\right|_{max}$ can be measured from either non-invasive MR or echocardiography imaging and has been proved to be superior to conventional LVEF [3, 59]. It has also been shown that $d\sigma^*/dt_{max}$ was impaired in patients with HFpEF as compared to normal subjects [3]. Further, $d\sigma^*/dt_{max}$ has been found to decrease in thalassaemia major patients with severe iron overload. These severe iron-loaded patients have preserved LVEF until late stage of HF. The detailed study is shown in the Appendix. However, its loading dependence is still debatable [60].

Figure 2-9 Linear regression analysis demonstrates good correlation between $d\sigma^*/dt_{max}$ vs dP/dt_{max} ($r = 0.88$, $p < 0.01$), E_{es} ($r = 0.88$, $p < 0.01$) and $E_{a,max}$ ($r = 0.89$, $p < 0.01$). (Figures adopted from Zhong et al. [59])

The heart can also be viewed as a mechatronic organ. Ghista et al [56] have modelled the heart muscle, at its microscopic structural level, as a mechatronic system. Each sarcomeric contractile element that makes the LV myocardial wall develop stress is represented by a 3-element myocardium model, developed based on Hill's three-element model [61] and Huxley's cross bridge theory [62]. Each myocardial structural unit (MSU) consists of an LV myocardial mass, series-elastic element (SE), viscous-elastic element (VE) and the contractile-element (CE) as shown in Figure 2-10C. Each myofiber comprises two MSUs. There are, supposedly, N myocardial fibers, located helically within the model's wall: one set of fibers ($N/2$) oriented clockwise, and the other set ($N/2$), counter-clockwise (Figure 2-10A). The vertical components of the fiber forces exert pressure on the top and bottom surfaces of the LV chamber, while the horizontal components produce a torque (T_t) in the LV (Figure 2-10B) that is given by:

$$T_t = \frac{N}{2} F_t \cos \alpha_t = \frac{\frac{N}{2} \pi R_i^2 P_t \cos \alpha_t}{\frac{N}{2} \sin \alpha_t} = \pi R_i^2 P_t \cot \alpha_t$$

(Eq. 2.11)

where F_t is the force within each fiber, α_t is the instantaneous fiber angle, N is determined by the cross-sectional area of the cylindrical myocardium model divided by the cross-sectional area of MSU (approximately $7.85 \times 10^{-5} \text{ cm}^2$ [63]). A constant fiber angle α of 35.26° was adopted from the analysis of Pietrabissa et al. [64].

This torque T_t results in a twist of the LV by angle θ_t :

$$\theta_t = \frac{T_t L_t}{JG} = \frac{\pi R_i^2 P_t L_t \cot \alpha_t}{JG}$$

(Eq. 2.12)

where L_t is the instantaneous length at time t of the LV cylindrical model, $\alpha_t (= \alpha) = 35.26^\circ$, J is the polar moment of inertia, G is the shear modulus of LV myocardium ≈ 100 GPa [65].

Figure 2-10 (A) A cylindrical model depicting a typical myocardial fiber arranged as helix within the LV wall, L , R_i and R_o are the length, inner and outer radii of the LV cylindrical, respectively, α is the fiber angle; (B) Equilibrium of fiber forces and LV pressure of the LV cylindrical model at the top circular cross-sectional plane and across the longitudinal plane in the circumferential direction; (C) Myocardial fibril model, composed of two symmetrical MSUs, which are mirror images of each other. Each MSU is composed of an effective mass

(m) that is accelerated, connective tissue series element (SE), the parallel viscous element of sarcolemma (VE), the contractile element (CE) which generates contractile force between myosin and actin filaments. (Figures adopted from Ghista et al. [56])

The governing differential equation for MSU dynamics and the generated MSU contractile force, F_{CE} , is expressed as:

$$m\ddot{x}_2 + B_V\dot{x}_2 - F_{CE} + kx_1 = 0$$

or

$$m\ddot{x}_1 + B_V\dot{x}_1 + kx_1 = F_{CE} - B_V\dot{x}_T - m\ddot{x}_T$$

(Eq. 2.13)

where F_{CE} is the applied force exerted by the contractile element of MSU, m is the muscle mass per unit cross-sectional area ($= \pi(R_0^2 - R_i^2)L\rho/2N$), B_V is the viscous damping parameter of the parallel viscous element (VE), k is the elastic stiffness (or modulus) of the series elastic element (SE), x_T is the shortening displacement of the myocardial fiber unit relative to its centerline, determined from LV dimensional changes, x_2 is the displacement of m relative to centerline due to CE contraction ($= x_1 + x_T$). Rearranging the terms, (Eq. 2.13) becomes:

$$F_{CE} = m\ddot{x}_2 + B_V\dot{x}_2 + kx_1, \text{ or } F_{CE} = m(\ddot{x}_1 + \ddot{x}_T) + B_V(\dot{x}_1 + \dot{x}_T) + kx_1$$

(Eq. 2.14)

The term $m\ddot{x}_2$ is of a small order of magnitude compared to the other two terms, and is hence neglected in the analysis.

The MSU shortening velocity ($\dot{x}_2$) is given by:

$$\dot{x}_2 = \dot{x}_1 + \dot{x}_T$$

(Eq. 2.15)

where x_1 is determined from monitored LV pressure and dimensions, $\dot{x}_1$ is the first time-derivative of x_1 , x_T is determined from LV dimensional changes during isovolumic contraction and ejection phases, and $\dot{x}_T$ is its first time-derivative.

x_T is computed as:

$$x_T = \frac{L_{t+1} - L_t}{2 \sin \alpha} \quad (\text{Eq. 2.16})$$

F_{CE} is expressed as a time-varying cyclic expression:

$$F_{CE} = F_{CE_0} \sin(\omega_{CE} t) e^{-Z_{CE} t} \quad (\text{Eq. 2.17})$$

where F_{CE_0} , ω_{CE} and Z_{CE} are the additional parameters to be determined, and $t = 0$ corresponds to the start of isovolumic contraction phase. Upon substituting (Eq. 2.16) and (Eq. 2.17) into the governing (Eq. 2.14), the differential equation is obtained:

$$B_V \dot{x}_1 + k x_1 = F_{CE_0} \sin(\omega_{CE} t) e^{-Z_{CE} t} - B_V \dot{x}_T \quad (\text{Eq. 2.18})$$

The solution of this differential equation is expressed as:

$$x_1 = f(m, k, B_V, F_{CE_0}, \omega_{CE}, Z_{CE}, t) \quad (\text{Eq. 2.19})$$

The parallel series element force, F_{SE} , is given by:

$$F_{SE} = k \times (\text{total SE deformation}) = k \times x_1 = \frac{2\pi R_i^2 P_i}{N \sin \alpha}$$

(Eq. 2.20)

Matching this above expression for kx_1 with the value of $\frac{2\pi R_i^2 P_i}{N \sin \alpha}$ calculated using instantaneous LV pressure and dimensional data obtained during ventriculography, parameters k , B_V , F_{CE_0} , ω_{CE} and Z_{CE} can be determined. F_{CE} , x_1 , x_2 and $\dot{x}_2$ can then be obtained. From the values of sarcomere contractile force, F_{CE} , and shortening velocity $\dot{x}_2$, Ghista et al. [56] proposed a power index for LV contractility, expressed as:

$$Power = N(F_{CE} \times \dot{x}_2)$$

and the myocardial power index (*MSPI*), expressed as:

$$MSPI = \frac{Power_{max}}{V_m}$$

where $Power_{max}$ is the maximal value of power and V_m is myocardial volume.

Both maximal power generated by CE, $Power_{max}$, and the *MSPI* contractility index were demonstrated to be lower in patients with myocardial infarct [56]. These may help to quantify how myocardial infarct impairs the LV performance. However, these 2 parameters require invasive LV pressure data.

2.1.3.4 Summary of contractility indices and gap identified

The modelling and formulation of contractility indices at different LV physiological levels have been discussed in detail. Their dependence on loading conditions, heart rate, sensitivity to inotropic changes, as well as their ease of use in clinical practice (in terms of requirement of invasive procedures or sophisticated devices that are not readily available in clinical settings) are summarized in Table 2-1.

Although the above mentioned studies have covered a wide range of physiology of LV contraction, from micro to macro level, the clinical applicability of these indices is somewhat limited due to the need for haemodynamic data which, at present, can only be acquired by invasive catheterisation. Strain and strain rate imaging, although gaining popularity in clinical research to assess LV performance in various cardiac diseases, are measures of deformation, and not of contractility. Thus, it is crucial to develop indices which are intrinsic measures of LV contractility based on sound mathematical formulations and, at the same time, can be easily applied in routine clinical settings using readily available non-invasive imaging modalities or devices.

Table 2-1 Summary of contractility indices, their preload and afterload dependence, sensitivity to inotropic changes and applicability in clinical settings

Indices	Preload dependent	Afterload dependent	Sensitive to inotropic changes	Easy to use in clinical settings
Left ventricular ejection fraction, $LVEF$ (%)	yes	yes	yes	yes
Maximal velocity of shortening, V_{max} (mm/s)	yes	yes	yes	no
Maximal rate of LV pressure rise, dP/dt_{max} (mmHg/s)	yes	minimal	yes	no
End-systolic ventricular elastance, E_{es} (mmHg/ml)	minimal	yes	yes	yes
Preload-adjusted maximal power, $PAMP$ (W/ml ²)	minimal	minimal	yes	yes
Strain (%)	yes	yes	yes	yes
Strain rate (s ⁻¹)	yes	yes	yes	yes
Maximal active elastance, $E_{a,max}$ (mmHg/ml)	no	no	yes	no
Maximal rate-of-change of LV pressure-normalized wall stress, $d\sigma^*/dt_{max}$ (s ⁻¹)	yes	no	yes	yes
Myocardial power index, $MSPI$ (W/ml)	no	no	yes	no

2.2 Overview of Cardiac Imaging Modalities

Cardiac imaging is an indispensable tool for disease diagnosis, evaluation of morphology and function to guide treatment. The non-invasive imaging modalities used in routine clinical settings are: echocardiography (echo), cardiac magnetic resonance (CMR), cardiac computed tomography (CT), and nuclear cardiology, which includes single-photon emission CT (SPECT) and positron emission tomography (PET). The summary of their clinical applications, advantages and limitations are shown in Table 2-2.

Table 2-2 Summary of cardiac imaging modalities

Modality	Principles	Advantages	Limitations	Applications
Echo	Piezoelectric crystalline transducer that converts electrical energy to ultrasound and vice versa.	• Affordable, portable • Assessment of cardiac structure, function and haemodynamic by manipulating the transducer without any risk to patient • Good temporal resolution	• Operator dependent • Limited acoustic window due to the position of the transducer on the chest wall • Poor spatial resolution	• First diagnostic test ordered whenever cardiac disease is suspected • Cardiac structure from transthoracic (TTE) or transoesophageal (TEE) 2D/3D echo • Cardiac function from 2D/3D, M-mode, colour Doppler, tissue Doppler imaging (TDI), stress echo • Cardiac haemodynamic from colour Doppler • Acute circulatory failure and haemodynamically unstable patient

				in emergency room and intensive care • Guide procedures and assessment of results in operation and interventional suites
CMR	Atomic nuclei (hydrogen-1) which is abundant in water and fat in the body with radiofrequency pulses in the presence of magnetic field	• Safe, no radiation • Excellent views of heart, pericardium, great vessels and adjacent structures	• Expensive and not readily available in some centres • Contraindications: pacemakers, metal implants, claustrophobia, arrhythmia or unable to carry out breath-holds	• Quantification of chamber volumes, mass and function • Assessment of cardiac structure • Viability and myocardial fibrosis assessment using late-gadolinium enhancement • Myocardial perfusion • Assessment of tissue iron loading
CT	Multiple x-ray images	• Superior spatial resolution • Short exam time	• Side effects due to iodine-containing	• Assessment of cardiac structure and coronary arteries • Calcium score

		• High sensitivity for calcified tissues	contrast media, ionizing radiation • Breath holding • Lower heart rates	
Nuclear (SPECT, PET)	Injection of radionuclide agents as tracers, followed by image acquisition by gamma camera with rest, exercise or medication-induced stress testing		• Poor spatial resolution • Exposure to radiation	• Myocardial perfusion

2.3 Heart Failure with Preserved and Reduced Ejection Fractions

HF, a disease that causes LV dysfunction, involves high healthcare cost and has high mortality. It is one of the most common diseases in the developed world and is increasingly prevalent in developing countries, especially among the ageing population [1].

HF patients are stratified into two groups, based on their LVEF. A patient who has signs and symptoms of HF, while LVEF is preserved, is characterized as HFpEF, otherwise, classified as HFrEF. In the past, HFpEF was referred to as diastolic HF (DHF) while systolic HF (SHF) corresponded with HFrEF. However, the terms DHF and SHF have been abandoned as diastolic dysfunction has been observed in all symptomatic HF patients, regardless of EF [66] and in recent years, evidence of systolic dysfunction, to a lesser extent, has even been demonstrated in patients with HFPEF [2-4]. It is still debatable whether HFpEF and HFrEF exist as part of one HF spectrum with HFpEF preceding HFrEF or represent two distinct syndromes of HF: HFpEF has concentric remodelling with high LV mass/volume ratio and mainly diastolic dysfunction, while HFrEF has eccentric remodelling with low LV mass/volume ratio [67, 68] and a combination of systolic-diastolic dysfunction (HFrEF) [5]. The characteristics of concentric remodelling are high peripheral resistance, low cardiac index and increased arterial stiffness which affect the diastolic function. Remodeling occurs in chronic volume overload associated with mitral or aortic regurgitation which induces LV chamber dilatation characterized by eccentric hypertrophy. The remodelling progress from normal to HF with characteristics of concentric remodelling and eccentric remodelling is shown in Figure 2-11. The complex mixture of systolic and diastolic dysfunction and variable degrees of LV remodelling underlying HFpEF poses challenges to diagnose and provide pharmacological treatment for HFpEF. Although HFpEF is fast becoming the most prevalent HF phenotype, with its prevalence relative to HFrEF is rising at a rate of about 1% yearly, research and clinical

trials have not lead to a single effective treatment, and prognosis of HFrEF has remained unaltered for the past 3 decades [69].

Recent evidence suggests that HFpEF may be developed from a number of individual abnormalities in cardiovascular reserve function – diastolic, systolic, chronotropic and vascular [70, 71].

Figure 2-11 Remodeling progress from normal to HF

2.3.1 Diastolic Dysfunction

LV diastolic dysfunction in HFpEF, which consists of abnormal relaxation and increased diastolic LV stiffness, has been well documented [72]. It results from interrelated stiffness change in extracellular matrix and cardiomyocytes of the myocardium, transmitted from one to the other via matricellular proteins.

