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Biomechanical Engineering Indices for Cardiac Function & Dysfunction during Filling and Ejection Phases

Zhong Liang

School of Mechanical and Aerospace Engineering

A thesis submitted to the Nanyang Technological University

in fulfillment of the requirement for the degree of

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This thesis is dedicated to my dear parents, Zhong Juti and Zeng Yuying, to my wife Chen Yan. Their caring love and enduring encouragement have been around me. I would like to share all my success and happiness with them

Abstract

The performance of the left ventricle (LV) is determined not only by its intrinsic properties, it is also determined by the arterial system afterload (in systole) and by the left atrium (in diastole) during its filling process. These mechanisms work in concert to govern the beat-to-beat cardiovascular function. This dissertation investigates their dynamic interrelations under physiological and medical conditions, using biomechanical engineering models for (i) left ventricular diastolic and systolic indices, using clinical data (involving simultaneous recordings of aortic pressure, LV pressure, LV volume and electrocardiogram from patients from National Heart Center at Singapore), and (ii) the aortic blood pressure profile using auscultatory cuff diastolic and systolic pressures along with the blood flow rate from the LV into the aorta.

The first biomechanical engineering (BME) model involves development of a time-dependent active-elastance and volume-dependent passive-elastance. The total elastance (sum of active and passive elastance) varies throughout the cardiac cycle. The active elastance contributes to the pressure increases during the isovolumic contraction and the LV suction during the rapid-filling phase characterized by a temporal drop in LV pressure after mitral valve opening. The passive elastance depicts the myocardial constitutive property. The active-elastance time-dependent function can be looked upon as a contractility index, while the volume-dependent passive-elastance function can help to characterize LV-stiffening and hence resistance-to-filing.

Next, we have investigated the effect of ventricular shape on contractility and ejection function. In this study, a new contractility index is developed in terms of the wall-stress (σ^* , normalized with respect to LV pressure)) in LV ellipsoidal model. Using cine-ventriculography data, the LV ellipsoidal model (LVEM) major (B) and minor axes (A) are derived for the entire cardiac cycle. Thereafter, a new contractility index (CONT1) was derived as $d\sigma^* / dt$ incorporating the LV ellipsoidal shape factor. Also, another contractility index (CONT2) was developed in terms of the generated σ^* at the start of ejection phase, and maximized with respect to B/A shape parameter to obtain the optimal value of B/A over the physiological range of values of the ratio of myocardial volume and LV volume. The in vivo value of B/A at the start of ejection is compared with this optimal value, and the LV contractility is evaluated in terms of the proximity of the in vivo B/A to the optimal B/A. The results indicate that a non-optimal less-ellipsoidal shape (or more spherical) is associated with decreased contractility (and poor systolic function) of the LV, associated with a failing heart.

In chapter 5, we have developed the analysis to determine the aortic pressure-time profile, along with aortic volume-elasticity and peripheral resistance. The input to the model consists of auscultatory cuff diastolic and systolic pressures and cineangiographically measured ejection volume-time profile (or volume input into the aorta). The model obtained aortic pressure-time profile is compared with the catheter based pressure profile, to provide credibility to the model and to the computed values of aortic volume-elasticity (or stiffness) and peripheral resistance. Then based on this aortic pressure profile and the computation of the pressure drop across the aortic valve (in terms of the outflow tract geometry), we can noninvasively determine the LV pressure profile during the ejection phase.

In chapter 6, we have developed a LV myocardial sarcomere model to characterize the intrinsic contraction capacity of the LV. In this model, the sarcomere stress and displacement are related to the LV pressure and volume in terms of the sarcomere elements' parameters. By simulating this model to the clinical data of LV pressure and volume, the sarcomere parameters are evaluated. We then determine the sarcomere contractile-element (the actin-myosin unit) 'stress vs. shortening-velocity' characteristics as well as the power generated by the sarcomere (CE) element. These are deemed to be useful LV functional indices.

The model parameters derived from all of the analyses constitute a matrix of diagnostic indices, which can significantly contribute to cardiac assessment. Hence, in chapter 7, we have analyzed several patients case-by-case by depicting their history and the computed functional indices. Each patient's clinical diagnosis is compared with our BME indices-based assessment, to help reveal the efficacy of these indices.

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Glossary of Abbreviations

<i>BME</i>	biomedical engineering
<i>BP</i>	blood pressure
<i>CE</i>	contractile element
<i>CO</i>	cardiac output
<i>DAP</i>	diastolic arterial pressure
<i>ECG</i>	electrocardiogram
<i>EDP</i>	end-diastolic left ventricular pressure
<i>EDPVR</i>	end-diastolic pressure-volume relation
<i>EDV</i>	end-diastolic left ventricular volume
<i>EF</i>	ejection fraction
<i>ESP</i>	end-systolic left ventricular pressure
<i>ESPVR</i>	end-systolic pressure-volume relation
<i>ESV</i>	end-systolic left ventricular volume
<i>CONT</i>	contractility
<i>2-D</i>	two dimension
<i>HR</i>	heart rate
<i>LA</i>	left atrial
<i>LAP</i>	left atrial pressure
<i>LV</i>	left ventricular
<i>LVCi</i>	left ventricular contractility index
<i>LVFPI</i>	left ventricular filling performance index
<i>MAP</i>	mean arterial pressure
<i>MV</i>	myocardial volume
<i>PP</i>	pulse pressure
<i>PWV</i>	pulse wave velocity
<i>RMSE</i>	root mean square error
<i>RTF</i>	resistance-to-filling
<i>SE</i>	series element
<i>TPR</i>	total peripheral resistance
<i>VE</i>	viscous element

Glossary of Symbols

A	major axis for ellipsoidal model [cm]
B	minor axis for ellipsoidal model [cm]
B_v	viscous damping parameter of parallel viscous element [g/s]
c	pulse wave velocity [cm/s]
C	Compliance [ml/mmHg]
dP/dt	first derivative of left ventricular pressure [mmHg/s]
E	elastance [mmHg/ml]
E_v	young's modulus of the blood vessel wall [mmHg]
E_a	active elastance [mmHg/ml]
E_p	passive elastance [mmHg/ml]
F_{CE}	myocardial-unit contractile-element force [$\text{g}\cdot\text{cm}^3/\text{s}^2$]
G	Geometry term ($= R_i^2 (5R_o^2 + 2R_i R_o + R_i^2) / (R_o^2 - R_i^2) (R_o + R_i)^2$) for cylindrical model
h	thickness of myocardium [cm]
h_a	thickness of aortic wall [cm]
$I(t)$	inflow rate to aorta [ml/s]
k	elastic stiffness (or modulus) of series element [g/s^2]
l	length of blood vessel [cm]
m	mass per unit cross-section area [g/cm^2]
m_a	stiffness of aorta [mmHg/ml]
m_s	myocardial surface-density or mass per unit surface area [g/cm^2]
M	$= \rho_s h$ [mmHg/(ml/s ²)]
$Q(t)$	outflow rate from aorta [ml/s]

Glossary of symbols

Q_m	mean flowrate [ml/s]
Q_p	pulse-flow [ml/s]
P_a	= $P - P_{ed}$, active pressure [mmHg]
P_{el}	elastic recoil pressure [mmHg]
P_{LV}	left ventricular pressure [mmHg]
$P_d(t)$	diastolic pressure of aorta [mmHg]
$P_s(t)$	systolic pressure of aorta [mmHg]
P_p	pulse pressure [mmHg]
P_m	mean arterial pressure [mmHg]
r_a	radius of aorta [cm]
r_v	radius of vessel [cm]
R	radius of left ventricle [cm]
R_i	inside radius of cylindrical model [cm]
R_m	Middle radius of cylindrical model [cm]
R_o	outside radius of cylindrical model [cm]
R_p	peripheral resistance [mmHg.s/ml]
s	shape factor (=B/A)
t	time [s]
t_m	= t_2 , time for peak aortic pressure [s]
t_a	= $t - t_{iso}$ during systolic ejection [s]
t_s	time for systolic contraction [s]
t_{iso}	time for isovolumic contraction [s]
t_e	time for ejection [s]
T_a	flow acceleration period [s]
x_I	Added deformation of series element during systole [cm]
x_I^c	x_1 at isovolumic contraction [cm]
x_I^e	x_1 at ejection phase [cm]
x_{Ied}	end-diastolic x_1 [cm]
x_2	displacement of muscle mass m relative to centre-line [cm]
x_T	displacement of muscle half-unit relative to centre-line [cm]

Glossary of symbols

$\bar{u}$	mean velocity-pulse of blood [cm/s]
u_w	wall displacement [cm]
V	volume of left ventricle [ml]
V_a	volume of aorta [ml]
V_{ed}	end-diastolic volume [ml]
V_{es}	end-systolic volume [ml]
ΔP	pressure drop across the aortic valve [mmHg]
Z_0	arterial impedance [mmHg.s/ml]
σ_{SE}	stress exerted by the series-element [g.cm/s ²]
σ	$= \sigma_{SE}$ [g.cm/s ²]
σ^*	$= \sigma / P$
σ_{VE}	stress-resistance exerted by the viscous-element [g.cm/s ²]
σ_{CE}	applied stress exerted by the contractile-element [g.cm/s ²]
ρ	myocardial density [g/cm ³]
ρ_f	blood density [g/cm ³]
μ	viscosity of blood [g/(cm.s)]
λ	$= m_a / R_p$ [s ⁻¹]
$\dot{\epsilon}$	strain rate [s ⁻¹]
ρ_s	myocardial surface density [g/cm ⁵]
η	myocardial efficiency

CHAPTER 1

INTRODUCTION

1.1 Background and Statement of Problem

Heart failure is a leading cause of death in developed countries, including Singapore. This clinical syndrome may be a manifestation of filling abnormalities and/or inadequate left ventricular (LV) myocardial contraction (due to myocardial ischemia or infarct and/or electrical contraction abnormality). Cardiologists have been using simple clinical measurements such as heart rate, ECG patterns, blood pressure and ejection fraction to diagnose cardiac pathologies. However, these measurements do not provide adequate insight into the heart's complex electro-mechanical machinery involved in its functional performance and clinical syndromes. This dissertation constitutes study of biomechanical mechanisms and phenomena of the heart function, leading to the development of new indices of assessment of heart function and impairment.

In a bioengineering sense, the heart can be described as a blood pump and its biomechanical behavior can be understood in terms of the time-varying relationship between ventricular blood pressure and volume. For many years, clinicians have used this relationship as a measure of cardiac function (Grodins, 1959; Elzinga et al., 1972; Suga

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and Sagawa, 1974; Vaarjes and Boom, 1987; Palladino et al., 1998; Kass et al., 2002; Ishida et al., 2004). Concomitant with this approach has been the concept of LV myocardial stress and modulus (Ghista et al., 1971, 1973, 1975), to characterize both diastolic and systolic performance.

Recently, it has become apparent that an understanding of LV mechanisms in terms of its myocardial properties is important to characterize the underlying ventricular pump function. Pressure and volume are the fundamental measurable physical variables, from which to derive and express the biomechanical properties of the LV. Some of the earlier works of Ghista, on this intrinsic characterization of LV function (Ghista et al., 1971, 1975), have in fact been adopted clinically.

Characterizing the LV as a pump is not simple, as the LV action is a complex phenomenon. It depends both on its myocardial properties and chamber geometry, as well as the preload (i.e., end-diastolic pressure) and afterload (i.e. aortic pressure). Therefore, it is necessary to know the characteristics of LV shape-dynamics and LV muscle contraction during physiological and pathological conditions. In an intact beating heart, it is still impossible to measure these parameters and to relate them with the different diseases. Hence, we need to develop appropriate LV models, to characterize its in-vivo anatomy and physiology as well as its sarcomere properties, and link them to its clinical performance.

Analytical modeling will be necessary for such a quantitative understanding of the cardiac function and dysfunction during diastolic-filling and ejection phases. In this regard, the primary objectives of this thesis have been to (i) develop time-dependent active-elastance and volume-dependent passive-elastance model, (ii) investigate the effect of ventricular shape on contractility and ejection function, (iii) determine the aortic pressure noninvasively, along with aortic volume-elasticity and peripheral resistance, (iv) develop

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the LV myocardial sarcomere model to characterize the intrinsic contraction capacity of the LV, and (v) use the model parameters to assess cardiac function and dysfunction case by case. Our work is intended to enable comprehensive, convenient and reliable diagnosis of cardiac performance and disorders, in terms of these functional model parameters.

1.2 Objectives and Scope

Left ventricular function is characterized by its performance in both the diastolic and systolic phases. It responds to the combined effects of several underlying mechanisms, such as early diastolic suction and isovolumic contraction to generate the high pressure required for ejection. The aim of this research is to provide insight these phenomena by modeling their mechanisms and formulating associated indices of cardiac dysfunction leading to heart failure.

Diastole and systole constitute the two primary events of a cardiac cycle. Hence, cardiac dysfunction is associated with irregularities of one or both of these events and phenomena. Intrinsic measures of the LV pumping performance can be deemed to be associated with (i) LV filling and contraction, in terms of LV nonlinear passive and active elastance, (ii) LV shape-based contractility index, as a substitute for the traditional $dP/dt_{\max}$, and (iii) LV ejection, in terms of LV sarcomere contraction development. On the other hand, the LV also has to respond to the arterial system characteristics (i.e., aortic stiffness and peripheral resistance) in the form of afterloaded. Thus this study also investigates the determination of aortic pressure profile noninvasively.

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The specific aims of this study are as follows:

1. Develop non-linear volume-dependent passive-elastance and time-dependent active-elastance model, in terms of the new definition of elastance change ($= VdE + EdV$), in relation to left-ventricular pressure and volume.
2. Establish a new cardiac LV shape-based contractility index in terms of the wall-stress (σ^* normalized with respect to LV pressure)) in LV ellipsoidal model.
3. Provide the analysis for the aortic pressure waveform non-invasively, as well as indicate how it can be employed to determine aortic stiffness (m_a), peripheral resistance (R_p), and even a new cardiac contractility index.
4. Construct a LV myocardial sarcomere model, in terms of its series element, viscous element and contractile element, relate LV myocardial sarcomere contraction dynamics to LV systolic function, in terms of the ability of the myocardium to shorten against the aortic pressure load, for ejection of blood into the high-pressure aorta.

1.3 Significance of Proposed Project

1.3.1 Non-linear Passive and Active Elastance

Description of the heart as a pump has been dominated by models based on a time-varying elastance, or its inverse the compliance. However, the time-dependency of active-elastance and volume-dependent passive elastance are poorly understood. We have developed a biomathematical model to define the active elastance as a function of time, and passive elastance as a function of LV volume. Both the passive and active elastance govern the pressure-volume relation throughout the cardiac cycle. A computation procedure was used to evaluate these nonlinear elastances. The results show that it is the

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active elastance that contributes to the pressure increase during the isovolumic contraction. During early filling, the decreasing active elastance makes it possible for LV suction of blood from the left-atrium, characterized by a temporal drop in LV pressure after mitral valve opening. Its maximal value is seen to decrease with the poorly contracting LVs. Hence it can be deemed as a contractility index. The passive elastance have an exponential relationship with the volume of LV, and characterizes the myocardial constitutive property. It becomes steeper in a less distensible LV, which implies a stiff myocardium offering resistance to filling.

1.3.2 Left Ventricular Shape-based Contractility Index

That the shape of LV is related closely with heart performance has long been recognized by cardiologists, but never formulated biomechanically. The optimal LV shape and its normalized wall-stress change-rate have not been thus far investigated. Herein, we have established an ellipsoidal model from the cineangiography, and defined its shape factor (in terms of the ratio of minor and major axis). Based on this model, we have biomathematically established the optimal LV shape and its related normalized wall stress. Our results show that the optimal shape is a function of the MVN (ratio of myocardial volume and volume of LV).

The failing heart's shape factor is far away from this optimal shape and the corresponding normalized stress change-rate also decreases. It is concluded that a healthy LV shape factor is more akin to an optimal-ellipsoidal shape factor, but transforms towards a more spherical shape in a poorly contracting LV in LV failure. Since the LV normalized wall stress depends on its shape, hence the LV contractile capacity also depends on the LV shape. This is the rationale behind our LV shape-based contractility index.

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1.3.3 Non-invasive Determination of Aortic Pressure and Aortic Pressure Drop

That the aortic pressure measurement is of significant clinical importance has long been recognized. In data, no one has investigated the aortic waveform profile determination noninvasively throughout the cardiac cycle, along with aortic stiffness and peripheral resistance. Herein, we have provided the analysis for the aortic pressure waveform to be determined non-invasively, as well as indicated this method of determining aortic stiffness and peripheral resistance (and even cardiac contractility).

For this purpose, we have developed a biomathematical model to simulate aortic pressure response to LV output flowrate, along with aortic stiffness (m_a) and peripheral resistance (R_p). In addition, the aortic pressure drop across aortic valve is also formulated, in terms of the outflow tract geometry, which can be obtained noninvasively. Together, the aortic pressure and the pressure-drop across the aortic valve can contribute to the determination of LV pressure during the ejection. Since accurate measurement of aortic blood pressure waveform requires catheterization of the aorta, a noninvasive determination of aortic as well as LV blood pressure is thus most welcome news in cardiology.

1.3.4 Systolic Modeling of the Left Ventricle

‘How to assess the systolic function of the LV’ has long been the major problem in physiology and cardiology, and this problem has remained unsolved. In systole, the myocardial cells in the ventricular wall must generate adequate contractile force to provide sufficient pressure to open the aortic valve, and then shorten and thicken the wall to pump an appropriate stroke volume. For this purpose, we link the myocardial contractile properties to its organ-level function. For this purpose, we have analyzed the dynamics of the LV sarcomere. The stress-shortening velocity relationship and power generated by sarcomere (CE) element are obtained, and linked to LV function namely its

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pressure and volume-change. In so doing, we have expressed LV disability in terms of the dynamic characteristics of the LV myocardial fiber.

1.3.5 Clinical Application of Our Modeling Effort

The most impact of the current investigation is to apply the models and corresponding functional parameters in clinical application. Each patient's clinical diagnosis is compared with our bioengineering (BIE) indices-based assessment, to help develop and reveal the efficiency of these indices.

1.4 Organization of the Thesis

The above goals are achieved and explained in detail in seven chapters. The Chapter 2 presents a literature review in relation to LV diastolic filling and systolic function, modeling cardiac function and aortic pressure, cardiac properties and clinical indices for cardiac function. It also highlights the gaps between existing approaches and our current work.

In Chapter 3, a nonlinear volume-dependent passive elastance and time-dependent active elastance model is established. With this model, the relation between passive-elastance and LV volume, active-elastance and time have been studied, demonstrating the impact of total elastance in characterizing LV diastolic and systolic during a complete cardiac cycle. This chapter also analyzes several patients case-by-case, by depicting their history and the computed functional indices.

Chapter 4 investigates the effect of left ventricular shape alternation on contractility and function. Cardiologists have been observing for some time that an infarcted LV becomes less ellipsoidal as compared to a normally contracting LV shape. This resultant distorted

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shape of an impaired LV does not allow it to contract and deform (in an optimal twisting mode), so as to perform its pumping function and deliver the requisite cardiac output efficiently. In concordance with this clinical observation, a new LV shape-based contractility index (CONT1) has been formulated as $d\sigma^*/dt_{\max}$, incorporating the LV ellipsoidal shape factor (ratio of B/A). Also another contractility index (CONT2) is developed based on the derivation from this optimal shape factor. The results confirm that a non-optimal less-ellipsoidal shape is associated with decreased LV contractility.

Chapter 5 develops a biomathematical model to simulate aortic pressure response to LV output flowrate, along with aortic stiffness (m_a) and peripheral resistance (R_p). The aortic stiffness (m_a) may be an indication of arteriosclerosis, while peripheral resistance (R_p) can be an indication of atherosclerosis. Then, based on this aortic pressure profile and the computation of the pressure drop across the aortic valve (in terms of the outflow tract geometry), we can determine the LV pressure profile during the ejection phase noninvasively.

Chapter 6 develops a LV systolic-phase model in terms of the myocardial sarcomere model. The resulted “stress-velocity” relationship and power generated by the sarcomere (CE) element are investigated as indices of LV function and impairment.

Chapter 7 applies all of these models to clinical cases. Each patient’s clinically made diagnosis is compared with our indices-based assessment, to help reveal the efficacy of these indices.

Finally, Chapter 8 summarizes the main conclusions reached in this work. It also proposes the direction for future work.

CHAPTER 2

LITERATURE REVIEW

During the last one hundred years a number of specific properties of the ventricle have been investigated. Several of these attained (i.e., ejection fraction & stroke output) universal acceptance. Others were never fully validated. A number of properties (i.e., chamber compliance & myocardial compliance) were used for the construction of models in the analysis of cardiac function. Many cardiac performance indices were then generated either from adaptation of these models to the clinical application or from simple intuitive considerations.

Essentially, the work reported in this thesis focuses on developing bioengineering indices for reliable diagnosis of cardiac dysfunction modalities due to filling and contractility abnormalities, as well as aortic stiffness for arteriosclerosis and peripheral resistance for atherosclerosis. In previous research, numerous approaches about cardiac function model have been studied for the diastolic filling, systolic and arterial system. Accordingly, this chapter presents a literature review in the following perspectives: left ventricular (LV) function in diastolic and systole, modeling of cardiac function and aortic blood pressure, cardiac properties and clinical indices derived for cardiac function and arterial system. As

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a result, the review enables the gaps pertaining to the research in cardiac performance, provides the motivations for an in-depth investigation.

2.1 Left Ventricular Function in Diastole and Systole

LV diastolic function can be defined as filling phase that is sufficient to produce a cardiac output with the needs of the body. On the other hand, LV systolic function can be defined, as myocardial cell must generate adequate coordinated contractile force to provide sufficient LV pressure to open the aortic valve and then contracting and shortening the wall to pump an appropriate stroke volume. This means systole is a process of converting chemical energy into mechanical energy in crossbridges for contraction (Suga, 1994).

From a physiological point of view the LV is an integrated muscle-pump system. The term diastole is interpreted as division, notch, or separation between two contraction-relaxation cycles (Brutsaert et al., 1984). In this interpretation its meanings is restricted to the passive properties of the LV (Gillebert et al., 1994). LV Diastole starts when active relaxation has been completed and includes the diastasis and the left atrial (LA) contraction phase. In the English medical literature, diastole is interpreted as “the dilatation or period of dilatation of the LV, coinciding with the interval between the second and first heart sounds” (Brutsaert et al., 1984). In this interpretation it is the part of the cardiac cycle, which starts with the isovolumic relaxation phase and ends with cessation of mitral flow (Arrighi et al., 1995).

The functional properties of the LV during diastole have mostly been described in terms of either the rate at which it relaxes in early diastole or its stiffness when it is fully relaxed in the later part of diastole. Hence diastolic dysfunction can be divided into relaxation abnormalities (i.e., ischemia, cardiomyopathy), decreased compliance (i.e., hypertrophy,

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myocardial fibrosis) and abnormal high heart rate (Brutsaert et al., 1993; Rusconi, 1998). However, the filling pattern of the LV depends on a complex and continuous interaction of multiple factors, of which only some relate directly to the diastolic properties of the LV itself. Other factors relate purely to hemodynamic conditions imposed on the LV, including venous return, suction, resistance-to-filling and LA contraction and so on.

The functional properties of the LV during systole have most been described in terms of contractility term on different levels. Hence, systolic dysfunction can be defined, as LV is not able to contract and eject the adequate stroke volume into the circulation. LV performance is the result of two independent but interrelated functions (diastolic and systolic function), as shown in Figure 2.1. Systole is defined as the capacity of the LV to contract and then eject the stroke volume at the high pressure existing in the aorta. Diastole is defined as the capacity of the LV to relax and then to accept the stroke volume at the low pressure existing in LA and pulmonary veins.

Figure 2.1 : Diagram illustrating the concept of LV diastolic and systolic function.

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Hemodynamic phases during diastole and systole can be elaborated as follows:

2.1.1 Diastolic phases

The LV diastole phase consists of isovolumic relaxation, rapid filling, diastasis and atrial contraction will be discussed briefly (Figure 2.2). Rapid filling starts after relaxation is completed. A relatively small volume portion of blood is shifted into the LV during diastasis. In the atrial contraction phase, intra-ventricular blood volume increases again.

Isovolumic Relaxation: LV pressure first falls below the pressure in the aortic root, which causes the aortic valve to close. The decline of pressure in time approximates an exponential curve, but in the non-filling heart the LV pressure frequently reaches a negative asymptote due to elastic recoil (Yellin et al., 1986; 1994; Gilbert et al., 1989). The rate of myocardial relaxation is influenced by several independent factors in the LV (Brutsaert et al., 1980; 1984) such as preload, afterload, and inactivation. Closure of the aortic valve marks the beginning of the isovolumic relaxation phase. Valve closure can be detected as the second heart sound. After closure of the aortic valve there is a rebound wave of pressure against the valve in the aorta. This rebound wave occurs due to the distension of the aorta's walls during the ejection phase. During the isovolumic relaxation phase both the mitral and aortic valves are closed and the pressure in the ventricle falls rapidly.

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Figure 2.2: LV diastolic and systolic phases with different definition (Wiggers, Clinical and Muscle-pump). MVC=mitral valve close; AVO=aortic valve open; AVC=aortic valve close; MVO=mitral valve open.

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Rapid filling phase: when LV pressure falls below LA pressure the mitral valve opens. The LV will then be filled with the blood, which is accumulated in the LA in the previous systole. During early filling, blood enters the LV passively with the atrio-ventricular pressure gradient mainly developed by, and related to, the rate of ventricular relaxation and impedance of the mitral valve (MV) (Ishisa et al., 1986, Yellin et al., 1990; 1992; 1994). The faster the ventricular relaxation, the lower the LV minimal pressure, and the higher the atrio-ventricular pressure gradient during early filling. In cardiac diseases with impaired ventricular relaxation, the atrio-ventricular pressure gradient is decreased during early filling because of a higher level of the LV minimal pressure. In this condition, an increased LA pressure can maintain the stroke volume. On the other hand, an enhance rate of ventricular relaxation and suction effect without increasing of the LA pressure also can maintain the stroke volume (Cheng et al., 1993). It has been suggested that this mechanism, of enhanced ventricular relaxation, could be the basic phenomenon of the so-called ventricular suction (Udelson et al., 1990).

At first, LV pressure will continue to decrease due to continue decreasing of sarcomere despite early LV filling, thus accelerating blood into the LV. With increasing LV volume, LV pressure will rise according to the passive filling characteristics that are determined by viscoelastic properties of the myocardium (i.e. passive elastance or compliance), myocardial thickness, and external constraints (i.e., pericardium, right ventricle and lungs) (Yellin et al., 1990, Little et al., 1990; 1995). Once relaxation and elastic recoil are complete, LV filling will continue because of inertia (i.e., the mass of flow blood) (Yellin et al., 1990). Early LV filling rate (i.e. the first derivative of volume-time curve), will diminish when atrio-ventricular pressure is reversed (Courtois et al., 1988). When LV chamber stiffness increases, the early diastolic filling deceleration time decreases (Little et al., 1995; Rich et al., 1999). Conversely, early diastolic filling deceleration time may

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increase in the presence of mitral stenosis as a consequence of increased impedance of the mitral valve with prolonged atrio-ventricular pressure difference associated with elevated LA pressure (Meisner et al., 1991). As a result of these three processes: ventricular relaxation, ventricular filling and atrial emptying, the atrio-ventricular pressure gradient decreases until a point is reached when the pressure in both chambers equilibrate, and ventricular rapid filling stops.

Diastasis phase: this is the phase in diastole when LA and LV pressures are essentially in equilibrium following the rapid filling phase, and little or no filling occurs. Flow from the pulmonary veins may continue to contribute slightly to ventricular filling, with the LA acting as a passive conduit. The duration of this period depends mainly on the heart rate. If the heart rate does not exceed 90 to 100 beats per minute, a near zero flow occurs (Rusconi et al., 1998). According to Brutsaert (1993), true diastole begins with diastasis when ventricular relaxation is physiologically completed and passive LV diastolic compliance is the main determinant of the diastolic pressure-volume curve morphology. In this phase and during atrial contraction, the true passive properties of the ventricular myocardium can properly be studied, provided a normally short LV relaxation exists without interfering with end-diastolic events (Gibert et al., 1989, Yellin et al., 1990; Zile, 1996).

Late filling phase: In the presence of sinus rhythm, synchronous electrical activation of the LA is followed by atrial contraction and the ejection of the further amount of blood into the LV. The percentage of its contribution to total ventricular filling largely depends on the age from around 10% in children to more than 50% above the age of 80 years (Rusconi et al., 1998). The proportion of LA contribution to LV filling increases in a

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variety of cardiac diseases with delayed ventricular relaxation and decreased early filling (Little et al., 1990, Pai et al., 1994). Because of Frank-Starling mechanism of the LA, the reduction in early LV filling induces a more forceful LA contraction and a compensatory increase of its ejection volume into the LV; the normal LV filling volume is thus maintained. This result can be obtained with or without an increase of LV end-diastolic pressure depending on the passive properties of the LV. Normally, very little retrograde flow of blood into the pulmonary veins occurs, but the retrograde will occur in patients with LV hypertrophy or fibrosis in which atrial contraction faces a stiffer LV (Little et al., 1990).

2.1.2 Systolic Phases

Systole is divided (isovolumic contraction and ejection) will be discussed briefly (Figure 2.2). Isovolumic contraction starts after diastolic filling is completed. During the isovolumic contraction phase, both the mitral and aortic valves are closed and the pressure in the ventricle increases rapidly. In the systolic ejection phase, LV ejects blood into the aorta and thus its circulation through the body.

Isovolumic Contraction: The QRS complex of the ECG, which represents ventricular depolarization, initiates this phase of the cardiac cycle (Figure 2.2). As the ventricles depolarize, excitation-contraction coupling leads to myocyte contraction and the development of ventricular wall tension and a rapid increase in intraventricular pressure (Lakatta, 1992). As the ventricle begins to contract, the pressure in the ventricle soon exceeds that of the atrium and the mitral valve closes, which marks the end of diastole and the beginning of ventricular systole. Closure of this valve also marks the beginning of

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the isovolumic phase of contraction and is detectable as the first heart sound. During the isovolumic phase of contraction, since both the mitral and aortic valves are closed, the volume of blood in the ventricle is constant and pressure inside the ventricle increases. Individual myocyte contraction, however, is not necessarily isometric (Fozzard et al., 1991). Individual fibers contract isotonicly (i.e., concentric, shortening contraction), while others contract isometrically (i.e., no change in length) or eccentrically (i.e., lengthening). Therefore, ventricular chamber geometry changes considerably as the heart becomes more spheroid in shape (Juznic, 1998); LV circumference increases and base-to-apex length decreases. As contraction of the ventricle proceeds, the pressure in the ventricle further increases rapidly until it equals the pressure in the aorta.

Ejection: When the pressure in the ventricle exceeds the pressure in the aorta, the aortic valve opens and the ejection phase begins. Note that during ejection, aortic pressure is slightly less than LV pressure, which is why the aortic valve remains open. This pressure drop across the aortic valve is useful to identify the performance of an aortic valve. Initially, contractile force and hence ventricular pressure continues to increase causing rapid ejection of blood from the ventricle. Aortic blood flow increases and ventricular volume rapidly decreases during this rapid ejection period.

Contractile force peaks and begins to decline due to the beginning of repolarization of the ventricle, marked by the T wave (Figure 2.2), and due to decreased volume in the ventricle and a length-tension related reduction in force. When force declines the ejection rate declines. As pressure in the ventricle falls below that in the aorta, the aortic valve closes. This concludes the systolic period of the cardiac cycle.