Delayed relaxation is common in normal aging but is more prominent in HF and with hypertrophy. Relaxation can be quantified invasively by the rate of pressure decay, expressed by a time constant using various mathematical models to fit the invasive pressure data. However, these model may not adequately describe certain types of HF and may lead to erroneous conclusions. This approach has yet been applied in routine clinical practice. Instead, Doppler echo is currently being used to approximate relaxation [73].

Similarly, passive diastolic LV stiffness is rarely measured directly in clinical settings. The most accurate estimation of the LV diastolic pressure-volume relationship (DPVR) involves acquisition of multiple PV loops over a loading range to connect the points at late-diastole from these cycles. Single heart-beat estimation of DPVR is most often used. However, in patients who have genetic hypertrophic cardiomyopathy, single loop approach markedly underestimated LV stiffness [74]. Other non-invasive surrogate of diastolic stiffness measured using echo will be discussed in detail in the next section.

2.3.2 *Systolic Dysfunction*

In recent years, evidence of systolic dysfunction, to a lesser extent, has even been demonstrated in patients with HFpEF. Normal EF, apparently, does not necessarily indicate normal contractility. Regional measures of systolic function assessed by echo tissue Doppler imaging are impaired in HFpEF [4]. Other measures of myocardial contractility, assessed by midwall fractional shortening and particularly wall-stress-based contractility index, $d\sigma^*/dt_{max}$ formulated as maximal rate-of-change of pressure-normalized wall stress [5] obtained from echo images, are also reduced in HFpEF, compared to healthy subjects [2, 3]. However, end-systolic elastance (E_{es}), an intrinsic measure of contractile function, defined by the slope and intercept of the end-systolic pressure-volume relationship, is elevated in HFpEF [2]. From these findings, it is postulated that the same processes such as myocyte hypertrophy and stiffness and contribute to reduced myocardial contractility and limited systolic reserve [75].

2.3.3 Chronotropic Incompetence

Impairment in chronotropic reserve has been reported in HFpEF patients. It is depressed even compared with older, age-matched controls and independent of rate-slowing medication use [70, 71]. This is likely related to downstream deficits in β -adrenergic stimulation, similar to HFrEF, reduction in baroreflex sensitivity and impaired heart rate recovery [70, 76].

2.3.4 Vascular Dysfunction

Vascular stiffening is characteristic of aging, hypertension and diabetes, which are the common risk factors for HFpEF. It is further attenuated in patients with HFpEF [77, 78]. Vascular dysfunction in HFpEF is not only confined to systemic circulation. It is also frequently observed in patients with pulmonary hypertension which is due to both elevated left heart pressures and high pulmonary vascular resistance [79]. The impairments of both vascular and contractile function in HFpEF result in abnormal ventricular-arterial coupling. Arterial elastance (E_a) and ventricular elastance (E_{es}) are elevated in tandem in HFpEF.

2.4 Echocardiographic Assessment of Left Ventricular Systolic and Diastolic Functions

Echocardiography (echo) is the first imaging tool employed for diagnosis of heart failure. Conventional echo approaches to evaluate systolic and diastolic functions in clinical settings are discussed below.

2.4.1 Assessment of Systolic Function

LVEF is the most universally accepted measure of systolic function. There are several techniques to measure LVEF from echo: i) M-mode of the parasternal long-axis view, ii) Biplane Simpson's using 2D 4-chamber and 2-chamber views and iii) area-length method. Although criticized for its insensitivity to abnormal wall motion, LVEF measured from M-mode is believed to be the most reproducible method. In this method, LVEF was calculated as:

$$LVEF = \frac{\frac{LVID_d^3}{2.4+LVID_d} - \frac{LVID_s^3}{2.4+LVID_s}}{\frac{LVID_d^3}{2.4+LVID_d}} \times 100$$

(Eq. 2.21)

where $LVID_d$ and $LVID_s$ are LV internal diameter at diastole and systole, respectively, measured from M-mode.

Other measures of myocardial contractility, namely endocardial fractional shortening (eFS) and midwall fractional shortening (mFS) are also determined from parasternal long-axis M-mode images.

$$eFS = 100 \times \frac{LVID_d - LVID_s}{LVID_d}$$

(Eq. 2.22)

$$mFS = 100 \times \left(1 - \frac{\frac{LVID_s}{2} + \frac{PW_s}{2}}{\frac{LVID_d}{2} + \frac{PW_d}{2}} \right)$$

(Eq. 2.23)

2.4.2 Assessment of Diastolic Function

To assess myocardial relaxation, velocity of mitral annular during early filling, E' , was measured, as shown in Figure 2-12. The normal values in healthy controls for E' is above 10cm/s, at septal annulus, and above 15cm/s at lateral annulus, and will increase with exercise to achieve lower LV diastolic pressure and thus, increase early filling.

Figure 2-12 Pulsed tissue Doppler image for measurement of mitral septal annulus velocity during contraction (S'), rapid filling (E') and atrial contraction (A')

Diastolic dysfunction is classified into 3 groups, based on mitral inflow velocities during early filling (E) and atrial contraction (A), as well as deceleration time (DT), measured from pulsed Doppler flow image (Figure 2-13).

Figure 2-13 Pulsed colour Doppler flow image with sample size placed at the tip of the mitral leaflet for measurement of peak rapid filling (E) and atrial contraction (A) velocities and deceleration time (DT)

Grade 1 diastolic dysfunction is characterized by $E/A < 1$ and $DT > 240$ ms. This diastolic pattern is also commonly seen in elderly individuals due to reduced myocardial relaxation with ageing. Grade 2 diastolic dysfunction is characterized by $E/A > 1$ and DT from 160-240 ms, like the normal flow pattern. However, this pseudo-normal stage is often present with increased E/E' ratio and shorter duration of antegrade atrial flow compared to pulmonary atrial reversal flow. Grade 3 diastolic dysfunction, which is the most advanced stage is characterized by increased $E/A > 2$ and short $DT < 160$ ms. The changes in mitral inflow velocities and tissue Doppler mitral annulus velocities with deterioration of diastolic function are shown in Figure 2-14.

Figure 2-14 Changes in mitral Doppler velocity and tissue Doppler velocity with LV filling patterns from normal to impaired relaxation (grade 1 DD) , pseudonormal (grade 2 DD) and restrictive physiology (grade 3 DD)

Another parameter for assessment of diastolic function is LA size. Patients with increased filling pressure were found to have enlarged LA size [80].

Further, isovolumic relaxation time (IVRT) is used to estimate LA pressure. Short IVRT (< 60 ms) suggests increase LA pressure [81].

The above mentioned echo parameters are currently being routinely used to assess systolic and diastolic functions in HF in clinical settings. These measurements, however, are based on simplified haemodynamic assumptions and varied with loading conditions. Hereby, novel echo approaches to determine intrinsic measures of systolic and diastolic functions would be developed.

CHAPTER 3. INTRA-LEFT VENTRICULAR DIASTOLIC AND SYSTOLIC FLOW DISTRIBUTIONS

3.1 Background²

Intra-cardiac flow is useful for evaluating cardiac function as it is the end-result of cardiac myocardial abnormalities. The vortex flow that forms during left ventricular filling is a critical determinant of direct blood flow during ejection, and can offer a novel index of cardiac dysfunction.

CMR has been used for examining detailed blood flow patterns in the heart and great vessels for a range of clinical conditions [6-8]. In parallel with non-invasive imaging techniques, computational fluid dynamics (CFD) has been used for examining the global flow patterns and pressure distribution since the 1970s and 1980s [9, 10]. The early models were confined to one- or two-dimensions with simplified geometries and fluid-ventricular wall interactions were subsequently incorporated into the CFD models to obtain velocity and pressure distributions in the LV, as well as stress distributions within the wall [11-13].

However, CMR is relatively expensive and not readily available. Further, this phase contrast velocity mapping technique has limited spatio-temporal resolution, requires additional scans and is time consuming. It is thus not a routinely used technique in clinical settings.

Recent developments in echocardiography enable assessment of intra-cavitary blood flow patterns by tracking the patterns produced by contrast agent particles, called particle imaging velocimetry (echo-PIV) technique [16, 17, 82]. However, this technique requires injection of

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² The content of this chapter is published in Le et al: Intra-Left Ventricular Flow Distributions in Diastolic and Systolic Phases, Based on Echo Velocity Flow Mapping of Normal Subjects and Heart Failure Patients, to Characterize Left Ventricular Performance Outcomes of Heart Failure. *Journal of Mechanics in Medicine and Biology* 2012, 12(5), 1240029 (19 pages). Permission to use as part of the thesis has been obtained from co-authors.

contrast agent, which might lead to serious side effects and has limited velocity range due to tracking algorithm.

Vector flow mapping (VFM) technique has been recently developed to generate flow velocity vector fields by post-processing colour Doppler echo images. There are several algorithms proposed to compute vector fields from Doppler flow. Ohtsuki and Tanaka [83] have deconstructed the flow into a basic non-vortical laminar motion and a vertical component. The colour Doppler velocity (axial velocity, u) profile was analysed across an arc as shown in Figure 3-1 at each echo depth.

The Doppler velocity u along the beam line is composed of basic non-vortical laminar flow (u_b) and vortex flow (u_v) components. If the Doppler velocity profile on the arc has both negative and positive fractions, it is considered to be a combination of non-vortical and vertical laminar flows. The vortex feature is assumed to be bilaterally symmetric so that the negative and positive components of u_v perpendicular to the arc negate each other.

Figure 3-1 Velocity generated by VFM, using method described by Ohtsuki and Tanaka [83], along an arc at each echo depth with a combination of single laminar flow and vortex flows (Top left). Colour Doppler flow data are separated into basic and vortex flow components so that vortex flow component is bilaterally symmetrical on each arc (Top right); At a given pixel, colour Doppler velocity u along the beam line is a sum of its vortex flow component u_v and basic flow component u_b . The vortex flow component consists of colour Doppler velocity u_v and radial velocity v_v . Likewise, the basic flow component consists of colour Doppler velocity u_b and radial velocity v_b . Flow vector is the sum of flow vectors of basic and vortex flow components (Bottom).

The basic flow component u_b is computed as:

$$u_b = u - u_v$$

(Eq. 3.1)

The radial vortex flow component v_v is computed as:

$$v_v = -\frac{\partial \psi}{\partial \theta} \quad (\text{Eq. 3.2})$$

where r and θ are radial and angle coordinates expressing the location of the pixel, and stream function $\psi(r, \theta)$ can be expressed as:

$$\psi(r, \theta) = \int_0^\theta u_v(r, \theta) r d\theta \quad (\text{Eq. 3.3})$$

The radial basic flow component v_b can then be found as:

$$v_b = u_b \tan \theta \quad (\text{Eq. 3.4})$$

However, boundary conditions were not considered in this algorithm and thus, near-wall flow affected by the LV wall motion was not included. Garcia *et al.* [18] proposed an algorithm based on the continuity equation and incorporated wall tracking as boundary conditions. A polar coordinate system was assumed, with its center located at the head of the probe. The radial component of the blood velocity (V_r) was measured by colour Doppler. The azimuthal component was derived from 2D continuity equation:

$$\frac{\partial V_\theta}{\partial \theta} = -r \frac{\partial V_r}{\partial r} - V_r \quad (\text{Eq. 3.5})$$

The azimuthal velocities at the two opposite walls ($V_{\theta}^{-}(r)$ and $V_{\theta}^{+}(r)$) of the LV were determined from echo speckle tracking algorithm as boundary condition. The flow velocity fields are acquired:

$$V_{\theta+} = \int_{\theta}^{\theta+} \left(r \frac{\partial V_r}{\partial r} + V_r \right) d\theta$$

(Eq. 3.6)

$$V_{\theta-} = \int_{\theta-}^{\theta} \left(-r \frac{\partial V_r}{\partial r} - V_r \right) d\theta$$

(Eq. 3.7)

To reduce the error in calculation of V_{θ} , $V_{\theta}^{-}(r)$ and $V_{\theta}^{+}(r)$ were combined with a weight function:

$$V_{\theta} = wV_{\theta}^{-} + (1 - w)V_{\theta}^{+}$$

(Eq. 3.8)

The above method involve solving the differential equation. However, as colour Doppler data are known to be noisy, sufficient data smoothing is required. Therefore, Itatani et al [19] applied Gaussian averaging filter to stabilize the differential term.

This 2D velocity reconstruction algorithm has shown good correlations with in vitro laser particle image velocimetry (PIV) measurements, in terms of vortex radius ($r = 0.72$), vortex circulation ($r = 0.85$) and relative distance from the vortex to the mitral valve ($r = 0.91$), and in vivo phase contrast MR, with relative error bound between 15-20% [18]. Validation of the VFM algorithm with CFD by Itatani et al. has also shown good correlation in both horizontal ($r^2 = 0.772$) and vertical ($r^2 = 0.982$) components.

As blood flow in the LV is complex three-dimensional (3D), assumption of 2D planar flow obtained from echo three-chamber long-axis plane which passes through the LV apex, the centre of the mitral and the aortic valves was made. Phase-contrast MR experiments have shown that through-plane flow components are relatively smaller than the in-plane components and are thus negligible [18, 84].

3.2 Aim

To obtain intra-LV flow patterns for patients with HFrEF, HFpEF with different degrees of diastolic dysfunction and controls, in order to characterize the LV performance outcomes of normal subjects and HF patients.

3.3 Methodology

3.3.1 Subject Recruitment

3 HFpEF patients with Grade 1, 2 and 3 diastolic dysfunction (DD), 1 HFrEF patient and 2 normal controls were recruited. Subjects who met 2 major or 1 major plus 2 minor modified Framingham criteria (Table 3-1) were diagnosed to have HF and enrolled in the study. Patients were then stratified based on LVEF measured from echo, into HFpEF (LVEF $\geq$ 50%) and HFrEF (LVEF < 50%). Written informed consent was obtained prior to scan and the study protocol had been approved by the hospital's ethics review board³.

Table 3-1 Modified Framingham criteria for diagnosis of chronic heart failure

Major	Minor
History of heart failure	Extremity edema
Paroxysmal nocturnal dyspnea	Night cough
Pulmonary or interstitial edema (on chest X-ray)	Dyspnea on exertion
Rales	Hepatomegaly

³ Singhealth Centralised Institutional Review Board, study number CIRB 2009/1003/C.

S3 gallop	Pleural effusion
Cardiomegaly	Tachycardia (≥ 130 beats per min)
Jugular venous distention	
Positive hepatjugular reflux	

3.3.2 Echocardiography

All subjects underwent echocardiography (Alpha 10, Hitachi Aloka). The LVEF and LV mass was measured from echo M-mode images at the parasternal long-axis view using standard methodology. Stroke volumes (SV), Mitral E and A velocities, deceleration time (DT), systolic (PVs) and diastolic (PVd) pulmonary vein velocities were measured from pulsed wave Doppler images, while the septal E' velocity was measured from pulsed tissue Doppler images. Isovolumic relaxation time (IVRT) was measured from continuous wave Doppler images with cursor placed between aortic and mitral valves.

Grading of diastolic dysfunction was based on EAE/ASE guidelines [85, 86] for values of E/A ratio and DT as shown in Chapter 2 (Figure 2-14).

Colour Doppler flow images were captured at the 3-chamber view for VFM analysis (Hitachi Aloka, F75). Manual de-aliasing was performed to double the velocity range input to remove aliasing and noise. The pixel-wise Doppler velocity values were extracted from Doppler flow images. The velocity vector distributions throughout the cardiac cycle were then computed from these pixel-wise Doppler velocity values using the algorithm described in Section 3.1 (Hitachi Aloka, RS-DAS1) and compared among all subjects. The LV outflow rates during systole and inflow rates during diastole were determined by computing the flow rates passing through a line drawn across the LV outflow tract (LVOT) during systole (Figure 3-2) and a line across the MV annulus during diastole (Figure 3-3).

Figure 3-2 illustrates measurement of maximal flow rate into the aorta using VFM. The figure on the left shows the velocity vector distribution in the LV during systole; therein, the arrows denote velocity vectors, and the red dots indicate heads of the arrows; a line is drawn at the LVOT to determine the maximum flow rate ejected into the aorta. In the figure on the right, we can see the flow profile through the line drawn at the LVOT at a time instant.

Figure 3-2 Measurement of flow rate into the aorta using vector flow mapping (VFM) at a time instant marked on the ECG signal. (Left) Velocity vector distribution in the LV during systole. Arrows denote velocity vectors. Red dots indicate heads of the arrows. A line was drawn at the LVOT to determine the maximum flow rate ejected into the aorta. (Right) Flow profile through the line drawn at LVOT at a time instant.

Figure 3-3 Measurement of flow rate across the mitral valve using vector flow mapping (VFM) at a time instant marked on the ECG signal. (Left) Colour Doppler flow image of the LV is captured at the 3-chamber long-axis view. A line is drawn across the mitral annulus. (Right) Vector flow profile across the line drawn, at a time instant, is computed by VFM. Qtotal (as shown in the bottom right) is the total flow rate measured across the mitral annulus line.

3.4 Results

3.4.1 Baseline demographics, clinical characteristics and conventional echo parameters

Baseline demographics, clinical characteristics as well as echo parameters of all subjects are shown in Table 3-2.

Table 3-2 Baseline demographics, clinical characteristics and echo parameters of all subjects

	Normal	Normal	HFpEF	HFpEF	HFpEF	HFrEF
		ageing	DD Grade 1	DD Grade 2	DD Grade 3	
Age (years)	47	70	67	47	73	56
Sex	M	M	M	M	F	M
SBP (mmHg)	124	155	134	83	98	110
DBP (mmHg)	70	73	63	62	64	80
Heart rate (bpm)	53	88	82	86	67	98
LVEF (%)	72	54	62	76	77	11
LVMl (g/ m²)	91	54	97	90	115	138
LVEDVI (ml/m²)	64	38	46	87	70	103
SV (ml)	84	63	44	36	34	34
E/A	1.5	0.7	0.7	1.5	2.7	1.72
Septal E/E'	8.1	7.0	12.5	17.5	27.7	17.9
PVs/PVd	1.2	1.4	-	0.6	0.6	0.4
DT (ms)	198	246	265	188	116	112
IVRT (ms)	72	72	114	108	78	90

3.4.2 *Systolic flow patterns*

Systolic flow patterns for each of the 6 subjects: young normal, normal ageing, HFpEF DD1, HFpEF DD2, HFpEF DD3, HFrEF are shown in Figure 3-4.

At isovolumic contraction (frame 1), LV contraction produced recirculating flow patterns and directed flow towards the aortic valve. At early systole (frame 2), flow was seen to be pouring out of the LV; however, recirculating flow was observed at the proximal posterior wall, near the MV area, in all subjects. In normal controls, peak outflow velocity was observed at early systole (frame 2) while for the rest of the subjects, the flow ejected more rapidly at mid systole (frame 3) and gradually reduced at the end of systole (frame 4). In subject HFpEF DD3 and HFrEF, persistent low velocity recirculating flow was seen throughout the systolic phase.

At isovolumic relaxation (frame 5), there was virtually no flow in the LV of HFpEF patients and normal subjects. However, some flow circulation was still present in HFpEF DD1, HFpEF DD2 and HFrEF, who had prolonged IVRT (as seen in Table 3-2).

Figure 3-4 Systolic flow patterns for (from top to bottom) normal, normal ageing, HFpEF with abnormal relaxation (grade 1 diastolic dysfunction), HFpEF with pseudonormal filling pattern (grade 2 diastolic dysfunction), HFpEF with restrictive physiology (grade 3 diastolic dysfunction), and HFrEF at (from left to right) isovolumic contraction (frame 1), early systole (frame 2), mid systole (frame 3), late systole (frame 4), and isovolumic relaxation (frame 5). Arrow represents velocity flow vector. Red dot indicates the head of the arrow.

3.4.3 Diastolic flow patterns

Diastolic flow patterns for each of the 6 subjects: young normal, normal ageing, HFpEF DD1, HFpEF DD2, HFpEF DD3, HFrEF are shown in Figure 3-5.

After MV opened, in the rapid filling phase (frame 1), straight flow was seen rushing into the LV from the LA. Circulating flow patterns were seen at the anterior and posterior walls of the LV in all subjects. In ageing, HFpEF DD1 and HFrEF subjects, the rapid filling phase started later in the cardiac cycle (near onset of P wave).

As inflow propagated further towards the apex, the circulating patterns at both anterior and posterior walls became bigger (frame 2).

In the diastasis phase (frame 3, marked by P wave on the ECG), the flow patterns differed between young normal control versus ageing and HF subjects. In young normal control, there was virtually no flow during this phase. In ageing and HF subjects, inflow continued to enter the LV, with 2 circulating flows seen at both anterior and posterior walls. The circulating flow was more prominent at the anterior wall in all these subjects.

At atrial contraction, after P wave on the ECG (frame 4), as LA contracted, the flow started to enter LV in normal control subject, after a period of no flow. Profound circulating pattern at the anterior wall was observed in the rest of the subjects. These circulating flow features remained until the end of the atrial contraction (frame 5).

Figure 3-5 Diastolic flow patterns for (from top to bottom) normal, normal ageing, HFpEF with abnormal relaxation (grade 1 diastolic dysfunction), HFpEF with pseudonormal filling pattern (grade 2 diastolic dysfunction), HFpEF with restrictive physiology (grade 3 diastolic dysfunction), and HFrEF at (from left to right) the start of rapid filling phase (frame 1), late rapid filling (frame 2), diastasis (frame 3), start of atrial contraction (frame 4), and end of atrial contraction just before mitral valve closes (frame 5). Arrow represents velocity flow vector. Red dot indicates the head of the arrow.

3.5 Discussion and Conclusion

3.5.1 *Intra-left ventricular flow patterns in HF patients versus controls*

Herein, the use of VFM technique to visualize blood flow patterns in HF patients versus normal subjects have been demonstrated.

At the start of systole, when MV closes, LV pressure increases without a change in volume during isovolumic contraction, until LV pressure exceeds the aortic pressure and AV opens. LV will then start to eject blood into the aorta. In ageing and HF subjects, velocity of blood ejected from the LV reached its peak later in the ejection phase, as compared to normal control subject. This might be due to: i) increased in aortic pressure (in the case of ageing, and HFpEF DD1 subjects, of which SBPs were in the higher range) and/or ii) reduced contractility which needs to be evaluated in later work.

In isovolumic relaxation, when both valves close, LV pressure falls without a change in volume, until it is below the LA pressure. The LA-LV pressure gradient opens the MV and rapid filling phase starts. In ageing, HFpEF DD1 and HFrEF subjects, there was delay in the start of rapid filling, which might be due reduced elastic recoil (in the case of ageing and HFpEF DD1) and/or dilated LV (in the case of HFrEF).

During diastasis phase, marked by P wave on ECG, the pressure in LV and LA equilibrates, thus flow through mitral valve nearly ceases. However, mitral inflow was observed in all subjects except for normal control, indicating possible increased LA pressure or shortened diastolic filling time (due to increased isovolumic relaxation time).

In atrial contraction, LV continued to be filled. The contribution of LA systole to LV filling shall be investigated separately in the next chapter. Large circulating flow features seen at the anterior wall may help to direct flow from the apex towards aorta, in preparation for LV ejection.

Due to small sampling size, statistical significance was not achieved.

3.5.2 Intra-left ventricular flow patterns variation

The VFM analysis has provided similar common flow patterns to those obtained from combination of CFD and MRI [15] and contrast echo [17]. Even though colour Doppler images have much lower temporal resolution compared to two-dimensional echo images used for echo PIV, the current frame rates of 20-30 frames/seconds are quantifiably comparable to those obtained by phase-contrast MRI. This technique, thus, is potential applicable in clinical applications, as colour Doppler echo is widely used in routine clinical practice.

3.5.3 Conclusion

In conclusion, flow patterns in HF patients with various degrees of diastolic dysfunction, as well as controls, were visualized using novel VFM technique, derived from echo Doppler flow images. This offers quick understanding into haemodynamic changes brought on by disease progression. It would also provide quantitative tool for functional assessment of chambers which will be explored in the following chapters.

CHAPTER 4. NON-INVASIVE ASSESSMENT OF LEFT ATRIAL CONTRACTILE FUNCTION IN TERMS OF MAXIMUM LOAD-ADJUSTED LEFT ATRIAL EJECTION FORCE

4.1 Background

Assessment of LV diastolic function is usually focused on determining LV filling, neglecting the LA contraction component which accounts for 10 – 20% of LV filling at rest in healthy people. However, in the presence of heart diseases or with normal aging, LA contribution to LV filling changes. Association between HFpEF and LA dysfunction has been demonstrated in cross-sectional [87] and longitudinal studies [88]. However, non-invasive determination of LA contractile dysfunction to evaluate the changes in LA haemodynamics and its contribution to LV diastolic performance is difficult. LA functional parameters, including LA ejection fraction, septal and lateral mitral annulus A' velocities measured from pulsed tissue Doppler echo, and systolic LA strain and strain rate measured from colour tissue Doppler echo, assessed by pulsed wave Doppler measurements of late mitral A diastolic filling velocity [89], are dependent on age and loading conditions [90, 91]. These indices do not adequately characterize LA contractility because they are not intrinsically representing the contractile force exerted by LA. There is hence a need to develop an intrinsic index of LA contractile function.

The concept of LA ejection force (LAEjF) was first introduced by Manning [92] based on Newton's second law of motion, with the assumptions of constant acceleration and circular mitral orifice. It is measurable by echo using the formula of $\frac{1}{2} \times \rho \times \text{Mitral orifice area} \times (\text{Peak A velocity})^2$. Unlike conventional LA functional parameters, LAEjF is a measure of biomechanical function which takes into account both acceleration and mass of blood ejected

by LA to LV. Later on, Tokushima [93] formulated LAEjF based on the principle of hydrodynamics, as $\frac{1}{3} \times \rho \times \text{Mitral orifice area} \times (\text{Peak A velocity})^2$.

Refined echo techniques, using 3D echo to compute area of the ellipsoidal-shaped mitral orifice and A velocity measured at the mitral valve annulus, were then developed by Zhong et al [94, 95] to compute LAEjF from the latter formula. However, there were limitations in using these formulae due to (i) non-simultaneous measurements of mitral orifice area and A velocity and (ii) assumption of uniform velocity distribution across the valve (plug flow).

4.2 Aim

To formulate instantaneous LAEjF and propose a novel index of LA contractility in HF patients and controls.

4.3 Methodology

4.3.1 Subject recruitment

Seventy subjects (30 controls, 20 HFpEF and 20 HFrEF patients) were recruited for the study. All controls did not have history of hypertension, diabetes mellitus and not under any cardiac medications. The HF patients were identified based on the presence of signs and symptoms of congestive HF, from modified Framingham criteria as shown in Table 3-1 [96]. HFpEF and HFrEF were then stratified based on LVEF ($\geq 50\%$ for HFpEF and $<50\%$ for HFrEF), measured from echo imaging. Each of the HF patients represents a different grade of diastolic dysfunction: Grade 1 – Abnormal relaxation, Grade 2 – Pseudo-normal filling pattern, Grade 3 – Restrictive filling pattern. Grading of diastolic dysfunction was done using echo parameters, based on EAE/ASE guidelines [86]. Written informed consent was obtained prior to scan and the study protocol had been approved by the hospital's ethics review board.

4.3.2 Echocardiography

All subjects underwent echo scans (Hitachi-Aloka Alpha 10). LVEF and mass (LVM) were measured from M-mode images at the parasternal long-axis view using standard methodology. Mitral E and A velocities, DT, systolic (PVs) and diastolic (PVd) pulmonary vein velocities were measured from pulsed wave Doppler images, while septal E' velocity was measured from pulsed tissue Doppler images.

The LA volumes at end-systole (LAV_{max}), end-diastole (LAV_{min}) and before atrial contraction, measured at onset of P wave (LAV_{pre-A}) were measured using biplane area-length method [67].

The LA passive emptying fraction, LApEF, was calculated as:

$$100 \times \frac{LAV_{max} - LAV_{pre-A}}{LAV_{max}} \quad (\text{Eq. 4.1})$$

The LA active emptying fraction, LAaEF, was calculated as:

$$100 \times \frac{LAV_{pre-A} - LAV_{min}}{LAV_{pre-A}} \quad (\text{Eq. 4.2})$$

All the volume and mass measurements were indexed to body surface area.

Colour Doppler flow images were captured at three-chamber long-axis views for VFM analysis (DAS-RS1, Aloka).

4.3.3 Calculation of Left Atrial Ejection Force

Based on Newton's law of motion, the force exerted by the fluid is equal to the rate of change of momentum. Therefore, left atrial ejection force, LAEjF, at time instant i is:

$$LAEjF_i = \frac{m_i v_i - m_{i-1} v_{i-1}}{\Delta t} \quad (\text{Eq. 4.3})$$

where m is mass of blood ejected by LA across the mitral valve, v is blood velocity at the mitral valve annulus, and Δt is time difference between 2 instants.

In order to determine m and v , a line was drawn across the mitral annulus at each time instant, as shown in Figure 3-3. The flow rate, F [cm^2/s], across this line was computed by VFM software. The details of VFM calculation of velocity vectors can be found in Chapter 3 and in previous publications [18, 19].