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2.2 Modeling Cardiac Function

Many models have been constructed for the whole cardiovascular circulation by simplifying each subsystem. Only those models that shed some light on cardiac function, however, need to be reviewed here.

Earlier in 1895, Frank (1895) for the first time characterized ventricular function in the pressure-volume (P-V) diagram with frog experiments. He viewed the heart as a compression chamber. Starling (1918) first viewed the heart as a pump to generate flow against afterload as a function of preload, and proposed that cardiac tone (contractility) could be assessed by the height of the cardiac output versus preload curve. The cardiac output curve is the basis of the Starling law of the heart, and its mechanisms have been searched for into molecular levels such as crossbridge (ter Keurs et al., 1988). According to this law we can predict the mechanical performance of the cardiac muscle from a group of isotonic or isometric curves in response to a given stimulation. Thus, the tension at a given instant in the action should be dependent on the length at that instant.

In 1955 Guyton illustrated how venous return can be equated with cardiac response, by equating these curves both the cardiac output and the right atrial (RA) pressure are simultaneously determined. Relations between cardiac output and RA pressure were obtained from physiological experiments. Hence he also derived an empirical equation for venous return but without physiological meaning coefficients. However, the model still embodies the common line of thinking in the daily clinical practice.

In 1959 Grodins represented the cardiovascular system as a feedback regulator. He analyzed the steady-state operation of the isolated LV in terms of an “emptying process” and a “filling process” using “Starling’s law of the heart”. Grodins derived appropriate differential equation during the filling phase on the assumption that any atrial contribution can be neglected. Therefore, Grodins’ analysis was confined to the steady state by

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assuming a continuous and linear starling curves with zero y-intercept (Defares et al, 1963). However, the cardiovascular system is a complex multivariate feedback regulator and the objective investigated is thus limited.

Robinson (1963) constructed the cardiovascular system using the equivalent circuit theory, based on the feedback mechanism of Grodins (1959). The study focused on modeling of the LV by considering it in isolation from the rest of the circuit. He attempted to link the cardiac performance with the myocardial behavior by treating the LV as a cylinder model. As a result, the relationships between the flow and venous pressure, as well as the flow and arterial pressure are determined.

Later, some approaches emphasize the LV as an energy source for the circulation. They usually represented LV as the combination of a pressure source and series of impedance. Elzinga (1972) studied selective changes in capacitive and resistive load under constant LA filling pressure. Isolated cat heart was loaded with a hydraulic model simulating the input impedance of the systemic arteries. Aortic and LV pressure and aortic flow were measured under different impedances. However, LV stroke output is mainly controlled by the oxygen needed of the tissues, which is not affected by the input impedance of the arterial system. Therefore the behavior of a normal LV in an intact circulation in response to changes in impedance may be quantitatively different. Similarly, Meisner (1986) represented a ventricle as the combination of a pressure source and a series of impedances. He constructed an electric analogue, lumped parameter model of the circulation from the right ventricle (RV) to the aorta. Based on his work, Zhu (1996) investigated the factors (i.e., pulmonary bed, LA and mitral valve and LV itself) that affect the LV performance based on the animal experimental results. These models can provide an insight to the diastolic and systolic processes. Many researchers still simulated

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the cardiovascular system in recent years by using an equivalent electronic circuit (Podnar et al., 2002; 2004; Rupnik et al., 2002; Segers et al., 2003).

There are some models in the description of the LV as an elastic reservoir, of which the compliant properties are function of time.

Warner (1959) appeared to be the first to adopt a compliance description for a dynamic heart. He assigned two values to the compliance: a higher value during diastole and a lesser value during the systole with abrupt transitions between diastolic and systolic phases. Defares (1963) avoided the stepwise transition between the diastolic and systolic compliance by treating elastance as a continuously varying function in time without the stepwise transitions between the diastolic and systolic compliance values. The change in elastance allows the ventricle to fill during diastole and to eject during systole. This work ushered in the era of time-varying compliance or elastance based ventricle models. Later, the concept of a continuously varying compliance or elastance was adopted by a number of investigators with diverse variations (Suga and Sagawa, 1974; Kennish et al., 1975; Mulier, 1994; Palladino et al., 1998). They all shared the preconceived model of a simple compliance as an adequate description of ventricular mechanics during the cardiac cycle.

As to the elastance model, Suga (1969) confirmed this property in isolated ventricles and in the intact animal. Working with the isolated, supported canine heart, series of experiments suggested that elastance essentially followed the same time course for the entire cardiac cycle. Subsequently, more accurately executed experiments restricted the applicability of elastance to systole (Sagawa, 1978), and to only small ejection fraction (Sagawa, 1980) in order to investigate the relationship between the elastance and contractile state

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Suga and Sagawa thereafter defined a time-varying elastance as ventricular pressure divided by a corrected ventricular volume ($P/(V-V_d)$) and applied actual pressure and volume into the experiments. However, this is valid only if the relation between pressure and volume is linear. This requirement has also never been investigated for the total compliance curve. Suga and Sagawa found a linear relation for the end-ejection moment when they shifted the intersection point on the x-axis by a volume called V_d . A simple calculation of the elastance using their definition, of a ventricle pumping against different arterial loads revealed that ($P/(V-V_d)$) changed and was therefore load dependent.

Noordergraaf (1994) also pointed that the ventricle model in terms of a pure compliance has some inherent difficulties. Because basic aspects of pressure-flow relations in arteries reveal the other properties (i.e., initial effect & viscous effect) may be of important.

Instead of describing the whole ventricle as the behavior of only one system, some researchers have used a model of cardiac muscle built in a geometric construction, taking muscle and geometric properties into consideration.

Robinson (1963) used a model built in a cylinder wall with Laplace's law. Beneken (1965) extended further by integrating the three-element muscle model as described by Hill (1938), to obtain a mathematical relationship between LV volume and pressure in a sphere with a thick incompressible wall.

The reconstruction for the orientation of the muscle fibers in the LV wall are too complicated to give a simple model of LV function unless geometric considerations are strongly simplified. The subsequent calculation of shortening and force development during contracting was thus too difficult and time-consuming; therefore the finite element method (FEM) was a major tool in this endeavor.

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One of the earliest FE models of ventricular mechanics was formulated by Gould, Ghista, Brombolich and Mirsky (1972), who incorporated a realistic longitudinal cross-section of the LV wall into an axisymmetric FE representation. The effects of the extra geometric complexity were examined using rings of isotropic, homogeneous shell elements. The additional geometric flexibility allowed the changes in wall curvature sign and hence a shift in the peak wall stress from the endocardial to the epicardial surface, which the previous geometrically simple models (i.e., Robinson, 1963) could not predict. Later FE analysis was used widely for the experimental studies of the LV by many researchers.

Tozeren (1983) modeled the LV as a thick hollow tube composed of solid fibers. He represented the relative thickness of the ventricle, inner volume of the ventricle and the various tension-extension relations proposed for the fibers of the heart muscle. The pumping efficiency was shown to increase with increasing thickness of the modeled LV and with increasing contractility of the muscle fibers. But the computations for the stimulated heart muscle were not applicable during ejection systole when the fiber tension depends strongly on the velocity of contraction. Guccione (1991) modeled the equatorial region of LV as a thick-walled cylinder consisting of an incompressible hyper-elastic material with homogeneous exponential properties. This model also took the orientation of the muscle fibers in the myocardium into consideration. Taylor (1994) developed a spherical LV model using the computational fluid dynamics (CFD) method. Costa (1996) represented a thick-walled ellipsoidal model for LV using high-order mesh scheme. He provided the first practical opportunity to solve large-scale anatomically detailed models for cardiac stress analysis. Okamoto (2000) later described the passive ventricular wall using a nonlinear, three-dimensional, finite element (FE) model, assessing the material parameters of the intact passive canine LV wall using an exponential, transversely isotropic constitute relation. He suggested a new approach to obtain parameters for three-

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dimensional relations of the LV wall. Recently, researchers applied FEM into the visualization and measurement of the LV deformation with a visualization toolkit to recognize and predict heart diseases (Wunsche et al., 2003).

The FEM is the most powerful among the numerical and analytical methods, but it is difficult and heavy to use mostly when, to achieve a higher and higher fitness to the describing ventricle, a very high number of elements are employed. Furthermore, the already mentioned difficulties in obtaining an accurate three-dimensional reconstruction of the intact heart strongly limit the theoretical power of the method.

There were many researchers who modeled the ventricle from micro-structural dynamics. In the review by Sagawa (1978), he derived that instantaneous pressure and instantaneous volume of the ventricle in the P-V plane was derived from some fundamental properties of heart muscle. Experimental investigation of the behavior of isolated strips of skeletal and cardiac muscles revealed the existence of force-length as well as of force-velocity relationship by Hill (1938). These indicated that the force of contraction increases with length under isometric conditions within the physiological range. Under shortening conditions this force is diminished in relation to the velocity of shortening. For the next 50 years since 1938, Hill's model of muscle contraction has dominated the field. During the period, many ideas have been added to the model in order to accommodate newly discovered facts. Originally rather simple, gradually the "series elastic" element became a very complex entity. Then the "active state" function was introduced, the exact meaning of which turned out to be elusive.

Huxley and Niedergerke (1954) proposed the sliding filament theory in 1954. They showed that mechanisms underlying lengthening and shortening of striated muscle have

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been correlated with altering overlap of thin and thick filaments that constituted the sarcomere.

With the advent of the sliding theory, the main stream of muscle research has been centered on the theory of cross-bridges. The cross-bridge is a description of the interaction of actin and myosin filaments. The myosin filaments were shown to be composed of a light-meromyosin and a heavy-meromyosin part (Huxley, 1974). Without definitive structural data and a fundamental atomic approach, the theory has to be stated under various sets of hypotheses such that the lengths of the actin and myosin filaments are unaltered by stretch or contraction. Prior to actual observation of cross-bridges, Huxley devised the crossbridge model based on the structural assumption such that bonds between myofilaments were controlled via rate constants f and g , indicating attachment and detachment, respectively.

Subsequent models became more complex in an effort to describe muscle's dynamic behavior (Julian et al., 1973; Eisenberg et al., 1980). These approaches consisted of attachment and detachment rate. Julian (1973) represented the model as a volume of muscle with one half-sarcomere in length and one cm^2 in cross section. Length changes are confined to the plateau region of the sarcomere length-tension relation. Eisenberg (1980) further proposed cross-bridge model based on Huxley's description of a single sarcomere. This cross-bridge model consisted of two cross-bridge states detached from actin and two cross-bridge states attached to actin. This model also illustrated the inter-relationship between the biochemical and physiological data necessary for the development of a complete cross-bridge model. However, these approaches have never described all types of contractile loading conditions. In addition, the models rely on nonlinear f and g rate functions, hence shifting the emphasis away from crossbridge and myofilaments mechanics to rate function.

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Recently, Palladino (1997) proposed a structural mechanism for the origin of muscle's complex mechanical properties using a distributed model. Some important factors influencing the property of contraction such as the masses of myofilaments and cross-bridge bonds were taken into account. The contractile force was generated by viscoelastic crossbridge bonds that formed between the interdigitating matrix of myofilaments. The number of bonds formed depended upon the degree of overlap between thick and thin filaments and was dictated spatially and temporally because of finite electrical and chemical activation rates.

In brief, these investigations have explained the muscle contraction mechanism from the micro-structural dynamics. The models presented here together with the values given for the parameters and rate constants (i.e., f and g), is not necessarily final. How to integrate it into a LV geometry model for modeling LV still remain to be resolved. Also, it would be interesting to test the model's generality by determining the extent of the modifications required to obtain a satisfactory fit to myocardial behavior.

2.3 Modeling of Aortic Blood Pressure

The monitorable aortic blood pressure waveform can be directly used to derive valuable indices of cardiac and cardiovascular function, such as systolic time intervals, ejection duration (Westerhof et al., 1995), arterial compliance (Liu et al., 1986; Burattini et al., 1987; Machenzie et al., 2002), peripheral resistance (Ocasio et al., 1993). Also, it can be indirectly used to derive indices such as myocardial oxygen supply and demand (Sunagawa et al., 1983), wave reflection (Chiu et al., 1991), the augmentation indices (Chen et al., 1996), and end-systolic elastance (Lee et al., 2002). In addition, the waveform can be combined with aortic flow or ventricular volume to facilitate assessment of cardiac performance as presented by O'Rourke (1984). Recently, Kyriazis (2001)

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proposed a term, $dP/dt_{\max}$ (traditional contractility index) from the brachial pulsation signal with the use of an inflated cuff.

Estimation of these indices of ventricular and arterial pressure waveform measurements should be done closer to the heart, in the ascending aorta. Due to practical and ethical reasons, however, the arterial pressure waveform is rarely recorded in the ascending aorta but in a peripheral artery. Since the arterial pressure wave contour is site-dependent (due to wave propagation/reflection phenomenon), the use of peripheral arterial wave contour for diagnostic purpose is hence somewhat limiting.

The models for the aortic pressure determination vary in their complexity and accuracy, depending on the assumptions being used in the model development and their applications. There exist two classes of model: mathematical model and physical model with hydrodynamic or electrical analogues. Some of the models in both classes emphasize the properties that the arterial tree transforms intermittent or pulsatile inflow to more constant or steady outflow. The simplest form was the ‘Windkessel’ model, which assumed all pressure fluctuations in the arterials occurred synchronously.

Otto Frank (1899) established the well-known “Windkessel” theory, which considered the arteries as a system of interconnected tubes with fluid storage capacity. Fluid is pumped in at one end in an intermittent (ventricular ejection), while outflow at the other end through the peripheral resistance is constant. The “Windkessel” model of the arterial tree consists of two compartments: the aorta as a compliant vessel with storage properties and peripheral vessels as stiff tubes that drain blood during the diastole. For the last century, “Windkessel” model of arterial system has dominated the field. Since then, many ideas have been added to the model in order to accommodate newly discovered facts (Ocasio et al., 1993; Fogliardi et al., 1994 & 1996; Lambermont et al., 1997; Molino et al., 1998; Stergiopulos et al., 1999; Scharfschwerdt et al., 2004) with different sets of parameters

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(i.e., arterial compliance, peripheral resistance). The most limiting aspect of these models was the assumption used in obtaining the aortic pressure.

Eater researchers developed methods to generate the ascending aortic pressure wave from the radial or brachial pressure wave through a generalized transfer function (Karamanoglu et al., 1993, 1995; Pauca et al., 2001; Soderstrom et al., 2002). A transfer function is a mathematical description of the change in pulsatile phenomena between two sites, expressed in the frequency domain in terms of modulus and phase. The methods were based on the determination of an “averaged” pressure transfer function between the peripheral and aortic locations. Differences between individual patients and the averaged pressure transfer function may exist and thus the use of a generalized “averaged” transfer function may result in errors for the prediction of aortic pressure.

2.3.1 Aortic Pressure Waveform

In a review of Karamanoglu (1997), different features in the arterial pulse contour are described. These features consist of five relative points on the arterial pressure wave contour: the wave foot, first shoulder, second shoulder, incisura, and duration of the pulse (Figure 2.3). The wave foot and first shoulder coincide with the onset of LV ejection and the peak flow, respectively. The second shoulder is considered to be associated with reflected pressure wave originating from the periphery and occurs later in systole. This shoulder is followed by the sharp incisura, which coincides with the closure of the aortic valve and cessation of LV ejection. The second shoulder that is higher than the first shoulder augments the systolic pressure and is seen mostly in the elderly patients. The second shoulder, which is equal to or less than the first shoulder, obviously has no systolic pressure augmentation (Kelly, 1989; Karamanoglu et al., 1997).

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Figure 2.3: The basic features of the aortic pressure profile. P_1 and P_2 are diastolic pressure and systolic pressure, respectively.

2.3.2 Assessment of Non-invasive Arterial Pressure

The generally applied noninvasive methods to assess arterial pressure include auscultatory, oscillometry and arterial tonometry. The principles of measuring arterial pressure with these methods are discussed here. Arterial catheterization is an invasive method of assessing arterial pressure properties and will be mentioned first.

Invasive catheterization method: Early in 1733, Reverend Stephen Hales inserted a long glass tube upright into an incision of a horse's artery. The pumping action of the heart generated a pressure force, causing the blood level to rise in the tube. These early surgical procedures were dangerous for patients, due to the risk of infection and excessive blood loss. Even today, invasive catheterization procedures are seldom done for blood pressure measurement. Instead, non-invasive methods sacrifice a degree of accuracy for patient safety, comfort and convenience.

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The auscultatory method: In 1905, Korotkoff described the auscultatory sounds, which became the foundation for the auscultatory technique. This is the most common method of blood pressure measurement today (Maurer, 1976; Drzewiecki et al., 1987, 1989; Karamanoglu et al., 1997). An air-filled cuff is wrapped around the patient's upper arm. The cuff is inflated to occlude the brachial artery. As the cuff is allowed to deflate, a stethoscope is placed over the patient's brachial artery (distal to the cuff). The clinician uses the stethoscope to listen for the Korotkoff sounds as the cuff deflates. The conventional site for the Korotkoff method is the upper arm and brachial artery since it is closer to the heart. Thus, the pressure recorded is relative close to aortic pressure, which is of primary interest (Shenoy et al., 1993). Based on the diastolic and systolic pressures obtained, Chemla (2002) formulated empirical equation for mean aortic pressure (MAP). The auscultatory technique is based on the ability of the human ear to detect and distinguish sounds. This is a great advantage since it allows the clinician to determine the quality of each measure. However, inherent in this method is the possibility of measuring error due to differences in hearing acuity from clinician to clinician. In an attempt to increase reproducibility, some automated devices have replaced the human ear with a microphone.

The oscillometry method: Oscillometric measurement of blood pressure predates the method of Korotkoff with its introduction by the French physiologist Marey (1885). This method allowed blood pressure measurement for critical care and intensive care patients with muted Korotkoff sounds (Yong et al., 1990; Ursino et al., 1995; Drzewiecki et al., 1998). Unlike auscultatory techniques, which measure systolic and diastolic and estimate the mean arterial pressure, oscillometric devices measure the mean but estimate systolic and diastolic pressures. An air-filled cuff is wrapped around the patient's upper arm. The cuff is inflated to occlude the brachial artery. As the cuff is allowed to deflate, pressure

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data is recorded by the device. Over time, the pressure data is recorded as a waveform. The point of maximum amplitude is considered the mean arterial pressure. Systolic and diastolic pressures are estimated from the mean arterial pressure (MAP). Therefore, erroneous determination of MAP may produce inaccurate values for systolic and diastolic pressures.

In brief, the auscultatory and oscillometric methods (Brinton, 1997) provide only two features of the complex arterial pressure wave contour: the peak systolic and diastolic pressures. These values are routinely used in diagnosis and treatment of hypertension. However, there are other features of the aortic pressure wave contour, which are also of interest to the clinician.

The arterial tonometry method: the method of arterial tonometry was introduced to record noninvasively the pressure in superficial arterial (i.e., the radial artery) and provide direct pressure calibration (Drzewiecki et al., 1983). It uses a very different approach. The artery is flattened by applying pressure non-invasively to squeeze the artery against bone. The applied pressure required to maintain the flattened shape are recorded by an array of sensors (Moubarak et al., 1989; Bansal et al., 1994). The output is a waveform similar to the catheter measurements. In general, excellent pulse waveform quality is obtainable (Sato et al., 1993). However, it has two limitations. Firstly, it is a measure of the peripheral circulation, which has different pressure from more centrally located sites (such as the brachial artery). Secondly, tonometry has a high sensitivity to the sensor position and angle. Therefore, reproducibility among different operators is low (Drzewiecki et al., 1998).

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2.4 Cardiac Properties

2.4.1 Geometry of the Left Ventricle

The geometry of the LV plays a major role in modeling the LV mechanics (Arts, 1988). Generally, the strategy in designing a mathematical model of LV mechanics begins with interpretation of a number of physiological findings as obtained in experiments. These findings are combined with a more general idea, which is described in mathematical terms. As a result, the designed model can describe the physiological situation most accurately in the vicinity of the physiological conditions.

Thin-walled ventricular models

In a review by Mirsky (1973), one of the earliest models of ventricular stress was formulated by Woods (1892), based on a simple thin sphere with uniform internal pressure. In the absence of computers, the model was based on analytical techniques. The model approximated myocardial tension to be proportional to the product of pressure and radius. Several decades later, some investigators took the same idea to model the LV as a thin-wall sphere (Stillwell, 1973), in which the basic equation between pressure and stress within the myocardium was obtained. Contrasted to the spherical model, Sandler and Sandler (1963) modeled the LV using an axisymmetric ellipsoid. Ventricular wall stress was expressed in terms of wall thickness, the principal radii and the cavity pressure.

Although these thin-walled models did not consider the material properties of the tissue, estimation of principal wall stresses could be obtained throughout the cardiac cycle by means of simple measurements of the ventricular pressure and geometry.

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Thick-walled ventricular model

Early attempts to predict the regional variation in wall stress were proposed by Wong and Rautaharju (1968). They formulated the first LV thick wall model. Transmural variations in myocardial stress were based on ellipsoidal shells of compressible, isotropic, linearly elastic and homogeneous tissue. They matched material properties (the Young's modulus and Poisson's ratio) with the experimental data to estimate the time-varying myocardial stress distributions. Later ellipsoid (Ghista et al., 1971; 1973), thick-wall sphere (Fung, 1981), and thick-wall cylinder geometry (Arts et al., 1988; Shoucri et al., 1994, 2000) were analysed. These analyses yield nonlinear stress distributions through the wall thickness, a result that cannot be predicted by thin-walled ventricular models.

Realistic geometry ventricular model

The models discussed thus far have approximated LV geometry with simple axisymmetric sphere or ellipsoid, which is at best appropriate only for a global analysis of ventricular function. More accurate regional variations in myocardial stress can be incorporated into the models using realistic geometry. In order to analyse stress with this added complexity, the FEM is most suited for the analysis of stress and strain in the beating heart (Gould et al., 1972; Hunter, 1988; Guccione et al., 1991; Costa et al., 1996; Nash, 1998).

However, the LV shape changes during the heart cycle as well as during different physiological and pathological conditions (Tischler, 1993). For example, during diastole, the LV length increases in dimension with small changes in LV circumference. The LV varies from a small to a large ellipsoid. On the other hand, during isovolumic contraction, the LV becomes more spherical again. During ejection, the LV changes again from sphere to ellipsoid. The consequence is the alternating of small and large ellipsoids. The

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mechanism derived is thus varying in different pathological cases (i.e., concentric, eccentric hypertrophy), and the outcome is a disturbance, especially in the filling phases of the LV (Juznic, 1998). The alternating shape of the LV is not only referred to the pattern changes, but also associated with the filling and emptying sequences (Knap et al., 2003). Hence the timing of size and shape of the LV plays a vital role in the process of pumping function.

2.4.2 Hill's Three-Element model

In a review by Fung (1981), the Hill's three-element model (1938) was narrated again. Hill represented an active muscle as composed of three elements: (1) an active contractile element which generates force and shortening, (2) a passive series elastic element that transmits the force (T) generated by the contractile element to the exterior, and (3) a passive parallel elastic element that supports resting tension (Figure 2.4). The basic equation of a force-velocity relation was obtained. It stated that when compared to the isometric force at the same length, the generated force of contraction decreased by the velocity of shortening. For a long time there was no consensus among muscle physiologists. The ultra-structural basis of this phenomenon is likely to be an enhancement of cross-bridge attachment as compared to isometric force development.

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Figure 2.4: Hill's functional model of the muscle. Representative of an active muscle with three elements: contractile, elastic and parallel elements.

2.4.3 Huxley's Cross-bridge Theory

Cross-bridge is a description of the interaction of actin and myosin filaments. Huxley (1954; 1974) proposed the basic theory of sliding element, and focused on the cross-bridges. The essentials of the theory are illustrated in Figure 2.5.

The interaction between actin and myosin is visualized as it is to take place between the globular head and actin molecule. During shortening, therefore, the actin filament moves to the left relative to the myosin filament. Muscle force is generated as a result of cross-bridge bonds formed between thick (myosin) and thin (actin) filaments. The details of the bond formation and detachment are still subjected to considerable debate. Without definitive structural data and a fundamental atomic approach, the theory is derived with

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some hypothesis. Prior to the actual observation of crossbridge, Huxley devised the crossbridge model based on the structural and energetic assumptions. Bonds between myofilaments are controlled via rate constants f and g , dictating attachment and detachment, respectively. One major shortcoming of the theory is its inability to describe transients resulted from rapid changes in muscle length or load (Palladino et al., 1998).

Figure 2.5: Schematic diagram of the cross-bridge mechanism with an assumed tension. (Arrows give the direction of the relative motion between the filaments when the muscle shortens).

2.4.4 Ghista's Three-Element Myocardial Model

Ghista (1971) characterised the myocardial constitutive properties by relating the LV instantaneous stress and strain by means of the Hill-type 3-parameter constitutive model comprising of series-elasticity, parallel-elasticity and contractile elements. The instantaneous LV modulus, expressed in terms of the instantaneous chamber geometry and pressure (by invoking elasticity theory), was also related to the parameters of these elements. This was then clinically implemented to determine those parameters,

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representing the rheological parameters of the LV myocardium, and then related to LV pumping energies (Ghista et al, 1971; 1973).

The constitutive properties constitute averaged properties for the entire LV, and provide a gross evaluation of the normal-pathological state of the LV (Ghista et al., 1980). Conceivably, more representative myocardial characteristics are obtained by applying the alternative 3-element model wherein the series and parallel elastic elements are replaced by viscoelastic elements and the contractile element force is time-dependent. The prime extension and benefit of the Ghista's 3-element model is to make it regionally representative, by developing a myocardial finite-element incorporating these 3-elements. In this way, one can determine the regional values of these elements, and relate them pathologically.

2.4.5 Ventricular Suction

Physiologists have been intrigued by the observation that the relaxing ventricle seems somehow to suck blood into its chamber. With pioneering physical intuition, Katz (1930) proposed that the early rapid filling of the heart is due to mechanical suction of blood by the ventricle. The concept of the heart as a suction pump has over the years been suggested by many researchers (Katz, 1930; Brutsaert et al., 1984; Covell et al., 1995; Bleasda et al., 2003) and is no longer questioned, however, the underlying mechanisms are still not entirely clear. Many believed that ventricular suction did exist as a result of some sort of activity during relaxation (i.e., elastic recoil), a sudden stretching resulting from the filling of the coronary arteries, a marked asynchronous cessation of contraction, or even an actual contraction of some fibers (Brutsaert et al., 1984). Sabbah (1981) confirmed that early rapid filling of the LV is due to forces within the ventricular wall

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that act to restore the ventricle to its diastolic dimensions. This means that the suction is resulted from the contribution of elastic recoil and restoring loads due to the compression of sarcomeres.

Later, work by Robinson and colleagues (1986) contributed in an important way. Robinson et al proposed that the connective tissue matrix of the heart and the heart as a whole (including its connection to the vessel) stores contractile strain during systole. This strain is recovered as elastic recoil in diastole, and performs external work on the atrial blood by sucking it into the LV. This physiological phenomenon of the heart muscle shortening, storing elastic strain in its structures, and then re-lengthening to cause suction has also been expressed by Prewitt (1993) and Kovács (1995).

However, these explanations are quite ambiguous. It is in fact the rapid increase in LV wall compliance that causes a decrease in LV pressure below the value of LA pressure, to thereby create a suction effect on the LA blood. The LV pressure continues to decrease because of continuing sarcomere relaxation, associated with increase in LV compliance and rapid filling of blood resulting in negative values of volume acceleration.

2.5 Clinical Indices for Cardiac Function

The use of indices, mathematically derived from the measurements, in principle facilitates the monitoring and the follow-up of cardiac function. Nonetheless, some indices measure more than one cardiac properties, while others were never derived from a cardiac property and do not associate to any cardiac model. They thus serve mainly for the rapid provision of simple information on the heart in a clinical situation.

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2.5.1 Indices in Describing the Passive Ventricle

The LV end-diastolic pressure remains the most commonly used clinical parameter to describe the passive elastance of the ventricle. A higher-than-normal filling pressure is considered an index of LV dilatation and systolic failure. This parameter is easily measured by catheterization. However, elevated filling pressure does not distinguish between overfilling, venoconstriction, absence of atrial contraction or a changed compliance of the ventricle. Therefore, there are needs to develop some other indices to describe the passive ventricle.

Later, chamber stiffness and myocardial stiffness were investigated (Gaasch et al., 1976; Mirsky et al., 1979; 1984; 1990; Smith et al., 1992). Chamber stiffness is derived from the relationship between pressure and volume during diastole. The operation stiffness at any point along a given pressure-volume curve is equal to the slope of a tangent drawn on the curve at that point. Thus, the shape and position of the entire pressure-volume relation can be used to calculate the overall chamber stiffness. As shown in Figure 2.6, operating chamber stiffness changes throughout the filling phase; stiffness (dP/dV) is less with a smaller volume (point 'a') and greater with larger volume (point 'b'). Since diastolic pressure-volume data can be assumed by an exponential relation, a module of chamber stiffness (k_c) can thus be derived as the slope of the linear relation between dP/dV and pressure (Smith et al., 1992). When overall chamber stiffness increases, the pressure-volume curve shifts to the left, the slope of the dP/dV versus pressure relation becomes steeper, and k_c increases. In order to decrease complexity, Lissauskas (2001) developed the average and passive ventricular diastolic stiffness from transmitral flow using a simple equation $(\Delta P / \Delta V)_{avg}$.

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Figure 2.6: Schematic diagram of LV diastolic pressure-volume relation. On the left, a progressive increase in volume will increase chamber stiffness (dP/dV). On the right, a leftward shift of the pressure-volume relation will also increase chamber stiffness. As the pressure-volume relation is assumed exponential, the relation between dP/dV and pressure is linear; the slope of this relation represents the chamber stiffness constant (k_c).

Corresponding with chamber stiffness, the myocardial muscle of the LV behaves as an elastic material, developing a resisting force as it is stretched by ventricular filling. The greater the change in muscle length (strain), the greater the increase in the force (wall stress) that resists this deformation and the stiffer the myocardium becomes. Myocardial stiffness can be estimated by examining the relation between LV wall stress and strain during diastole. At any given strain throughout filling, myocardial stiffness is equal to the slope ($d\sigma/d\varepsilon$) of a tangent drawn to the stress-strain curve at that strain.

Most investigators considered the diastolic pressure-volume relation and stress-strain relation as curvilinear and exponential, hence the relationships between dP/dV versus pressure and between $d\sigma/d\varepsilon$ versus stress are linear (Mirsky, 1984). It is a common practice to curve-fit diastolic P-V or stress-strain data from minimum pressure (stress) to end diastole in exponential or power form, and then use the exponent as an index of

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chamber or myocardial stiffness. Such approaches are however limited for several reasons, namely, (1) the data are sparse and often scattered in the clinical setting, particularly when angiographic measurement are used; (2) the exponent used is often size dependent and therefore not always suitable for patient-to-patient comparisons; and (3) events that occur during the early rapid filling phase are completely ignored in the analysis (Mirsky et al., 1990).

2.5.2 Indices in Describing Contractility

Most cardiac models deal with the measurement of contractility (Sarnoff, 1955; Mason, 1969; Little, 1989; Kass et al., 1993; Shroff et al., 1995; Greenberg et al., 2002; Xiao et al., 2003; Kara et al., 2004). Then what is the meaning of contractility? Conceptually cardiac contractility is the potential for contraction that cardiac muscle possesses by virtue of the physicochemical environment of the muscle cell, e.g., calcium handling and contractile proteins. It is what the muscle (heart) is capable of doing (Slinker, 1995). But how does one measure the total physicochemical environment of the cell in order to measure contractility? Obviously, one does not. Thus, to use the concept of contractility in evaluating LV performance, one needs an operational definition of contractility. In the past years, contractility has been described as among others in different ways.

Sarnoff (1955) described it as shifts between members of families of function curves. Based on the Hill's theory on activated muscle, Sonnebblick (1962; 1969) has since extended this study to cardiac muscle. He suggested that a hyperbolic relation existed between the velocity of shortening of the contractile element and the developed force. In particular, the results indicated that $V_{\max}$ (the contractile element shortening velocity at

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zero load) was independent of the initial muscle length or preload and seemed as a good contractility index.

However, Mirsky and Ghista (1974) gave a summary review of the existing formulae available for conducting force-velocity analyses derived from animal experimental studies and the development of indices for the assessment of heart muscle function. On the basis of this study, it is concluded that $V_{\max}$ is sensitive to the relatively high preloads and may not be a reliable index of contractility. A more reliable parameter for assessing cardiac muscle function $(dP/dt/kP)_{\max}$ is thus proposed (P is LV pressure and k is its stiffness constant).

Anderson (1973) proposed a new index of cardiac contractility index $\dot{F}_{\max}$. He found that the ratio of two values of $\dot{F}_{\max}$ obtained by perturbing the rate of stimulation at one length is exactly the same as the ratio obtained from the same perturbation at any other length. However, to achieve this goal one must begin with the isolated preparation in which the entire force-frequency relationship can be determined. They are thus associated with some limitations for clinical state.

Later Little (1989) proposed that the changes in the slope of a relation between some output variables, such as ejection fraction, cardiac output, stroke volume, stroke work, or dP/dt , and one of the determinants of function, including end-diastolic pressure, end-diastolic volume, systolic wall stress, or mean aortic pressure. Most studies have indicated the peak of the first time derivative of the ventricular pressure $(dP/dt_{\max})$ was the most sensitive cardiac index of inotropic changes (Kass et al., 1987) in the last three decades. With respect to the loading conditions, it is minimally dependent on afterload for physiological and high resistance ranges, as experimentally observed (Kass et al., 1987) while showing a marked dependence on preload.

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Some other models describe the ventricle as an elastic reservoir, of which the compliant properties vary in time. Suga and Sagawa (1974) defined a time-varying elastance as ventricular pressure divided by a corrected ventricular volume. Maximum elastance ($E_{\max}$) during isovolumic contraction seemed comparable to the elastance at end-ejection as well as independent of end-diastolic volume. This model gave an impetus to the development of several new indices, such as the end-systolic pressure volume relation (ESPVR) as a measure of contractility. However, the complexity of measuring LV $E_{\max}$ requiring a pressure-volume loop recording and at least two different hemodynamic states, which limits seriously its clinical applicability. In addition, a simple calculation of the elastance, using modified definition $P/(V - V_d)$, where V_d is the intersection point on the x-axis when pressure is zero, against different arterial loads reveals in the work that $P/(V - V_d)$ changes and is therefore load dependent. Hence those derived indices such as $E_{\max}$ and ESPVR lose their attractiveness, as a result (Mulier, 1994).

Later, many researchers tried to develop new indices as a surrogate for the slope of the LV end-systolic pressure-volume relationship (ESPVR) such as “LV outflow tract mean systolic acceleration” proposed first by Bennett (1984) and “power index” proposed by Kass (1993). Consequently ascending aortic blood flow velocity and acceleration have been reported to be sensitive to inotropic and little affected by changes in loading conditions by many researchers (Wallmeyer et al., 1986; Redaelli et al., 1998; Bauer et al., 2002). The “power index”: preload-adjusted maximal power accomplished by dividing by end-diastolic volume squared, has been recently shown to be relatively independent of preload, afterload and resistance (Kass et al., 1993; Sharir et al., 1994; William et al., 1998). Because the calculation of power does not require assessment over a wide range of pressure and volume values like pressure-volume loop studies, it appears

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to be an alternative attractive load-independent to assess contractility. However, power inherently is not a parameter describing to heart or arterial system alone. Power also does not characterize the heart such as what the end-systolic pressure-volume relation does. Hence, inherently, it runs into the danger that changes may not pertain to the cardiac changes exclusively.

Some researchers have assessed the cardiac function using cardiac reserve concept (Shoucric et al., 1994; 2000; Xiao et al., 2003; Kara et al., 2004). Shoucric (1994) proposed the external work reserve (EWR), or external energy reserve (EER), as a possible index with potential for clinical application. He considered that the work performed by the myocardium to be: (i) the potential energy which seems to be related to the internal metabolism to develop tension in the active fibres of the myocardium; (ii) the external work delivered to the LV cavity; (iii) the contraction work that seems to correspond to the work needed for the elastic deformation of the passive medium of the myocardium. Xiao et al (2003) also assessed the cardiac function from cardiac reserve measurement where a realizable cardiac contractility reserve index (CCRI) was hence proposed. Kara (2004) proposed that the calculated area under each cardiac cycle of the blood pressure curve as a heart contractility power parameter. However, these indices didn't give much detail information for muscle contractility.

With the advent of FEM, Subbaraj (1987) provided instantaneous distributions of intra-LV flow and differential pressure during the ejection phases and in turn derived an intrinsic index of contractility-pressure gradient field. A uniform pressure gradient towards the aortic outflow tract will contribute to an efficient pump. On the other hand, a non-uniform pressure gradient, caused by asynchronous myocardium contraction due to coronary lesions or infarcts, would give rise to poor pumping performance. In this area, Computational fluid dynamics (CFD) has also been shown to be a powerful tool in

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investigating cardiac mechanics because of its ability to provide data not easily attainable with experimental techniques (Georgiadis et al., 1992; Schoepfhoerster et al., 1994; Taylor et al., 1994; Redaelli et al., 1998). However, this method is a weakly coupled approach, which only approximates the equilibrium of the cardiac wall once its movement is calculated from the fluid velocity field.

Recently, with the advent of new technology, noninvasive index characterizing contractility, myocardial fiber strain rate, obtained by tissue Doppler echocardiography (TDE) and strain rate imaging (SRI), have been proposed by Greenberg (2002) and Costa (2004), respectively. Myocardial strain reflects the deformation of tissue in response to an applied force. The first temporal derivative of strain, strain rate, is the velocity-change in myocardial length. One limitation of TDE, however, is that regional TDE velocities are affected by heart translation and tethering of adjacent myocardial segments. The method of SRI has eliminated the tethering effect as a powerful tool for assessing segmental LV dysfunction such as coronary disease. However, Slinker (1995) believed that none of these has been particularly robust because the approaches used to define them have been too narrowly focused. He summarized it in two reasons: Firstly, the regulated cardiac pump is too complex. The functional capability of cardiac muscle or the heart ultimately derives from the interaction of crossbridges in myocytes. However, the heart functions at any point in time in the range of possibilities available to it will depend on a multitude factors. Secondly, the indices must also be “load independent”. In fact, they are inextricably linked to the load and rate. Thus, given the complexity of the regulated cardiac pump, the multiple interacting determinants of cardiac performance, and the marvelous adaptive ability of cardiac muscle, it is not surprising that a robust, simple load-independent index have not been found. For these reasons, we developed a matrix of diagnostic indices in this thesis to assess the cardiac dysfunction during filling and

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ejection phases other than a single index. Each patient's clinical diagnosis is compared with our biomechanical engineering (BME) indices based-assessment to help in revealing the reliability of these new indices.

2.5.3 Indices in Describing the Arterial system

Aortic Stiffness

There have been much recent interests in the relationship between arterial stiffness and cardiovascular diseases including hypertension, diabetes mellitus, hypercholesterolaemia and end-stage renal failure (Glasser et al., 1997). The aorta, being the largest artery and the one nearest to the heart, is the central conduit from the heart to the body. Acute dilation occurs at aortic walls and this may cause damages to the aorta if it is stiff. This is when most of the cardiovascular diseases begin. As changes can be detected before the appearance of clinically apparent vascular disease, aortic stiffness may act either as a marker for the development of future arteriosclerosis disease, or may be more directly involved in the process of arteriosclerosis.

Arterial stiffness may be measured using a variety of different techniques, although at present the majority of measurements are made for experimental and physiological studies rather than in clinical practice. There are several different methods of assessing arterial stiffness such as pulse pressure (Nakayama et al., 2000) and pulse wave velocity (PWV) (Asmar et al., 1999). Arterial stiffness can also be estimated from oscillometric blood pressure measurement. However, noninvasive determining the aortic stiffness has not been investigated.

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Total Peripheral Resistance (TPR)

The total peripheral resistance (TPR) is the resistance from the arteries and capillaries. As blood is pumped out of the heart into the resistance network of systemic circulation, pressure is generated. In reality, this pressure is pulsatile because of the cardiac output is intermittent in nature. If we were to assume that the cardiac output was continuous (i.e., non-pulsatile), then the mean arterial pressure (MAP) is determined using the cardiac output (CO) and total peripheral resistance (TPR), with equation (2-1), which is based upon the relationship between flow, pressure and resistance (Ocasio et al., 1993; Fogliardi et al., 1996; Segers et al., 2001):

$$MAP = CO \times TPR \quad (2.1)$$

Therefore, changes in either *CO* or *TPR* will affect MAP.

MAP was estimated at the brachial artery level by adding a fraction of pulse pressure (form factor=0.33) to diastolic pressure by Chemla (2002).

$$MAP = DAP + (form\ factor \times PP) \quad (2.2)$$

$$\therefore form\ factor = (MAP - DAP)/PP \quad (2.3)$$

where DAP is diastolic arterial pressure, MAP is mean arterial pressure, PP is pulse pressure.

Based on the experimental results, an improved and empirical estimation of MAP was given as:

$$MAP = DAP + PP/3 + 5\ mmHg \quad (2.4)$$

In practice, from the aortic pressure trace over time, the shape of the pressure trace yields a mean pressure value (geometric mean) that is less than the arithmetic average of the

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systolic and diastolic pressures as shown in Figure 2.3. Therefore, in this thesis, we adopt the mean arterial pressure as

$$MAP = \frac{1}{T} \int P(x,t) dt \quad (2.5)$$

where T is the period of one cardiac cycle, $P(x,t)$ is the aortic pressure.

2.6 Chapter Summary

The current review focuses on models for cardiac functions and indices that are characterizing the performance of LV and arterial system. It covers a broad topics ranging from LV function during diastole and systole, modeling cardiac function and aortic pressure, to cardiac properties and the associated indices. The review enables the gaps pertaining to research in modeling of cardiac function to be identified, and accordingly, provides the motivations for the subsequent investigations.

CHAPTER 3

NONLINEAR PASSIVE AND ACTIVE ELASTANCE

3.1 Background

The human left ventricle (LV) is the chamber of the heart that is responsible for pumping blood through the circulatory system to provide nutrition to the cells of the organ systems. During diastole, the ventricular wall must be appropriately compliant to allow rapid filling at low filling pressure. During systole, however, the LV-wall myocardium must generate adequate coordinated contractile force to develop sufficient intra-LV pressure to open the aortic valve (in contracting and thickening the LV myocardial wall) to pump an appropriate stroke volume.

In a bioengineering sense, the LV can be described as a blood pressure pump, and its biomechanical behavior is expressed by the time-varying relationship between ventricular blood cavity volume and pressure. For many years, clinicians have used this relationship as a measure of cardiac function (Grodins, 1959; Elzinga, 1972; Suga and Sagawa, 1974; Vaartjes and Boom, 1987; Palladino, 1998, 2002). The description of this relationship has been dominated by models based on a time-varying elastance (or its inverse, compliance).

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The change in elastance allows the ventricle to fill during diastole and to eject during systole. However, how these elastance changes regulate LV pressure and filling has not hitherto been explained. Herein, we introduce the new concept of passive (volume-dependent) elastance and active (time-dependent) elastance.

This study develops the analysis and computation of the volume-dependent passive elastance and the time-varying active elastance during cardiac cycle, determines the temporal relationship of elastance to the generated LV pressure, and shows how this active-elastance profile can explain the intra-ventricular pressure increase during the isovolumic contraction phase as well as the LV suction effect during the rapid-filling phase of diastole. We have then studied some cases with different heart diseases (such as myocardial infarct, hypertension and valvular disease) by computing their volume-dependent passive elastance and the time-dependent active elastance, and employed them to assess LV performance.

3.2 Methods

3.2.1 Data Acquisition

The subjects in this study were studied in a resting recumbent (baseline) state, by retrograde aortic catheterization. Left ventricular chamber pressure was measured by a pigtail catheter and pressure transducer; the pressure was recorded immediately during angiocardiology.

Angiography was performed by injecting 30-36 ml of iodinated contrast into the LV at 10 to 12 ml/s. None of the subjects included in this study demonstrated a change in heart rate or pressure during the cineangiocardiology. It has been found, by using biplane

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angiocardiograms, that the calculated orthogonal chamber diameters are nearly identical (Sandler and Dodge, 1963). These findings are used to justify the use of single-plane cine techniques, which enable beat-to-beat analysis of the chamber dimensions. Monoplane cineangiocardiograms were recorded in a RAO 30° projection from a 9 in image intensifier using 35 mm film at 50 frames/s using INTEGRIS Allura 9 system or Philips V5000 from the National Heart Centre (NHC), Singapore. Automated LV analysis was carried out to calculate LV volume and myocardial wall thickness. The variables derived from the cineangiographic films are shown in Figure 3.1; they consist of a measured volume and myocardial thickness of the chamber, as well as the corresponding pressure. All measurements are corrected for geometric distortion due to the respective recordings systems. Figure 3.2 gives an example of measured LV pressure and volume. Note that during the early filling phase, LV pressure decreases immediately after the commencement of LV filling. This phenomenon, is defined as suction effect, has been explained by the decreasing value of active-elastance even in the filling phase.

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Figure 3.1: An example case of measured LV pressure, volume and wall thickness during a cardiac cycle. Seconds is measured from start-of-isovolumic contraction. In this figure, 1-5 is isovolumic contraction phase, 5-17 is ejection phase, and 17-21 is isovolumic relaxation phase, 21-37 is diastolic filling phase.

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Figure 3.2: Same example case of relationship between LV volume and pressure.

3.2.2 Establishing the Nonlinear Passive and Active Elastance Model

At the start of diastolic-filling phase, the LV incremental pressure dP_{LV} is the response to (i) LV myocardial sarcomere force (between its actin and myosin elements) continuing to decrease well into the filling phase, (ii) the inflow of blood, and (iii) the associated increase in LV passive volume-dependent elastance. The associated governing differential equation A-11 derived is:

$$M\ddot{V} + d(V/C) = M\ddot{V} + d(EV) = M\ddot{V} + VdE + EdV = dP_{LV} \quad (3.1)$$

where V represents volume of the LV (ml)

P_{LV} represents pressure of the LV, (hereafter symbolized by P) (mmHg)

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M represents the inertia coefficient, $=[\text{LV wall-density } (\rho)/(\text{LV surface-area/wall-thickness})] = \rho h / 4\pi R^2$, for a spherical LV model (in mmHg/(ml/s²))

C represents LV compliance (ml/mmHg)

E represents LV elastance (mmHg/ml)

The instantaneous LV elastance (E) is the sum of (i) the volume-dependent passive elastance (E_p) and (ii) the active elastance (E_a) due to the activation of the sarcomere. Hence,

$$E = E_a + E_p \quad (3.2)$$

Since filling (and ejection phase) pressure-volume data can be fitted by an exponential relation (Mirsky, 1990), and the classical definition of elastance is defined as the pressure change (dP) due to a change in its distending volume (dV), hence the passive elastance can be adopted as

$$E_p = E_{p0} e^{z_p V} \quad (3.3-a)$$

where E_{p0} is the passive elastance coefficient, z_p is the passive elastance exponent, and V is the LV volume.

On the other hand, the active elastance (E_a) shapes the LV pressure curve, and hence could be represented by an analogous under-damped function, such as:

$$E_a = E_{a0} e^{-z_a t} \sin(\omega_a t) \quad (3.3-b)$$

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

Now we will first determine the active-elastance (E_a) values during isovolumic contraction and relaxation phases.

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a) Active elastance determination during isovolumic contraction and relaxation

During isovolumic contraction, the governing equation (3.1) simplifies to $VdE = dP_{LV}$,

which can be numerically frame-wise represented as:

$$V_i(E_{a,i} + E_{p,i} - E_{a,i-1} - E_{p,i-1}) = V_i(E_{a,i} + E_{ped} - E_{a,i-1} - E_{ped}) = dP_{LV,i} \quad (3.4)$$

where i is a time instant during the isovolumic contraction and relaxation, V_i and $P_{LV,i}$ are the known LV volume and pressure at this instant, and E_{ped} is the passive elastance at end-diastole.

During isovolumic relaxation, the governing equation (3.1) also becomes $VdE = dP_{LV}$,

which can be detailed as:

$$V_i(E_{a,i} + E_{p,i} - E_{a,i-1} - E_{p,i-1}) = V_i(E_{a,i} + E_{pes} - E_{a,i-1} - E_{pes}) = dP_{LV,i} \quad (3.5)$$

where E_{pes} is the passive elastance at end-systole.

For the case shown in the **Figure 3.1**, we have

1. For isovolumic-contraction

$$E_{a,1}(E_a @ t = 0) = 0 \quad (3.6-a)$$

Based on the data values of P_1 , P_2 and V_2 ,

$$E_{a,2}(= E_a @ t = 0.02) = (P_2 - P_1)/V_2 + E_{a,1} = 0.029477 \text{ mmHg/ml} \quad (3.6-b)$$

Similarly,

$$E_{a,3}(= E_a @ t = 0.04) = (P_3 - P_2)/V_3 + E_{a,2} = 0.103771 \text{ mmHg/ml} \quad (3.6-c)$$

$$E_{a,4}(= E_a @ t = 0.06) = (P_4 - P_3)/V_4 + E_{a,3} = 0.253584 \text{ mmHg/ml} \quad (3.6-d)$$

$$E_{a,5}(= E_a @ t = 0.08) = (P_5 - P_4)/V_5 + E_{a,4} = 0.463599 \text{ mmHg/ml} \quad (3.6-e)$$

Now, we can substitute these values into equation (3.3-b) to obtain:

$$E_{a,2}(= E_a @ t = 0.02) = 0.029477 = E_{a0}e^{-0.02z_a} \sin(0.02\omega_a) \quad (3.7-a)$$

$$E_{a,3}(= E_a @ t = 0.04) = 0.103771 = E_{a0}e^{-0.04z_a} \sin(0.04\omega_a) \quad (3.7-b)$$

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$$E_{a,4}(= E_a @ t = 0.06) = 0.253584 = E_{a0} e^{-0.06z_a} \sin(0.06\omega_a) \quad (3.7-c)$$

$$E_{a,5}(= E_a @ t = 0.08) = 0.463599 = E_{a0} e^{-0.08z_a} \sin(0.08\omega_a) \quad (3.7-d)$$

from equations (3.7-a & 3.7-b), we have

$$\frac{E_{a,2}}{E_{a,3}} = e^{0.02z_a} \frac{\sin(0.02\omega_a)}{\sin(0.04\omega_a)} = e^{0.02z_a} \frac{\sin(0.02 \times \pi / 0.72)}{\sin(0.04 \times \pi / 0.72)} = \frac{0.029477}{0.103771}$$

$$\therefore z_a(3) = -28.2687 \text{ (1/s)} \quad (3.8)$$

Also, another two values of z_a are obtained from equations (3.7-b & 3.7-c), (3.7-c & 3.7-d)

$$z_a(4) = -24.3995 \text{ (1/s)}$$

$$z_a(5) = -15.7848 \text{ (1/s)} \quad (3.9)$$

We adopt the average of $z_a(3)$, $z_a(4)$ and $z_a(5)$, to be the value of z_a . We can then obtain the average value of E_{a0} by substituting the value of z_a into equations (3.7), to obtain

$$\bar{E}_{a0} = 0.2305 \text{ mmHg/ml, for } \bar{z}_a = -22.8177 \text{ s}^{-1} \quad (3.10)$$

where $\bar{z}_a$ and $\bar{E}_{a0}$ are the average values of z_a and E_{a0} .

Hence, we can now represent E_a (equation 3.3-b) as:

$$E_a = 0.2305 e^{22.8177t} \sin(\pi / 0.72t) \quad (3.11)$$

2. For Isovolumic relaxation, we have

$$E_{a,18}(= E_a @ t = 0.34) = (P_{18} - P_{17}) / V_{18} + E_{a,17} = E_{a,17} - 0.058954 \text{ mmHg/ml} \quad (3.12-a)$$

$$E_{a,19}(= E_a @ t = 0.36) = (P_{19} - P_{18}) / V_{19} + E_{a,18} = E_{a,17} - 0.177824 \text{ mmHg/ml} \quad (3.12-b)$$

$$E_{a,20}(= E_a @ t = 0.38) = (P_{20} - P_{19}) / V_{20} + E_{a,19} = E_{a,17} - 0.312656 \text{ mmHg/ml} \quad (3.12-c)$$

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$$E_{a,21}(=E_a @ t = 0.4) = (P_{21} - P_{20}) / V_{21} + E_{a,20} = E_{a,17} - 0.463599 \text{ mmHg/ml} \quad (3.12-d)$$

By substituting these values into equation (3.11), we can obtain the average value of $E_{a,17} = 1204 \text{ mmHg/ml}$. The resulting function given by equation (3.11) causes E_a to peak vary steeply during isovolumic contraction relative to it's the computed values, as depicted in **Figure 3.3**.

Figure 3.3: The active elastance during isovolumic contraction and relaxation for same example case at $E_{a,17} = 1204 \text{ mmHg/ml}$. The solid line is model computed as equation (3.11). Second is measured from the start-of-isovolumic contraction.

The active elastance during isovolumic contraction and relaxation with different end-ejection (ee) active elastance ($E_{a,ee} = E_{a,17}$) is shown in **Figure 3.4**.

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Figure 3.4: The active elastance during isovolumic contraction and relaxation for same example case at $E_{a,17} = 0.9 \text{ mmHg/ml}$, $E_{a,17} = 1.1 \text{ mmHg/ml}$, $E_{a,17} = 1.4 \text{ mmHg/ml}$. The solid line is fitted by 6th-order polynomial. Seconds is measured from the start-of-isovolumic contraction.

We hence represent active-elastance (E_a) by a double exponential function, such as:

$$E_a = E_{a0} \left(1 - e^{-\left(\frac{t}{\tau_c}\right)^{Z_c}} \right) \left(e^{-\left(\frac{t-d}{\tau_R}\right)^{Z_R}} \right), (t-d)=0 \text{ when } t < d \quad (3.13)$$

In this equation, the time coefficient (τ_c) describes the rate of elastance rise during the contraction phase, while (τ_R) describes the rate of elastance fall during the relaxation phase. The exponents " Z_c " and " Z_R " are introduced in the expression for E_a to make it better conform to the LV pressure curve. In equation (3.13), E_{a0} is the active elastance

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coefficient, d is a time interval. This equation can satisfy the data with one condition that $t-d$ is set to zero when $t < d$ (from the start of isovolumic contraction to more or less mid-ejection instant). When equation (3.13) is used to fit the computed values in equations (3.6 & 3.12), the resultant computed E_a function is illustrated in **Figure 3.5**. The values of the parameters and the resulting RMS ($=0.024$ mmHg/ml) are listed in **Table 3.1** below.

Table 3.1: Parameters related to sample case shown in Figure 3.1

parameter	value	unit
E_{a0}	1.5	mmHg/ml
τ_C	0.1221	second
Z_C	2.356	non-dimension
d	0.2	second
τ_R	0.1575	second
Z_R	3.728	non-dimension
$E_{a,17}$	1.1	mmHg/ml
RMS	0.024	mmHg/ml

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Figure 3.5: The same sample case is now fitted with equation (3.13). The resulting parameters values are listed in Table 3.1.

In fact, E_a can be adopted as a measure of LV contractility.

b) Passive elastance determination during diastolic filling

Now, during the diastolic filling phase, equation (3.1) becomes

$$M\ddot{V}_i + V_i(E_{a,i} - E_{a,i-1} + E_{p,i} - E_{p,i-1}) + (E_{p,i} + E_{a,i})(V_i - V_{i-1}) = P_i - P_{i-1} \quad (3.14)$$

Because the passive elastance is constant at a particular volume V_i , hence equation (3.14) becomes

$$M\ddot{V}_i + V_i(E_{a,i} - E_{a,i-1}) + (E_{p,i} + E_{a,i})(V_i - V_{i-1}) = P_i - P_{i-1} \quad (3.15)$$

$$\therefore E_{p,i} = \frac{(P_i - P_{i-1}) - M\ddot{V}_i - V_i(E_{a,i} - E_{a,i-1})}{V_i - V_{i-1}} - E_{a,i} \quad (3.16)$$

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where i is a time-instant during diastolic filling, V_i and $P_{LV,i}$ are the monitored LV volume and pressure at this time, and $M = \rho h / 4\pi R^2$. For this sample case (shown in **Figure 3.1**), we can get the mean value for M during diastolic filling, $M = 8.03 \times 10^{-6} \text{ mmHg}/(\text{ml}/\text{s}^2)$. Therefore, from equation (3.16), we can calculate the values of E_p at various instants during filling phase. We then plot E_p versus V , as shown in **Figure 3.6**, fit the data by equation (3.3-a), and obtain the values of the parameters E_{p0} and z_p , as:

$$z_p = 0.0395 \text{ ml}^{-1}, E_{p0} = 4.375 \times 10^{-3} \text{ mmHg/ml} \quad (3.17)$$

Hence, we can now represent E_p (equation 3.3-a) as:

$$E_p = 4.375 \times 10^{-3} e^{0.0395V} \quad (3.18)$$

where E_p can be looked upon as a measure of resistance-to-filling, while E_a can represent LV contractility index.

Figure 3.6: Passive elastance E_p vs. LV volume V for sample case shown in Figure 3.1.

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Figure 3.7: LV Pressure, active elastance E_a , passive elastance E_p , and total elastance $E = E_a + E_p$ for the same sample case shown in Figure 3.1. In this figure, 1-5 is isovolumic contraction phase, 5-17 is ejection phase, and 17-21 is isovolumic relaxation phase, 21-37 is diastolic filling phase.

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Figure 3.8: Active elastance vs. active pressure for same sample case shown in Figure 3.1, Arrow direction indicates progression of time. Note that rapid decrease in E_a during the isovolumic relaxation that also extends into the filling phase, and causes suction of blood into the LV even before initiation of left atrial contraction.

The variations of active and passive elastance (during a cardiac cycle) are shown in **Figure 3.7**. It is to be noted that E_a is not zero during the filling phase, but is gradually decreasing up to end-diastole, after which it again increases. Likewise E_p is not zero during the ejection phase, because it represents the effect of decreasing LV volume on the LV pressure. Hence, as shown, it decreases during the ejection phase.

We can also get the relationship between the active elastance and the systolic pressure ($P-P_{ed}$) generated by LV contraction, as shown in **Figure 3.8**. Indeed, this rapid decrease in elastance during isovolumic relaxation and extended into the filling phase can explain the

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suction effect during the rapid filling sub-phase, as illustrated by the decrease in LV pressure (in **Figure 3.7**) immediately after LV filling has commenced. Let us show this happens, by rewriting equation (3.16) (and neglecting the $M\ddot{V}_i$ term) as follows:

$$P_i - P_{i-1} = (E_{p,i} + E_{a,i})(V_i - V_{i-1}) + V_i(E_{a,i} - E_{a,i-1}) \quad (3.19)$$

It is seen that P_i can be less than P_{i-1} (or that $P_i - P_{i-1} < 0$) only if $(E_{a,i} - E_{a,i-1})$ is negative, which can occur if the active elastance is decreasing. Let us then evaluate $(P_{22} - P_{21})$ or $[P(t@0.42) - P(t@0.40)]$. Based on equations (3.13 & 3.18), we have

$$\begin{aligned} V_{22} &= 105 \text{ ml}, V_{21} = 90.6 \text{ ml}; E_{p,22} = 0.1086 \text{ mmHg/ml}, E_{a,22} = 0.0422 \text{ mmHg/ml}, \\ E_{a,21} &= 0.1266 \text{ mmHg/ml}, \end{aligned} \quad (3.20)$$

Substituting these values into equation (3.19) gives $(P_{22} - P_{21}) = -6.69 \text{ mmHg}$. Hence, it is our novel concept of decreasing active elastance that is able to explain the phenomenon of decreasing LV pressure during early stage of filling.

Likewise, the increase in E_a during isovolumic contraction is responsible for the increase in LV pressure or for LV pressure generation at constant volume. Finally, both the concepts of E_a and E_p are made possible by our redefining the concept of elastance and compliance as

$$dP = d(EV) = d(V/C) = VdE + EdV \quad (3.21)$$

3.3 Clinical Applications

The analysis is now applied to the clinically obtained data, of the subject's left ventricular (instant-of-instant) dimensions (obtained by cineangiocardiology) and chamber pressure (obtained by cardiac catheterization). In so doing, for each subject's left ventricular data, the passive and active elastance are determined. **Tables 3.2** and **3.3** summarize the

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measured and model derived hemodynamic parameters for three subjects (subject H.E.L., D.D.M, and T.P.S), respectively. Subject **H.E.L** serves as an example of a patient with inferior myocardial infarct (MI) and double vessel disease (DVD), subject **D.D.M** with DVD and hypertension (HTN), treated with PTCA; subject **T.P.S** with native LAD, ischemia in anterior territory and mitral regurgitation (MR). The subjects’ medical histories are provided in **Appendix B**.

Table 3.2 Clinical history, measured hemodynamic data from subjects (H.E.L, D.D.M and T.P.S). Where LVP: left ventricle chamber pressure, AOP: aortic pressure, EDV: end-diastolic volume, ESV: end-systolic volume, EF: ejection fraction, MI: myocardial infarct, MR: mitral regurgitation, DVD: double vessel disease, HTN: hypertension, LAD: left artery disease.

Subject	H.E.L	D.D.M	T.P.S
Disease	MI, DVD	DVD, HTN	LAD, MR and Ischemia
LVP (mmHg)	122/18	170/24	147/22
AOP (mmHg)	125/75	169/99	140/71
EDV/ESV (ml)	132.5/84.3	121.7/41.3	112/44.8
EF	0.36	0.66	0.60

Shown in **Figure 3.7** are the model-derived nonlinear passive and active elastance during one cardiac cycle for the subject H.E.L. The diastole, isovolumic-contraction, ejection and isovolumic-relaxation periods are marked in the figure. We can see clearly that passive and active elastance vary continuously throughout the cardiac cycle. In this particular example (subject H.E.L), the maximum active elastance is 1.33 mmHg/ml.

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Figure 3.8 plots E_a versus active pressure ($P-P_{ed}$) generated; the computed E_a is maximum during more or less mid-ejection and the E_a -LV pressure makes a loop during mid-ejection. That is the sarcomere shortening is maximum and it generates maximum stress during mid-ejection. Even after end-of relaxation, the active elastance continues to decrease with the filling phase, reaching its minimum value at the end of filling phase. This continuing decrease of active elastance can explain the suction effect during the rapid filling sub-phase.

Figures 3.9 and **3.10** give the nonlinear passive and active elastance for subject **H.E.L** (MI, DVD), **D.D.M** (DVD, HTN), and **T.P.S** (LAD, MR & Ischemia). The nonlinear passive and active elastance follow the same shape for all the subjects. The passive elastance versus volume (shown in **Figure 3.9**) clearly reveals that elastance increases with increasing LV volume with an exponential relationship. The parameters (E_{p0} and z_p) characterize this relationship are obtained. The passive elastance curve is steeper for the stiffer (and infarcted) myocardium (subject T.P.S).