Flow volume at time instant i , V_i :

$$V_i = \left(\frac{\pi}{4}\right) D_i \cdot D_i \cdot \text{vel} = \pi \frac{D_i}{4} F_i \Delta t \quad (\text{Eq. 4.4})$$

The velocity across the mitral annulus line (Figure 3-3) at time instant i is computed as:

$$v_i = \frac{F_i}{D_i} \quad (\text{Eq. 4.5})$$

Combining (Eq. 4.4) and (Eq. 4.5), (Eq. 4.3) becomes:

$$LAEjF_i = \frac{\rho \pi \frac{D_i}{4} F_i \Delta t \frac{F_i}{D_i} - \rho \pi \frac{D_{i-1}}{4} F_{i-1} \Delta t \frac{F_{i-1}}{D_{i-1}}}{\Delta t} = \frac{\pi}{4} \rho (F_i^2 - F_{i-1}^2) \quad (\text{Eq. 4.6})$$

where ρ , the blood density, equals to 1.06 g/cm^3 .

The maximum LAEjF, $\text{LAEjF}_{\max}$, was determined from the instantaneous LAEjF. $\text{LAV}_{\text{pre-A}}$ can be considered as a measure of atrial preload before LA contraction. E/E' ratio, which is a surrogate marker of LV filling pressure, can be considered as a measure of atrial afterload.

Therefore, to adjust for atrial preload and afterload, $\text{LAEjF}_{\max}$ was divided with $\text{LAV}_{\text{pre-A}}$ and E/E' ratio, respectively. Maximum load-adjusted $\text{LAEjF}_{\max}$ was proposed to be an index of LA contractility.

4.3.4 Biomarkers

Blood analysis was performed within 7 days from the date of echo scan to measure the following biomarkers:

- N-terminal-pro-brain natriuretic peptide (NT-proBNP), which is produced from the atria and ventricles and is released into the circulation in response to increased wall tension [97]. NT-proBNP is raised in both symptomatic and asymptomatic patients with LV dysfunction [98].
- Creatinine kinase (CK) and CK-MB, for diagnosis of acute myocardial infarction.
- Troponin T (TnT), protein involved in the regulation of cardiac and skeletal muscle contraction and is released from injured myocardium.

4.3.5 Statistical analysis

Non-parametric Mann-Whitney U test was performed for pairwise comparison between the groups. Non-parametric correlation was used to assess linear association between parameters. All tests were done using SPSS software (version 20, IBM).

4.4 Results

4.4.1 Baseline demographics and clinical characteristics

Baseline demographics and clinical characteristics of HFrEF, HFpEF patients and controls are shown in Table 4-1 and Table 4-2. Values are expressed as median (interquartile range). There were no significant difference between the groups.

Table 4-1 Baseline demographics of patients with HFrEF, HFpEF and controls. § denotes statistically significant difference compared to controls (p<0.05).

	HFrEF	HFpEF	Controls
	(n = 20)	(n = 20)	(n = 30)
Gender (M:F)	14:6	10:10	16:14
Age (years)	61 (52 – 68) §	66 (49 – 78)	50 (45 – 59)
Height (m)	1.63 (1.53 – 1.71)	1.58 (1.49 – 1.65)	1.63 (1.57 – 1.70)
Weight (kg)	66.5 (57.5 – 82.5)	66.7 (61.0 – 73.3)	68.5 (63.8 – 76)
SBP (mmHg)	117 (110 – 136)	137 (107 – 156)	128 (118 – 139)
DBP (mmHg)	65 (58 – 82)	64 (59 – 72) §	74 (68 – 78)
Heart rate (beats/min)	76 (57 – 90)	67 (55 – 79)	69 (64 – 76)

Table 4-2 Clinical characteristics of patients with HFrEF versus HFpEF

	HFrEF	HFpEF
	(n = 20)	(n = 20)
NYHA class (I:II:III:IV)	5:5:5:5	5:9:6:0
Hypertension (n (%))	16 (80)	18 (90)
Diabetes mellitus (n (%))	13 (65)	15 (75)
Hyperlipidaemia (n (%))	16 (80)	16 (80)
Left ventricular hypertrophy on ECG (n (%))	8 (40)	5 (25)
Troponin T (µg/l)	0.05 (0.03 – 0.07)	0.07 (0.03 – 0.12)
CK-MB (µg/l)	3.6 (2.5 – 5.3)	4.2 (2.9 – 8.7)
CK (u/l)	105 (63 – 181)	161 (70 – 308)
NT-proBNP (pg/ml)	5818 (1703 – 15813)	3668 (1838 – 8164)

4.4.2 Diastolic echo parameters

Conventional diastolic echo parameters as well as load-adjusted $\text{LAEjF}_{\max}$ are shown in Table 4-3.

Compared to controls, HFpEF and HFrEF patients had higher E/E' ratio, lower S/D ratio, prolonged IVRT. It is of note that increased E/E' is associated with increased LV filling pressure [99] and increased pre-atrial contraction (pre-A) pressure in the LA [100]. Indexed-LA volumes at the start of LV diastole, pre-A and end of LV diastole were larger while LAaEF is reduced in HFpEF patients.

$\text{LAEjF}_{\max}$ was adjusted for loading conditions by dividing with $\text{LAV}_{\text{pre-A}}$ (LA preload) and E/E', as it is considered as a measure of LV filling pressure (LA afterload). The load-adjusted $\text{LAEjF}_{\max}$ was reduced in both groups of HF patients, as compared to controls.

Table 4-3 Conventional diastolic echo parameters and load-adjusted maximum left atrial ejection force in patients with HFrEF, HFpEF and controls. § and # denote statistically significant difference compared to controls and HFpEF patients, respectively ($p < 0.05$).

	HFrEF	HFpEF	Controls
	(n = 20)	(n = 20)	(n = 30)
LVMI (g/m^2)	120 (104 – 149) ^{§#}	82 (64 – 101)	65 (54 – 74)
E/A	2.94 (1.37 – 4.62) [§]	1.22 (0.90 – 2.49)	1.04 (0.78 – 1.40)
DT	156 (108 – 184) ^{§#}	202 (149 – 234)	201 (179 – 241)
E/E'	19.9 (16.0 – 31.4) [§]	15.2 (12.5 – 24.0) [§]	7.0 (6.0 – 8.1)
S/D	1.3 (0.5 – 1.4)	0.7 (0.6 – 1.2) [§]	1.4 (1.1 – 1.6)
IVRT (ms)	103 (84 – 126) [§]	114 (93 – 123) [§]	78 (70 – 86)
LApEF (%)	19 (14 – 23) [§]	21 (14 – 30)	36 (23 – 43.8)
LAaEF (%)	10 (5 – 16) ^{§#}	29 (19 – 40) [§]	44 (35 – 50)
LAVI _{max} (ml/m^2)	46.6 (36.1 – 53.5) [§]	42.4 (35.4 – 53.6) [§]	27.9 (22.3 – 31.8)
LAVI _{pre-A} (ml/m^2)	39.0 (30.0 – 44.4) [§]	32.8 (24.7 – 41.5) [§]	16.8 (14.7 – 23.1)
LAVI _{min} (ml/m^2)	33.9 (23.6 – 41.8) [§]	22.4 (15.4 – 33.4) [§]	10.0 (8.4 – 13.2)
Load-adjusted LAEjF _{max} ($\times 10^{-3} \text{N}/\text{m}^3$)	0.48 (0.04 – 1.26) [§]	1.52 (0.66 – 4.00) [§]	7.63 (3.22 – 11.67)

4.4.3 Maximum load-adjusted left atrial ejection force across diastolic dysfunction grades

Grading of diastolic dysfunction in HF patients was done based on EAE/ASE guidelines [85, 86] for values of E/A ratio and DT: i) Grade 1 ($n = 8$), impaired relaxation, $E/A < 0.8$, $DT > 240\text{ms}$, ii) Grade 2 ($n = 14$), pseudo-normalization, $0.8 < E/A < 1.6$, $160\text{ms} < DT < 240\text{ms}$, and iii) Grade 3 ($n = 18$), restrictive filling, $E/A > 1.6$, $DT < 160\text{ms}$.

Among the 30 normal controls, 6 subjects who are above 60 years of age were classified as normal ageing.

Median (interquartile range) of LAaEF and load-adjusted LAejF_{max} across diastolic dysfunction grades, normal ageing and controls were plotted in Figure 4-1 and , respectively.

Compared to controls, there were a tendency of reduced LAaEF and load-adjusted LAejF_{max} in HF patients as diastolic function worsened. LAaEF appeared to increase in normal ageing subjects as compared to younger controls. However, load-adjusted LAejF_{max} of ageing subjects reduced.

Spearman's correlation tests showed negative association of LAaEF ($\rho = -0.673$, $p < 0.001$) and load-adjusted LAejF_{max} ($\rho = -0.702$, $p < 0.001$) versus severity of diastolic dysfunction and ageing.

Figure 4-1 Left atrial active emptying fraction in HF patients with different diastolic dysfunction grades, normal ageing and controls

Figure 4-2 Maximum load-adjusted left atrial ejection force in HF patients with different diastolic dysfunction grades, normal ageing and controls

4.5 Discussion and Conclusion

4.5.1 *Maximum load-adjusted left atrial ejection force at different stages of diastolic dysfunction*

In a normal heart, as the LV relaxes during early diastole, LV pressure falls rapidly below that of LA and thus creates a suction force to pull blood from the LA to the LV. This early diastolic phase is responsible for the majority of LV filling volume. In ageing or diastolic dysfunction cases, the LV relaxation rate reduces due to increased LV stiffness, and results in reduction in early diastolic filling and prolonged duration to reach LV-LA pressure equilibrium. In these cases, the LA contraction contributes a substantial proportion of the diastolic filling volume.

As LV early diastolic filling reduces (in ageing or diastolic dysfunction cases), more blood is left in the LA before its contraction phase, and hence results in increased LAV_{pre-A} (LA preload). Based on the Frank-Starling mechanism, as demonstrated in a previous study [101], there is an increase in LA contractility, as measured by LAaEF, in response to an increase in LA preload up to a point, beyond which the LAaEF decreased. This compensatory mechanism is used to explain the delay in appearance of symptoms in early stage of HF [102, 103], when LA can compensate well to the increased haemodynamic load of increased LAV_{pre-A} . Similar trend is observed with LAaEF in this study, with LAaEF slightly increased in normal ageing, which indicated increased LA contractility based on conventional approach, and decreased as diastolic dysfunction progressed.

Interestingly, the proposed novel LA contractility index, load-adjusted $LAEjF_{max}$, did not act in tandem with LAaEF. Load-adjusted $LAEjF_{max}$ gradually reduced in normal ageing and worsened as diastolic dysfunction became more severe. This is due to different physiological interpretation of the two indices, although both have been proposed as indicators of LA contractility. LAaEF, which is analogous to LVEF, is determined by the change in pre- and post-contraction volumes of the chamber and is highly dependent on volume measurements and loading conditions; this is the conventionally employed LA contractility index. On the other hand, $LAEjF_{max}$ is defined as maximum LA generated force during its contraction phase. In terms of mechanical definition of force, it is dependent on both chamber size and pressure generated by the chamber to eject blood. Herein, $LAEjF_{max}$ was normalized with chamber size before contraction, LAV_{pre-A} , to adjust for preload and E/E' ratio, which is a measure of LV filling pressure, to adjust for afterload. The load-adjusted $LAEjF_{max}$ thus can be considered as an intrinsic measure of contractility of LA. It is to be noted that in HF patients, increased LA stiffness may hinder the ability of LA to generate pressure during its contraction, despite augmented stroke volume, due to Frank-Starling mechanism [104]. It has been well

documented that LV and arterial stiffness increase in normal ageing. However, it is not known if LA stiffness also increases with ageing and as the result, contractile function of LA reduces.

From the results, it is postulated that decrease in load-adjusted $\text{LAEjF}_{\max}$ may precede decrease in LAaEF and is thus, might be more sensitive in assessing LA contractile function and its role in disease progress in ageing and early stage of HF.

4.5.2 Flow measurement by VFM

Flow through a surface is a product of surface area and mean velocity across it. In the previous formulae of the LAEjF, the flow across the mitral annulus was computed from pulsed Doppler peak A velocity, assuming that peak A velocity was equal to mean velocity across the annulus. However, this would be true only if flow through mitral annulus had uniformly distributed velocity vector (uniform plug flow). In fact, the flow profile across the valve has been shown be skewed from both magnetic resonance imaging [105] and echo vector mapping, as shown in Figure 3-2 and Figure 3-3. The shape of flow profile, therefore, compromises the use of local velocity measurements.

VFM, on the other hand, computes velocity vector at each pixel along the line drawn across the mitral annulus. The flow volume at each pixel is then calculated as the product of the mitral valve annulus area (of diameter equal to the length of this mitral annulus line) and velocity across this line, or, as shown in (Eq. 4.4), the product of mitral annulus line length, flow rate and pixel length. This calculation, therefore, takes into account different shapes of flow profile, which are dependent on multiple factors such as wall shear force, blood viscosity, interactions with mitral leaflets, etc.

4.5.3 Limitations of the study

To compute LAEjF in this study, the mitral annulus was assumed to have a circular shape of diameter D equal to the mitral annulus length (as shown in (Eq. 4.1)). However, applying circular geometry to calculate CSA may give similar results to elliptical CSA [106].

Besides, although echo Doppler temporal resolution, ranging from 20-25 Hz, is comparable to that of MRI, it is relatively low compared to pulsed echo Doppler. Therefore, instantaneous changes in LAEjF may not be detectable in subjects with short duration of LA contraction.

To adjust for afterload, LAEjF_{max} was normalized with E/E' ratio. To accurately determine LA afterload, invasive measurement of LV filling pressure needs to be performed. However, it is widely acceptable in clinical practice to use E/E' ratio as a surrogate for LV filling pressure [99].

Lastly, the effect of medications used in treatment of HF (vasodilator, beta-blocker) which alter LA compliance and loading conditions was not studied in this study. These shall be done in subsequent studies to compare LA contractility between a pool of HF patients and controls, and validate with invasive haemodynamic data.

4.5.4 Conclusion

In this chapter, a novel LA contractility index, load-adjusted LAEjF_{max}, was formulated and computed from instantaneous flow from the LA to the LV during LA contraction, obtained from novel VFM technique. The contribution of LA contraction during diastole has not been well quantified. By using load-adjusted LAEjF_{max}, this study has demonstrated a trend of gradual reduction in LA contractile performance in normal ageing subjects and across the diastolic dysfunction grades.