The active elastance versus active or generated pressure $P_a (=P-P_{ed})$ is shown in **Figure 3.10**. Subject **D.D.M** contractile mechanism has to generate high E_a in order to develop the requisite LV pressure to meet the high pressure in the aorta. Subject **H.E.L** has MI, and hence less contracting myocardium; this is manifest by a lower amount of E_a invoked, compared to D.D.M. Subject **T.P.S** with a stiffer myocardium, has to generate comparable high E_a in order to maintain the stroke volume and ejection fraction (EF), which indicates an adjusting mechanism to the disease.

Figure 3.11 shows the active elastance versus normalized time for these three subjects, their values decrease with less contracting LV, especially for subjects (H.E.L)

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Table 3.3 summarizes the results of these three subjects. The maximum active elastance values can be correlated with the values of the traditional contractility index $dP/dt_{\max}$. The passive elastance exponent z_p can be correlated with the stiffness of myocardium.

Table 3.3: Calculated passive and active elastance parameters from subjects (H.E.L, D.D.M and T.P.S). $E_{a, \max}$: maximum active elastance

Subject	H.E.L	D.D.M	T.P.S
E_{p0} (mmHg/ml)	4.375×10^{-3}	6.74×10^{-5}	5.072×10^{-10}
z_p (ml ⁻¹)	0.0395	0.07499	0.1989
E_{a0} (mmHg/ml)	1.50	4.40	3.66
τ_c (s)	0.1221	0.2070	0.2458
Z_c	2.356	1.536	2.306
d (s)	0.20	0.26	0.30
τ_R (s)	0.1575	0.1536	0.1838
Z_R	3.728	2.943	3.096
$E_{a, \max}$ (mmHg/ml)	1.33	3.58	3.22
$dP/dt_{\max}$ (mmHg/s)	985	1475	1234

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Figure 3.9: LV volume and the corresponding volume-dependent passive elastance for the subject H.E.L, D.D.M, and T.P.S.

Figure 3.10: Active elastance versus systolic pressure generated (or active pressure) for subject H.E.L, D.D.M, and T.P.S.

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Figure 3.1: Active elastance versus normalized time of subjects H.E.L, D.D.M, and T.P.S. The t_s is duration from start-of-isovolumic contraction phase to end-of-isovolumic relaxation.

Now E_a constitutes the effort put in by the LV to raise its pressure just adequate to overcome the afterload. Hence, let us conceive of a new elastance per unit pressure generated ($=E_a/P$). Its cyclic plot is illustrated in **Figure 3.12**. The maximal value of E_a/P can represent LV ability to raise the elastance per unit pressure. The higher the value of $(E_a/P)_{\max}$, the more competently is the LV operating.

Additionally, in order to characterize the myocardium stiff, we define another index E_p per maximal filling pressure ($E_{p,\max}/P_{ed}$). These two indices will be applied to more clinical data in Chapter 7.

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Figure 3.12: Active elastance per unit pressure E_a/P vs. time of subjects H.E.L, D.D.M, and T.P.S.

3.4 Conclusion and Discussion

Most previous attempts to describe the elastance were focused on the value of elastance based on the definition $P/(V - V_d)$. However, this definition of $P/(V - V_d)$ changes against different arterial loads and is therefore load dependent (Mulier, 1994). Derived indices such as E_{max} and end-systolic pressure-volume relation (ESPVR, as a measure of contractility) loose their sensitivity, as a result. This chapter’s novelty is in presenting the formulation of the nonlinear volume-dependent passive elastance and time-dependent active elastance during the cardiac cycle. The active elastance can be described by a special double exponential equation, while the passive elastance can be described by an

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exponential equation. We can say that the LV pressure is shaped by the active elastance curve. Further, active elastance (E_a) is not zero during the filling phase, but is gradually decreasing up to end-diastole, after which it again increases. The decrease of E_a during the isovolumic relaxation that also extends into the filling can explain the suction effect, as illustrated by the decrease in LV pressure immediately after commencement of the filling phase. Likewise, E_p is also not zero during the ejection phase, because it represents the effect of decreasing volume in the LV pressure.

In conclusion, the manner in which the analysis is to be employed to calculate the in vivo values of the volume-dependent passive elastance and active elastance from routinely obtained cineangiocardigraphic data is demonstrated. We have obtained insight into the mechanism of how time-dependent E_a shapes that LV generated pressure and accounts for the lowering of LV pressure following the opening of the mitral valve. The maximum active elastance ($E_{a,max}$) could be correlated with the traditional contraction index dP/dt_{max} , while high passive elastance exponent z_p could relate to a stiffer myocardium. Hence we can give a preliminary conclusion that active elastance can represent the contractility of myocardium as an intrinsic index, while the passive elastance can present the resistance-to-filling index. We will continue to apply this analysis to more clinical data in Chapter 7 (clinical application).

CHAPTER 4

LEFT VENTRICULAR SHAPE-BASED CONTRACTILITY INDICES

4.1 Background

Over the past decades, several indices for estimating the ventricular contractile state have been proposed, based on either empirical evidence or theoretical considerations (Mason et al., 1969; Peterson et al., 1974; Lambert et al., 1983; Kass et al., 1987; 1993; Greenberg et al, 2002; De Stefano et al., 2004). A great deal of effort has been made to assess their specificity and prediction capability. Most studies have indicated that the peak of the first time derivative of the ventricular pressure ($dP/dt_{\max}$) to be the most sensitive cardiac index of inotropic changes (Kass et al., 1987). The maximum of dP/dt is reached soon after aortic valve opening, after the myocardial fibers have started to shorten and expend part of their energy in providing both pressure and kinetic energy to the ejection blood. However, the intraventricular LV pressure is obtainable only by cardiac catheterization. To avoid the risk, expense and inconvenience of catheterization, many researchers have sought non-invasive methods for assessing the LV contractility, say, in term of ejection

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blood acceleration, expressed as the peak of the time derivation of the aortic flow rate (f), $df/dt_{\max}$ (Bettett et al., 1984; Lazarus et al., 1988; Redaelli, 1998), myocardial systolic strain rate (Greenberg et al., 2002) and isovolumic contraction time (Tsuyoshi et al., 2003).

To the best of our knowledge, very few studies have been dedicated to the influence of the LV shape factor on its contractility. It has been observed that the shape of the LV is of clinical relevance for prognosis of heart patients (Tischler et al., 1993; Devereux, 1994; Krumholz et al., 1995; Juznic et al., 1998; Knap et al., 2002; 2003). Thus some investigators have associated a more spherically-shaped and less-ellipsoidal shaped LV with the failing heart (Lee et al., 1993). Invasive animal experiments have indicated that the shape of the LV is somewhat like a prolate ellipsoid (De Anda et al., 1995). From echo-ventriculography, we can obtain the 2-dimensional shape of the LV, and therefrom, the ellipsoidal shape of LV. This information has been applied, herein, to develop a left-ventricular ellipsoidal geometry model and LV ellipsoidal-model wall stress. Now, we can define a LV contractility index (LVCI) to represent the capacity of the LV to generate necessary and sufficient intra-myocardial stress to provide necessary and sufficient pressure and kinetic energy to the ejected blood. Hence, we could gauge LV contractile capability in terms of the maximum value of generated intra-myocardial stress, or $d\sigma / dt_{\max}$. Thus LVCI can help provide more insight into the LV shape-based contractile stress for its ejection function.

The current study is based on the premise that LV contractility index is a measure of the capacity of the LV myocardium to generate wall-stress that will adequately raise intra-LV pressure to eject the blood. Now since the LV wall stress depends on its shape, hence the LV contractile capacity also depends on the LV shape. This is the rationale behind the LV

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shape-based contractility index. Based on clinical observations, it is concluded that a healthy LV shape factor is more akin to the optimal-ellipsoidal shape factor, but transforms towards a more spherical shape in a poorly contracting LV as well as in LV failure.

4.2 Methods

4.2.1 Model Geometry

In this study, the LV is modeled as an ellipsoidal shell that is truncated at its base (**Figure 4.1**). The crescentic right ventricle wraps circumferentially around the LV about 180 degrees and extends longitudinally about two thirds of the distance from the base to the apex. Using such a model, the LV can be defined by the major and minor radii of its two surfaces: the endocardium of the LV, and a surface defined by the epicardium of the free wall and the endocardium of the septum. Streeter and Hanna (1973) described the position of the basal plane using a “truncation factor” f_b , which is defined as the ratio between the longitudinal distances from equator to base (A) and from equator to apex (A/2), as illustrated in **Figure 4.1**. The overall longitudinal distance from the base to apex ($=3A/2$) is thus $(1+f_b)$ times the major radius of the ellipse. Because variations in f_b are relatively small between the diastole and systole (0.44 to 0.5) (Streeter and Hanna, 1973), we propose a constant value of $f_b = 0.5$ in this study.

The volumes of myocardial wall and LV are given as:

$$MV = 9\pi[(A+h)(B+h)^2 - AB^2]/8 \quad (4.1)$$

$$V = 9\pi AB^2 / 8 \quad (4.2)$$

Simplifying equation (4.1) by neglecting $(9\pi/8(Ah^2 + 2Bh^2 + h^3))$ term, we obtain

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$$MV = 9\pi[2AB + B^2]h/8 \tag{4.3}$$

Figure 4.1: Comparison of the cine of the LV geometry with the corresponding analytic model. (a) at an instant during the diastolic filling stage (b) at an instant during the systolic ejection stage (c) measured LV dimensions (d) LV model geometry, shown are the major and minor radii of the inner surface of the LV (A & B) and the wall-thickness (h)

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Now, LV volume, wall-thickness and myocardial volume are measured by cineangiography. Hence, by using equations (4.2 & 4.3), we can calculate the major and minor radii A and B. Firstly, from equation (4.2), we have

$$A = 8V / (9\pi B^2) \quad (4.4)$$

Then, by substituting (4.4) into equation (4.3), we get $MV = \frac{9\pi}{8} \left[\frac{16V}{9\pi B} + B^2 \right] h$, which giving us a equation in B: $B^2 + \left(\frac{16V}{9\pi B} \right) - \left(\frac{8MV}{9\pi h} \right) = 0$ to obtain the value of B.

4.2.2 Determination of Wall Stress

Of importance in assessing cardiac function is an understanding and knowledge of the stress developed within the wall of the LV during a cardiac cycle. The generated wall-stress (GWS) is a measure of the effectiveness of the contractile machinery of the LV myocardium. The GWS is adjusted to be necessary and sufficient for carrying out its ejection function. Hence, the normalized wall stress σ/P ($=\sigma^*$) can provide a more intrinsic measure of its contractile capacity.

For an ellipsoidal shell, the circumferential wall stress σ_θ (referred to as σ) is given by (Mirsky et al., 1973):

$$\sigma = P \frac{B}{h} \left[1 - \frac{B(B/A)^2}{(2B+h)} \right] = P \frac{B}{h} \left[1 - \frac{(B/h)(B/A)^2}{2(B/h)+1} \right] \quad (4.5)$$

From equations (4.2 & 4.3), we can have

$$\frac{B}{h} = \frac{V}{MV} \left(2 + \frac{B}{A} \right) = \frac{V}{MV} (2 + s) \quad (4.6)$$

where B/A constitutes the LV shape factor, denoted by 's'.

Combining equations (4.5 & 4.6), we can express the normalized stress σ^* as:

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$$\begin{aligned}
 \sigma^* &= \frac{\sigma}{P} = \frac{B}{h} \left[1 - \frac{(B/h)(B/A)^2}{2(B/h)+1} \right] \\
 &= \frac{V}{MV} (2+s) \left[1 - \frac{Vs^2(2+s)}{2V(2+s)+MV} \right] = \frac{V(2+s)}{MV} \left[\frac{MV + 4V + 2VS - 2Vs^2 - Vs^3}{2V(2+s)+MV} \right] \quad (4.7) \\
 &= f(V, MV, s)
 \end{aligned}$$

We can now compute σ^* during ejection in terms of V , MV and s . Equation (4.7) is a function of s for a given V & MV .

Figure 4.2 indicates the cyclic range of variation of h , s ($=B/A$) and σ^* versus time during ejection phase for 3 of our patients.

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Figure 4.2 (to be continued on next page)

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Figure 4.2: Variation of h , B/A and σ^* versus time for subjects (H.E.L with myocardial infarct (MI) and Double vessel disease (DVD), subject D.D.M with DVD and hypertension (HTN), subject S.K.S with Triple vessel disease (TVD)) during the ejection phase. $t=0$ represents start-of-ejection. Subject S.K.S has the lower generated σ^* , while subject D.D.M has the maximal unloading of σ^* during the ejection phase, and hence the higher value.

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4.3 New Contractility Index

4.3.1 Contractility Index (CONT1)

A well-known definition of contractility is dP/dt_{max} . However, we can more intrinsically characterize contractility in terms of the max rate of generation of the LV normalized stress σ^* using equation (4.7), as:

$$\begin{aligned}
 \text{Contractility index} - I(\text{CONT1}) &= \left| (d\sigma^* / dt) \right|_{\max} \\
 &= \left| \frac{\dot{V}(2+s) + V\dot{s}}{MV} - \frac{V^2 s \left(s\dot{V}(16+8MV/V + (24+8MV/V)s + (12+2MV/V)s^2 + 2s^3) \right. \right. \\
 &\quad \left. \left. + V\dot{s}(32+8MV/V + (56+12MV/V)s + (32+4MV/V)s^2 + 6s^3) \right)}{MV(4V+2Vs+MV)^2} \right|_{\max} \\
 &= F(s, \dot{s}, V, \dot{V}, MV)
 \end{aligned} \tag{4.8}$$

Equation (4.7) indicates that corresponding to a patient's $V(t)$ and $\dot{V}(t)$ variation, the contractility index value for that patient is a function of the LV's s . Now cardiologists have been observing that an infarcted LV becomes less ellipsoidal as compared to a normally contracting LV shape. This resultant distorted shape of a contractility-impaired LV does not allow it to contract and deform in an optimal twisting mode (Yeo, 2004), so as to perform its pumping function and deliver the requisite cardiac output efficiently. In accordance with this clinical observation, our contractility index (equation 4.8) incorporates the LV shape factor ($s = B/A$), and the influence of the distorted shape of an infarcted LV to its impaired pumping function.

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4.3.2 Optimal LV Shape Factor and Corresponding Contractility Index (CONT2)

Let us designate the optimal shape factor s ($=B/A$) to be that value for which the generated myocardial wall stress σ^* for a given LV volume (at the start of ejection $V=V_{se}=V_{ed}$) is maximum.

For this purpose, we can maximize σ^* from equation (4.7) as

$$\frac{d\sigma^*}{ds} = \frac{V}{MV} - \frac{V^2}{MV} \frac{[(8s + 12s^2 + 4s^3)(MV + 4V + 2Vs) - (4s^2 + 4s^3 + s^4)(2V)]}{(MV + 4V + 2Vs)^2} = 0 \quad (4.9)$$

Simplifying equation (4.9), we can have

$$6s^4 + (4MV/V + 32)s^3 + (12MV/V + 52)s^2 + 4(MV/V + 4)s - (MV/V + 4)^2 = 0 \quad (4.10)$$

for which we obtain the optimal shape factor s is a function of MV/V , as shown in **Figure 4.3**. It may appear that s is linear proportional to MV/V : ($s = 0.053(MV/V) + 0.39$), this line can be called the optimal- s line.

The significance of this optimal- s line is that one can adjudge the cardiac health state merely in terms of how close the shape-factor s ($=B/A$) corresponding to his/her MV/V value at the start of ejection is to the optimal value obtained from Figure 4.3. We do not even need to compute σ^* or $d\sigma^*/dt$ in order to evaluate how efficiently a particular LV is pumping.

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Figure 4.3: Optimal shape factor s versus MV/V . We can get the optimal line: $s = 0.053(MV / V) + 0.39$.

Hence, another way to define LV contractility would be in a non-dimensional form at the start of ejection (s_e), as follows

$$CONT2 = \frac{s_{se} - s_{se}^{op}}{s_{se}^{op}} \tag{4.11}$$

where s_{se} is the measured shape factor value, s_{se}^{op} is the corresponding optimal value at the start-of-ejection. So, as $CONT2$ value increases the LV contractility becomes poorer. Then, from equation (4.10), the ($CONT2$) for data shown in **Figure 4.2** is obtained to be 0.2062 for subject H.E.L, 0.057 for subject D.D.M, and 0.1082 for subject S.K.S, as shown in **Table 4.1**. Note that both our new indices of contractility of the 3 subjects,

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DDM has the higher EF; correspondingly CONT1 is maximum for D.D.M and CONT2 is minimum for D.D.M.

Table 4.1: Clinical history, calculated s_{se} , CONT1 and CONT2 from subjects (H.E.L, D.D.M, and S.K.S).

Subject	Disease	s_{se}	CONT1	CONT2	EF
H.E.L	MI, DVD	0.56	3.84	0.2062	0.36
D.D.M	DVD,HTN	0.4781	6.90	0.057	0.66
S.K.S	TVD	0.5534	1.72	0.1082	0.24

The variation of s with MV/V for these three cases is depicted in **Figure 4.4**. Somewhat below the optimal line, the shape of the LV becomes somewhat physiological unnatural in order to support a reasonable value of V_{se} , the volume at the start of ejection. We can postulate that if the shape factor s is located on A zone, it can be a tolerable shape to provide a reasonable LV contractility; then the B zone could portray a poorly contracting LV, while the C zone could represent a failing heart, as shown in Figure 4.4, show the same trend as the ejection fraction (EF) index.

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Figure 4.4: s vs MV/V for subjects (H.E.L, D.D.M, and S.K.S), the corresponding CONT2 are shown in Table 4.1. We can postulate LVs to be normal contracting, poorly contracting and failing heart, as illustrated in the above figure.

Now let us see how an optimally shaped LV looks like, for different values of normal V variation with age. In other words, for various age groups, we take normal V values for Asian and American populations, based on the data shown in **Table 4.2**. The below **Figure 4.5** illustrates the LV(s) for the same value of A in each age group, for 3 different values of V at the start of ejection. For each such V value, we compute the value of B , corresponding to $s=s_{op}$, determine s , and then plot the LV shape.

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Table 4.2: Normal values of LV volumes and mass for adults and children [Dodge and Sandler, 1973]

End-diastolic volume (ml/m ²)	Volume (ml/m ²)	End-systolic volume (ml/m ²)	Ejection fraction (SV/EDV)	Thickness (mm)	Left ventricle mass (gm/m ²)
Adults [Kennedy, 1966]					
70±20	45±13	24	0.67±0.08	10.9±2.0	92±11
Children and infants less than 2 years of age [Graham, 1966; 1968]					
42±10	28.6	13.4	0.68±0.05		96±11
More than 2 years of age					
73±11	44±5	27±7	0.63±0.05		86±11

The anatomically abnormal LV(s) (to the left of the optimal LVs) have less than normal EDV as well as less than optimal contractility. Hence they would not be able to meet the SV demand of the circulatory and organ systems. The physiologically abnormal LV(s) (to the right of the optimal LVs) have bigger B values and bigger (s) values for the same value of A as the optimal LVs. Hence, as shown equation (4.6), these enlarged LVs will have higher values of myocardial tension ($= \sigma^* h$) than the optimal LVs. They will hence have a higher O₂ demand and will be more prone to be susceptible to supply-demand mismatch and hence to angina pains.

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Figure 4.5: Schematics of (1) anatomically abnormal, (2) optimal, and (3) physiological abnormal LV(s) for children less than 2 years of age, more than 2 years of ages and adults.

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4.4 Clinical Applications

4.4.1 Measurements

All subjects included in this study were in resting recumbent state, after premedication. The LV chamber pressure was measured with catheterization; the pressure recording was conducted immediately before or during the angiocardiology in all cases. Single plane cineangiocardiology were recorded in a posteroanterior projection from an image intensifier at 50 frames/s using INTEGRIS Allura 9 with Dynamic Flat Detector (Philips Inc.). For a sample subject (H.E.L), the LV ellipsoidal model's pressure, volume, wall thickness (as derived from the cineangiocardiology films) are presented in **Figure 4.6**, along with the calculated ellipsoid major and minor axis (A and B from equations 4.1 & 4.3), and calculated absolute value of $d\sigma^*/dt$ (from equation 4.7).

4.4.2 Subjects

Ten subjects, with $EF=0.63\pm0.05$ and $dP/dt_{\max}=1406\pm51$ mmHg/s were selected to comprise Group 1. They did not use nicotine, caffeine or alcohol. The age profiles were very similar in this group (around 58.7 years). Anthropometric data, blood pressure, heart rate and ejection fraction (EF) were within the expected range.

Ten patients (with coronary and/or valvular disease), with $EF=0.49\pm0.13$ and $dP/dt_{\max}=1183\pm62$ mmHg/s were classified as Group 2, having mean-age of 57.4 years. Finally, we have Group 3 (of having $EF=0.38\pm0.12$ and $dP/dt_{\max}=948\pm78$ mmHg/s hospitalized patients with poor contractility).

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Figure 4.6: Pressure, volume and dimensions during a cardiac cycle with ellipsoidal model, absolute value of $d\sigma^*/dt$ is calculated using equation (4.7) during ejection phase (subject H.E.L).

4.4.3 Results

For each subject, the chamber pressure and dimensions are monitored at 20ms intervals during the cardiac cycle. A typical set of pressure and chamber variations for a subject (H.E.L) is shown in **Figure 4.6**. The time-derivative of normalized stress and the shape factor (s) are calculated for each 20ms during the cardiac cycle (**Figure 4.6-e**). **Figure 4.6-f** presents the variation of absolute value of $d\sigma^*/dt$ during the ejection phase. During ejection, the maximum value of CONT1 is found to be $3.84 s^{-1}$.

Table 4.3 summarizes the patients' history, which includes patient age, heart rate (HR), EF, myocardial volume of LV (MV), start-of-ejection volume (V(SE)) and end-ejection volume (V(EE)). **Figure 4.7** depicts the mean and standard-deviation of MV, EF and

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V(SE) & V(EF) for all the patients analyzed by us. There exists a substantial difference ($p<0.05$) between the average values of EF, MV, V(EF) in normal contractility patients compared to patients with inadequate and poor contractility patients. We take the average value of V(SE) and s(SE), and then show the shaped LV looks like for these three groups. The LV in Group3 (poor contractility) has bigger B value and bigger s value compared with Group1. As a result, the enlarged LVs have a bigger CONT2 and lower CONT1 (Table 4.4). This may be concluded that a more-spherical shape is associated with poor systolic function and decreased contractility of the LV.

Table 4.3: Data: Group 1 (normal contractility), group2 (inadequate contractility) and group 3 (poor contractility). * $p<0.05$ compared with normal contractility group.

	Group 1	Group 2	Group 3
Age (years)	58.7±6.65	57.4±5.85	58.20±9.11
dP/dt _{max}	1406±51	1183±62*	948±78*
HR (beats/min)	72.69±9.20	67.70±10.04	74.02±10.09
MV (ml)	146±43	189±78	216±80*
V(SE) (ml)	119.26±31.75	148.7±68.32	177.41±90
V(EF) (ml)	43.64±9.87	79.45±53.75*	116.73±54.01*
EF	0.63±0.05	0.49±0.13*	0.38±0.12*

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Figure 4.7 to be continued next page

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Figure 4.7: Comparison of the EF, MV (wall volume) and V(SE), V(EF) in the group of 1 (normal contractility), 2 (inadequate contractility) and 3 (poor contractility). First bar=start-of-ejection(SE) and second bar=end-ejection (EE).

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Figure 4.8 illustrates the values of $s(SE)$, $s(EE)$, dP/dt_{max} , $CONT1$ and $CONT2$ for the three groups: Group 1 (normal contractility subjects), Group 2 with inadequate contractility and hospitalized Group 3 with poor contractility. The values of $CONT1$ and $CONT2$ in group 1 are considered to be normal contractility. Group 3 (patients with poor contractility) has comparatively lower values of $CONT1$ ($p < 0.05$) and bigger $CONT2$ as compared to those of normal group ($p < 0.05$). Similarly, group 2 (patient with inadequate contractility) also has lower values of $CONT1$ ($p < 0.05$) compared to those of normal group, while the $CONT2$ has shown smaller difference between the group 2 and group 1.

The average values of $CONT1$ decreases and $CONT2$ increases in group 2 and group 3, in relation to $CONT1$ and $CONT2$ for normal contractility group 1. The average values of $CONT1$ and $CONT2$ for normal contractility group are $8.75 \pm 2.30 s^{-1}$ and 0.09 ± 0.07 (**Table 4.4**). In the group of patients with poor contractility (group 3) the values of the indices are significantly different compared to group 1 ($p < 0.05$). The index $CONT2$ is biggest in group 3, suggesting that this group is having a more spherical or distorted LV shape. Therefore it may be concluded that a less ellipsoidal and more-spherical shape is associated with poor systolic function and decreased contractility of the LV, which is in agreement with the EF and $CONT1$ (**Figure 4.8**). In support of this, it is also noted that an infarcted LV becomes less ellipsoidal as compared to a normally contracting LV shape.

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Table 4.4: Mean values with standard deviations of s(SE), s(EF), CONT1 and CONT2 for group1 (normal contractility), group 2 (inadequate contractility) and group 3 (poor contractility). *p<0.05 compared with normal contractility group.

	Group 1	Group 2	Group 3
s(SE)	0.50±0.03	0.51±0.05	0.565±0.08*
s(EF)	0.44±0.02	0.47±0.05	0.53±0.1*
CONT1 (1/s)	8.75±2.3	5.78±1.30*	3.9±1.30*
CONT2	0.09±0.07	0.11±0.09	0.23±0.12*

Figure 4.8 (to be continued on next page)

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Figure 4.8: Comparison of the shape factor s at start-of-ejection ($s(SE)$) and end-ejection ($s(EE)$), dP/dt_{max} , CONT1, CONT2, for the group of 1 (normal contractility), 2 (inadequate contractility) and 3 (poor contractility). First bar=start-of-ejection (SE) and second bar=end-ejection (EE). Note that lower CONT2 denotes high contractility.

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4.4.4 Comparison with Traditional Invasive LV Contractility Index $dP/dt_{\max}$

For the 3 groups of patients, the comparisons between the indices (*CONT1* & *CONT2*) and EF, stroke volume per unit myocardial wall volume (SVMV), and $dP/dt_{\max}$ are summarized in **Figures 4.9-4.12**. In Figure 4.9-a, $dP/dt_{\max}$ is shown to correlate with EF at an r-value of 0.732 ($dP/dt_{\max} = 980 \times EF + 680$, $r=0.732$, $p<0.0001$). This result agrees well with the observation of Kyriazis (Kyriazis, 2001).

Similarly, $dP/dt_{\max}$ versus SV/MV, as presented in **Figure 4.9-b**, provides a similar conclusion ($r=0.6878$). Then, when the new index *CONT1* is compared with EF and SV/MV in **Figures 4.10-a & 4.10-b**, we note a similar order of correlation: $CONT1=14 \times EF - 1.37$, $r=0.7668$; $CONT1=14 \times SV/MV + 0.66$, $r=0.7785$, $p<0.0001$.

The index *CONT2*'s correlation with EF and SV/MV, as depicted in **Figures 4.11-a & 4.11-b**, gives negative r values of 0.6925 (for $CONT2 = -0.492 \times EF + 0.397$, $r=-0.6925$, $p<0.05$) and -0.5794 (for $CONT2 = -0.42 \times SV/MV + 0.31$, $r=-0.5794$, $p<0.05$). A higher *CONT2* was related with a lower value of ejection fraction (EF) and SV/MV.

Further comparisons between the *CONT1* and $dP/dt_{\max}$, *CONT2* and $dP/dt_{\max}$ are displayed in **Figures 4.12-a & 12-b**. **Figure 4.12-a** shows a good correlation of $r=0.7300$ between *CONT1* and $dP/dt_{\max}$ as $CONT1 = 0.0096 \times dP/dt_{\max} - 5.1$, $r=0.7300$, $p<0.0001$, while **Figure 4.12-b** suggests a fair correlation: $CONT2 = -0.00033 \times dP/dt_{\max} + 0.54$, $r=-0.6029$, $p<0.05$.

Our new non-invasively determinable contractility indices *CONT1* relate well to the traditional and invasively determinable contractility index of $dP/dt_{\max}$. The advantage of

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our contractility index is that it enables very convenient computation. However, CONT2 does not provide as good correlation with $dP / dt_{\max}$ as CONT1 .

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Figure 4.9: Relating traditional contractility index $dP/dt_{\max}$ to EF factor, SV/MV, with r being the correlation coefficient.

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Figure 4.10: Relating new developed contractility index CONT1 to EF factor, SV/MV, with r being the correlation coefficient.

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Figure 4.11: Relating new developed contractility index CONT2 to EF factor, SV/MV, with r being the correlation coefficient.

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Figure 4.12: Relating new developed contractility indices CONT1, CONT2 to traditional contractility index $dP/dt_{\max}$, with r being the correlation coefficient.

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4.5 Conclusion and Discussion

The shape of LV has intrigued physiologists as well as clinicians in attempting to gain a better understanding of its mode of operation (Sandler and Ghista, 1969; Rankin et al., 1976; Gaudron et al., 1993; Devereux, 1994; Knap, 2002), and trying to obtain diagnostic information on its performance. In this study, we have developed new contractility indices CONT1 and CONT2 based on the LV wall stress (normalized with respect to LV pressure) and the LV shape-factor.

The advantage of CONT1 and CONT2 is that we do not need to monitor the LV pressure; further they can be obtained noninvasively, from ventricular echocardiographic measurements. We have also obtained the optimal shaped LV corresponding to $(s)=(s)_{op}$ and the associated value of CONT2. We have further evaluated CONT1, CONT2, and their correlations with EF, SV/NV and dP/dt_{max} . However, CONT2 does not provide as good correlation with dP/dt_{max} as CONT1. Hence, we can employ CONT2 to get an initial inference of LV contractility. However, for a more accurate assessment, we need to use CONT1 as the contractility index.

CHAPTER 5

NON-INVASIVE DETERMINATION OF AORTIC PRESSURE, ALONG WITH AORTIC STIFFNESS AND PERIPHERAL RESISTANCE

5.1 Background

The aortic blood pressure waveform can be directly used to derive valuable indices of cardiac and cardiovascular function, such as arterial compliance (Liu et al., 1986), and the peripheral resistance (Ocasio et al., 1993). In addition, the waveform can be combined with aortic flow or ventricular volume to facilitate assessment of cardiac performance in terms of ventricular/vascular coupling (O'Rourke et al., 1984). Since accurate measurement of aortic blood pressure waveform requires catheterization of the aorta, noninvasive methods would of course be more convenient for obtaining a lot of diagnostic information.

The auscultatory and oscillometric methods provide only two features of the complex arterial pressure wave contour: the peak systolic and diastolic pressures (Brinton, 1997).

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These values are routinely used in diagnosis and treatment of hypertension. However, there are other features of the aortic pressure wave contour, which are also of interest to the clinician. Indeed, the analysis of aortic pressure waveforms can provide extra information about left ventricular function through assessment of end-systolic elastance (Lee et al., 2002). Furthermore, the entire aortic pressure waveform is required for studying of arterial function. Also, the peripheral resistance (Ocasio et al., 1993), arterial stiffness (Yin et al., 1987; Fogliardi et al., 1996; Brinton et al., 1997) and wave reflection (Murgo et al., 1980; Wei and Chow, 1985; Kelly et al., 1989) are indices available only by analysis of arterial pressure waveforms.

Estimation of these indices of ventricular and arterial pressure waveforms measurements should be done closer to the heart, in the ascending aorta. Due to practical and ethical reasons, however, the arterial pressure waveforms are rarely recorded in the ascending aorta but in a peripheral artery. Since the arterial pressure wave contour is site-dependent (due to wave propagation/reflection phenomenon), the use of peripheral arterial wave contour for diagnostic purpose is somewhat limiting. On the other hand, the aortic pressure waveform in the upper aorta was shown to be relative consistent under a wide variety of conditions (Karamanoglu et al., 1993). Herein, we are analyzing the ascending aortic (diastolic and systolic) pressure profile, in order to avoid the effects of pulse wave reflection.

Past studies have indicated that meaningful features can be obtained from a much smaller subset of five time-relative points on the aortic pressure wave profile: the wave foot, first shoulder, second shoulder, incisura, and the duration of the pulse (as shown in **Figure 5.1**). The wave foot and first shoulder coincide with the onset of left-ventricular (LV) ejection and the peak flow, respectively. The second shoulder is considered to be associated with reflected pressure waves originating from the periphery, and occurs later

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in systole. This shoulder is followed by the sharp incisura, which coincides with the closure of the aortic valve and cessation of ventricular ejection. A higher second shoulder than the first shoulder, which augments the systolic pressure, is seen mostly in elderly patients (Murgo et al., 1980). However, the second shoulder is equal or less than the first shoulder in young patients.

During the left ventricular (*LV*) ejection phase, as the blood is pumped into the aorta, the aortic pressure rises and the aorta distends (Ghista, 1986). However, not all of the blood pumped into the aorta is distributed into the peripheral circulation immediately, and a portion of it is stored in the distended aorta. The equation governing the modulation of aortic pressure can be formulated by considering that the rate-of-change of aortic pressure in terms of the volume elasticity (or distensibility of the aorta), the blood inflow-rate into the aorta, and the rate-of-outflow from the aorta into the systemic circulation.

After closure of the aortic valve, no more blood enters the aorta, but the distended vessel now recoils, according to its volume elasticity, and blood is propelled into the peripheral circulation. The rate of fall of aortic pressure in the elastic aortic chamber during this phase (predominantly during cardiac diastole) is equal to the product of the volume elasticity of the aorta and the outflow rate, which in turn is equal to the aortic pressure divided by the flow resistance.

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Figure 5.1: The basic features of the aortic pressure profile. P_1 and P_2 are diastolic pressure and systolic pressure, respectively. P_3 is the pressure corresponding to the instant of aortic valve closure.

5.2 Methodology

For a blood control-volume, shown in **Figure 5.2**, we have

$$\begin{aligned} \frac{dV}{dt} &= (\text{inflowrate}) - (\text{outflow}) \\ &= \left[I(t) + T_a \frac{dI}{dt} \right] - Q(t) = I(t) + T_a \frac{dI}{dt} - \frac{P(t)}{R_p} \end{aligned} \quad (5.1)$$

wherein (i) $I(t)$ and $Q(t)$ are inflow and outflow rates of the aorta, respectively, (ii) R_p is the resistance to flow in the aorta, (iii) T_a is the volume (or flow) acceleration period. This equation is based on the assumption that the outflow-acceleration is damped out.

We also have the relationship

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$$\frac{dP}{dt} = \frac{dP}{dV} \bullet \frac{dV}{dt} = m_a \frac{dV}{dt} \quad (5.2)$$

Figure 5.2: LV-aorta blood flow tract.

By combining equations (5.1 & 5.2), we obtain

$$\frac{dP}{dt} + \frac{m_a}{R_p} P = m_a \left[I(t) + T_a \frac{dI}{dt} \right] \quad (5.3)$$

Putting $\lambda = \frac{m_a}{R_p}$, equation (5.3) becomes,

$$\frac{dP}{dt} + \lambda P = m_a \left[I(t) + T_a \frac{dI}{dt} \right] \quad (5.4)$$

where λ is a parameter reflecting the aortic volume-elasticity and flow-resistance.

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Figure 5.3: Schematics for (i) $V_{LV}(t)$, the LV volume (ii) $V_a(t)$, volume input into the aorta (iii) $I(t)$, aortic inflow-rate (iv) $\ddot{V}_a(t) (= d^2V_a / dt^2)$, volume acceleration. $0-t_e$ is period for systolic phase, t_e-T is period for diastolic phase.

The LV outflow-rate is schematized in **Figure 5.3**. Since the left ventricle pumps blood into the aorta only during systole phase, the inflow rate into the aorta is approximated by the following function:

$$\begin{aligned}
 I(t) &= ae^{-bt} \sin(\omega t), & 0 < t < t_e \text{ (systole)} \\
 &= 0; & t_e < t < T \text{ (diastole)}
 \end{aligned} \tag{5.5}$$

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where a & b are constants related to the rate-of-inflow and $\omega = \pi / t_e$, t_e is the duration of the cardiac ejection phase.

By integrating equation (5.5) with respect to time, we obtain the expression for the blood-volume input to the aorta during the systolic phase:

$$V_a = -\frac{a}{b^2 + \omega^2} (b \sin(\omega t) + \omega \cos(\omega t)) e^{-bt} + \text{constant} \quad (5.6)$$

In equation (5.6), by imposing the initial condition that at the start of the ejection phase, the aortic volume $V_a(t=0)=0$, we obtain:

$$V_a = -\frac{a}{b^2 + \omega^2} (b \sin(\omega t) + \omega \cos(\omega t)) e^{-bt} + \frac{a\omega}{b^2 + \omega^2} \quad (5.7)$$

This aortic volume V_a can be expressed in terms of LV volume (V_{LV}) as

$$V_a(t) = V_{ed} - V_{LV}(t) \quad (5.8)$$

where V_{ed} is end-diastolic volume.

By matching equation (5.7) with the LV volume data, we can evaluate a and b . This procedure is exemplified later in section 5.4.

5.2.1 Diastolic Pressure $P_d(t)$ Analysis

During diastole, the aortic valve is closed with zero inflow into the aorta. Hence, $I(t)=0$.

From equation (5.4), we have

$$\frac{dP}{dt} + \lambda P = 0 \quad (5.9)$$

The solution of equation (5.9) is

$$P = P_d(t) = C_2 e^{-\lambda t} \quad (5.10)$$

Which describes the variation of aortic pressure $P_d(t)$ during the ventricular diastole phase.

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From **Figure 5.1**, we have:

$$P_d(t = t_e) = P_3 \quad (5.11)$$

$$P_d(t = T) = P_1 \quad (5.12)$$

where P_3 is the aortic pressure at the end of cardiac ejection or the start of aortic diastole, and P_1 is the diastolic pressure. Combining equations (5.10, 5.11, 5.12), we obtain the expression for the parameter λ in terms of the diastolic pressure P_1 and end-systolic pressure P_3 , in the form of:

$$\lambda = \frac{\ln(P_3 / P_1)}{(T - t_s)} = \frac{m_a}{R_p} \quad (5.13)$$

From equations (5.10 & 5.12), we have

$$C_2 = P_1 e^{\lambda T} \quad (5.14)$$

Hence equation (5.10), for diastolic pressure, becomes:

$$P_d(t) = P_1 e^{\lambda(T-t)} \quad (5.15)$$

It is to be noted that while P_1 is obtained as cuff-auscultatory diastolic pressure, we need to derive P_3 in order to determine λ .

5.2.2 Systolic Pressure $P_s(t)$ Analysis

During systole, when the ventricle pumps blood into the aorta, the inflow rate can be represented by the function $I(t) = ae^{-bt} \sin(\omega t)$. Hence, from equations (5.4 & 5.5), we obtain:

$$\frac{dP}{dt} + \lambda P = m_a a e^{-bt} (T_a \omega \cos(\omega t) + (1 - T_a b) \sin(\omega t)) \quad (5.16)$$

Upon solving equation (5.16), we obtain an expression for the variation of the aortic pressure $P_s(t)$ during systole,

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$$P_s(t) = C_1 e^{-\lambda t} + e^{-bt} [A_1 \cos(\omega t) + A_2 \sin(\omega t)] \quad (5.17)$$

$$\text{wherein } A_1 = \frac{m_a a \omega (T_a \lambda - 1)}{(b - \lambda)^2 + \omega^2}; \quad A_2 = \frac{m_a a [(\omega^2 + b^2) T_a + \lambda - b - T_a b \lambda]}{(b - \lambda)^2 + \omega^2}$$

and m_a and λ are the model parameters, which can be determined by making equation (5.17) match the actual aortic pressure waveform data.

From **Figure 5.1**, we have $P_s(t=0) = P_1$

Therefore, we have from equation (5.17):

$$C_1 = P_1 - A_1 \quad (5.18)$$

Upon substituting the expression (5.19) into equation (5.17), we get the total expression for $P_s(t)$ as follows:

$$P_s(t) = (P_1 - A_1) e^{-\lambda t} + e^{-bt} [A_1 \cos(\omega t) + A_2 \sin(\omega t)] \quad (5.19)$$

In this equation, the parameters m_a and R_p (or m_a and A) is still unknown.

5.2.3 Determination of P_3

Now, after determining the coefficients a and b in equation (5.7), we can evaluate the model parameters m_a & λ . For this purpose, we note that we can determine the pressures P_1 and P_2 by cuff-auscultation procedure (Figure 5.1). However, in order to determine λ (by equation 5.13), we also need to know the value of P_3 , the end-systole value of $P_s(t)$. Firstly, by differentiating equation (5.17) and equating to zero, we obtain the time t_m (i.e., t_2), when $P_s(t)$ is maximum, and equal to P_2 :

$$\frac{dP_s(t)}{dt} = -C_1 \lambda e^{-\lambda t} + e^{-bt} [A_3 \cos(\omega t) - A_4 \sin(\omega t)] \quad (5.20)$$

$$\text{wherein } A_3 = \frac{m_a a (T_a \omega (\omega^2 + b^2) + m_a \lambda (1 - 2T_a b))}{(b - \lambda)^2 + \omega^2},$$

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$$A_4 = \frac{m_a a (T_a (\omega^2 \lambda + \omega^2 b + b^3 - b^2 \lambda) - \omega^2 - \lambda b - b^2)}{(b - \lambda)^2 + \omega^2}, \text{ and } C_1 \text{ is given by equation (5.19).}$$

Now, at $t = t_m$, $P_s = P_2$. Hence, from the above equation, we get:

$$\frac{dP_s(t)}{dt}(t = t_m) = -C_1 \lambda e^{-\lambda t_m} + e^{-b t_m} [A_3 \cos(\omega t_m) - A_4 \sin(\omega t_m)] = 0 \quad (5.21)$$

$$P_s(t = t_m) = P_2 = C_1 e^{-\lambda t_m} + e^{-b t_m} [A_1 \cos(\omega t_m) + A_2 \sin(\omega t_m)] \quad (5.22)$$

In addition, for continuity between the $P_d(t)$ and $P_s(t)$ expressions (5.15 and 5.19), the diastolic pressure is to equal the systolic pressure at time t_e , i.e.,

$$\overset{\text{equation (5.15)}}{P_3} = \overset{\text{equations (5.19)}}{P_d(t = t_e)} = P_s(t = t_e)$$

$$\text{or, } P_1 e^{\lambda(T-t_e)} = (P_1 - A_1) e^{-\lambda t_e} + e^{-b t_e} [A_1 \cos(\omega t_e) + A_2 \sin(\omega t_e)] \quad (5.23)$$

Equations (5.21-5.23) constitute 3 equations to determine the 3 unknown parameters: m_a , λ and t_m .

5.2.4 Determination of Coefficients a , b and T_a

In order to evaluate the coefficients a , b and T_a , associated with $I(t)$, we need to monitor the ejected volume from the LV or the blood volume input to the aorta $V_a(t)$. For this purpose, the LV geometry and volume data can be obtained from cineangiography measurements; a sample data (of subject D.D.M) is displayed in **Figure 5.4-a**. Therefrom, we determine the aortic volume data during systole, and present it in **Figure 5.4-b**. We also keep in mind that aortic diastolic pressure (P_1) and systolic pressure (P_2) values can be obtained from the non-invasive cuff-auscultatory, with sufficient accuracy.

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Figure 5.4: (a) Cineangiography-derived data on LV volume vs. time during ejection. (b) Volume input into the aorta from the LV, as derived from 5.4-a during systolic phase.

Now, by using equation (5.7) to match the derived aortic volume (from the measurable LV volume) in **Figure 5.4-b**, we can determine the coefficients a , b (as shown in **Figure 5.5**). The values of these parameters are given in **Table 5.1**. Figure 5.5-a shows that the model equation (5.7) fits the data well, with $\text{RMS}=1.4732$ ml.

By twice differentiating this volume data, we obtain the LV output flow-acceleration curve depicted in **Figure 5.5-c**. Therein, the instant T_a , is found by locating a zero crossing of flow-acceleration from positive-to-negative. At this point, we also propose a new index of LV contractility ($EBFA$):

$$EBFA = \left[\frac{d^2 V_a}{dt^2} \right]_{\max} = \left[\frac{dI}{dt} \right]_{\max} \quad (5.24)$$

For the above case in **Figure 5.4-a**, $EBFA = 11865.3.1 \text{ ml/s}^2$,

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Figure 5.5: Upper panel: Plot of computed aortic volume vs. time, during the systolic phase of the aorta, this is the same curve as in Figure 5.4-b. Therein, (o) represents the measured data, (-) represents the computed curve $a=1209\text{ ml/s}$, $b=8.308\text{ s}^{-1}$. **Middle panel:** first-differentiate curve of volume- flow rate. **Below panel:** second-differentiate curve of volume vs. t, $T_a=0.088\text{ s}$ and $EBFA=11865.3\text{ ml/s}^2$. The prediction bounds define the width of the interval with a level of 95%.

5.2.5 Determination of Model Parameters m_a & λ

We now note that we can monitor P_1 (equation 5.19) and P_2 (equation 5.22) by cuff-auscultation. In order to determine m_a & λ from equations (5.21, 5.22 and 5.23), we also

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need to evaluate t_m . We thus have three unknowns: (m_a , λ and t_m) to be determined from three equations (5.21, 5.22 & 5.23), which involve monitored values of P_2 and P_1 . For the patient (D.D.M) whose LV volume, $V_{LV}(t)$, is displayed in **Figure 5.4-a**, the corresponding monitored auscultatory pressure are $P_2 = 170\text{mmHg}$, and $P_1 = 99\text{ mmHg}$. By solving equations (5.21, 5.22 & 5.23), we evaluate: $t_m=0.16\text{ s}$, $m_a=1.0313\text{ mmHg/ml}$, $\lambda=0.649\text{ s}^{-1}$, and hence $R=1.5891\text{ mmHg}\bullet\text{s} / \text{ml}$. Then, by substitution of these values of m_a and λ , into $P_d(t)$ and $P_s(t)$ expressions (5.15 & 5.17), we obtain the aortic pressure-time profile, as shown in **Figure 5.6**. The goodness of current model analysis is noted by comparison of the model profile with the catheterization data. This subject's parameters are shown in **Table 5.1**.

Figure 5.6: Plot of aortic pressure (of subject D.D.M) during one cardiac cycle, $t_e=0.32\text{s}$. Herein, $0-t_e$ represents the systolic phase, and t_e-1 represents the diastolic phase. The scatter points are the data measured from catheterization. The solid line is the model-computed profile. $\text{RMS}=2.41\text{ mmHg}$.

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Table 5.1: Measured haemodynamic data and model parameters of subject D.D.M

	Subject D.D.M
Measured haemodynamic data	
SBP (mmHg)	170
DBP (mmHg)	99
PP (mmHg)	37.38
T (s)	0.92
T _e (s)	0.32
Model parameters	
a (ml/s)	1209
b (s ⁻¹)	8.308
T _a (s)	0.088
MAP (mmHg)	132.62
Peripheral resistance R_p (mmHg·s/ml)	1.5891
Aortic stiffness m_a (mmHg/ml)	1.0313
λ (s ⁻¹)	0.6490
t _m (s)	0.16
LV contractility index (<i>EBFA</i>) (ml/s ²)	11865.3

5.3 Clinical Applications

5.3.1 Subjects

Altogether, 30 patients (age range 48-77 years) were studied. For each subject the aortic pressure and dimensions are monitored at 20 ms intervals during the cardiac cycle using cineangiography. The model aortic pressure, along with aortic stiffness m_a and peripheral resistance R_p were similarly calculated as indicated earlier (See section 5.2), as shown in Table 5.1. They will be analyzed case by case later in Chapter 7.

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5.3.2 Inferences for Parameters m_a & R_p

With reference to the literature review on cardiovascular diseases in the chapter 2, large artery damage is a major contributor to the cardiovascular diseases. In this section, we will present a detail analysis using biofluid mechanics to show how the two key parameters—aortic stiffness and peripheral resistance, can be used to assess the cardiovascular risk with reference made to the aortic pressure profile.

Figure 5.7: Schematic of relationship between peak systolic pressure (P_2), pulse pressure (P_p) and mean arterial pressure P_m (MAP).

In systemic circulation, an increase in pressure pulse (P_p) can result from decreased arterial compliance, reflection of the pressure waves backward from branches, and an increase in pulse wave velocity (PWV) (Machenzie et al., 2002). Therefore, the elastic

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nature of the aorta, which acts as a cushion to dampen the pressure oscillations resulting from intermittent ventricular ejection, plays an important role in all of these phenomena. The increase in pressure pulse can be referred to an increase in peak systolic pressure (P_2) or an increase in pulse pressure (P_p). This is presented in **Figure 5.7** below

$$P_2 = P_m + P_p \quad (5.25)$$

Correspondingly, we have $Q = Q_m + Q_p$, and $\bar{u} = \bar{u}_p + \bar{u}_m$.

a) Wave propagation in blood vessels

Figure 5.8: Free-body diagram of an arterial element, showing pressure, velocity, and wall displacement. $\bar{u}$ is the mean velocity-pulse of blood across cross section of the blood vessel tube. In other words, $\bar{u}_p$ is the response to P_p .

Before taking up the full complexity of pulse-wave propagation in arteries, let us consider first an infinitely long, isolated, circular, cylindrical, elastic tube containing a homogenous, incompressible, and nonviscous liquid. When this tube is disturbed at one place, the disturbance will be propagated as waves along the tube at a finite speed. The flow is assumed to be essentially one-dimensional, with a longitudinal mean velocity

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component $\bar{u}(x, t)$, which is a function of the axial coordinate x and time t . In comparison with u , other velocity components are negligibly small. Then the basic equations can be obtained (conservation of mass, momentum et al).

Consider first the conservation of mass in a segment of the tube of length dx as is illustrated in **Figure 5.8**. In a unit time, the mass influx at the left end is equal to $\rho_f \bar{u} \pi r_a^2$;

the efflux at the right is $\rho_f (\pi r_a^2) (\bar{u} + \frac{\partial \bar{u}}{\partial x} dx) + \rho_f (2\pi a dx) u_w$. Hence we get expression

for the velocity of fluid at the wall u_w

$$u_w = \frac{-a}{2} \frac{\partial \bar{u}}{\partial x} \quad (5.26)$$

Next, consider the balance of forces acting in the axis direction on a fluid element of length dx and cross section, as shown in **Figure 5.9**. Since the fluid is nonviscous, there is no shear stress acting on it. Hence, we have

$$P_p A + P_p \frac{\partial A}{\partial x} dx + m \left(\frac{\partial \bar{u}}{\partial t} + \bar{u} \frac{\partial \bar{u}}{\partial x} \right) = \left(P_p + \frac{\partial P_p}{\partial x} dx \right) \left(A + \frac{\partial A}{\partial x} dx \right) \quad (5.27)$$

where A is cross section area ($=\pi r_a^2$), m is mass ($=\rho_f A dx$), $P_p A$ is the force acting on the left end toward the right, $P_p (\partial A / \partial x) dx$ is the force acting on the lateral sides,

$\left(P_p + \frac{\partial P_p}{\partial x} dx \right) \left(A + \frac{\partial A}{\partial x} dx \right)$ is force acting on the right end toward the left. According to

Newton's law the net force will cause acceleration $\left(\frac{\partial \bar{u}}{\partial t} + \bar{u} \frac{\partial \bar{u}}{\partial x} \right)$. By neglecting the

second-order $\bar{u}(\partial \bar{u} / \partial x)$ term, we have

$$\frac{\partial P_p}{\partial x} + \rho_f \frac{\partial \bar{u}}{\partial t} = 0 \quad (5.28)$$

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Figure 5.9: The balances of forces in an arterial wall.

Next, because the material of tube obeys Hooke's law, then for a small change in radius η the circumference is changed by $2\pi\eta$ and the circumferential strain is η/r_a . If E_v is the Young's modulus of the wall material, the circumferential stress due to P_p ($=P_p r_a/h$). The circumferential strain (due to the pressure pulse dilating the aortic wall) $=\eta/r_a$. Hence

$$E_v = \frac{P_p r_a/h}{\eta/r_a}, \text{ or } E_v \frac{\eta}{r_a} h = r_a P_p \quad (5.29)$$

By requiring that the fluid velocity at the wall, u_w , equals the wall motion velocity, $\dot{\eta}$, and assuming the variation of wall displacement η in the axial direction is negligible, the subsequent equations can be obtained:

$$u_w(x, t) = \dot{\eta}(x, t) \quad (5.30)$$

From equations (5.26 5.29 & 5.30), we have

$$-\frac{r_a}{2} \frac{\partial u}{\partial x} = \frac{r_a^2}{Eh} \frac{\partial P_p}{\partial t} \quad (5.31)$$

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From equation (5.28 & 5.31), we have

$$\frac{\partial^2 P_p}{\partial x^2} = \frac{1}{\left(\frac{Eh}{2r_a} \rho_f\right)} \frac{\partial^2 P_p}{\partial t^2} \quad (5.32)$$

$$\frac{\partial^2 \bar{u}}{\partial x^2} = \frac{1}{\left(\frac{Eh}{2r_a} \rho_f\right)} \frac{\partial^2 \bar{u}}{\partial t^2} \quad (5.33)$$

Both equations 5.32 & 5.33 can be used to form the following pulse wave velocity (PWV) equation; the quantity c is the wave speed:

$$c = \sqrt{\frac{E_v h}{2r_a \rho_f}} \quad (5.34)$$

Equation (5.32) shows that the pressure in the elastic vessel is governed by a wave equation. Based on Fung (1984), the pressure and velocity satisfy the same wave equation.

We can show that the wave equation is satisfied by

$$P_p = P_0 f(x - ct) + P_0' g(x + ct) \quad (5.35)$$

$$\bar{u}_p = u_0 f(x - ct) - \bar{u}_0' g(x + ct) \quad (5.36)$$

On substituting equations (5.35 & 5.36) into equation (5.28), carrying out the differentiation, we obtain

$$P_0 = \rho_f c u_0 \quad (5.37)$$

for a wave that is moving in the position x direction and

$$P_0' = -\rho_f c \bar{u}_0' \quad (5.38)$$

for a wave which moves in the negative x direction.

This important relationship shows that the amplitude of pressure wave is proportional to the product of wave speed, the velocity disturbance (or pulse) and the fluid density, and nothing else (Fung, 1984).

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Therefore, we can continue to get

$$P_p = \rho_f c \bar{u}_p = \rho_f c \frac{Q_p}{A} = \rho_f c \frac{Q_p}{\pi r_a^2} \quad (5.39)$$

Let $Z_0 = \frac{P_p}{Q_p}$, then, we have

$$Z_0 = \frac{\rho_f c}{A} = \frac{\rho_f}{\pi r_a^2} \sqrt{\frac{Eh}{2r_a \rho_f}} = \sqrt{\frac{Eh \rho_f}{2\pi r_a^5}} \quad (5.40)$$

b) Aortic Stiffness (m_a) vs. Pulse Pressure (P_p), peripheral resistance (R_p) vs. mean arterial pressure (P_m)

By putting $E_v = m_a$, we have

$$c = \sqrt{\frac{m_a h}{2r_a \rho_f}} \quad (5.41)$$

From **Figure 5.7**, the mean pressure P_m and mean flow-rate can be represented as

$$P_m = Q_m \times R_p \quad (5.42)$$

where $R_p = 8\mu L / \pi r_a^4$, μ represents viscosity of blood, L represents the blood-column length.

On the other hand the pulse pressure and flow pulse (P_p and Q_p) are related follows:

$$P_p = Q_p \times Z_0 = Q_p \sqrt{\frac{m_a h \rho_f}{2\pi r_a^5}} \quad (5.43)$$

For a given Q_m , a high P_m is associated with a high R_p (i.e., with small radius or atherosclerotic-vessels) or high μ (due to smoking). On the other hand, anemia or low μ is associated with a low P_m .

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For a given Q_p , P_p is associated with the aortic stiffness m_a . For a normal P_m , a high is P_p associated with high Z_0 or high m_a or arteriosclerosis.

5.3.3 Comparison with traditional invasive LV contractility index dP/dt_{max}

For the subjects analyzed in this study, the comparison between $EBFA$ (equation 5.24) and dP/dt_{max} is summarized in **Figure 5.10** with a good correlation of $r=0.8779$ ($EBFA = 26 \times dP/dt_{max} - 190000$), which demonstrates that the index gives a good prediction to LV contractility. Further, $EBFA$ can be determined noninvasively. Thus, this new index $EBFA$ can be an excellent substitute to dP/dt_{max} for contractility measure.

Figure 5.10: Comparison between $EBFA$ versus dP/dt_{max} with r being the correlation coefficient.

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5.4 Determination of Pressure Drop Across Aortic Valve

5.4.1 Background

Transvalvular pressure drop (ΔP) is recognized as one of the key factors identifying the performance and disease states of a heart valve. During normal working conditions, ΔP is a function of time, depending upon several factors such as flow rate and its waveform, pulse rate, the overall geometry, and the opening/closing mechanism of the occluder (Fiore et al., 2002). Hence, according to different calculation methods, different characteristic values can be defined.

The ability to accurately and non-invasively quantify transvalvelar pressure drop is one of the most important applications of echocardiography (Stamm et al., 1983). The foundation of this application is the ability to measure a waveform velocity from routine pulsed Doppler echocardiography, and using the simplified Bernoulli equation to derive an estimated pressure gradient (Firstenberg et al., 1999). The simplified Bernoulli equation, which measures convective fluid energy, has been shown to be accurate in the setting of high flow across a stenosis valve, such as in mitral or aortic stenosis. However, unlike the complete, or unsteady, Bernoulli equation, the simplified version does not consider inertial or resistive forces (i.e. non-convective forces). Although poorly understood, the inertial energy across a cardiac valve has shown to be a significant component of the total transmitral gradient (Flachskampf et al., 1993). Another reason is the absence of flow-rate information (Baumgartner et al., 1993). Both criticisms are correct, but may not be an argument to reject Doppler echocardiography as a tool to evaluate pressure drop. In this study, we try to take into account all the needed variables.

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5.4.2 Bernoulli Theorem

When the work-energy relation is integrated between two points and along a streamline, a new relation is obtained (Bernoulli equation), expressing the variation of total energy of the fluid along a streamline in terms of the Bernoulli sum B_s , given by:

$$B_s = \frac{v^2}{2g} + \frac{P}{\rho g} + h \quad (5.44)$$

where h is the elevation with respect to a reference plane and the other two terms have also the dimension of a length. P is local static pressure, ρ is fluid density, g is gravitations acceleration and v is local velocity. This forms the physical basis for “pressure recovery”. As blood is forced to flow through a stenotic area formed for instance by the central zone of a valve, flow accelerates, kinetic energy increases and potential energy decreases as the total amount of energy is constant.

Briefly, three-dimensional flow in the cardiac cavities is governed by the Navier-Stokes equations for incompressible fluid. If we consider flow along a streamline, the Navier-Stokes equations can be rewritten as the Euler equation describing the local pressure (P) and velocity (v) relationship:

$$\frac{\partial P}{\partial s} = -\rho \left[\frac{\partial v}{\partial t} + v \frac{\partial v}{\partial s} \right] \quad (5.45)$$

Herein, v is a scalar quantity, the magnitude of velocity along the streamline at a given distance (s) and time (t). Integrating Euler equation between two points along the inflow path yields the unsteady Bernoulli equation

$$P_i(t) + \rho \frac{v_i^2(t)}{2} = P_j(t) + \rho \frac{v_j^2}{2} + \rho \int \frac{\partial v}{\partial s} ds + \phi \quad (5.46)$$

The third component on the right-hand side of the Bernoulli equation is the inertial term, also called the acceleration component of the total pressure difference across the valve-a

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term that requires knowing the length of the column of blood accelerated, and a term not available with pulsed Doppler. The last term ϕ is energy loss.

For steady incompressible non-viscous flow, equation (5.46) becomes

$$\Delta P_{ij} = P_i - P_j = \frac{\rho}{2}(v_i^2 - v_j^2) + \phi \quad (5.47)$$

Meanwhile,

$$A_i v_i = A_j v_j = Q \quad (5.48)$$

where Q is volume flow rate, A_i , A_j are orifice area.

5.4.3 Pressure Drop Across the Aortic Valve

Figure 5.11: LV longitudinal cross-section, showing the outflow tract.

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As shown in **Figure 5.11**, the inlet and outlet into and from the left ventricle (LV) is regulated by mitral and aortic valves. By applying Bernoulli's Theorem, we obtain pressure drop between section 1 and 2:

$$\begin{aligned} P_1 - P_2 &= \frac{\rho}{2} v_2^2 - \frac{\rho}{2} v_1^2 + \frac{\rho k_c v_1^2}{2} \\ &= \frac{\rho Q^2}{2} \left[\frac{1}{A_2^2} - \frac{1}{A_1^2} + \frac{k_c}{A_1^2} \right] \end{aligned} \quad (5.49)$$

where $\rho v_1^2 k_c / 2$ is energy loss ϕ due to contraction (5.50)

Similarly, the pressure drop between section 2 and 3 is:

$$\begin{aligned} P_2 - P_3 &= \frac{\rho}{2} v_3^2 - \frac{\rho}{2} v_2^2 + \frac{\rho}{2} (v_2 - v_3)^2 \\ &= \frac{\rho Q^2}{2} \left[\frac{1}{A_3^2} - \frac{1}{A_2^2} + \frac{1}{A_2^2} \left(1 - \frac{A_2}{A_3} \right)^2 \right] \end{aligned} \quad (5.51)$$

where $\frac{\rho}{2} (v_2 - v_3)^2$ is energy loss ϕ due to expansion.

Combining equation (5.49 and 5.51), we have

$$\begin{aligned} (P_1 - P_3) &= \frac{\rho Q^2}{2} \left[\frac{1}{A_3^2} - \frac{1}{A_1^2} + \frac{k_c}{A_1^2} + \frac{1}{A_2^2} \left(1 - \frac{A_2}{A_3} \right)^2 \right] \\ &= \frac{\rho Q^2}{2 A_2^2} \left[\left(\frac{A_2}{A_3} \right)^2 + \left(\frac{A_2}{A_1} \right)^2 (k_c - 1) + \left(1 - \frac{A_2}{A_3} \right)^2 \right] \end{aligned} \quad (5.52)$$

where ρ is blood density, k_c is coefficient (i.e. =0.36), Q can be measured noninvasively during cardiac cycle, $A_1 = \pi d_1^2 / 4$, $A_2 = \pi d_2^2 / 4$, $A_3 = \pi d_3^2 / 4$, d_1 , d_2 , and d_3 can be measured by echocardiography, as shown in **Figure 5.11**. Based on equation (5.52), we only need to accordingly know Q and A_2 . The ratios A_2 / A_1 and A_2 / A_3 can be obtained from echocardiographic views of the LV outflow tract.

Alternatively, if we can monitor Q , $P_1 - P_3$, and the ratios A_2 / A_1 and A_2 / A_3 , we can determine A_2 , the term of valvular stenosis.

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We have now developed the analysis of the aortic pressure (section 5.3) and pressure drop (section 5.4) across the aortic valve during the ejection phase. Hence from the aortic pressure and the computed pressure-drop, we can obtain the noninvasive LV pressure (i.e. $P_l(t)$ shown in **Figure 5.11**) during the ejection phase, which is very useful to determine the LV contractile capacity with the LV volume, as well as the sarcomere stress-shortening velocity characteristic in the next chapter (Chapter 6). So far we have not gotten the information of aortic valve for the subjects studied. Hence, this application will be finished as a future works.