CHAPTER 5. NON-INVASIVE ASSESSMENT OF LEFT VENTRICULAR CONTRACTILE FUNCTION IN TERMS OF MAXIMUM PRELOAD-ADJUSTED LEFT VENTRICULAR EJECTION FORCE

5.1 Background

Evidence of systolic dysfunction, to a lesser extent compared to HFrEF, has been demonstrated in patients with HFpEF despite normal LVEF. Measures of systolic function, such as midwall fractional shortening [2] and strain and strain rate, measured from echo images [4], were reduced in HFpEF patients, as compared to healthy subjects. However, these measures of LV contractile performance are highly dependent on loading conditions which are found to be increased in HF patients [2]. Therefore, it is desirable to develop novel intrinsic contractility index that is load-independent.

The idea of LV ejection force (LVEjF) was introduced by Isaaz et al. [107] based on Newton's law of motion as: $LVEjF = \text{mass} \times \text{acceleration}$, where mass and acceleration were obtained from echo pulsed Doppler image across the LV outflow tract (LVOT). Unlike conventional LVEF, LVEjF is a measure of biomechanical function of LV which takes into accounts both acceleration and mass of blood ejected by LV to the aorta. However, there were limitations in using this formula due to (i) non-simultaneous measurements of LVOT area and LVOT velocity and (ii) assumption of uniform velocity distribution across the valve (plug flow).

5.2 Aim

To formulate instantaneous LVEjF and to propose a novel index for assessment of LV contractility in HF patients versus controls.

5.3 Methodology

5.3.1 Subject recruitment

The same seventy subjects (20 HFrEF, 20 HFpEF and 30 controls), as described in Chapter 4, Section 4.3.1, were enrolled in the study. Written informed consent was obtained prior to scan and the study protocol had been approved by the hospital's ethics review board⁴.

5.3.2 Echocardiography

All subjects underwent echo scans (Hitachi-Aloka Alpha 10). LVEF, LV end-diastolic volume (EDV) and mass (LVM) were measured from M-mode images at the parasternal long-axis view using standard methodology.

Single-beat end-systolic elastance (E_{es}) was calculated based on formula developed by Chen et al. [41]. Effective arterial elastance (E_a), which is a measure of ventricular afterload, was calculated as:

$$E_a = \frac{0.9 \times SBP}{SV} \quad (\text{Eq. 5.1})$$

where SBP is systolic blood pressure, measured from cuff auscultatory, and SV is stroke volume, measure from pulsed Doppler flow across the left ventricular outflow tract (LVOT).

Another measure of ventricular afterload, circumferential end-systolic wall stress (cESS), was also calculated as [108]:

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⁴ Singhealth Centralised Institutional Review Board, study number CIRB 2009/1003/C.

$$cESS = \frac{SBP \times \left(\frac{LVID_{es}}{2}\right)^2 \times \left(1 + \frac{\left(\frac{LVID_{es}}{2} + PW_{es}\right)^2}{\left(\frac{LVID_{es}}{2} + \frac{PW_{es}}{2}\right)^2}\right)}{\left(\frac{LVID_{es}}{2} + PW_{es}\right)^2 - \left(\frac{LVID_{es}}{2}\right)^2} \quad (Eq. 5.2)$$

where $LVID_{es}$ is LV internal diameter at end-systole and PW_{es} is posterior wall thickness at end-systole. Both parameters were measured from parasternal long-axis M-mode images.

Measures of myocardial contractility, namely endocardial fractional shortening (eFS) and midwall fractional shortening (mFS) were determined from parasternal long-axis M-mode images [108].

$$eFS = 100 \times \frac{LVID_d - LVID_s}{LVID_d} \quad (Eq. 5.3)$$

$$mFS = 100 \times \left(1 - \frac{\frac{LVID_s}{2} + \frac{PW_s}{2}}{\frac{LVID_d}{2} + \frac{PW_d}{2}}\right) \quad (Eq. 5.4)$$

5.3.3 Calculation of left ventricular ejection force

Based on Newton's law of motion, the force exerted by the fluid is equal to the rate of change of momentum. Therefore, left ventricular ejection force, LVEjF, at time instant i is:

$$LVEjF_i = \frac{m_i v_i - m_{i-1} v_{i-1}}{\Delta t} \quad (Eq. 5.5)$$

where m is mass of blood ejected by LV across the aortic valve, v is blood velocity at the aortic valve annulus, and Δt is time difference between 2 instants.

In order to determine m and v , a line was drawn across the LVOT at each time instant, as shown in Figure 3-2. The flow rate, F [cm^2/s], across this line was computed by VFM software. The details of VFM calculation of velocity vectors can be found in Chapter 3 and in previous publications [18, 19].

Flow volume at time instant i , V_i :

$$V_i = \left(\frac{\pi}{4}\right) D_i \cdot D_i \cdot \text{vel} = \pi \frac{D_i}{4} F_i \Delta t \quad (\text{Eq. 5.6})$$

The velocity across the LV outflow tract line (Figure 3-2) at time instant i is computed as:

$$v_i = \frac{F_i}{D_i} \quad (\text{Eq. 5.7})$$

Combining (Eq. 5.6) and (Eq. 5.7), (Eq. 5.5) becomes:

$$\text{LVEjF}_i = \frac{\rho \pi \frac{D_i}{4} F_i \Delta t \frac{F_i}{D_i} - \rho \pi \frac{D_{i-1}}{4} F_{i-1} \Delta t \frac{F_{i-1}}{D_{i-1}}}{\Delta t} = \frac{\pi}{4} \rho (F_i^2 - F_{i-1}^2) \quad (\text{Eq. 5.8})$$

where ρ , the blood density, equals to 1.06 g/cm^3 .

The maximum LVEjF, $\text{LVEjF}_{\max}$, was determined from the instantaneous LVEjF. It was then adjusted for LV preload by dividing $\text{LVEjF}_{\max}$ with LVEDV. Maximum preload-adjusted $\text{LVEjF}_{\max}$ was proposed to be an index of LV contractility.

5.3.4 Biomarkers

All subjects had blood sample collected and analysed for NT-proBNP, CK, CK-MB and TnT, as described in Chapter 4, Section 4.3.4.

5.3.5 Statistical analysis

Non-parametric Mann-Whitney U test was performed for pairwise comparison between the groups. Non-parametric correlation was used to assess linear association between parameters. All tests were done using SPSS software (version 20, IBM). Curve fitting was performed using Matlab (R2014a).

5.4 Results

5.4.1 Baseline demographics and clinical characteristics

All subjects' baseline demographics and clinical characteristics are shown in Table 4-1 and Table 4-2.

5.4.2 Echocardiographic parameters and preload-adjusted maximum left ventricular ejection force preload-adjusted $LVEjF_{max}$

Echocardiographic parameters and preload-adjusted $LVEjF_{max}$ of HFrEF, HFpEF patients versus controls are shown in Table 5-1. Values are expressed as median (interquartile range).

LV afterload, which was measured by cESS and E_a increased significantly in patients with HFrEF compared to controls. In patients with HFpEF, while arterial afterload significantly increased compared to controls, afterload assessed by cESS was similar to that of controls.

There was no reduction in E_{es} in patients with HFpEF compared to controls, which was consistent with results obtain from other studies [2, 4]. E_{es} in patients with HFrEF was significantly lower than those with HFpEF and controls. E_a/E_{es} ratio in patients with HFpEF remained in the optimal range from 0.5 – 1 [2, 109].

Preload-adjusted $LVEjF_{max}$ was correlated with (i) other measures of contractility: LVEF (Spearman's $\rho = 0.484$, $p < 0.001$), eFS ($\rho = 0.539$, $p < 0.001$), mFS ($\rho = 0.516$, $p < 0.001$), (ii) ventricular arterial coupling: E_{es} ($\rho = 0.259$, $p = 0.037$), E_a/E_{es} ($\rho = 0.598$, $p < 0.001$), and (iii) measures of afterload: E_a ($\rho = 0.543$, $p < 0.001$), cESS ($\rho = -0.446$, $p < 0.001$).

Table 5-1 Systolic echo parameters and preload-adjusted maximum left ventricular ejection force in patients with HFrEF, HFpEF and controls. § and # denote statistically significant difference compared to controls and HFpEF patients, respectively (p<0.05).

	HFrEF	HFpEF	Controls
	(n = 20)	(n = 20)	(n = 30)
LVEF (%)	32 (23 – 40) ^{§#}	66 (63 – 75)	75 (70 – 78)
LVMI (g/m ²)	120 (104 – 149) ^{§#}	82 (64 – 101)	65 (54 – 74)
E _{es} (mmHg/ml)	2.28 (1.97 – 2.86) ^{§#}	3.00 (2.79 – 4.37)	2.96 (2.65 – 3.54)
E _a (mmHg/ml)	2.48 (2.89 – 3.99) [§]	2.52 (1.84 – 3.28) [§]	1.76 (1.41 – 3.54)
E _a /E _{es}	1.37 (1.13 – 1.61) ^{§#}	0.69 (0.57 – 0.88)	0.54 (0.51 – 0.65)
cESS (kdynes/cm ²)	314.0 (257.2 – 407.9) ^{§#}	156.2 (114.3 – 195.3)	141.6 (118.5 – 173.4)
eFS (%)	15.5 (10.7 – 20.0) ^{§#}	36.4 (33.5 – 43.4) [§]	43.6 (39.4 – 46.8)
mFS (%)	7.8 (4.6 – 9.6) ^{§#}	22.0 (17.1 – 23.2) [§]	25.7 (21.1 – 28.1)
Preload-adjusted LVEjF _{max} (N/m ³)	10.8 (2.4 – 43.0) [§]	59.0 (14.0 – 85.3) [§]	114.3 (77.6 – 175.1)

5.4.3 Preload-adjusted $LVEjF_{max}$ versus Troponin T

Preload-adjusted $LVEjF_{max}$ was plotted and curve-fitted against TnT, which is a biomarker of cardiac injury, in all HF subjects (as shown in Figure 5-1). Curve fitting between preload-adjusted $LVEjF_{max}$ and TnT showed an exponential relationship, in the form of $LVEjF_{max} = 156.8e^{-55TnT} + 7.395e^{0.897TnT}$, with $R^2 = 0.2783$, $RMSE = 31.79 \text{ N/m}^3$.

Figure 5-1 Maximum preload-adjusted left ventricular ejection force versus Troponin T in patients with heart failure. Solid line represents the curve fitted between preload-adjusted $LVEjF_{max}$ and TnT. Dashed line represents upper 95% prediction bound.

5.4.4 Preload-adjusted $LVEjF_{max}$ versus clinical outcomes

Cut-off value was chosen to be 43 N/m^3 , which was the 75th percentile of preload-adjusted $LVEjF_{max}$ in HFrEF patients. In the group with preload-adjusted $LVEjF_{max} \geq 43 \text{ N/m}^3$, 5 out of 16 HF subjects (31.3%) had cardiac related re-hospitalization or death. In the group with

preload-adjusted $\text{LVEjF}_{\max} < 43 \text{ N/m}^3$, 10 out of 23 HF subjects (43.5%) had cardiac related re-hospitalization or death.

5.5 Discussion and Conclusion

5.5.1 Contractility in HF

While LVEF is commonly used in clinical practice to assess systolic function, it is highly influenced by loading conditions and chamber size. Ventricular-arterial coupling, expressed by E_a/E_{es} ratio, has been proposed as a key determinant of cardiovascular performance [110]. The arterial component, E_a , is a lumped parameter reflecting total arterial afterload, while end systolic LV elastance, E_{es} , is a measure of contractility. As E_a increased significantly in both HF groups compared to controls, E_{es} in HFpEF group was similar to that of controls. The E_a/E_{es} ratio in HFpEF remained in the optimal range from 0.5 – 1, where cardiac work and efficiency are optimized [111].

While other measurements of contractility such as eFS, mFS and preload-adjusted $\text{LVEjF}_{\max}$ showed a worse contractile function in HFpEF patients compared to controls, E_{es} did not act in tandem with these indices. Noted that E_{es} is influenced by chamber geometry and passive stiffness, we speculate that impaired contractility coexists with impaired diastolic dysfunction and fibrosis.

5.5.2 Contractility versus cardiac injury and outcomes

Exponential relationship was observed between preload-adjusted $\text{LVEjF}_{\max}$ and TnT, which is a protein involved in the regulation of cardiac and skeletal muscle contraction. In this study, contractility assessed by preload-adjusted $\text{LVEjF}_{\max}$ was sharply reduced with TnT, which is linked to the presence of myocardial injury.

To access outcomes in this study, preload-adjusted $\text{LVEjF}_{\max}$ was set at the cut-off values of 43 N/m^3 . This cut-off value was chosen based on the 75th percentile of preload-adjusted

LVEjF_{max} in patients with HFrEF. Higher incidence rate of cardiac events and death was observed in HF patients with preload-adjusted LVEjF_{max} below the threshold level of 43 N/m³.

On the other hand, previous study has shown that TnT $\geq 0.03\mu\text{g/l}$ associated with worse outcomes [112]. By setting a cut-off value for TnT at $0.03\mu\text{g/l}$, median (interquartile range) of preload-adjusted LVEjF_{max} was 29.5 N/m³ (3.3 – 63.9) for HF patients with risk of worse clinical outcomes.

5.5.3 Limitations of the study

To account for loading conditions, LVEjF_{max} was normalized with LVEDV, which is a measure of preload. Afterload was not adjusted due to the complexity of various factors that could affect loading conditions. Further invasive haemodynamics and animal studies might be necessary to validate if this proposed novel contractility index is indeed load-independent.

5.5.4 Conclusion

In this chapter, a novel contractility index, LVEjF_{max}, has been formulated and calculated from instantaneous flow data across the LV outflow tract acquired using echo VFM technique. Using this index, reduced contractility has been demonstrated in patients with HFpEF and HFrEF. Relationship between reduction of contractile performance, assessed by LVEjF_{max}, and presence of cardiac injury, assessed by TnT biomarker, was also shown. This, combined with future studies on fibrosis, would be potentially helpful for disease classifications and monitoring of treatment therapies.

CHAPTER 6. NON-INVASIVE DETERMINATION OF INSTANTANEOUS INTRA-LEFT VENTRICULAR RELATIVE PRESSURE DISTRIBUTIONS

6.1 Background

Intra-LV pressure is the holy grail for HF diagnosis. This, however, requires invasive catheterisation. Qualitative and semi-quantitative non-invasive have been proposed to estimate LV filling pressure, such as ratio of mitral inflow E velocity and mitral annular E' velocity (E/E' ratio) [113], and ratio of E velocity and flow propagation velocity (E/Vp ratio) [114]. However, these parameters have limited accuracy.

Computational fluid dynamics (CFD) has been used for examining the global flow patterns and pressure distributions since the 1970s and 1980s using simplified geometries [9, 10]. With the development of high-performance computing, realistic geometries and fluid-ventricular wall interactions were subsequently incorporated into the CFD models [11-13].