5.5 Conclusion and Discussion

The auscultatory and oscillometric methods provide only features of the complex arterial pressure wave contour. It does not provide the entire arterial pressure wave contour; extra information contained in the arterial pulse is not available to the clinician. The clinical significance of arterial pressure waveform has been noticed from ancient times. In traditional Chinese and Ayurvedic medicines, physicians use fingers to feel the pulse waves of the radial artery on the forearm at the wrist. Through empirical information accumulated over the years, they have developed the art of diagnosis, which is often marvelous but not well understood. The use of pulse waves for diagnosis was discussed extensively in one of the most ancient classics of medicine, the Nei jing (Fung, 1984). The essential idea is that all disturbances in the function of any organ can be detected by changes in the pulse waves in the radial artery. The sensation felt by the fingers when pressing on the radial artery at specific points with varying degrees of pressure is used as the diagnostic criterion. However, these practices are qualitative. If instrumentation for

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recording the pressure waveforms can be utilized along with our analysis, we can begin to unravel the mysteries of Neijing.

The data required for our model consists of the aortic volume and the auscultatory pressures, which can be obtained non-invasively. The output of our model comprises of the aortic pressure waveform as well as the values of aortic stiffness m_a (to enable detection of arteriosclerosis) and peripheral (vascular) resistance R_p (or parameter λ) (to enable to detection of atherosclerosis). This model is very convenient for clinical practitioners, even who are not experienced. It also provides guidelines for treatment of hypertension in terms of selection of pharmacological therapy.

By carrying out large-scale clinical data, we can determine aortic pressure, m_a and R_p for patients with a wide disease spectrum. This can enable to further analyze the aortic pressure shape parameters and correlate them to various disease states. Based on this model, a novel contractility index EBFA has also been proposed. The result shows that there is good correlation between EBFA and traditional invasive contractility index $dP/dt_{\max}$.

In addition, in order to determine the LV pressure during the ejection phase noninvasively, the model for determination of pressure drop across the aortic valve is also developed. Once we obtain LV ejection pressure, we can then determine the LV sarcomere stress-shortening velocity properties with LV volume.

CHAPTER 6

SYSTOLIC MODELING OF THE LEFT VENTRICLE AS A MECHATRONICAL EXCITATION-CONTRACTION SYSTEM

6.1 Background

In Physiology, several systems are mechatronic in their functional operation, such as the musculo-skeletal (MS) system, Cardiac (CD) system, the gastro-intestinal (GI) system, and the uterus (UT). The MS system operates as a coupled excitation-contraction system, whereby the nervous system electrically stimulates and depolarizes the muscle, which responds to the stimulation by contracting. A contracted muscle develops internal force and shortens if its internal force is greater than the force acting on it. For example, when we want to lift a heavy load (W), we contract our biceps muscle. In this process, the muscle's sarcomere contractile element (CE) develops force (F_{CE}), which is transmitted to the muscle's elastic-element (EE) in series with it and hence to the load. When the

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developed force F_{CE} exceeds W , the biceps muscle shortens, causing the arm to flex at the elbow and lift the load W .

We can extend this simple mechanism to the heart. Herein, the bioelectrical depolarization wave is generated from the pacemaker cells and spreads over the heart muscle, thereby stepwise depolarizing the heart muscle (or the myocardium). So, as the bioelectrical wave spreads and propagates through the heart myocardial wall, it causes an analogous stress wave to propagate through the myocardium. The resulting radial stress acting on the inner surface of the heart-chamber equilibrates the pressure of the blood in the heart-chamber, thereby raising the pressure. When the heart-chamber pressure exceeds the pressure of blood in the aorta, then the aortic valve opens and the blood is ejected into the aorta and then pumped to the various organs.

We note that in all of bio-electro-mechanical physiological systems, the key phenomenon is excitation-contraction coupling mechanism of the myocardial sarcomere. In this chapter, we will present a model of the heart muscle, representing the sarcomere, sarcoplasmic reticulum and the connective tissue. We will analyze the model response to depolarization stimulus (simulated as an impulse function), and derive therefrom indices for left ventricle (LV) contractility and power.

6.2 Methods

6.2.1 Muscle Model

A microscopic structure of the heart muscle is shown in **Figure 6.1**. Therein, the sarcomere represents the functional unit of contraction, that makes the LV myocardial wall to develop stress and hence do work. The sarcomere can be represented by the

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Figure 6.1: Structure of the heart muscle is seen at different levels of magnification. In part C of this figure, the connective tissue is characterized by elastic and viscous elements of the 3-element model (in Figure 6.2), while the actin & myosin filaments constitute the contractile components or element of the 3-element in Figure 6.2. (This figure has been adopted from Fig. 2 of “Analysis and physiological monitoring of human left ventricle” by Ghista et al., Journal of Basic Engineering, June, 1971)

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contractile element of a 3-element myocardium model, while the connective tissue can be represented by the series elastic elements.

Based on the Hill three-element model (1938) and Huxley cross bridge theory (1957; 1974), we have developed a myocardial model involving the LV myocardial mass, series-elastic element (SE), viscous-elastic element (VE) and the contractile-element (CE) (as shown in **Figure 6.2**). We now link the anatomical associations of these myocardial model elements with the microscopic structure of the heart muscle.

Figure 6.2: Myocardial-fiber contractile model, involving: the effective mass (m) of the muscle tissue that is accelerated; elastic parameter k of the series element, having stress σ_{SE} (k =elastic modulus of the series element); viscous damping parameter B_v of the parallel viscous element, having stress σ_{VE} ; the contractile element (CE), which generates contractile stress σ_{CE} between myosin (thick) and actin (thin) filaments. The governing differential equation for this model is: $m\ddot{x}_2 + B_v\dot{x}_2 - \sigma_{CE} + kx_1 = 0$ or $m\ddot{x}_1 + B_v\dot{x}_1 + kx_1 = \sigma_{CE} - B_v\dot{x}_T - m\ddot{x}_T$.

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In **Figure 6.1**, the sarcomere represents the fundamental structural and functional unit of contraction. It is this unit that makes the muscle fiber contract, and generates stress within the wall. In **Figure 6.2**, the contractile element (CE) corresponds to the actin-myosin filaments of the sarcomere. The connective viscoelastic tissue between the fibers of the myocardium and the sarcolemma constitute the series element (SE) and the viscous element (VE).

In **Figure 6.2**, m denotes the LV myocardial mass, B_v is the viscosity parameter, k is the elastic-modulus parameter, x_T is the displacement of myocardial-fiber relative to the center line, x_2 is the displacement of the LV sarcolemma, x_1 is the displacement of SE ($=x_2 - x_T$), σ_{CE} denotes the stress generated by the CE, σ_{VE} denotes the stress by the VE, σ denotes the resulting total active stress which is related to the chamber pressure of LV.

The sarcomere unit consists of overlapping myosin and actin filaments (**Figure 6.3-a**). Myocardial shortening is generated by the relative sliding of the two filaments, driven by the working stroke in the myosin-head domain (**Figure 6.3-b, c**). The myosin filament is symmetrical about its midpoint and contains two regular arrays of myosin heads. Muscle contraction is driven by the motor protein **II**, which binds transiently to an actin filament, generates a unitary filament displacement or "working stroke", then detaches and repeats the cycle (Reconditi et al., 2004).

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Figure 6.3: Organization of myosin and actin filaments and myosin heads in the muscle sarcomere [This figure has been adopted from “The myosin motor in muscle generates a smaller and slower working stroke at higher load” by Reconditi et al., Nature, 2004, 428:578-581].

6.2.2 Thick-wall LV Cylindrical Model

In this study, the left ventricle (LV) is represented as a cylindrical shell contracting symmetrically. Transverse isotropy is assumed with respect to the axis of the cylinder. In **Figure 6.4**, the myocardial fiber model of Figure 6.2 is depicted within the LV cross-section. Therein, the activation of the sarcomeres within each cylindrical band develops active circumferential stress in that layer of the LV wall. The active circumferential stress (generated in the wall) acting on the cross-section of the band is denoted by $\sigma_{\theta\theta}$.

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Figure 6.4: Cross-section of a thick-wall cylinder representing the LV. The active wall stress $\sigma_{\theta\theta}$ generated by σ_{CE} due to the contraction of the sarcomere is given by:

$\sigma_{\theta\theta} = PR_i^2(1 + R_o^2 / R^2)/(R_o^2 - R_i^2)$, σ_m is the stress at the mid-radii. L is the length, R_i , R_m and R_o are the inner, middle and outer radii, h is the wall-thickness of cylinder model. There are 4 myocardial fiber units per band, and n (=10) bands in 1 cylinder.

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In **Figure 6.4**, subscripts i , o and m represent inside, outside and middle. The volume of myocardial wall (MV) and LV are given as:

$$MV = \pi(R_o^2 - R_i^2)L = 2\pi R_i hL \quad (6.1)$$

$$V = \pi R_i^2 L \quad (6.2)$$

where R_i and R_o are inside and outside radii of the cylindrical model. L and h are length and wall-thickness of the model.

Therein, the LV volume (V), wall thickness (h) and myocardial volume (MV) are measured by cineangiography. Using equations (6.1 & 6.2), we can calculate the radii R_i and length L ; then $R_o = R_i + h$. Hence if there n bands, the height of each band equals L/n (where n is fixed, =10, say)

In **Figure 6.4**, let the pressure acting on the inside be P (LV pressure) and that acting on the outside be P_0 (pressure from pericardium), both assumed to uniform. Here we assume that P_0 equals zero. Hence we can get the general expression of wall stress $\sigma_{\theta\theta}$ for the thick-wall cylinder as:

$$\sigma_{\theta\theta} = P \frac{R_i^2}{(R_o^2 - R_i^2)} \left(1 + \frac{R_o^2}{R^2}\right) \quad (6.3)$$

The stress varies through the wall, decreases from inside wall to outside wall (shown in Figure 6.4). By substituting $R = R_m = (R_i + R_o)/2$ into equation (6.3), we obtain the mid-wall circumferential stress (σ_m) as:

$$\sigma_m = P \frac{R_i^2 (5R_o^2 + 2R_o R_i + R_i^2)}{(R_o^2 - R_i^2)(R_o + R_i)^2} = P \cdot G \quad (6.4)$$

where “G” is for geometry ($G = \frac{R_i^2 (5R_o^2 + 2R_o R_i + R_i^2)}{(R_o^2 - R_i^2)(R_o + R_i)^2}$). Herein σ_m can be regarded

as the stress generated by the myocardial fiber (σ).

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In this cylindrical model, there are n bands along the length. Hence the height of each band equals L/n . Let us assume that there are just two big myocardial-fibers in every band, in order to deduce the mathematical complexity. The activation of the sarcomere within each band develops active stress ($\sigma_{\theta\theta}$) in that layer of the LV wall. The resulting stress raises the intra-ventricular pressure. When the pressure exceeds the pressure in the aorta, then the aortic valve opens; the LV shortens and thickens the wall to pump an appropriate stroke volume. Therefore, the displacement of myocardial-fiber unit (x_T), designated in Figure 6.2 relates with the change of radius of cylinder model and hence the LV volume during the ejection phase.

$$x_T = \pi \Delta R / 2 = \pi (R_{m,ed} - R_m(t)) / 2 \tag{6.5}$$

where $R_{m,ed}$ is the middle radius of the cylindrical model at end-diastole, and $R_m(t)$ is the middle radius of cylindrical model during the ejection phase.

Figure 6.5: Transfer function for determination of stress-shortening velocity of CE.

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From the clinical data LV volume, the cylindrical model's radii at different times can be derived and therefrom the displacements of myocardial-fiber unit ($x_T(t)$) using equation (6.5). Then the x_1 expression can be formulated using the myocardial-fiber model, as illustrated in Figure 6.2 and developed in the next section. On the other hand, from the LV pressure and cylindrical geometry, the generated myocardial fiber stress (σ or σ_m) using equation (6.4) can be determined, which can be related to the displacement x_1 of the series element. Therefore, from the expressions for x_T and x_1 and their values obtained in terms of $R_m(t)$ and $\sigma_m(t)$, we will determine the model parameters (i.e., elastic modulus k , viscous parameter B_v and the parameters of the contractile force σ_{CE}) will be evaluated. With these known parameters, the dynamic of sarcomere (i.e., stress-shortening velocity), as an important relationship representing cardiac contractility will be determined. This approach is summarized in **Figure 6.5**.

6.2.3 Analysis

A) Governing Equation of Myocardial Fiber Dynamics

From **Figure 6.6**, the governing differential equation for myocardial-fiber dynamic, due to the generated contractile stress (σ_{CE}), can be expressed as:

$$m\ddot{x}_2 + B_v\dot{x}_2 - \sigma_{CE} + kx_1 = 0 \quad (6.6)$$

$$\text{or, } m\ddot{x}_1 + B_v\dot{x}_1 + kx_1 = \sigma_{CE} - B_v\dot{x}_T - m\ddot{x}_T \quad (6.7)$$

where σ_{CE} is the applied stress exerted by the contractile-element

m is the muscle mass of per unit cross-section area $= \pi R \rho / 2$, ρ is muscle density.

B_v is the viscous damping parameter of parallel viscous element

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k is the elastic stiffness (or modulus) of SE

$$x_2 \text{ (the displacement of muscle mass } m \text{ relative to centre-line)} = x_T + x_1$$

x_T is the displacement of the myocardial-fiber unit relative to its centre-line

$$\sigma_{VE} = B_v \dot{x}_2, \text{ and } \sigma_{SE} = k(x_1 + x_{1ed})$$

x_{1ed} is x_1 at the end-diastole ($= (P_{ed} \cdot G_{ed}) / k$), P_{ed} is LV end-diastolic pressure,

$$G_{ed} \text{ is end-diastolic geometry } (= \left[\frac{R_i^2 (5R_o^2 + 2R_o R_i + R_i^2)}{(R_o^2 - R_i^2)(R_o + R_i)^2} \right]_{ed}).$$

Figure 6.6: Dynamic model of a myocardial-fiber unit: m is the effective mass of the myocardial sarcomere unit, there are 4 myocardial-fiber units within each band and n bands in the LV cylindrical model; k is the elastic modulus of series element; B_v is the viscous-damping parameter of parallel viscous element; σ denotes the total generated stress caused by the contractile stress σ_{CE} ; σ_{SE} is the stress in the series element ($=k(x_1 + x_{1ed})$), where x_{1ed} is the deformation of the SE at end-diastole; σ_{VE} is the stress in the viscous element ($=B_v \dot{x}_2$); x_1 then represents the added deformation of the SE during systole (over and above its deformation during the filling phase) due to the development of σ_{CE} .

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Because the terms $m\ddot{x}_1$ and $m\ddot{x}_T$ can be neglected due to small values when compared to other terms*, the equation (6.7) can thus be rewritten as:

$$B_v \dot{x}_1 + kx_1 = \sigma_{CE} - B_v \dot{x}_T \quad (6.8)$$

In this study, we just consider myocardial contraction during the systolic phase. The systolic contraction can be considered to comprise of two temporal phases. The first phase I, denoted by t_{iso} (and measured in seconds), corresponds to isovolumic contraction; it comprises the interval from the closing of the mitral valve until the aortic valve open (Phase I). The second phase II, (t_e), corresponds to the ejection phase of systole, as shown in **Figure 6.7**. The total duration of contraction t_s is given by

$$t_s = t_{iso} + t_e \quad (6.9)$$

Figure 6.7: Schematic of aortic pressure and LV pressure during cardiac cycle.

* for instance, $m\ddot{x}_1$ and $m\ddot{x}_T$ are of the order of 10^{0-1} while the other terms are of the order of 10^{3-4} .

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The QRS complex of the ECG that represents ventricular depolarization, initiates this phase of the cardiac cycle. As the LV depolarizes, excitation-contraction coupling leads to sarcomere contraction and the development of ventricular wall stress and a rapid increase in intraventricular pressure, as shown in **Figure 6.7**. During this phase of systolic contraction, the generated stress of CE σ_{CE} can be considered (analogous to the LV pressure wave shape) as:

$$\sigma_{CE} = \sigma_{CE0} \sin(\omega_{ce} t) e^{-z_{ce} t} \quad (6.10)$$

where $\omega_{ce} = \pi / t_s$, t_s is the contraction duration ($= t_{iso} + t$), σ_{ce0} and z_{ce} are coefficients, $t=0$ corresponds to the start of isovolumic contraction phase. It can be noted that this expression for σ_{CE} is similar to that for the active elastance as given by equation (3.3-b).

Phase I: Isovolumic contraction phase:

Since both the mitral and aortic valves are closed, the volume of blood in the ventricle is constant. Yet the pressure inside the ventricle is increasing due to the sarcomere contraction, i.e., due to σ_{CE} . Hence putting $x_T = \dot{x}_T = \ddot{x}_T = 0$, and employing σ_{CE} from equation (6.10), we can rewrite equation (6.8):

$$B_v \dot{x}_1 + kx_1 = \sigma_{CE0} \sin(\omega_{ce} t) e^{-z_{ce} t} \quad (6.11)$$

The solution of equation (6.11) is given by $x_1 (=x_1^c)$, as follows:

$$x_1(t) = x_1^c(t) = C_1 e^{-k/B_v t} + (a \sin(\omega_{ce} t) + b \cos(\omega_{ce} t)) e^{-z_{ce} t} \quad (6.12)$$

where $a = \frac{\sigma_{CE0} (k - z_{ce} B_v)}{(k - z_{ce} B_v)^2 + (B_v \omega_{ce})^2}$, $b = -\frac{\sigma_{CE0} B_v \omega_{ce}}{(k - z_{ce} B_v)^2 + (B_v \omega_{ce})^2}$.

For this phase of contraction, the initial conditions that we will impose are dictated by:

$$x_1^c(0) = C_1 + b = 0 \quad (6.13)$$

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Solving equation (6.13), we have

$$C_1 = -b \quad (6.14)$$

Hence, x_I during isovolumic contraction phase is given by

$$x_I(t) = x_I^c(t) = (-b)e^{-k/B_v t} + (a \sin(\omega_{ce} t) + b \cos(\omega_{ce} t))e^{-z_{ce} t} \quad (6.15)$$

Phase II: Ejection phase:

For mathematical convenience we make a shift in the time variable and redefine it as

$t_a = t - t_{iso}$. This changes the temporal region of interest to:

$$0 \leq t_a \leq t_e \quad (6.16)$$

In this phase, x_T is no longer zero, and hence we need to relate it to the LV volume as indicated by equation (6.5).

We now adopt (due to the flow-rate shape of LV)

$$\dot{x}_T = x_{T0} \sin(\omega_e t_a) e^{-z_e t_a} \quad (6.17)$$

where $\omega_e = \pi / t_e$, t_e is the duration of ejection as shown in Figure 6.7; x_{T0} and z_e are coefficients, and $t_a = 0$ corresponds to the start-of-ejection phase.

By employing initial condition of $x_T(t_a = 0) = 0$, we have

$$x_T = -\frac{x_{T0}}{z_e^2 + \omega_e^2} [z_e \sin(\omega_e t_a) + \omega_e \cos(\omega_e t_a)] e^{-z_e t_a} + \frac{x_{T0} \omega_e}{z_e^2 + \omega_e^2} \quad (6.18)$$

wherein the parameters x_{T0} & z_e are obtained, by matching x_T (equation 6.18) with the

clinical data on LV volume $V(t)$ and hence LV model $R(t)$ change ($= \frac{\pi}{2} (R_{ed,m} - R_m(t))$),

as equation (6.5).

Then, by substituting equation (6.10 & 6.17) into the governing equation (6.8), we have:

$$B_v \dot{x}_1 + kx_1 = \sigma_{CE0} \sin(\omega_{ce} (t_a + t_{iso})) e^{-z_{ce} (t_a + t_{iso})} - B_v x_{T0} \sin(\omega_e t_a) e^{-z_e t_a} \quad (6.19)$$

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The solution of equation (6.19) is given by $x_1 (= x_1^e)$:

$$x_1(t_a) = x_1^e(t_a) = C_2 e^{-k/B_v t_a} + [a \sin(\omega_{ce}(t_a + t_{iso})) + b \cos(\omega_{ce}(t_a + t_{iso}))] e^{-z_{ce}(t_a + t_{iso})} + [c \sin(\omega_e t_a) + d \cos(\omega_e t_a)] e^{-z_e t_a} \quad (6.20)$$

$$\text{where } c = -\frac{B_v x_{T0}(k - B_v z_e)}{(k - B_v z_e)^2 + (B_v \omega_e)^2}, \quad d = \frac{B_v^2 x_{T0} \omega_e}{(k - B_v z_e)^2 + (B_v \omega_e)^2}$$

Because the $x_I(t)$ between phases I and II is continuous, i.e., $x_1^e(t_a = 0) = x_1^c(t = t_{iso})$. This determines the initial condition for phase II. Hence, from equation (6.15 & 6.20),

$$\begin{aligned} x_1^e(0) &= C_2 + (a \sin(\omega_{ce} t_{iso}) + b \cos(\omega_{ce} t_{iso})) e^{-z_{ce} t_{iso}} + d = x_1^c(t = t_{iso}) \\ &= -b e^{-k/B_v t_{iso}} + (a \sin(\omega_{ce} t_{iso}) + b \cos(\omega_{ce} t_{iso})) e^{-z_{ce} t_{iso}} \end{aligned} \quad (6.21)$$

Solving equation (6.21), we have

$$C_2 = -b e^{-k/B_v t_{iso}} - d \quad (6.22)$$

Hence, the added SE deformation $x_1 (= x_1^e)$ during the systolic phase can be written as:

$$\begin{aligned} x_1(t_a) &= x_1^e(t_a) = (-b e^{-k/B_v t_{iso}} - d) e^{-k/B_v t_a} \\ &+ [a \sin(\omega_{ce}(t_a + t_{iso})) + b \cos(\omega_{ce}(t_a + t_{iso}))] e^{-z_{ce}(t_a + t_{iso})} \\ &+ [c \sin(\omega_e t_a) + d \cos(\omega_e t_a)] e^{-z_e t_a} \end{aligned} \quad (6.23)$$

B) Obtaining Solutions for All the Model Parameters

The expression for the LV myocardial stress generated (by σ_{ce}) is then given (on the basis of **Figures 6.4 & 6.6**)

$$\sigma_{SE} = \sigma = \sigma_m = k(\text{total SE deformation}) = k(x_1^e + x_{1ed}) \quad (6.24)$$

where σ_m is the stress at mid-radii, x_1^e is given by equation (6.23), x_{1ed} is x_1 at end-diastole. The resulting LV intra-cavity pressure P developed (by σ_m) is given by (refer to equation 6.4):

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$$P = \frac{\sigma_m (R_o^2 - R_i^2)(R_o + R_i)^2}{R_i^2 (5R_o^2 + 2R_o R_i + R_i^2)} = \frac{(R_o^2 - R_i^2)(R_o + R_i)^2}{R_i^2 (5R_o^2 + 2R_o R_i + R_i^2)} k(x_1^e + x_{1ed}) = \frac{k(x_1^e + x_{1ed})}{G} \quad (6.25-a)$$

$$\therefore k \cdot x_1^e = (P \cdot G - P_{ed} \cdot G_{ed}) \quad (6.25-b)$$

where, R_o and R_i are the outer and inner radii derived from clinical data, and the x_1^e expression is given by equation (6.23). Then we use the actual LV pressure and geometry term (G) derived from equation (6.4) at the same instant to obtain the right-hand side of equation (6.25-b). By matching the left side of equation (6.25-b) (kx_1^e) with the clinical derived data of the subject, and carrying out parameter-identification, we can determine the corresponding parameters k , B_v , σ_{CE0} , and z_{ce} .

Then in turn we can determine the contractile stress of CE σ_{CE} by equation (6.10), x_1 during isovolumic contraction (equation 6.15) and ejection (equation 6.23) and hence model derived pressure. On the other hand, displacement of CE, $x_2 (=x_1 + x_T)$ is also determined,

C) Power Generated by the Sarcomere Contractile-element and Pump Efficiency

Now, because we have incorporated 4 sarcomere units in each band (as illustrated in Figure 6.4), we now define LV myocardial contractile-element power (refer to Figure 6.4), as:

$$Power = 4(F_{CE} \times \dot{x}_2) \quad (6.26)$$

where (i) both F_{CE} and $\dot{x}_2$ are functions of time, (ii) F_{CE} is the contractile force generated by each contractile element in each band, is given by

$$F_{CE} = \sigma_{CE}(h \times L) \quad (6.27)$$

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and (iii) $\dot{x}_2$, the shortening velocity of the CE element, is given by $(\dot{x}_1 + \dot{x}_T)$. The generated σ_{CE} in each of the 4 sarcomere units is relates to the SE stress (kx_1), by equation (6.11), which in turn is related to LV wall stress σ_m by equation (6.24)

The energy input by contractile element is given by

$$W_{in} = 4 \int_{x_1}^{x_2} (F_{CE}) dx_2 \quad (6.28)$$

The work and power output (W_{out} and $Power_{out}$) by the series element that are relating chamber pressure and volume.

$$Power_{out} = 4(F_{SE} \times \dot{x}_T) \text{ and } W_{out} = 4 \int_{x_1}^{x_2} (F_{SE}) dx_T \quad (6.29)$$

where $F_{SE} = \frac{\int_{R_i}^{R_o} \sigma_{SE} dR}{h} (h \times L) \cong \sigma_m (h \times L)$

Hence the efficiency(η), the ratio between the work output and energy input, is given by

$$\eta = \frac{W_{out}}{W_{in}} \quad (6.30)$$

D) Defining New Contractility Index based on the Contractile Power

Herein, in quantifying the performance of the LV, contractility is defined as: the ability of the LV myocardium to produce a contractile force with a high shortening-velocity capability, so as to exert maximum contractile power ($Power_{max}$). In order to compare $Power_{max}$ between patients of differing LV size and mass, we define LV contractility index in terms of myocardial sarcomere power ($MSPI$) as:

$$MSPI = Power_{max} / MV \quad (6.31)$$

where MV is LV wall-volume.

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6.3 Clinical Application

The analysis is now applied to the clinically obtained data, of the subject's left ventricular (instant-of-instant) dimensions (obtained by cineangiocardigraph) and chamber pressure (obtained by cardiac catheterization). In so doing, for each subject's left ventricular data, the model parameters and corresponding new index MSPI are determined. **Table 6.1** summarized the measured and model derived hemodynamic parameters for three subjects (subject H.E.L., D.D.M, and T.P.S). Subject H.E.L serves as an example of a patient with myocardial infarct, subject D.D.M with double vessel disease (DVD) and hypertension, treated with PTCA; subject T.P.S with native LAD, ischemia in anterior territory and mitral regurgitation (MR). These three subjects studied are same as Chapter 3 (refer to **Table 3.2**). **Figure 6.8** depicts one-sample cineangiocardigraphically-derived LV dimensions and the derived cylindrical model dimensions during a cardiac cycle.

Table 6.1 Clinical history, measured hemodynamic data from subjects (H.E.L, D.D.M and T.P.S). Where LVP: left ventricle chamber pressure, AOP: aortic pressure, EDV: end-diastolic volume, ESV: end-systolic volume, EF: ejection fraction, MI: myocardial infarct, MR: mitral regurgitation, DVD: double vessel disease, HTN: hypertension, LAD: left artery disease.

Subject	H.E.L	D.D.M	T.P.S
Disease	MI, DVD	DVD, HTN	LAD, MR and Ischemia
LVP (mmHg)	122/18	170/24	147/22
AOP (mmHg)	125/75	169/99	140/71
EDV/ESV (ml)	132/84.3	121.7/41.3	112/44.8
EF	0.36	0.66	0.60

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Figure 6.8: Pressure and dimension during a cardiac cycle with thick-wall cylindrical model for subject H.E.L. MV=185 ml.

From the clinical data shown in Figure 6.8, we further calculate the clinical-derived model x_T using equation (6.5). This x_T versus time function during ejection is shown in Figure 6.9, as illustrated by the round points. We then use the expression of x_T given by equation (6.18) to fit the clinical derived data of x_T versus t , and determine the parameters x_{T0} and z_e , as shown in **Figure 6.9**. The model matches the clinical data very well with R-square=0.9944 and RMS=0.01 cm. The solid line is the model-computed displacement x_T (equation 6.18), the round points constitute the clinical derived data.

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We use the actual LV pressure data in Figure 6.8 and clinical-derived geometry term (G) to obtain the right-hand side of the equation (6.25-b), as illustrated by the round points shown in **Figure 6.10**. We then use the kx_1^e expression given by equation (6.25-b) to determine other parameters k , B_v , σ_{CE0} , and z_{ce} , as shown in **Table 6.2**.

Figure 6.9: From the data shown in Figure 6.8, we further calculate the model x_T using equation (6.5), as shown round points during the ejection phase in this figure. This data is now fitted with equation (6.18). The resulting parameters values are listed in Table 6.2.

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Table 6.2: Parameters related to the subject H.E.L shown in Figure 6.8, during ejection phase

Parameters	Values	Fitting		
$x_{T0}(\text{cm})$	4.584 ± 0.86	x_T fit during ejection phase using, equation (6.18)	RMS	0.01 cm
$z_e(\text{s}^{-1})$	9.517 ± 0.708		R-square	0.99441
$\sigma_{CE0}(\times 10^5\text{ g}\cdot\text{cm}/\text{s}^2)$	5.771 ± 1.285	kx_1^e fit during ejection phase, using equation (6.25)	RMS	4397 $\text{g}\cdot\text{cm}/\text{s}$
$z_{ce}(\text{s}^{-1})$	0.4333 ± 0.0425		R-square	0.9703
$B_v(\times 10^5\text{ g/s})$	1.584 ± 0.378			
$k(\times 10^6\text{ g/s}^2)$	1.709 ± 0.242

Figure 6.10: From the data shown in Figure 6.8, we further calculate the model $(P \cdot G - P_{ed} \cdot G_{ed})$ using equation (6.4), as shown the round points in this figure. The clinical-derived data is now fitted with equation (6.25-b). The resulting parameters values are listed in Table 6.2.

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Figure 6.11: Results of myocardial-fiber model for subject H.E.L. 0-0.32s: diastole; 0.32-0.4s: isovolumic contraction; 0.4-0.64s: ejection; 0.64-0.72s: isovolumic relaxation.

Shown in **Figure 6.11** are the results for subject H.E.L. In the **Figure 6.11-a** is the measured data from the experiment: LV pressure in one cardiac cycle. By means of the

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values of the parameters in **Table 6.2**, we have determined and plotted x_I versus time, x_2 versus time and x_T versus time in **Figure 6.11-b**.

For the sake of interest, if we add the maximum CE shortening x_2 by the 4 sarcomere units, it amounts to $4 \times 0.41 \text{ cm} = 1.64 \text{ cm}$. In other words, the x_2 shortening shortens the LV model circumference by 1.64 cm. Now let us look at the actual LV data on derived R_i and hence $R_m (= R_i + h/2)$ from **Figure 6.8**, which amounts to (1.68-2.0cm). The change in LV model circumference is $2\pi\Delta R = 2\pi(R_{m,ed} - R_m(t)) = 1.39 \text{ cm}$, which is of the same order of magnitude as the LV model circumferential change of 1.64cm caused by CE deformation x_2 .

The CE shortening velocity and stress are shown in **Figure 6.11-c & 6.11-d** respectively. Notice that the stress changes are similar to active elastance that we described in Chapter 3.