The integration of current state-of-art real-time CMR flow data and CFD enables subject-specific intra-LV flow simulations [14, 15, 115]. Intra-LV pressure distributions can be calculated from combined CMR and CFD or CMR phase contrast velocity mapping alone [116]. However, these requires additional scans which are time consuming and onerous. Thus, it is not a routinely used technique in clinical settings.

Intra-cardiac pressure gradients have also been measured by applying Euler equation to echo colour M-mode Doppler [117, 118]. However, due to its 1D flow hypothesis, the accuracy and applicability to various types of diseases and intra-LV locations are limited.

The use of VFM technique to obtain instantaneous 2D intra-LV flow distributions has been demonstrated in previous chapters. From intra-LV velocity vectors, intra-LV pressure gradient distribution can be computed using Navier-Stokes equation [119].

6.2 Aim

To determine instantaneous intra-left ventricular pressure distributions from velocity distributions.

6.3 Methodology

6.3.1 Pressure gradient calculation

From Navier-Stokes equation, the relationship between velocity $\mathbf{V}$ and pressure p in a 3-D flow can be expressed as:

$$\frac{D\mathbf{V}}{Dt} = \mathbf{F} - \frac{1}{\rho}\nabla p + \mu\nabla^2\mathbf{V} \quad (\text{Eq. 6.1})$$

where $\mathbf{F}$ is the external force per unit mass, ρ is density and μ is kinetic viscosity.

Assuming that kinetic viscosity and external force are negligible, (Eq. 6.1) becomes:

$$\frac{D\mathbf{V}}{Dt} = -\frac{1}{\rho}\nabla p \quad (\text{Eq. 6.2})$$

For $V(u, v, w)$ in the (x, y, z) directions, the scalar-component equations can be written as:

$$\frac{\partial u}{\partial t} + u\frac{\partial u}{\partial x} + v\frac{\partial u}{\partial y} + w\frac{\partial u}{\partial z} = -\frac{1}{\rho}\frac{\partial p}{\partial x} \quad (\text{Eq. 6.3})$$

$$\frac{\partial v}{\partial t} + u \frac{\partial v}{\partial x} + v \frac{\partial v}{\partial y} + w \frac{\partial v}{\partial z} = -\frac{1}{\rho} \frac{\partial p}{\partial y}$$

(Eq. 6.4)

$$\frac{\partial w}{\partial t} + u \frac{\partial w}{\partial x} + v \frac{\partial w}{\partial y} + w \frac{\partial w}{\partial z} = -\frac{1}{\rho} \frac{\partial p}{\partial z}$$

(Eq. 6.5)

Define the square of the magnitude of $V(u, v, w)$ as:

$$q^2 = u^2 + v^2 + w^2$$

(Eq. 6.6)

This equation is partially differentiated in the x, y, and z directions and multiplied by 1/2, we have:

$$\frac{1}{2} \frac{\partial q^2}{\partial x} = u \frac{\partial u}{\partial x} + v \frac{\partial v}{\partial x} + w \frac{\partial w}{\partial x}$$

(Eq. 6.7)

$$\frac{1}{2} \frac{\partial q^2}{\partial y} = u \frac{\partial u}{\partial y} + v \frac{\partial v}{\partial y} + w \frac{\partial w}{\partial y}$$

(Eq. 6.8)

$$\frac{1}{2} \frac{\partial q^2}{\partial z} = u \frac{\partial u}{\partial z} + v \frac{\partial v}{\partial z} + w \frac{\partial w}{\partial z}$$

(Eq. 6.9)

Substituting (Eq. 6.7), (Eq. 6.8), and (Eq. 6.9) into (Eq. 6.3), (Eq. 6.4), and (Eq. 6.5), then rearranging the terms:

$$\frac{1}{2} \frac{\partial q^2}{\partial x} + \frac{\partial u}{\partial t} - v \frac{\partial v}{\partial x} - w \frac{\partial w}{\partial x} = -\frac{1}{\rho} \frac{\partial p}{\partial x} \quad (\text{Eq. 6.10})$$

$$\frac{1}{2} \frac{\partial q^2}{\partial y} + \frac{\partial v}{\partial t} - u \frac{\partial u}{\partial y} - w \frac{\partial w}{\partial y} = -\frac{1}{\rho} \frac{\partial p}{\partial y} \quad (\text{Eq. 6.11})$$

$$\frac{1}{2} \frac{\partial q^2}{\partial z} + \frac{\partial w}{\partial t} - u \frac{\partial u}{\partial z} - v \frac{\partial v}{\partial z} = -\frac{1}{\rho} \frac{\partial p}{\partial z} \quad (\text{Eq. 6.12})$$

Thus, (Eq. 6.2) becomes:

$$\nabla \left(\frac{1}{2} q^2 \right) + \frac{\partial V}{\partial t} + \omega \times V = -\nabla \left(\frac{p}{\rho} \right) \quad (\text{Eq. 6.13})$$

where ω is the vorticity vector.

Noted in (Eq. 6.13) that pressure p is the scalar potential. In theory, the pressure values obtained by line integration should be independent of path ($\text{curl} \nabla p = 0$). The line integration, in this case, can be performed using only the acceleration components in the plane. However, due to inevitable noise in echo Doppler velocity, the pressure values depend on the integration path used. The pressure p can be represented by a vector potential P and a scalar potential Doppler pressure p_d . The pressure in the 2D observation plane fixed in 3D flow can thus be:

$$-\nabla \left(\frac{p_d}{\rho} \right) + \nabla \times P = \nabla \left(\frac{1}{2} q^2 \right) + \frac{\partial u}{\partial t} \mathbf{i} + \frac{\partial v}{\partial t} \mathbf{j} - \left(\frac{\partial v}{\partial x} - \frac{\partial u}{\partial y} \right) (v \mathbf{i} - u \mathbf{j}) + w \left[\left(\frac{\partial w}{\partial x} - \frac{\partial u}{\partial z} \right) \mathbf{i} + \left(\frac{\partial w}{\partial y} - \frac{\partial v}{\partial z} \right) \mathbf{j} \right] \quad (\text{Eq. 6.14})$$

As mentioned in Chapter 3, by selecting the apical three-chamber long-axis view, through-plane velocity can be assumed to be negligible, thus $w \approx 0$. (Eq. 6.14) becomes:

$$-\nabla\left(\frac{p_d}{\rho}\right) + \nabla \times P = \nabla\left(\frac{1}{2}(u^2 + v^2)\right) + \frac{\partial u}{\partial t}\mathbf{i} + \frac{\partial v}{\partial t}\mathbf{j} - \left(\frac{\partial v}{\partial x} - \frac{\partial u}{\partial y}\right)(v\mathbf{i} - u\mathbf{j})$$

(Eq. 6.15)

Now, the difficult problem is to eliminate the rotation component $\nabla \times P$ from the acceleration vector. To get through this difficulty, a method using Helmholtz' decomposition theorem in the 2D vector field that had been proposed by Ohtsuki and Tanaka [119] was applied. From Helmholtz' theorem, vector X in the vector field is expressed by both scalar potential ϕ and vector potential Q as:

$$\mathbf{X} = \nabla\phi + \nabla \times \mathbf{Q}$$

(Eq. 6.16)

Ohtsuki and Tanaka then obtained the scalar potential ϕ in the observation plane in the 3D vector field as:

$$\phi = -\int_S \nabla \cdot \mathbf{X} \left(\int \frac{dr}{2\pi r} \right) dS - \int_c \bar{X} dl$$

(Eq. 6.17)

where $\nabla \cdot \mathbf{X}$ is the divergence of vector X and is considered to be spread cylindrically, dS is the unit surface area of the cylinder $2\pi r dh$, $\bar{X}$ is the mean values of X in the area of interest, and dl is the line element of the path c .

To apply the Helmholtz's decomposition theorem to solve our problem, (Eq. 6.15) was first rearrange as:

$$-\nabla\left(\frac{p_d}{\rho} + \frac{1}{2}(u^2 + v^2)\right) + \nabla \times P = \frac{\partial u}{\partial t} \mathbf{i} + \frac{\partial v}{\partial t} \mathbf{j} - \left(\frac{\partial v}{\partial x} - \frac{\partial u}{\partial y}\right)(v\mathbf{i} - u\mathbf{j})$$

(Eq. 6.18)

Let the right hand side terms of (Eq. 6.18)

$$\frac{\partial u}{\partial t} \mathbf{i} + \frac{\partial v}{\partial t} \mathbf{j} - \left(\frac{\partial v}{\partial x} - \frac{\partial u}{\partial y}\right)(v\mathbf{i} - u\mathbf{j}) \equiv I$$

(Eq. 6.19)

where I is the vector field and, from the Helmholtz' theorem:

$$I = \nabla\phi + \nabla \times P$$

(Eq. 6.20)

where

$$\phi = - \int_S \nabla \cdot I \left(\int \frac{dr}{2\pi r} \right) dS - \int_c \bar{I} dl$$

(Eq. 6.21)

From (Eq. 6.18), (Eq. 6.19) and (Eq. 6.20), we have:

$$-\nabla\left(\frac{p_d}{\rho} + \frac{1}{2}(u^2 + v^2)\right) = \nabla\phi$$

(Eq. 6.22)

From (Eq. 6.22), Doppler pressure p_d can be calculated as:

$$p_d = -\rho \left(\frac{1}{2} (u^2 + v^2) + \phi \right)$$

(Eq. 6.23)

Substituting (Eq. 6.21) into (Eq. 6.23), p_d is:

$$p_d = -\rho \left(\frac{1}{2} (u^2 + v^2) + - \int_S \nabla \cdot I \left(\int \frac{dr}{2\pi r} \right) dS - \int_c \bar{I} dl \right)$$

(Eq. 6.24)

Noted that p_d is not the total pressure but the relative pressure compared to that at the reference point which in this case, was set at the apex.

To solve for p_d , numerical approaches for partial differentiation and line integration of u and v [120] were used to compute I , $\nabla \cdot I$ and $\bar{I}$ where:

$$\begin{aligned} \nabla \cdot I &= \left(\frac{\partial}{\partial x} \mathbf{i} + \frac{\partial}{\partial y} \mathbf{j} \right) \left[\frac{\partial u}{\partial t} \mathbf{i} + \frac{\partial v}{\partial t} \mathbf{j} - \left(\frac{\partial v}{\partial x} - \frac{\partial u}{\partial y} \right) (v\mathbf{i} - u\mathbf{j}) \right] \\ &= \frac{\partial}{\partial x} \frac{\partial u}{\partial t} + \frac{\partial}{\partial y} \frac{\partial v}{\partial t} - \frac{\partial}{\partial x} \left(\frac{\partial v}{\partial x} - \frac{\partial u}{\partial y} \right) v + \frac{\partial}{\partial y} \left(\frac{\partial v}{\partial x} - \frac{\partial u}{\partial y} \right) u \\ &= \frac{\partial}{\partial t} \left(\frac{\partial u}{\partial x} + \frac{\partial v}{\partial y} \right) - v \left(\frac{\partial^2 v}{\partial x^2} - \frac{\partial^2 u}{\partial x \partial y} \right) - \frac{\partial v}{\partial x} \left(\frac{\partial v}{\partial x} - \frac{\partial u}{\partial y} \right) + u \left(\frac{\partial^2 v}{\partial x \partial y} - \frac{\partial^2 u}{\partial y^2} \right) + \frac{\partial u}{\partial y} \left(\frac{\partial v}{\partial x} - \frac{\partial u}{\partial y} \right) \end{aligned}$$

Therefore,

$$\nabla \cdot I = \frac{\partial}{\partial t} \left(\frac{\partial u}{\partial x} + \frac{\partial v}{\partial y} \right) - v \left(\frac{\partial^2 v}{\partial x^2} - \frac{\partial^2 u}{\partial x \partial y} \right) + u \left(\frac{\partial^2 v}{\partial x \partial y} - \frac{\partial^2 u}{\partial y^2} \right) - \left(\frac{\partial v}{\partial x} - \frac{\partial u}{\partial y} \right)^2$$

(Eq. 6.25)

$$\int_S \nabla \cdot I \left(\int \frac{dr}{2\pi r} \right) dS = \int_0^{2\pi} \int_0^R \nabla \cdot I \cdot r \cdot \ln r dr d\theta$$

(Eq. 6.26)

$\bar{I}$ was calculated as mean of pixel-wise I values from point of interest to apex (reference point) and line integration was performed to calculate $\int_c \bar{I} dl$.

Values of u and v at each pixel were obtained from VFM technique as described in Chapter 3. Due to inevitable noise from echo Doppler velocity, to reduce the noise accentuated by differentiation of velocity vectors, smoothing method using Gaussian filter was added into the algorithm. A MATLAB program (Mathworks, version 2014a) was written to compute instantaneous pixel-wise p_d throughout the cardiac cycle.

6.3.2 Subject recruitment

Echo scans of the same 3 HFpEF patients with Grade 1, 2 and 3 diastolic dysfunction (DD), 1 HFrEF patient and 2 normal controls recruited as mentioned in Chapter 3 were used for pressure gradient calculation. Written informed consent was obtained prior to scan and the study protocol had been approved by the hospital's ethics review board⁵.

6.4 Results

6.4.1 Ejection pressure gradient distribution

Pressure gradient distributions during systole, with respect to reference point at the apex, for normal, normal control, HFpEF with abnormal relaxation (grade 1 diastolic dysfunction), HFpEF with pseudonormal filling pattern (grade 2 diastolic dysfunction), HFpEF with restrictive physiology (grade 3 diastolic dysfunction), and HFrEF are shown in Figure 6-1.

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⁵ Singhealth Centralised Institutional Review Board, study number CIRB 2009/1003/C.

In normal and normal ageing subjects, negative pressure gradient, or in another word, lower-pressure area was seen at the mid-anterior and outflow tract area during early and mid-systole. Higher-pressure area was seen at the apical and mid-posterior wall. Lower-pressure area was detected at the outflow tract area in all HF cases, most notably during mid-systole. However, the pressure gradients were smaller than those generated in controls. Areas of lower- and higher-pressure are scattered and not distributed specifically in any region in the LV.

Figure 6-1 Pressure gradient distributions, with respect to apex, for (from top to bottom) normal, normal ageing, HFpEF with abnormal relaxation (grade 1 diastolic dysfunction), HFpEF with pseudonormal filling pattern (grade 2 diastolic dysfunction), HFpEF with restrictive physiology (grade 3 diastolic dysfunction), and HFrEF at (from left to right) isovolumic contraction (frame 1), early systole (frame 2), mid systole (frame 3), late systole (frame 4), and isovolumic relaxation (frame 5). Arrow represents velocity flow vector.

6.4.2 Filling pressure gradient distribution

Pressure gradient distributions during diastole, with respect to reference point at the apex, for normal, normal control, HFpEF with abnormal relaxation (grade 1 diastolic dysfunction),

HFpEF with pseudonormal filling pattern (grade 2 diastolic dysfunction), HFpEF with restrictive physiology (grade 3 diastolic dysfunction), and HFrEF are shown in Figure 6-2.