Meanwhile, we also plot stress-velocity and stress-length for the contractile-element(CE) during the contraction phase, as shown in **Figures 6.12 & 6.13**. In **Figure 6.12**, the CE shortening velocity increases, along with increasing CE force. They both reach their maximum values at about one-third ejection. The stress-shortening velocity makes a loop during mid-ejection.

Figure 6.13 is the stress-displacement of the CE, where CE stress (σ_{CE}) is plotted against CE shortening displacement (x_2). The CE shortening reaches maximum at about end-ejection. The area encircled by stress-displacement curve and x-axis represent the energy input of CE. For our interest and in order to provide validation of the our computed values of σ_{CE} , we can compute the maximal $\sigma_{CE} = 5.33 \times 10^5 \text{ g} \cdot \text{cm} / \text{s}^2$ with the value of $\sigma_m = 2.37 \times 10^5 \text{ g} \cdot \text{cm} / \text{s}^2$ at the same instant, and note that σ_{CE} is about 2 times of σ_m .

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Figure 6.12: Stress-shortening-velocity relationship of contractile element (CE) for subject H.E.L. Arrow direction indicates progression of time, starts from diastolic filling phase.

From **Figures 6.12 & 6.13**, we can calculate the contractile power (Power) using equation (6.26) and work input (W_{in}) using equation (6.28) generated by CE. The corresponding maximum power ($Power_{max}$) is 8.12 Nm/s and MSPI is 0.044 Nm/s/ml.

This analysis is carried out for other two subjects listed in **Table 6.1**.

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Figure 6.13: Stress-length relationship of contractile element (CE) for subject H.E.L. Arrow direction indicates progression of time, starts from diastolic-filling phase.

Figures 6.14 and **6.15** give the stress-shortening velocity and stress-displacement of contractile element (CE) in myocardial-fiber model for subject H.E.L (with MI, DVD), D.D.M (DVD, HTN) and T.P.S (LAD, MR, Ischemia). In **Figure 6.14**, the stress-shortening velocity follows the same shape for all the subjects. The stress and shortening velocity both reach their maximal values at about one-third ejection. However, the loop made by stress and shortening velocity is a little different under different condition. **Figure 6.15** plots the stress-displacement for these three subjects with different heart disease. The area encircled by the curve and the x-axis along with the shape of the curve changes indicate the amount of work generated by the CE varying according to the demands.

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Figure 6.14: Stress-velocity relationship of contractile element (CE) for subject H. E. L, D. D. M and T. P. S. where MI: myocardial infarct, DVD: double vessel disease, HTN, hypertension, LAD: left artery disease, MR: mitral regurgitation.

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Figure 6.15: Stress-displacement of contractile element (CE) for subject H.E.L, D.D.M and T.P.S. where MI: myocardial infarct, DVD: double vessel disease, HTN, hypertension, LAD: left artery disease, MR: mitral regurgitation.

Subject H.E.L has myocardial infarct, and hence has less contracting myocardium. This is manifest by a lower maximal stress and shortening velocity of CE, in comparison with subject D.D.M and T.P.S (shown in **Table 6.3**). Hence, the values of maximum power generated by CE and corresponding contractility index MSPI are lower than other two subjects. Also, the area of stress-displacement decreases dramatically as compared with the other two subjects, and hence this subject generates less work. This indicates that the infarct part of the myocardium would impair the overall left ventricular performance by attenuating the heart work.

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Subject D.D.M has high maximal stress and shortening velocity and big area of stress-displacement, indicating that the LV has to generate more work to overcome the increased afterload (hypertension).

Subject T.P.S has myocardial ischemia, however, both the maximum stress and shortening velocity as well as the area of stress-displacement (σ_{CE} vs x_2) do not decrease as much with subject D.D.M. This perhaps reflects an adaptive mechanism attempting to restore the LV performance, which is in agreement with ejection fraction (EF=0.6). However, the efficiency η of this subject decreases a little bit.

Table 6.3 summarizes the results for these three results, where we compare their MSPI and η indices with the traditional contractility index dP/dt_{max} . However, we need to interpret the η index, as the capacity of the LV to respond to the clinical demand and its impairment. Our results show that the subject T.P.S' LV has not been able to respond to the disease states as well as the other two subjects.

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Table 6.3: Clinical history, $dP/dt_{\max}$, Maximal contractile stress, σ_{CE} , shortening velocity $\dot{x}_2$ of CE, area under σ_{CE} vs. x_2 , calculated maximum Power ($Power_{\max}$), myocardial volume (MV), left ventricular contractility index (MSPI), and myocardial efficiency η from subjects (H.E.L, D.D.M, and T.P.S).

Subject	H.E.L	D.D.M	T.P.S
Disease	MI, DVD	DVD, HTN	LAD, MR Ischemia
EF	0.36	0.66	0.60
$dP/dt_{\max}$ (mmHg/s)	984	1475	1234
Maximum σ_{CE} ($\times 10^5 \text{ g} \cdot \text{cm} / \text{s}^2$)	5.33	8.56	8.14
Maximal shortening velocity $\dot{x}_2$ (cm/s)	3.20	4.20	4.67
Area under σ_{CE} vs x_2 curve ($\times 10^5 \text{ g} \cdot \text{cm}^2 / \text{s}^2$)	1.75	4.88	4.77
Power _{max} (Nm/s)	8.12	13.88	14.84
MV (ml)	185	138	140
MSPI ((Nm/s)/ml)	0.044	0.10	0.11
η	0.34	0.32	0.26

6.4 Discussion and Conclusion

In most cases, left ventricular models are developed to evaluate wall stress as a function of intraventricular pressure. In this study, LV systolic performance is investigated by means of a mechatronic excitation-contraction system involving the ventricular wall (cylindrical model) composed of myocardial fibers. Each myocardial sarcomere unit is composed of three-elements: series element (analogue to connective tissue), viscous element (analogue to sarcolemma) and contractile element (analogue to sarcomere). The

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sarcomere contracting is associated with the relative sliding of the actin-myosin filaments. The contractile stress σ_{CE} and deformation x_2 of the LV myocardial-sarcomere unit are related to the LV pressure and volume data in terms of the model's parameters (k, m, B_v), and hence we can evaluate them. After that, we determine the in vivo characteristics of the LV sarcomere (CE), in terms of ' σ_{CE} versus $\dot{x}_2$ ' and ' σ_{CE} and x_2 ', as well as the power generated by the sarcomere (CE). Both ' σ_{CE} vs. $\dot{x}_2$ ' and sarcomere power generated by CE can be regarded as important LV functional indices.

Stress-shortening velocity and stress-displacement have been shown to be sensitive parameters to reflect changes in LV contractile function. Decreased stress-shortening velocity is associated with less contracting LV; also less area encircled by the stress-displacement and x-axis is associated with impaired LV contractility. This indicates that a LV with impaired contractility is not able to generate as much energy (required to provided) adequate EF and stroke volume as a well contracting LV. Furthermore, case studies results show that our new contractility index MSPI can be correlated with the traditional contraction index $dP/dt_{\max}$.

CHAPTER 7

CLINICAL APPLICATION

7.1 Background

Herein, we will quantitatively assess the overall ventricular performance of each patient, in terms of: (i) the intrinsic contractile state or contractility of myocardium, (ii) the passive elastance or filling compliance of the ventricle and (iii) the circulatory impedance (such as peripheral resistance and aortic stiffness) to ventricular ejection (afterload).

In chapter 3, we have developed the nonlinear volume-dependent passive and time-dependent active elastance during one cardiac cycle, which can explain the pressure increase during isovolumic contraction and the suction effect during rapid filling process. The corresponding parameters of the elastances are evaluated for our patient population. In the contracted LV, the maximum active elastance reflects the strength of contraction (or the contractile effort) needed to raise LV pressure to cope with the afterload and maintain a certain cardiac output. On the other hand, the passive elastance characterizes the material property of the relaxed LV myocardium. In Chapter 4, we have examined the effect of ventricular shape on contractility and ejection function. Therein, a contractility index is developed in terms of the left ventricular (LV) maximal normalized-stress

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change-rate. Also, another contractility index (*CONT2*) is developed based on the optimal shape-factor.

In Chapter 5, we have developed a model to determine the aortic pressure noninvasively, along with the aortic stiffness and peripheral resistance. The aortic stiffness and peripheral resistance can enable us to diagnose arteriosclerosis and atherosclerosis diseases, respectively. We also proposed that the derived maximum volume acceleration into the aorta, *EBFA*, reflects the strength of LV contraction.

In Chapter 6, a myocardial-fiber model was developed to incorporate the dynamics of the LV sarcomere contained within the wall of a cylindrical geometry model of the LV. Therein, we have determined the sarcomere contractile-element (the actin-myosin unit) 'stress vs. shortening-velocity' characteristics as well as the power generated by the sarcomere (CE) element. These are deemed to be important LV functional indices.

In this chapter, the following parameters are evaluated for each patient in our patient population, namely: maximal active elastance per unit pressure $(E_a/P)_{\max}$, passive elastance $E_{p,\max}/P_{ed}$, shape-based indices *CONT1* and *CONT2*, aortic stiffness (m_a), peripheral resistance (R_p), ejection blood-flow acceleration (*EBFA*), myocardial sarcomeric power index (*MSPI*) and efficiency (η). These indices, derived from all of the above analyses, constitute a diagnostic matrix, which can contribute to cardiac assessment.

In this Chapter, we will also analyze the patients case-by-case, by depicting their history, clinical diagnosis, and the computed bioengineering (BioE) indices. Each patient's clinical diagnosis is compared with our BioE Table indices-based assessment, to help reveal the efficacy of these indices.

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Table 7.1 summarizes the patients' history, which includes age, left ventricular and aortic pressure, wall-thickness at end-diastole and end-systole, end-diastolic volume (EDV) and end-systolic volume (ESV), myocardial volume (MV) and diagnosis by the cardiologist.

Table 7.1: Patients' history and clinical data, obtained from the National Heart Centre (NHC), Singapore.

Subject	Age	LVP (mmHg)	Aortic P (mmHg)	H S/D(mm)	EDV/ESV (cm ³)	MV (cm ³)	Disease
1 (H.B.S)	58	178/34	174/92	17.9/11	185/60	225	DM,HTN,TVD
2 (E.S)	66	102/10	116/75	8.8/5.4	86/38	86	MS
3 (W.K.K)	48	148/16	143/89	14.6/12	160/96	236	MI, DVD
4(A.T)	51	135/24	135/77	15.4/11.8	128/63	200	SVD
5 (V.G)	73	135/13	140/80	18/10	93/33	161	MS
6(S.E.I)	48	146/23	141/86	13.3/11.3	104/68	165	MI, TVD
7 (O.G.L)	56	142/19	139/82	13.5/9.6	82/33	118	LV tach.
8 (S.K.S)	77	162/53	159/82	16.3/14.7	131/100	271	TVD
9 (S.H.C)	56	118/37	117/63	15.5/12.7	103/59	200	MI, DVD
10 (L.K.J)	51	110/23	115/67	11.0/9	135/88	146	MI, TVD
11 (S.S)	62	115/7	125/85	17/10	117/52	200	MS, Mitral insufficiency
12(B.C)	63	162/20	165/72	16/11	105/37	171	SVD
13 (W.S.T)	65	154/23	147/80	11.2/9	98/63	125	MI, TVD
14 (T.T.L)	65	154/12	141/76	15/11	143/71.5	195.4	CAD
15 (H.B.O)	52	154/32	150/98	14/11	118/56	168	Normal coronary
16 (A.C.H)	53	182/24	183/93	12.0/8	138/47	128	Normal, HTN
17 (T.B.A)	67	171/28	173/74	15/11	126/57	187	TVD, HTN
18(A.R.A.R)	55	156/44	120/90	9.5/7.3	97.5/53.6	94	SVD
19(A.B.K.T)	60	114/14	112/56	12.4/9	129.6/31.5	142	DVD
20 (H.E.L)	50	122/18	125/75	13/11	132.5/84.3	185	MI, DVD
21 (C.J.P)	52	144/22	138/79	15/9.6	109/33	143	Normal coronary
22 (D.D.M)	56	170/24	169/99	14/9	121.7/41.3	138	DVD, HTN LAD, MR,
23 (T.P.S)	58	147/32	140/71	15/9.4	112/35	140	Ischemia
24 (C.C.Y)	51	156/26	157/77	14/8	148/53	137	Normal
25 (L.C.P)	58	178/26	178/82	14/10	121.9/48	163	CAD, HTN
26 (S.T.S)	54	110/18	110/68	13/7.4	100/31.1	100	Normal coronary
27 (J.C)	56	105/8	115/80	20/13	282/165	364	MS, Mitral insufficiency
28 (P.B)	60	198/25	160/80	12/8.5	263/184	257	AS
29 (M.L)	58	109/12	115/70	9.3/7.7	360/286	219	IHD
30 (V.B)	64	135/6	140/80	15/13	425/300	443	Post OPWV

MS: Mitral stenosis; AS: Aortic stenosis; MI: Myocardial infarct; MR. mitral regurgitation; AI: aortic insufficiency; TVD: Triple vessel disease; DVD: Double vessel disease; SVD: single vessel disease; LAD: left artery disease; DM: Diabetes mellitus; HTN: Hypertension; Tach.: Tachycardia; MD: Idiopathic heart disease.

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7.2 Establishing Normal Ranges of Bioengineering Indices Relative to Normal Ranges of Clinical Indices

For the entire group of patients studied here, 0.55 was selected as the lower limit of normal for the ejection fraction (EF). Previous hemodynamic studies from Children's Hospital Medical Centre have shown that the ejection fraction in almost all young patients in the age groups studied here exceeds 55%, unless the clinical diagnosis is myocardial pathology or rheumatic heart disease (Mirsky et al., 1973). This value has, therefore, been taken rather arbitrarily and employed in the regression equations in order to obtain the "cut-off" values for the various indices displayed in **Figures 7.1-9**.

As observed in **Figure 7.1**, E_a represents the effort made by the LV myocardium to raise the LV pressure as required to overcome the afterload. Hence, $(E_a / P)_{\max}$ can represent the LV ability to raise the elastance per unit pressure. The higher its value the more competently is the LV operating. Patients with values of elastance generated per unit pressure, $(E_a / P)_{\max}$, greater than 17.85 l^{-1} almost always had normal ejection fraction (12 of 13). Patients with low $(E_a / P)_{\max}$ and low EF are in the bottom left quadrant, while patients with high $(E_a / P)_{\max}$ and high EF are in top right quadrant. Thus the lower limit of $(E_a / P)_{\max}$ is established to be 17.85 l^{-1} . No doubt, the sensitivity of these parameters cannot be assessed until adequate data has been collected.

For the subjects listed in **Table 7.1**, the correlation between the indices $(E_a / P)_{\max}$ and the traditional contractility index $dP / dt_{\max}$ is plotted in **Figure 7.2**:

$$(E_a / P)_{\max} = 0.025 \times dP / dt_{\max} - 13, \quad r = 0.6731.$$

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Figure 7.1: The relationship between $(E_a / P)_{\max}$ and ejection fraction (EF) for 30 patients. Patients with low $(E_a / P)_{\max}$ and low EF are in the bottom left quadrant, while patients with high $(E_a / P)_{\max}$ and high EF are in top right quadrant. Adopting a value of 0.55 as lower limit of normal for EF, an average cut-off value of $(E_a / P)_{\max} = 17.85 \text{ l}^{-1}$ was obtained from the regression equation $(E_a / P)_{\max} = 39 \times EF - 3.6$.

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Figure 7.2: Relating contractility index $(E_a/P)_{\max}$ to the traditional contractility index $dP/dt_{\max}$, with $r=0.6731$.

In **Figure 7.3**, 15 mmHg was selected as the upper limit of normal for end-diastolic pressure (P_{ed}), because pressures above this value almost always indicate myocardial disease. Corresponding to P_{ed} of 15 mmHg, the average cur-off value of $E_{p,\max}$ is 1.5 mmHg/ml, based on the regression equation $E_{p,\max} = 0.086 \times P_{ed} + 0.18$, as shown in **Figure 7.3**. Patients with values of $E_{p,\max}$ greater than 1.5 mmHg/ml almost had abnormal end-diastolic pressure (11/15).

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Figure 7.3: The relationship between $E_{p,max}$ and P_{ed} for 30 patients. Adopting a value of 15 as upper limit of normal P_{ed} , an average cut-off value of $E_{p,max} = 1.50 \text{ mmHg} / \text{ml}$ is obtained from the regression equation $E_{p,max} = 0.086x P_{ed} + 0.18$.

In **Figure 7.4**, the lower limit of normal $CONT1$ is seen to be 6.39 s^{-1} , corresponding to EF of 0.55 and the regression equation between $CONT1$ and EF. In **Figure 7.5**, the regression equation between $CONT1$ and $(dP / dt)_{max}$ is $CONT1 = 0.0096x dP / dt_{max} - 5.1$, r-value of 0.73 indicates a good correlation between $CONT1$ and $(dP / dt)_{max}$. Then, in **Figure 7.6**, the normal range of $CONT2$ is seen to 0.13. Most patients (9 of 12) with $CONT2$ greater than 0.13 had abnormal ejection fraction (EF). It is noted that the same patients fall in the high $CONT1$ -EF quadrant in

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Figure 7.4 and in the low *CONT2-EF* quadrant in Figure 7.6. Thus, while *CONT2* is as effective as *CONT1*, it is easier to determine and apply clinically.

Figure 7.4: Relationship between *CONT1* (based on shape-factor) and EF. *CONT1* is defined by equation (4.8) in chapter 4. Patients with low *CONT1* and low EF are in the bottom left quadrant, while patients with high *CONT1* and high EF are in top right quadrant. An EF=0.55 yields a cut-off value for *CONT1*=6.39 s⁻¹. With one exception (#18), all patients with *CONT1* greater than 6.39 s⁻¹ have normal EF. However, there are 2 patients (#12 & #25) with varying cardiac diseases who have normal EF despite low value of *CONT1*.

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Figure 7.5: *CONT1* vs. dP/dt_{max} , with r (the correlation coefficient)=0.73.

Figure 7.6: Relationship between *CONT2* based on shape-factor and *EF*. *CONT2* is given by equation (4.11) in chapter 4. An $EF=0.55$ yields a cut-off value for $CONT1=0.13$. Most patients (9 of 12) with *CONT2* greater than 0.13 had abnormal *EF*.

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Figure 7.7: Relationship between *ejected blood-flow acceleration (EBFA)* and EF. *EBFA* is given by equation (5.24) in chapter 5. Patients with low *EBFA* and low EF are in the bottom left quadrant, while patients with high *EBFA* and high EF are in top right quadrant. An EF=0.55 yields a lower limit value for EBFA=14000 ml/s². Patients with *EBFA* greater than 14000ml/s² have normal EF.

As regards *EBFA* (equation 4.8), it is seed from **Figure 7.7** that its lower limit of the normal range is 14000 ml/s². As regards the myocardial sarcomere power index, *MSPI* (equation 6.31), the lower limit of *MSPI* is 69 Nm/s/l, in **Figure 7.8**. In **Figure 7.9**, *MSPI* is shown to correlate with $dP / dt_{\max}$ as: $MSPI = 0.08dP / dt_{\max} - 34$, $r = 0.544$. Then in **Figure 7.10**, the lower limit of the efficiency η is 33.8%.

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Figure 7.8: Relationship between myocardial sarcomere (CE) power (*MSPI*) and EF. *MSPI* is defined by equation (6.31) in chapter 6. Patients with low *MSPI* and low EF are in the bottom left quadrant, while patients with high *MSPI* and high EF are in top right quadrant. An EF=0.55 yields a cut-off value for *MSPI*=69 Nm/s/l.

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Figure 7.9: Relating myocardial sarcomeric power index (*MSPI*) to the traditional contractility index $dP / dt_{\max}$ with $r=0.544$.

Figure 7.10: Relationship between η and EF. The myocardial efficiency (η) is defined by equation (6.30) in chapter 6. Patients with low η and low EF are in the bottom left quadrant, while patients with high η and high EF are in top right quadrant. An $EF=0.55$ yields a cut-off value for $\eta=33.8\%$.

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7.3 Distribution of parameters

Figures 7.11-7.21 display the distribution of parameters, namely, elastance indices per unit pressure, $(E_a / P)_{\max}$, myocardial passive elastance per unit P_{ed} , $(E_{p,\max} / P_{ed})$, shape-based indices *CONT1* & *CONT2*, ejection blood-flow acceleration *EBFA*, myocardial sarcomeric power index *MSPI*, aortic property indices (m_a and R_p).

The distribution of is depicted in **Figure 7.11**, along with the ranges of normal, low and poor contractile effort capacity. Note that the normal range of $(E_a / P)_{\max}$ is greater than

17.85 l-1In **Figure 7.3**, we have established the upper limit of the normal range of $E_{p,\max}$ to be 1.5 mmHg/ml. Based on that, in **Figure 7.12**, $E_{p,\max} / P_{ed} < 60 \text{ l}^{-1}$ for normal myocardium, patients having $E_{p,\max} / P_{ed} > 100 \text{ l}^{-1}$ for stiff myocardium, and patients having $60 \text{ l}^{-1} < E_{p,\max} / P_{ed} < 100 \text{ l}^{-1}$ can be said to have borderline stiff myocardium.

Figure 7.11: Distribution of the index $(E_a / P)_{\max}$

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Figure 7.12: Distribution of the index $E_{p,max} / P_{ed}$.

The distribution of *CONT1* (equation 4.8) is depicted in **Figure 7.13**, along with the ranges of good, low and poor contractility. Note that the distribution of *CONT1* is somewhat Gaussian, with 6.39 s⁻¹ as its mean value. The distribution of *CONT2* index is shown in **Figure 7.14**, where the ranges of good, low and poor contractility based on shape factor are also designated.

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Figure 7.13: Distribution of the index *CONT1* (equation 4.8). The remarks on the plots

Figure 7.14: Distribution of the index *CONT2*.

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The distribution of the index *EBFA* (equation 5.24) is depicted in **Figure 7.15**; therein, the demarcated ranges of *EBFA* are based on Figure 7.7. In **Figure 7.16**, the distribution of *MSPI* has a mean value of 69 Nm/s/l, equal to its lower cut-off value; in other words, most of our patients have poor sarcomeric contractile capacity.

Based on **Figure 7.10**, the distribution of η is shown in **Figure 7.17**, along with the zones of high, low and poor sarcomere contractile efficiency.

Figure 7.15: Distribution of the index *EBFA*.

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Figure 7.16: Distribution of the index $MSPI$.

Figure 7.17: Distribution of the index η .

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No we proceed to aortic property parameters. In **Figure 7.18**, we have depicted the normal range of $m_a=0.45\text{-}1.05\text{mmHg/ml}$; patients having $1.05\text{mmHg/ml}<m_a<1.35\text{mmHg/ml}$ are deemed to be borderline atherosclerotic and patients having $m_a>1.35\text{mmHg/ml}$ to be severely atherosclerosis. Then, in **Figure 7.19**, we have depicted the normal range of peripheral resistance R_p to $0.8\text{-}1.2\text{ mmHg/(ml/s)}$, patients having $1.2\text{ mmHg/(ml/s)}<R_p<1.6\text{ mmHg/(ml/s)}$ are deemed to be borderline arteriosclerosis and patients having $R_p>1.6\text{ mmHg/(ml/s)}$ to be arteriosclerosis.

Figure 7.18: Distribution of the parameter m_a .

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Figure 7.19: Distribution of the parameter R_p .

Figure 7.20: Distribution of the parameter P_p .

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Figure 7.21: Distribution of the parameter P_m

The normal and abnormal ranges of the pulse pressure (P_p) and mean aortic pressure (P_m) are shown in **Figure 7.20** and **7.21**; the upper limits of P_p and P_m are 33 mmHg and 115 mmHg. Patients having $P_p > 33$ mmHg indicate high pulse pressure, which may relate to high aortic stiffness m_a . While patients having >115 mmHg indicate high mean aortic pressure, which may relate to high peripheral resistance R_p .

7.4 Evaluated Indices for all Patients

Patient H.E.L: The results for subject H.E.L are shown in **Figure 7.22**. **Figure 7.22-a** depicts the measured data of cyclic left ventricular pressure and volume. In **Figure 7.22-b**, the model-derived E_a is plotted versus time, starting from isovolumic contraction. In **Figure 7.22-c**, the model derived (volume-dependent) E_p is plotted against the LV

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volume, during diastolic phase. In **Figure 7.22-d**, the model derived E_a is plotted against the corresponding generated pressure $P_a (=P-P_{ed})$. **Figure 7.22-e** displays the stress vs. shortening velocity of the contractile element (CE) during the contraction phase. **Figure 7.22-f** depicts the model-computed aortic pressure and the actual catheterization pressure data with time, along with the corresponding mean pressure (P_m), pulse pressure (P_p).

In the below Table, we have displayed the derived indices: (i) the active and passive elastances ($(E_a / P)_{\max}$ and $E_{p,\max} / P_{ed}$), (ii) the maximum rate-of-change of normalized stress $CONT1 (= (d\sigma^* / dt)_{\max})$, $CONT2$ based on the optimal shape factor line, (iii) normalized maximum power generated by myocardial sarcomere (CE) $MSPI (= Power_{\max} / MV)$ and myocardial efficiency η , (iv) aortic stiffness m_a , peripheral resistance R_p , pulse pressure P_p , mean aortic pressure P_m , and maximal ejection volume acceleration ($EBFA$). Based on these distributions of the indices, for our patient population, the diagnosis and assessment is given in the Table. The remarks are based on the indices distribution plots (Figures 7.11-7.21), wherein the normal ranges are established from the plots (7.11-7.21) of our bioengineering indices vs. traditional indices of EF , H/B and $dP / dt_{\max}$. Wherein, N(normal), BL(borderline), BN (below normal), GC(good contractility), LC(low contractility), PC(poor contractility), GE(good efficiency), LE(low efficiency), PE(poor efficiency). These classifications are based on the ranges depicted in the distribution plots. Hence against each index remark, the corresponding figure # is indicted for reference.

Figures 7.23-7.51 display the results for the other two-nine patients as listed in **Table 7.1**.

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Elastances		Remarks	Shape-based Indices		Remarks	Sarcomeric-based index		Remarks
$(E_a/P)_{max} (l^{-1})$	10.90	PC (7.11)	$CONT1 (s^{-1})$	3.84	PC (7.13)	$MSPI (Nm/s/l)$	40	PC (7.16)
$E_{p,max}/P_{ed} (l^{-1})$	64.44	BL (7.12)	$CONT2$	0.21	PC (7.14)	$\eta (\%)$	34	LE (7.17)
Aortic properties		Remarks	Disease states Clinical parameter		This patient had an inferior myocardial infarction with impaired contractility. Angiography revealed 2-vessel disease.			
$m_a (mmHg/ml)$	1.04	N (7.18)						
$R_p (mmHg.s/ml)$	1.58	BL (7.19)						
$P_p (mmHg)$	23.89	N (7.20)	EF		0.36	L		
$P_m (mmHg)$	104.15	N (7.21)	H/B		0.40	N		
$EBFA (ml/s^2)$	9565.4	PC (7.15)	$dP/dt_{max} (mmHg/s)$		984.4	L		

Figure 7.22: Measured and model-derived result for subject H.E.L. The remarks are based on the indices distribution plots (7.11-7.21), wherein the normal ranges are established from the plots (7.11-7.21) of our bioengineering indices vs. traditional indices of EF, H/B and dP/dt_{max} . N(normal), BL(borderline), BN (below normal), GC(good contractility), LC(low contractility), PC(poor contractility), LE(low efficiency). These classifications are based on the ranges depicted in the distribution plots. Hence against each index remark, the corresponding figure # is indicted for reference.

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Elastances		Remarks	Shape-based Indices		Remarks	Sarcomeric-based index		Remarks
$(E_a/P)_{max} (l^{-1})$	14.38	LC (7.11)	$CONT1 (s^{-1})$	6.49	GC (7.13)	$MSPII (Nm/s/l)$	60	LC (7.16)
$E_{p,max}/P_{ed} (l^{-1})$	21.18	N (7.12)	$CONT2$	0.11	GC (7.14)	$\eta (\%)$	40	GE (7.17)
Aortic properties		Remarks	Disease states Clinical parameter	This patient had atherosclerotic lesions in all 3 major coronary arteries. The LVEF (left ventricular ejection fraction) was indeed normal on ventriculography.				
$m_a (mmHg/ml)$	1.67	Arteri. (7.18)						
$R_p (mmHg.s/ml)$	1.10	N (7.19)						
$P_p (mmHg)$	46.7	H (7.20)						
$P_m (mmHg)$	127.3	H (7.21)						
$EBFA (ml/s^2)$	19216.6	GC (7.15)	$dP/dt_{max} (mmHg/s)$	1399	N			

Figure 7.23: Measured and model-derived result for subject H.B.S.

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Elastances		Remarks	Shape-based Indices		Remarks	Sarcomeric-based index		Remarks
$(E_a/P)_{max} (l^{-1})$	28.53	N (7.11)	$CONT1 (s^{-1})$	13.36	GC (7.13)	$MSP11 (Nm/s/l)$	70	GC (7.16)
$E_{p,max}/P_{ed} (l^{-1})$	68	BL(7.12)	$CONT2$	0.19	LC (7.14)	$\eta (%)$	43	GE (7.17)
Aortic properties		Remarks	Disease states		Clinically patient had mitral stenosis with preserved LVEF.			
$m_a (mmHg/ml)$	0.99	N (7.18)	Clinical parameter					
$R_p (mmHg.s/ml)$	1.45	BL (7.19)						
$P_p (mmHg)$	21.3	N (7.20)	EF		0.56	N		
$P_m (mmHg)$	94.7	N (7.21)	H/B		0.24	N		
$EBFA (ml/s^2)$	13193.1	LC (7.15)	$dP/dt_{max} (mmHg/s)$		1445	N		

Figure 7.24: Measured and model-derived result for subject E.S.

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Elastances		Remarks	Shape-based Indices		Remarks	Sarcomeric-based index		Remarks
$(E_a/P)_{max} (\Gamma^1)$	9.86	PC (7.11)	$CONT1 (s^{-1})$	3.45	PC (7.13)	$MSPII (Nm/s/l)$	60	LC (7.16)
$E_{p,max}/P_{ed} (\Gamma^1)$	75.63	BL (7.12)	$CONT2$	0.09	GC (7.14)	$\eta (\%)$	27	LE (7.17)
Aortic properties			Remarks	Disease states		This patient had previous heart attack with impaired function.		
$m_a (mmHg/ml)$	1.01	N (7.18)	Clinical parameter					
$R_p (mmHg.s/ml)$	1.46	BL (7.19)						
$P_p (mmHg)$	29.78	BL (7.20)	EF		0.40	L		
$P_m (mmHg)$	113.21	BL (7.21)	H/B		0.44	H		
$EBFA (ml/s^2)$	13882	LC (7.15)	$dP/dt_{max} (mmHg/s)$		1175	L		

Figure 7.25: Measured and model-derived results for subject W.K.K.

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Elastances		Remarks	Shape-based Indices		Remarks	Sarcomeric-based index		Remarks
$(E_a/P)_{max} (l^{-1})$	11.78	PC (7.11)	$CONT1 (s^{-1})$	4.18	PC (7.13)	$MSPII (Nm/s/l)$	30	PC (7.16)
$E_{p,max}/P_{ed} (l^{-1})$	138.33	BN (7.12)	$CONT2$	0.08	GC (7.14)	$\eta (\%)$	36	LE (7.17)
Aortic properties		Remarks	Disease states Clinical parameter	Clinically patient had mildly impaired LVEF, with single vessel disease involving left circumflex artery. This was treated with coronary angioplasty.				
$m_a (mmHg/ml)$	1.10	BL (7.18)						
$R_p (mmHg.s/ml)$	1.29	BL (7.19)						
$P_p (mmHg)$	29.5	BL (7.20)	EF	0.51	L			
$P_m (mmHg)$	105.52	BL (7.21)	H/B	0.44	H			
$EBFA (ml/s^2)$	2697.2	PC (7.15)	$dP/dt_{max} (mmHg/s)$	840	L			

Figure 7.26: Measured and model-derived results for subject A.T.