Higher-pressure area was seen at the mitral annulus during both rapid filling and atrial contraction phases. The lowest-pressure area was seen at mid LV cavity, after the tips of the mitral valve leaflets. The low pressure areas were then spread out from mid LV cavity towards apical region and

At the start of rapid filling phase (frame 1), higher pressure gradient was found from mitral annulus to mid LV cavity. The high pressure gradient at the start of rapid filling phase was seen in normal controls, HFpEF subject with grade 2 DD, and HFrEF subject, who had grade 2 DD.

At late rapid filling phase (frame 2), pressure gradient between mitral annulus and mid LV cavity reduced in normal young control, while it was seen to increase in the rest of the subjects.

At diastasis (frame 3), minimal pressure gradient was detected in normal younger control. No flow entered the LV from LA. However, in the rest of the subjects, low-pressure area persisted and located from the central to anterior part of the LV.

At LA contraction phase (frame 4 and frame 5), pressure gradient between mitral annulus and LV cavity increased. The highest pressure gradient was observed in normal ageing and HFpEF subjects with grade 1 and 2 DD.

Figure 6-2 Pressure gradient distributions, with respect to apex, for (from top to bottom) normal, normal ageing, HFpEF with abnormal relaxation (grade 1 diastolic dysfunction), HFpEF with pseudonormal filling pattern (grade 2 diastolic dysfunction), HFpEF with restrictive physiology (grade 3 diastolic dysfunction), and HFrEF at (from left to right) the start of rapid filling phase (frame 1), late rapid filling (frame 2), diastasis (frame 3), start of atrial contraction (frame 4), and end of atrial contraction just before mitral valve closes (frame 5). Arrow represents velocity flow vector.

6.5 Discussion and Conclusion

Pressure distribution reflects how the myocardium generates force during contraction phase and relaxes during filling phase to effectively maintain cardiac output. Pressure gradients have been either directly measured from invasive catheterisation or computationally determined from CFD, CMR or combined CFD/CMR. This is the first study that attempted to compute pressure gradient distribution and visualize different patterns of pressure distribution in patients with HFpEF and HFrEF, versus normal controls. Although validation with invasive catheterization or non-invasive CFD was not carried out in this pilot study, the maximum pressure gradient values of normal controls, as seen from the pressure colour maps shown in Figure 6-1 and Figure 6-2 at systolic and diastolic phase, respectively, were compatible to those obtained from computation of phase-contrast CMR [84, 116], but higher than those obtained from CFD/CMR techniques [121]. Noted that the LV models used for CFD/CMR pressure calculation, although patient-specific, did not include realistic structures of LV such as valve leaflets and papillary muscles. These features are expected to greatly alter the flow patterns, and thus, the pressure distributions.

We acknowledge that colour Doppler echo has its own shortcomings in estimating flow velocities. Firstly, there is an upper limit of the Doppler shift that can be displayed, known as Nyquist limit. When blood flow velocity exceeds the Nyquist limit, aliasing occurs. To eliminate aliasing, imaging depth and velocity scale need to be optimized during image acquisition. When aliasing cannot be removed completely from image, before VFM analysis, manual de-aliasing by doubling the velocity range input for VFM will be performed. Secondly, the original colour Doppler dataset is noisy and thus, spatial averaging is necessary to process the data. And lastly, the calculation of VFM was based on 2D flow instead of 3D flow due to the 2D echo plane. The negligible through-plane velocity component was the assumption made for computing the velocity vectors in the 2D. Previous study by Garcia et al. [18], validated

with in vitro PIV and in vivo phase-contrast MR, has shown the through-plane component is small enough in the apical long-axis plane of the LV. This plane cuts through the LV apex, the centre of the mitral and of the aortic valves. In clinical practice, the acquisition of true apical plane is dependent on operator and patient's anatomy.

Despite these limitations, this method allows estimation of 2D pressure in unsteady flow with the presence of vortex. The pressure p_d obtained is not the total pressure but the relative pressure compared to the reference point which is set at the apex. In this study, pressure gradient between two points in the LV cavity is of interest. The larger the difference in pressure, the greater the energy to move blood. This has different interpretations in systolic and diastolic phases. In systolic phase, higher pressure gradient would better facilitate blood ejection from the LV to the aorta. In diastolic phase, higher pressure gradient between mitral annulus and LV cavity could be due to (i) drop in LV intra-cavitary pressure or (ii) increase in LA pressure. In this study, higher pressure gradient between mitral annulus and mid-LV cavity during filling phase was found in normal controls and HFpEF with grade 2 and 3 DD, while HFpEF with grade 1 DD had the lowest pressure gradient among the subjects. This finding is in agreement with previous results shown by Ohara et al. [118], obtained using echo colour M-mode Doppler with Dobutamine infusion. In normal young control, high pressure gradient was seen at the start of early filling phase, while it appeared much later in the rest of the subjects. This may indicate a higher and faster drop in intra-LV pressure, after isovolumic relaxation, which aspirate blood from LA to LV effectively. The delayed and yet, persistently high pressure gradient found in HF subjects with grade 2 and 3 DD may indicate both prolonged relaxation and increased LA pressure. Finally, the above observations may not be significant due to the very limited statistical sampling.

This method offers fast, non-invasive assessment of intra-LV flow and pressure gradient distributions. Although comprehensive validation studies are required, this proposed method

makes study of non-invasive intra-LV haemodynamic in large number of patients with various disease conditions possible in the clinical settings where high throughput is desired.

CHAPTER 7. ASSESSMENT OF DIFFUSE MYOCARDIAL FIBROSIS BASED ON CARDIAC MAGNETIC RESONANCE T1-MAPPING AND EXTRACELLULAR VOLUME FRACTION MEASUREMENT

7.1 Background

In the previous chapters, methods to deduce instantaneous intra-LV flow and pressure gradient distributions, as well as indices of systolic and diastolic performance have been proposed to assess the severity of HF patients. Changes to intra-LV pressure gradient patterns to effectively eject blood during contraction and to facilitate filling during diastole have been demonstrated. However, myocardial stiffness which plays an important role in determining LV performance has not been studied. Myocardial fibrosis, which is both a cause and a consequence of HF, has been shown to be associated with increased myocardial stiffness [122]. There are two types of myocardial fibrosis: (i) replacement fibrosis and (ii) interstitial fibrosis. Replacement fibrosis occurs as a result of myocyte necrosis after myocardial infarction. Interstitial fibrosis occurs as a result of localized formation of collagenous scars due to cellular apoptosis and induced inflammatory responses from recurring toxic insults. Interstitial fibrosis can be found in several non-ischaemic conditions such as hypertrophic cardiomyopathy and amyloidosis. Increased interstitial fibrosis can also be due to age-related fibrotic remodelling or conditions such as hypertension, pressure and volume overload events, diabetes mellitus, and obesity [123], which are common risk factors for HF. Currently, the gold standard to assess myocardial fibrosis is myocardial biopsy. However, this method is invasive, susceptible to sampling errors and unable to assess fibrosis of the whole heart. CMR is, at the moment, the only non-invasive imaging modality for assessment of myocardial fibrosis. There are two approaches: conventional late gadolinium enhancement (LGE) and novel myocardial T1 mapping.

In LGE imaging, areas of scarring and fibrosis have higher contrast accumulation and delayed contrast wash out. Therefore, these areas appeared as bright spots compared to surrounding normal tissue in T1-weighted image. However, this technique, which relies on the difference in signal intensity between scarred and normal tissue. Interstitial fibrosis has more diffuse patterns and thus, LGE often shows no regional scarring (Figure 7-1).

Figure 7-1 Late gadolinium enhancement shows bright spots (see arrows) at apical septum and lateral wall, compared to surrounding normal tissue in ischaemic heart disease (left) and no increased signal intensity in hypertrophic cardiomyopathy case (right).

The novel myocardial T1 mapping, which generates a parametric T1 map by calculating signal intensity of each voxel in the myocardium, has been used to assess diffuse fibrosis. Currently, there are several T1 mapping indices to estimate interstitial fibrosis, using native T1, post-contrast T1, partition coefficient, and extracellular volume (ECV) fraction [124]. Increased diffuse myocardial fibrosis, either assessed by ECV fraction [125] or post-contrast T1 [126], has been found to be associated with worse systolic and diastolic function. Unlike replacement fibrosis which is believed to be irreversible, there is increasing interest to reverse diffuse interstitial fibrosis using pharmacological therapy [127, 128]. Thus, it is desirable to evaluate diffuse fibrosis in HF to gain mechanistic insights into the relationship between myocardial

fibrosis and cardiac performance and better understanding of the underlying physiology and disease progression of HF.

Among the current T1 mapping approaches, Chin et al. [125] has reported that ECV fraction offers better reproducibility (including scan-rescan repeatability) compared to native and post-contrast T1 and is able to differentiate between normal and diseased myocardium. However, to date, post-processing and interpretation of ECV maps remain underdeveloped with no commercial clinical software available nor standardized image acquisition and post-processing techniques [123].

7.2 Aim

To develop pixel-wise extracellular volume fraction mapping from native and post-contrast CMR T1-weighted images for assessment of diffuse interstitial myocardial fibrosis.

7.3 Methodology

7.3.1 Cardiac magnetic resonance image acquisition

Scan was done on a 3T system (Philips Ingenia, Netherlands). T1 mapping was performed using the Modified Look-Locker Inversion sequence (MOLLI) with 5s(3s)3s scheme for native T1 and 4s(1s)3s(1s)2s scheme for post-contrast T1. SENSE factor of 2.2.

T1 maps were acquired for 3 short-axis slices at the base, mid and apical level, and 1 four-chamber long-axis view at late diastole. Post-contrast T1 maps were acquired approximately 20 min after administration of 0.1mmol/kg of gadobutrol (Gadovist/Gadavist, Bayer Pharma AG, Germany). Subject's blood was taken just before the scan to determine haematocrit value.

7.3.2 T1 mapping

During MOLLI acquisition, patients are required to hold their breath for 11s. However, in patients who have difficulty with breath-hold or when there is diaphragmatic drift due to

residual respiratory motion, artifacts will occurred and if uncorrected, this would lead to errors in the pixel-wise estimation of T1 and affect the T1 maps quality. Motion correction (MOCO) algorithm described by Kabus et al [129] was applied to the original acquired inversion recovery images and T1 maps were generated by pixel-wise curve fitting using MATLAB. To evaluate the quality of T1 estimate after MOCO, a standard deviation (SD) map was created by transforming the SD of the residual fitting error into the SD of T1 estimate. Median absolute deviation approach was used to estimate the SD (σ) from the fit residuals $\epsilon_i = (\text{fit} - \text{meas})$ as proposed by Kellman et al. [130]:

$$\sigma = \frac{\text{median}(\text{abs}(r_i))}{0.6745} \quad (\text{Eq. 7.1})$$

where r_i are the residuals ϵ_i after discarding 2 values with lowest magnitude.

7.3.3 ECV measurement

The ECV in the myocardium is calculated as:

$$ECV = (1 - \text{haematocrit}) \frac{\left(\frac{1}{T1_{\text{myo post}}} - \frac{1}{T1_{\text{myo native}}} \right)}{\left(\frac{1}{T1_{\text{blood post}}} - \frac{1}{T1_{\text{blood native}}} \right)} \quad (\text{Eq. 7.2})$$

As T1 native and post-contrast images are acquired in separate breath-holds at 20 minutes apart, changes in respiratory and patient's positions would cause significant misalignment of the images. Therefore, co-registration of native and post-contrast images was performed using non-rigid image registration of the longest inversion time MOCO images [129].

To calculate the change in blood relaxation rate, $\Delta R1_{blood} = \frac{1}{T1_{blood\ post}} - \frac{1}{T1_{blood\ native}}$, blood region was created from native T1 map using threshold of 1300ms. The values for native and post-contrast blood T1 were calculated as median of all T1 values inside the region of interest. The ECV map was then calculated at every pixel from the native and co-registered post-contrast T1 maps at the same slice location using MATLAB.

7.4 Results

7.4.1 *Quality of T1 and ECV maps*

Figure 2-1 shows improved T1 map after MOCO, especially at the septum area, between myocardium and blood, and at the anterior area, between myocardium and pericardium (marked by the arrows).

Figure 7-2 T1 and SD maps with (left) and without (right) motion correction (MOCO).

Figure 7-3 shows improved ECV map before and after co-registration. In this case, there was significant shift between native and post-contrast T1 maps, as shown by overlaying the two maps. After co-registration, the native and post-contrast T1 maps were aligned and ECV map was markedly improved, removing the high ECV areas.

Figure 7-3 ECV and overlay native and post-contrast T1 maps with (left) and without (right) co-registration.

7.4.2 ECV maps of normal and diseased myocardium

ECV maps of normal control and patient with dilated cardiomyopathy (DCM) after MOCO and co-registration are shown in Figure 7-4. Haematocrit values of control and DCM patients are 42.8% and 46.5%, respectively. Mean ECV values of the myocardium in control and DCM patient were 28.2% and 37.3%, respectively. Noted the area of increased fibrosis at the lateral and inferior wall (increased ECV) which was not detectable on LGE image (Figure 7-5).

Figure 7-4 ECV maps of normal control (top) and patient with dilated cardiomyopathy (bottom) at the mid slice

Figure 7-5 Late gadolinium enhancement image of patient with dilated cardiomyopathy at the mid slice

7.5 Discussion and Conclusion

Motion correction and co-registration have been shown to be crucial to ensure more accurate measurement of T1 and ECV. To demonstrate the feasibility of this technique, 2 representative cases of normal and DCM were analysed. From LGE image of the same patient, difference in signal intensity was not detectable, indicating absence of scar tissue. Region of increased ECV in DCM was detected from ECV map, indicating presence of increased fibrosis. ECV values have been shown to be correlated with histologically determined diffuse interstitial fibrosis in the myocardium [131].

This proposed technique has been developed as an in-house application and is being used as a clinical tool at our centre for characterization of various myocardial diseases such as

cardiomyopathies, hypertrophic cardiomyopathies, and infiltrative diseases such as amyloidosis. The prognosis values of ECV, however, remained to be explored in the future.

CHAPTER 8. CONCLUSION AND FUTURE DIRECTIONS

The work covered in this thesis involved biomechanics, mathematical formulation and image processing to (i) determine the intra-LV blood flow and pressure gradient distributions, (ii) develop quantitative indices to assess cardiac systolic and diastolic performance, (iii) employ LV Ejection force as a useful contractility index to detect HF, and (iv) determine extracellular volume fraction for assessment of diffuse myocardial fibrosis in HF patients.

In particular, intra-LV blood flow and pressure gradient distributions were determined from echo Doppler flow images using VFM technique and demonstrated in representative cases of HF patients who had reduced and preserved ejection fraction, and exhibited different severity of diastolic dysfunction, versus young healthy as well as ageing controls. This is the first study that attempted to compute pressure gradient distribution and visualize different patterns of pressure distribution in patients with HFpEF and HFrEF, versus normal controls. Although validation with invasive catheterization or non-invasive CFD was not carried out in this pilot study, the maximum pressure gradient values of normal controls were compatible to those obtained from computation of phase-contrast CMR.

Echo is a safe, fast, readily available and relatively inexpensive non-invasive imaging modality used routinely in clinical practice. Although colour Doppler echo has its own shortcomings in estimating flow velocity, this technique offers fast, non-invasive assessment of intra-LV flow and pressure gradient distributions to evaluate haemodynamic changes due to disease progression and treatment.

In addition, the indices, load-adjusted $LA E_j F_{\max}$, and preload-adjusted $LVE_j F_{\max}$, derived from echo Doppler flow, have been proposed to quantitatively assess diastolic function and systolic function, respectively.

Conventionally employed LA contractility index, LAaEF, which is analogous to LVEF, is determined by the change in pre- and post-contraction volumes of the chamber and is highly dependent on volume measurements and loading conditions. LAEjF_{max} is defined as maximum LA generated force during its contraction phase. The LAEjF was formulated based on Newton's second law of motion where the force exerted by the fluid is equal to the rate of change of momentum. In terms of mechanical definition of force, it is dependent on both chamber size and pressure generated by the chamber to eject blood. Herein, LAEjF_{max} was normalized with chamber size before contraction, LAV_{pre-A}, to adjust for preload and E/E' ratio to adjust for afterload. To accurately determine LA afterload, invasive measurement of LV filling pressure needs to be performed. However, it is widely acceptable in clinical practice to use E/E' ratio as a surrogate for LV filling pressure. The load-adjusted LAEjF_{max} thus can be considered as an intrinsic measure of contractility of LA. By using load-adjusted LAEjF_{max}, this study has demonstrated a trend of gradual reduction in LA contractile performance in normal ageing subjects and across the diastolic dysfunction grades.

The proposed LVEjF in this thesis is a direct and very effective measure of biomechanical contractile function of LV, because it incorporates the parameters of the mass and acceleration of the blood ejected by the LV to the aorta, which are both the result of myocardial contraction. To account for loading conditions, LVEjF_{max} was normalized with LVEDV, which is a measure of preload. Afterload was not adjusted due to the complexity of various factors that could affect loading conditions. In systole, reduced contractility has been demonstrated in both HFpEF and HFrEF patients, with association with presence of cardiac injury assessed by biomarker.

Lastly, an algorithm for post-processing of the CMR T1-weighted contrast images and computation of ECV maps as well as ECV values of the myocardium, has been developed. The ECV values have been shown to be correlated with histologically determined diffuse interstitial

fibrosis, which presents in HF patients, and to alter the myocardial stiffness from animal studies.

Therefore, in future, by combining the flow and pressure gradient distributions and myocardial fibrosis, estimated from ECV, insights into how changes in myocardial stiffness due to increased myocardial fibrosis, as the results of disease progression and pharmacological therapies, affect the ability of LV (i) to contract to generate adequate pressure during ejection phase and (ii) to relax to create pressure drop in LV to facilitate filling. Flow pattern, which is the manifestation of the interaction between myocardial stiffness and intra-LV pressure gradient, and performance indices derived from flow velocities would offer both visualization and quantitative approaches for assessment of cardiac performance and would be potentially useful for diagnosis and prognosis of HF and other cardiac diseases.

For future studies, further invasive haemodynamics and animal studies might be necessary to validate if the proposed novel measurements of LA and LV contractility are indeed load-independent. The effect of medications used in treatment of HF such as vasodilator, beta blocker, etc. which alter myocardial compliance and loading conditions shall be studied in subsequent studies with larger cohorts of patients. The methods to compute pressure gradient distributions as well as these proposed performance indices can also be applied in CMR phase contrast flow images, if available.

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APPENDIX – ASSESSMENT OF ARTERIAL STIFFNESS AND LEFT VENTRICULAR CONTRACTILITY IN PATIENTS WITH SIDEROTIC CARDIOMYOPATHY

Introduction

Thalassaemia is a common genetic disorder in the world, due to under- or no production of the globin chains that leads to unbalanced haemoglobin synthesis. Patients with β -thalassaemia major, which is the most severe type, require life-long blood transfusion that results in iron overload in various body tissues. Iron overload has been considered to be the main factor leading to the development of cardiomyopathy [132] and vascular involvement in TM patients [133, 134]. Cardiomyopathy, which is the leading cause of death in TM patients [135], presents with 2 distinct clinical phenotypes: dilated cardiomyopathy with impaired contractility in about 83% of cases and restrictive cardiomyopathy in the remaining 17% of cases [136]. Traditional LVEF to assess systolic function is usually preserved till late stage [137] and thus, is not ideal for early identification of cardiac failure due to iron overload.

A novel stress-based contractility index, $d\sigma^*/dt_{max}$, that has recently been proposed [59], has proved to be a reliable indicator of heart failure with preserved EF. This index, $d\sigma^*/dt_{max}$, defined as maximal rate-of-change of pressure-normalized stress, can be easily measured from non-invasive echocardiography or cardiac MR. We hypothesized that $d\sigma^*/dt_{max}$ would be sensitive for detecting early myocardial dysfunction due to iron overloading.

Increased arterial stiffness due to increased iron deposition in the vascular system described in TM [133, 138] may also cause LV mismatch that contributes to impairment of LV performance. Timely diagnosis of cardiac involvement for intensification of iron chelation therapies is crucial to reverse this siderotic cardiomyopathy [139, 140].

In this study, by first determining the myocardial iron status in a cohort of TM using current gold standard T2* measurement and stratifying them into groups based on their T2* results, we then compared arterial stiffness and contractility index of these groups of patients.

Methods

Patient Population

Fifty-three TM patients (age range from 10 to 32 years) were included in the study. All patients had been regularly transfused with pre-transfusion haemoglobin concentration maintained at 8-9 g/dl. All patients were on one of the following iron chelation therapies: deferoxamine, deferiprone, deferasirox as monotherapy or combination of deferoxamine and deferiprone. Serum ferritin level was recorded for each patient.

Cardiac Magnetic Resonance

Patients were scanned using a 1.5T Avanto scanner (Siemens). For assessment of cardiac iron, a single breath-hold short-axis mid-ventricular slice was acquired at 8 different echo times using previously described methodology [137, 141]. Patients are stratified into 2 groups based on their cardiac T2* results: Group 1, severe cardiac iron overload, T2* <10 ms, and Group 2, T2* ≥10 ms.

In each patient, a parallel stack of fast imaging in steady-state precession (trueFISP) short-axis cine images was acquired. Measurements of left and right ventricular (RV) volumes, LV mass and EFs were performed with standard MR techniques involving manual contouring. All volumes and LV mass measurements were then indexed to body surface area.

In each patient, a velocity-encoded gradient echo pulse sequence was performed at the aortic root perpendicular to the ascending aorta, which yielded magnitude and quantitative flow images. The former provided temporally-resolved visualization of the contours of the

ascending aorta, which were then automatically traced for area analysis. The latter were used for aortic flow measurement analysis (ARGUS software, Siemens, Erlangen) using conventional methodology [142].

Calculation of LV stress-based contractility index

Maximal rate-of-change of pressure-normalized stress, $d\sigma^*/dt_{max}$, was calculated using the following equation [59]:

$$d\sigma^*/dt_{max} = 1.5 \frac{dV/dt_{max}}{V_m}$$

where dV/dt_{max} is maximal flow rate into the aorta, determined from flow analysis of velocity encoded image of aorta as described above; V_m is LV myocardial volume.

Calculation of aortic stiffness indices

Maximal, A_{max} , and minimal, A_{min} , aortic areas were measured from the area analysis of the aortic cine images as described above.

Aortic strain, ε , is defined as relative change in area of the aorta:

$$\varepsilon = \frac{A_{max} - A_{min}}{A_{min}}$$

Aortic distensibility coefficient, DC , is calculated [143] as:

$$DC = \frac{A_{max} - A_{min}}{A_{min} \cdot \Delta P}$$

Where ΔP is central pulse pressure, defined as the difference between aortic systolic blood pressure (SBP) and aortic diastolic blood pressure (DBP). Aortic SBP is estimated to be $0.9 \times$ brachial SBP [41]. Aortic DBP was assumed to be similar to brachial DBP.

Statistical analysis

Statistical analysis was performed using SPSS 15.0 software package. Independent samples t-tests were used to compare variables between two groups of patients. Data are expressed as mean $\pm$ SD for continuous variables or percentages for discrete variables. P value <0.05 was considered statistically significant.

Results

Patient Characteristics

Severe myocardial iron overload was found in 16 TM patients. There were no significant differences in age and gender between the 2 groups of patients. Liver T2* and serum ferritin were markedly different between the groups (Table).

LV mass index, indexed ventricular volumes and ejection fractions were not significantly different between severe and non-severe myocardial iron overload TM patients.

Compared to Group 2, contractility index $d\sigma^*/dt_{max}$ was reduced in Group 1. Aortic strain, ϵ , was also found significantly lower in Group 1, although no difference in distensibility DC was detected.

Table. Patient clinical characteristics, CMR measurements, stress-based contractility index and aortic stiffness parameters

	Group 1 (n = 16)	Group 2 (n = 37)	P
<i>Clinical Characteristics</i>			
Age (years)	21 $\pm$ 6	20 $\pm$ 6	0.413
Gender (% female)	50	49	
Body surface area (m²)	1.26 $\pm$ 0.17	1.41 $\pm$ 0.20	0.011
Serum Ferritin (g/dl)	5985 $\pm$ 3676	3087 $\pm$ 2737	0.002

Chelation therapy (%)			
Deferoxamine monotherapy	43.8	62.2	
Deferiprone monotherapy	6.3	5.4	
Deferasirox monotherapy	0	2.7	
Deferoxamine + deferiprone	50	29.7	
Heart T2* (ms)	6.13 ± 1.59	30.94 ± 12.87	<0.001
Liver T2* (ms)	1.87 ± 1.77	4.42 ± 5.52	0.022
MR Parameters			
LV mass index (g/m²)	55.36 ± 9.78	50.89 ± 9.67	0.129
LVESVI (ml/m²)	38.28 ± 10.72	37.03 ± 9.91	0.683
LVEDVI (ml/m²)	95.72 ± 19.15	94.11 ± 13.85	0.732
LVEF (%)	60.51 ± 5.30	61.05 ± 5.99	0.759
RVESVI (ml/m²)	37.04 ± 13.15	35.61 ± 12.13	0.693
RVEDVI (ml/m²)	91.84 ± 20.23	89.80 ± 15.76	0.702
RVEF (%)	60.22 ± 6.09	61.13 ± 7.33	0.662
Indices			
$d\sigma^*/dt_{max}$ (s⁻¹)	6.86 ± 1.38	7.76 ± 1.51	0.05
ε (%)	32.73 ± 20.19	48.37 ± 14.87	0.003
DC (kPa⁻¹.10⁻³)	92.79 ± 64.84	102.43 ± 36.81	0.584

Discussion

Aortic stiffness

Based on the fundamental concept of stress and strain used in engineering physics, aortic strain and distensibility determine the stiffness condition of the aorta, based on the increase in relative

lumen area resulting from increase in pressure. Aortic strain decreased significantly in TM patients with severe iron overload while no significant difference was found in aortic distensibility as compared to patients with non-severe iron loading. Previous studies have reported significant decrease in aortic stiffness in TM patients, compared to normal volunteers [144, 145], using echo and applanation tonometry. Ours is the first study which assessed aortic stiffness of TM patients with reference to different levels of iron loading based on cardiac T2* measurement. The reported values of aortic strain in TM patients ($9 \pm 3.6\%$) derived from aortic diameters, acquired by echo, were lower than those obtained from MR in this study. The variation might be due to different techniques used. Our aortic strain values were comparable to values obtained in healthy volunteers using MR technique [146] albeit older age. Mean aortic strain of 21 healthy subjects, aged 20-29 years, was $33 \pm 10\%$ and values decreased significantly with increase in age.

We applied a simple formula to estimate aortic systolic and diastolic pressures from brachial systolic and diastolic pressures to avoid invasive catheterization for pressure measurement. This estimation of pressures might introduce some errors while calculating aortic distensibility.

Stress-based contractility index

Compared to TM patients with T2* <10ms, stress-based contractility index, $d\sigma^*/dt_{max}$, was significantly decreased in those with severe iron loading, while their LVEF values were similar. Patients who have cardiac T2* < 10ms are known to have higher relative risk of progression to heart failure [147].

We previously reported significantly reduced $d\sigma^*/dt_{max}$ in heart failure patients with preserved ejection fraction, measured with echo technique [3]. This underscores some extent of myocardial contractile dysfunction while LVEF remains preserved. $d\sigma^*/dt_{max}$ was formulated

based on maximal rate of wall stress with respect to pressure. Wall stress, which is generated by sarcomere contraction and results in development of pressure, can be considered as an intrinsic indicator of contractile function. In this formula, wall stress was normalized with pressure to eliminate the pressure term, which is not always easily measurable; hence, calculation of the index became simpler. $d\sigma^*/dt_{max}$ has been shown to correlate well with peak first-time derivative of LV intracavity pressure, dP/dt_{max} , [59] an established cardiac index which requires invasive procedure. Calculation of $d\sigma^*/dt_{max}$ requires myocardial volume and maximal LV flow rate into the aorta. These two determinants can readily be obtained from echocardiography or cardiac MR. Volume quantification using MR remains the most reproducible and reliable method. Besides, determination of maximal flow rate using pulsed Doppler echo is subjected to errors due to Doppler insonation angle and the location of the sample volume.

The formulation of $d\sigma^*/dt_{max}$ was based on a simplified pressurized spherical model. Normal LV shape is, however, more ellipsoidal than spherical. A shape-based contractility index has been formulated based on an ellipsoidal model [148], which is more accurate but somewhat more complicated to compute. Besides, the spherical model has long been used for determination of LV wall stress [149]. This model alleviates the complex mathematical calculation and thus, makes the index more applicable in clinical settings.

Conclusion

In conclusion, aortic strain and contractile function, assessed using stress-based contractility index, decrease significantly in patients with severe myocardial iron loading. These may constitute early signs of cardiac failure, although ventricular volumes and ejection fractions remained normal. Serial follow-ups of aortic strain and contractility index, together with

myocardial MR T2*, in future studies, might reveal the relationship between iron loading and cardiac disease progression.