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Elastances		Remarks	Shape-based Indices		Remarks	Sarcomeric-based index		Remarks
$(E_a/P)_{max} (l^{-1})$	26.22	N (7.11)	$CONT1 (s^{-1})$	10.63	GC (7.13)	$MSPI (Nm/s/l)$	40	LC (7.16)
$E_{p,max}/P_{ed} (l^{-1})$	218.46	BN (7.12)	$CONT2$	0.07	GC (7.14)	$\eta (\%)$	42	GE (7.17)
Aortic properties		Remarks	Disease states Clinical parameter	This patient had an inferior myocardial Clinically patient had mitral stenosis and hypertrophied LV with preserved LVEF.				
$m_a (mmHg/ml)$	1.15	BL (7.18)						
$R_p (mmHg.s/ml)$	0.81	N (7.19)						
$P_p (mmHg)$	31.76	BL (7.20)						
$P_m (mmHg)$	108.24	BL (7.21)						
$EBFA (ml/s^2)$	16971.4	GC (7.15)	$dP/dt_{max} (mmHg/s)$	1417	N			

Figure 7.27: Measured and model-derived result for subject V.G.

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Elastances		Remarks	Shape-based Indices		Remarks	Sarcomeric-based index		Remarks
$(E_a/P)_{max} (l^{-1})$	10.89	PC (7.11)	$CONT1 (s^{-1})$	2.81	PC (7.13)	$MSPI (Nm/s/l)$	27	PC (7.16)
$E_{p,max}/P_{ed} (l^{-1})$	86.52	BL (7.12)	$CONT2$	0.3	PC (7.14)	$\eta (\%)$	4	GE (7.17)
Aortic properties		Remarks	<div><div>Disease states</div><div>Clinical parameter</div></div>		Clinically patient had moderately impaired LVEF of 35%, having had previous anterior heart attack in LAD territory. There was new narrowing in LCX artery, which was treated with angioplasty.			
$m_a (mmHg/ml)$	1.43	Arteri.(7.18)						
$R_p (mmHg.s/ml)$	2.45	Ather. (7.19)						
$P_p (mmHg)$	31.76	BL (7.20)	EF		0.35	L		
$P_m (mmHg)$	109.3	BL (7.21)	H/B		0.43	H		
$EBFA (ml/s^2)$	2536.37	PC (7.15)	$dP/dt_{max} (mmHg/s)$		1025	L		

Figure 7.28: Measured and model-derived result for subject S.E.I.

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Elastances		Remarks	Shape-based Indices		Remarks	Sarcomeric-based index		Remarks
$(E_a/P)_{max}$ (l^{-1})	22.46	N (7.11)	$CONT1$ (s^{-1})	6.42	GC (7.13)	$MSPI$ (Nm/s/l)	52	LC (7.16)
$E_{p,max}/P_{ed}$ (l^{-1})	80	BL (7.12)	$CONT2$	0.19	LC (7.14)	η (%)	37	GE (7.17)
Aortic properties		Remarks	Disease states Clinical parameter	Patient's main problem was that of ventricular tachycardia (a type of abnormal heart rhythm.) There was no significant atherosclerosis coronary artery disease. The LVEF was normal.				
m_a (mmHg/ml)	1.42	Arteri. (7.18)						
R_p (mmHg.s/ml)	1.79	Ather. (7.19)						
P_p (mmHg)	29	BL (7.20)						
P_m (mmHg)	110	BL (7.21)	EF	0.60	N			
$EBFA$ (ml/s ²)	17654.1	GC (7.15)	H/B	0.39	N			
			dP/dt_{max} (mmHg/s)	1371	N			

Figure 7.29: Measured and model-derived result for subject O.G.L.

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Elastances		Remarks	Shape-based Indices		Remarks	Sarcomeric-based index		Remarks
$(E_a/P)_{max} (l^{-1})$	6.05	PC (7.11)	$CONT1 (s^{-1})$	1.72	PC (7.13)	$MSPI (Nm/s/l)$	23	PC (7.16)
$E_{p,max}/P_{ed}(l^{-1})$	96.41	BL (7.12)	$CONT2$	0.11	GC (7.14)	$\eta (\%)$	24	PE (7.17)
Aortic properties			Remarks	Disease states		Patient had severely impaired LVEF of 20-25% with TVD. He subsequently underwent a coronary artery bypass surgery (CABG).		
$m_a (mmHg/ml)$	2.71	Arteri. (7.18)	Clinical parameter					
$R_p (mmHg.s/ml)$	2.28	Ather. (7.19)						
$P_p (mmHg)$	41	H (7.20)		EF	0.24			
$P_m (mmHg)$	117.69	H (7.21)	H/B	0.54	H			
$EBFA (ml/s^2)$	3593.26	PC (7.15)	$dP/dt_{max} (mmHg/s)$	897	L			

Figure 7.30: Measured and model-derived result for subject S.K.S.

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Elastances		Remarks	Shape-based Indices		Remarks	Sarcomeric-based index		Remarks
$(E_a/P)_{max}$ (l^{-1})	13.22	LC (7.11)	$CONT1$ (s^{-1})	2.93	PC (7.13)	$MSPI$ (Nm/s/l)	33	PC (7.16)
$E_{p,max}/P_{ed}$ (l^{-1})	135.14	BN (7.12)	$CONT2$	-0.10	PC (7.14)	η (%)	23	PE (7.17)
Aortic properties		Remarks	Disease states Clinical parameter		Patient had mild-to-moderately impaired LVEF of ~40%. He recently had an anterior heart attack.			
m_a (mmHg/ml)	0.98	N (7.18)						
R_p (mmHg.s/ml)	1.55	BL (7.19)						
P_p (mmHg)	34	H (7.20)	EF		0.43	L		
P_m (mmHg)	83	N (7.21)	H/B		0.54	H		
$EBFA$ (ml/s ²)	2002.46	PC (7.15)	dP/dt_{max} (mmHg/s)		850	L		

Figure 7.31: Measured and model-derived results for subject S.H.C.

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Elastances		Remarks	Shape-based Indices		Remarks	Sarcomeric-based index		Remarks
$(E_a/P)_{max} (l^{-1})$	12	PC (7.11)	$CONT1 (s^{-1})$	4.63	LC (7.13)	$MSPI (Nm/s/l)$	32	PC (7.16)
$E_{p,max}/P_{ed} (l^{-1})$	238.26	BN (7.12)	$CONT2$	0.18	LC (7.14)	$\eta (\%)$	31	LE (7.17)
Aortic properties		Remarks	Disease states Clinical parameter	Patient had moderately impaired LVEF of 35% with recent infero-posterior MI. Found to have TVD. Likely to have diastolic dysfunction from IHD as well.				
$m_a (mmHg/ml)$	1.20	BL (7.18)						
$R_p (mmHg.s/ml)$	1.92	Ather. (7.19)						
$P_p (mmHg)$	25.2	N (7.20)						
$P_m (mmHg)$	89.8	N (7.21)						
$EBFA (ml/s^2)$	2705.2	PC (7.15)						
			$dP/dt_{max} (mmHg/s)$		850	L		

Figure 7.32: Measured and model-derived result for subject L.K.J.

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Elastances		Remarks	Shape-based Indices		Remarks	Sarcomeric-based index		Remarks
$(E_a/P)_{max}$ (l^{-1})	21.04	(7.11)	CONT1 (s^{-1})	9.21	GC (7.13)	MSPI (Nm/s/l)	45	LC (7.16)
$E_{p,max}/P_{ed}$ (l^{-1})	60	BL (7.12)	CONT2	0.10	GC (7.14)	η (%)	40	GE (7.17)
Aortic properties		Remarks	Disease states Clinical parameter		Clinically patient had mitral stenosis, mitral insufficiency, and hypertrophied LV with preserved LVEF.			
m_a (mmHg/ml)	0.71	N (7.18)						
R_p (mmHg.s/ml)	1.26	BL (7.19)						
P_p (mmHg)	20.46	N (7.20)	EF		0.56	N		
P_m (mmHg)	104.5	N (7.21)	H/B		0.40	H		
EBFA (ml/s ²)	21488.8	GC (7.15)	dP/dt_{max} (mmHg/s)		1300	N		

Figure 7.33: Measured and model-derived result for subject S.S.

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Elastances		Remarks	Shape-based Indices		Remarks	Sarcomeric-based index		Remarks
$(E_a/P)_{max} (l^{-1})$	28.27	N (7.11)	CONT1 (s ⁻¹)	5.67	LC (7.13)	MSPI (Nm/s/l)	45	LC (7.16)
$E_{p,max}/P_{ed} (l^{-1})$	63	BL (7.12)	CONT2	0.02	GC (7.14)	η (%)	40	GE (7.17)
Aortic properties		Remarks	Disease states Clinical parameter	Patient had normal LVEF of 65%. Also had single vessel disease involving LCX artery and hypertrophied LV.				
m_a (mmHg/ml)	1.42	Arteri. (7.18)						
R_p (mmHg.s/ml)	1.63	Ather. (7.19)						
P_p (mmHg)	44	H (7.20)	EF	0.65	N			
P_m (mmHg)	121.03	H (7.21)	H/B	0.44	H			
$EBFA$ (ml/s ²)	11402.7	LC (7.15)	dP/dt_{max} (mmHg/s)	1393	N			

Figure 7.34: Measured and model-derived result for subject B.C.

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Elastances		Remarks	Shape-based Indices		Remarks	Sarcomeric-based index		Remarks
$(E_a/P)_{max} (l^{-1})$	13.25	LC (7.11)	$CONT1 (s^{-1})$	4.81	LC (7.13)	$MSPI (Nm/s/l)$	55	LC (7.16)
$E_{p,max}/P_{ed} (l^{-1})$	87.39	BL (7.12)	$CONT2$	0.27	PC (7.14)	$\eta (\%)$	23	PE (7.17)
Aortic properties		Remarks	Disease states Clinical parameter	Patient had moderately impaired LVEF of 35%, with recent inferolateral MI. He had TVD. PTCA was done to one of his narrowed LCX.				
$m_a (mmHg/ml)$	2.39	Arteri. (7.18)						
$R_p (mmHg.s/ml)$	2.72	Ather. (7.19)						
$P_p (mmHg)$	34.3	H (7.20)						
$P_m (mmHg)$	112.7	BL (7.21)	EF		0.35	L		
$EBFA (ml/s^2)$	11466	LC (7.15)	H/B		0.37	N		
			$dP/dt_{max} (mmHg/s)$		1120	L		

Figure 7.35: Measured and model-derived result for subject W.S.T

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Elastances		Remarks	Shape-based Indices		Remarks	Sarcomeric-based index		Remarks
$(E_a/P)_{max}$ (Γ^1)	13.11	LC (7.11)	$CONT1$ (s^{-1})	5.05	LC (7.13)	$MSPI$ (Nm/s/l)	26	PC (7.16)
$E_{p,max}/P_{ed}$ (Γ^1)	143.33	BN (7.12)	$CONT2$	0.09	GC (7.14)	η (%)	28	LE (7.17)
Aortic properties		Remarks	Disease states Clinical parameter	Patient had stable angina. Coronary angiography revealed minor coronary artery disease, with near-normal LVEF of 5-%.				
m_a (mmHg/ml)	1	N (7.18)						
R_p (mmHg.s/ml)	1.21	BL (7.19)						
P_p (mmHg)	35.35	H (7.20)						
P_m (mmHg)	105.65	BL (7.21)	EF	0.5	L			
$EBFA$ (ml/s ²)	10972.2	PC (7.15)	H/B	0.43	H			
			dP/dt_{max} (mmHg/s)	1200	L			

Figure 7.36: Measured and model-derived result for subject T.T.L.

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Elastances		Remarks	Shape-based Indices		Remarks	Sarcomeric-based index		Remarks
$(E_d/P)_{max} (l^{-1})$	15.06	LC (7.11)	CONT1 (s^{-1})	5.47	LC (7.13)	MSPI (Nm/s/l)	57	LC (7.16)
$E_{p,max}/P_{ed} (l^{-1})$	141.87	BN (7.12)	CONT2	0.06	GC (7.14)	η (%)	33	LE (7.17)
Aortic properties		Remarks	Clinical parameter		Normal coronaries and normal left ventricular EF			
m_a (mmHg/ml)	0.97	N (7.18)						
R_p (mmHg.s/ml)	1.72	Ather. (7.19)						
P_p (mmHg)	25.66	N (7.20)						
P_m (mmHg)	122.34	H (7.21)	EF		0.53	L		
$EBFA$ (ml/s ²)	11604.1	LC (7.15)	H/B		0.42	H		
			dP/dt_{max} (mmHg/s)		1152	L		

Figure 7.37: Measured and model-derived result for subject H.B.O

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Elastances		Remarks	Shape-based Indices		Remarks	Sarcomeric-based index		Remarks
$(E_d/P)_{max}$ (l^{-1})	14.67	LC (7.11)	$CONT1$ (s^{-1})	13.76	GC (7.13)	$MSPI$ (Nm/s/l)	110	GC (7.16)
$E_{p,max}/P_{ed}$ (l^{-1})	26.67	N (7.12)	$CONT2$	0.21	LC (7.14)	η (%)	34	GE (7.17)
Aortic properties		Remarks	Disease states		Patient had normal LVEF of 60%. No significant coronary artery disease.			
m_a (mmHg/ml)	1.19	BL (7.18)	Clinical parameter					
R_p (mmHg.s/ml)	1.44	BL (7.19)						
P_p (mmHg)	46.56	H (7.20)	EF		0.71	N		
P_m (mmHg)	136.44	H (7.21)	H/B		0.29	N		
$EBFA$ (ml/s ²)	22224.9	GC (7.15)	dP/dt_{max} (mmHg/s)		1469.3	N		

Figure 7.38: Measured and model-derived result for subject A.C.H.

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Elastances		Remarks	Shape-based Indices		Remarks	Sarcomeric-based index		Remarks
$(E_d/P)_{max} (l^{-1})$	8.88	PC (7.11)	$CONT1 (s^{-1})$	4.70	LC (7.13)	$MSPI (Nm/s/l)$	40	LC (7.16)
$E_{p,max}/P_{ed} (l^{-1})$	15	N (7.12)	$CONT2$	0.15	LC (7.14)	$\eta (\%)$	49	GE (7.17)
Aortic properties		Remarks	Disease states Clinical parameter	Patient had severely impaired LVEF of 25% with TVD. Recent heart attack. Recommended for CABG treatment.				
$m_a (mmHg/ml)$	1.75	Arteri. (7.18)						
$R_p (mmHg.s/ml)$	1.44	BL (7.19)						
$P_p (mmHg)$	52.6	H (7.20)						
$P_m (mmHg)$	120.40	H (7.21)						
$EBFA (ml/s^2)$	11093	LC (7.15)	$dP/dt_{max} (mmHg/s)$	1000	L			

Figure 7.39 Measured and model-derived result for subject T.B.A.

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Elastances		Remarks	Shape-based Indices		Remarks	Sarcomeric-based index		Remarks
$(E_a/P)_{max} (l^{-1})$	16.35	LC (7.11)	$CONT1 (s^{-1})$	6.58	GC (7.13)	$MSPI (Nm/s/l)$	63	LC (7.16)
$E_{p,max}/P_{ed} (l^{-1})$	105	BN (7.12)	$CONT2$	0.10	GC (7.14)	$\eta (\%)$	46	GE (7.17)
Aortic properties		Remarks	Disease states Clinical parameter	Patient had chronic total occlusion of 1 of the coronary arteries (LAD), causing mildly impaired LVEF of 45%. He was treated with PTCA.				
$m_a (mmHg/ml)$	1.39	Arteri. (7.18)						
$R_p (mmHg.s/ml)$	2.14	Ather. (7.19)						
$P_p (mmHg)$	25.77	N (7.20)						
$P_m (mmHg)$	114.22	BL (7.21)	EF	0.45	L			
$EBFA (ml/s^2)$	11179.5	LC (7.15)	H/B	0.31	N			
			$dP/dt_{max} (mmHg/s)$	1100	L			

Figure 7.40: Measured and model-derived result for subject A.R.A.R.

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Elastances		Remarks	Shape-based Indices		Remarks	Sarcomeric-based index		Remarks
$(E_a/P)_{max} (l^{-1})$	19.04	GC (7.11)	CONT1 (s ⁻¹)	5.81	LC (7.13)	MSPI (Nm/s/l)	93	GC (7.16)
$E_{p,max}/P_{ed} (l^{-1})$	179.29	BN (7.12)	CONT2	0.16	LC (7.14)	η (%)	28	LE (7.17)
Aortic properties		Remarks	Disease states Clinical parameter	Patient had double vessel disease causing stable angina. Both arteries causing narrowing were treated with stenting.				
m_a (mmHg/ml)	1	N (7.18)						
R_p (mmHg.s/ml)	1.19	N (7.19)						
P_p (mmHg)	28.58	BL (7.20)	EF	0.52	L			
P_m (mmHg)	83.42	N (7.21)	H/B	0.34	N			
EBFA (ml/s ²)	5727.2	PC (7.15)	dP/dt_{max} (mmHg/s)	1015	L			

Figure 7.41 : Measured and model-derived result for subject A.B.K.T

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Elastances		Remarks	Shape-based Indices		Remarks	Sarcomeric-based index		Remarks
$(E_a/P)_{max} (l^{-1})$	25.76	GC (7.11)	CONT1 (s ⁻¹)	7.96	GC (7.13)	MSPI (Nm/s/l)	46	LC (7.16)
$E_{p,max}/P_{ed} (l^{-1})$	184.09	BN (7.12)	CONT2	0.21	LC (7.14)	η (%)	46	GE (7.17)
Aortic properties		Remarks	Disease states Clinical parameter		Normal coronaries and left ventricular EF, however, had also hypertrophied LV.			
m_a (mmHg/ml)	0.90	N (7.18)						
R_p (mmHg.s/ml)	1.59	BL (7.19)						
P_p (mmHg)	31.17	BL (7.20)	EF		0.70	N		
P_m (mmHg)	106.84	BL (7.21)	H/B		0.38	N		
EBFA (ml/s ²)	16765.8	GC (7.15)	dP/dt_{max} (mmHg/s)	1250	L			

Figure 7.42: Measured and model-derived result for subject C.J.P.

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Elastances		Remarks	Shape-based Indices		Remarks	Sarcomeric-based index		Remarks
$(E_a/P)_{max} (l^{-1})$	21.06	GC (7.11)	$CONT1 (s^{-1})$	6.90	GC (7.13)	$MSPI (Nm/s/l)$	100	GC (7.16)
$E_{p,max}/P_{ed} (l^{-1})$	34.17	N (7.12)	$CONT2$	0.06	GC (7.14)	$\eta (\%)$	31	LE (7.17)
Aortic properties		Remarks	Disease states Clinical parameter	Patient had normal LVEF of 55 with DVD (RCA and LCX). Both the vessels were treated with PTCA successfully.				
$m_a (mmHg/ml)$	1.03	N (7.18)						
$R_p (mmHg.s/ml)$	1.59	BL (7.19)						
$P_p (mmHg)$	36.38	H (7.20)						
$P_m (mmHg)$	132.62	H (7.21)						
$EBFA (ml/s^2)$	21865.3	GC (7.15)	$dP/dt_{max} (mmHg/s)$	1475	N			

Figure 7.43: Measured and model-derived result for subject D.D.M.

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Elastances		Remarks	Shape-based Indices		Remarks	Sarcomeric-based index		Remarks
$(E_a/P)_{max}$ (l^{-1})	21.90	GC (7.11)	$CONT1$ (s^{-1})	7.28	GC (7.13)	$MSPI$ (Nm/s/l)	110	GC (7.16)
$E_{p,max}/P_{ed}$ (l^{-1})	85	BL (7.12)	$CONT2$	0.05	GC (7.14)	η (%)	26	PE (7.17)
Aortic properties		Remarks	Disease states Clinical parameter	Patient had normal LVEF of 55%. He previously had CABG. One of the bypass grafts had occluded.				
m_a (mmHg/ml)	0.92	N (7.18)						
R_p (mmHg.s/ml)	1.52	BL (7.19)						
P_p (mmHg)	38.59	H (7.20)						
P_m (mmHg)	101.42	N (7.21)						
$EBFA$ (ml/s ²)	9401.5	PC (7.15)	dP/dt_{max} (mmHg/s)	1234	L			

Figure 7.44: Measured and model-derived result for subject T.P.S.

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Elastances		Remarks	Shape-based Indices		Remarks	Sarcomeric-based index		Remarks
$(E_a/P)_{max}$ (l^{-1})	19.36	GC (7.11)	$CONT1$ (s^{-1})	10.96	GC (7.13)	$MSPI$ (Nm/s/l)	170	GC (7.16)
$E_{p,max}/P_{ed}$ (l^{-1})	28.46	N (7.12)	$CONT2$	0.01	GC (7.14)	η (%)	27	LE (7.17)
Aortic properties		Remarks	<div><div>Disease states</div><div>Clinical parameter</div></div>		Patient had normal LVEF of 55-60%. His RCA was 100% occluded. This was successfully treated with PTCA after 3 attempts.			
m_a (mmHg/ml)	1.08	BL (7.18)						
R_p (mmHg.s/ml)	0.97	N (7.19)						
P_p (mmHg)	39.16	H (7.20)	EF		0.64	N		
P_m (mmHg)	117.84	H (7.21)	H/B		0.30	N		
$EBFA$ (ml/s ²)	19741	GC (7.15)	dP/dt_{max} (mmHg/s)		1241	L		

Figure 7.45: Measured and model-derived result for subject C.C.Y.

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Elastances		Remarks	Shape-based Indices		Remarks	Sarcomeric-based index		Remarks
$(E_a/P)_{max} (l^{-1})$	19.21	GC (7.11)	CONT1 (s ⁻¹)	5.85	LC (7.13)	MSPI (Nm/s/l)	110	GC (7.16)
$E_{p,max}/P_{ed} (l^{-1})$	43.85	N (7.12)	CONT2	0.08	GC (7.14)	η (%)	25	PE (7.17)
Aortic properties		Remarks	Disease states Clinical parameter	Patient had normal LVEF of 55% with very minor coronary artery disease. Was continued on medical therapy.				
m_a (mmHg/ml)	1.67	Arteri. (7.18)						
R_p (mmHg.s/ml)	1.44	BL (7.19)						
P_p (mmHg)	50.93	H (7.20)						
P_m (mmHg)	127.07	H (7.21)						
$EBFA$ (ml/s ²)	15165	GC (7.15)	dP/dt_{max} (mmHg/s)	1380	N			

Figure 7.46: Measured and model-derived result for subject L.C.P.

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Elastances		Remarks	Shape-based Indices		Remarks	Sarcomeric-based index		Remarks
$(E_a/P)_{max}$ (l^{-1})	34.73	GC (7.11)	CONT1 (s^{-1})	7.79	GC (7.13)	MSPI (Nm/s/l)	100	GC (7.16)
$E_{p,max}/P_{ed}$ (l^{-1})	39.44	N (7.12)	CONT2	0.03	GC (7.14)	η (%)	24	PE (7.17)
Aortic properties		Remarks	Disease states		Normal coronaries and left ventricular EF			
m_a (mmHg/ml)	0.64	N (7.18)	Clinical parameter					
R_p (mmHg.s/ml)	1.20	BL (7.19)						
P_p (mmHg)	22.53	N (7.20)	EF		0.69	N		
P_m (mmHg)	87.47	N (7.21)	H/B		0.33	N		
EBFA (ml/s ²)	17296.5	GC (7.15)	dP/dt_{max} (mmHg/s)		1400	N		

Figure 7.47: Measured and model-derived result for subject S.T.S.

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Elastances		Remarks	Shape-based Indices		Remarks	Sarcomeric-based index		Remarks
$(E_a/P)_{max}$ (l^{-1})	11.71	PC (7.11)	$CONT1$ (s^{-1})	5.23	LC (7.13)	$MSPI$ (Nm/s/l)	6	PC (7.16)
$E_{p,max}/P_{ed}$ (l^{-1})	100	BL (7.12)	$CONT2$	0.16	LC (7.14)	η (%)	24	PE (7.17)
Aortic properties			Remarks	Disease states		Clinically patient had mitral stenosis and mitral insufficiency with mild impaired LVEF		
m_a (mmHg/ml)	0.33	N (7.18)	Clinical parameter					
R_p (mmHg.s/ml)	0.93	N (7.19)						
P_p (mmHg)	18.38	N (7.20)	EF		0.41	L		
P_m (mmHg)	96.62	N (7.21)	H/B		0.38	N		
$EBFA$ (ml/s ²)	12689.1	LC (7.15)	dP/dt_{max} (mmHg/s)		1167	L		

Figure 7.48: Measured and model-derived result for subject J.C.

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Elastances		Remarks	Shape-based Indices		Remarks	Sarcomeric-based index		Remarks
$(E_a/P)_{max} (l^{-1})$	6.26	PC (7.11)	$CONT1 (s^{-1})$	7.95	GC (7.13)	$MSPI (Nm/s/l)$	60	LC (7.16)
$E_{p,max}/P_{ed} (l^{-1})$	100	BL (7.12)	$CONT2$	0.23	PC (7.14)	$\eta (\%)$	28	LE (7.17)
Aortic properties		Remarks	Disease states		Clinically patient had aortic stenosis, enlarged chamber, and with severe impaired LVEF			
$m_a (mmHg/ml)$	1.13	BL (7.18)	Clinical parameter					
$R_p (mmHg.s/ml)$	1.27	BL (7.19)						
$P_p (mmHg)$	43.65	H (7.20)						
$P_m (mmHg)$	116.35	H (7.21)	H/B		0.25	N		
$EBFA (ml/s^2)$	13550.6	LC (7.15)	$dP/dt_{max} (mmHg/s)$		1135	L		

Figure 7.49: Measured and model-derived result for subject P.B.

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Elastances		Remarks	Shape-based Indices		Remarks	Sarcomeric-based index		Remarks
$(E_a/P)_{max} (l^{-1})$	5.23	PC (7.11)	$CONT1 (s^{-1})$	5.50	LC (7.13)	$MSPI (Nm/s/l)$	22	PC (7.16)
$E_{p,max}/P_{ed} (l^{-1})$	170	BN (7.12)	$CONT2$	0.82	PC (7.14)	$\eta (\%)$	30	LE (7.17)
Aortic properties			Remarks	Disease states		Clinically patient had idiopathic heart disease with severe impaired LVEF		
$m_a (mmHg/ml)$	0.63	N (7.18)	Clinical parameter					
$R_p (mmHg.s/ml)$	1	N (7.19)						
$P_p (mmHg)$	25.06	N (7.20)	EF		0.30	L		
$P_m (mmHg)$	89.94	N (7.21)	H/B		0.18	N		
$EBFA (ml/s^2)$	13118.2	LC (7.15)	$dP/dt_{max} (mmHg/s)$		1135	L		

Figure 7.50: Measured and model-derived result for subject M.L.

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Elastances		Remarks	Shape-based Indices		Remarks	Sarcomeric-based index		Remarks
$(E_a/P)_{max} (l^{-1})$	4.15	PC (7.11)	$CONT1 (s^{-1})$	2.87	PC (7.13)	$MSPI (Nm/s/l)$	81	LC (7.16)
$E_{p,max}/P_{ed} (l^{-1})$	83.33	BL (7.12)	$CONT2$	0.37	PC (7.14)	$\eta (\%)$	29	LE (7.17)
Aortic properties			Remarks		<div><div>Disease states</div><div>Clinical parameter</div></div>		Clinically patient had mitral stenosis with severe impaired LVEF, treated with percutaneous mitral valvuloplasty.	
$m_a (mmHg/ml)$	0.46	N (7.18)						
$R_p (mmHg.s/ml)$	0.86	N (7.19)						
$P_p (mmHg)$	34.88	H (7.20)	EF		0.29	L		
$P_m (mmHg)$	105.12	BL (7.21)	H/B		0.31	N		
$EBFA (ml/s^2)$	10574.9	PC (7.15)	$dP/dt_{max} (mmHg/s)$		1000	L		

Figure 7.51: Measured and model-derived result for subject V.B.

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7.5 Tabulation of Indices for all Patients

Table 7.2 summarizes the ranges of the contractility indices: $(E_a/P)_{\max}$,
 $CONT1=(d\sigma^*/dt)_{\max}$, $CONT2=(s_{se}-s_{se}^{op})/s_{se}^{op}$, $EBFA=(d^2V/dt^2)_{\max}$,
 $MSPI=Power_{\max}/MV$.

Table 7.2: Ranges for contractility indices based on those distributions plots,
 $CONT1=(d\sigma^*/dt)_{\max}$, $CONT2=(s_{se}-s_{se}^{op})/s_{se}^{op}$, $EBFA=(d^2V/dt^2)_{\max}$,
 $MSPI=Power_{\max}/MV$.

	$(E_a/P)_{\max}$ (I^{-1})	$CONT1$ (s^{-1})	$CONT2$	$EBFA$ (ml/s^2)	$MSPI$ (Nm/s)/l
Good contractility	>17.85	>6.39	<0.13	>14000	>70
Low contractility	12.5-17.85	4.40-6.39	0.13-0.21	11000-14000	40-70
Poor contractility	<12.5	<4.40	>0.21	<11000	<40
Reference figure #	7.11	7.13	7.14	7.15	7.16

Table 7.3 lists the results of all indices and parameters evaluated for each patient, namely, maximum active elastance per unit pressure generated ($(E_a/P)_{\max}$), passive elastance per unit P_{ed} ($E_{p,\max}/P_{ed}$); shape factor indices $CONT1$ & $CONT2$; myocardial sarcomeric power index $MSPI$ and myocardial efficiency η ; aortic stiffness parameter (m_a), peripheral resistance parameter (R_p) and ejection blood-flow acceleration ($EBFA$). Based on these indices, the model-based diagnosis and assessment is given.

Table 7.3 Biomechanical engineering (BME) parameters for 30 patients

Subject	Elastances		Shape-based indices		Sarcomere-based indices		Aortic properties			Model-based Diagnosis & Assessment
	$(E_s / P)_{mc}$ (l^{-1})	$E_{s,mc} / P_{ad}$ (l^{-1})	$CONT1$ (s^{-1})	$CONT2$	$MSPI$ (Nm/s)/l	η (%)	R_p (mmHg /(ml/s))	m_a (mmHg/ml)	$EBFA$ (ml/s ²)	
1 (H.B.S)	14.38	21.18	6.49	0.11	59.73	39.8	1.07	0.67	19216.6	Normal myocardium, good contractility, arteriosclerosis
2 (E.S)	28.52	68	11.35	0.19	68.84	42.86	1.45	0.99	13193.1	Borderline stiff myocardium, good contractility borderline arteriosclerosis
3 (W.K.K)	9.86	75.63	3.45	-0.09	56.27	27.2	1.47	1.01	13882	Borderline stiff myocardium, poor contractility, borderline arteriosclerosis,
4(A.T)	11.77	138.33	4.18	0.08	27	35.7	1.29	1.10	2697.2	Stiff myocardium, poor contractility, borderline arteriosclerosis and arteriosclerosis
5 (V.G)	26.22	218.46	10.63	0.07	35.28	41.8	1.43	1.15	16971.4	Stiff myocardium, good contractility, borderline arteriosclerosis
6(S.E.I)	10.89	86.52	2.81	0.3	26.91	40	2.45	1.43	2536.37	Borderline stiff myocardium, poor contractility, arteriosclerosis, arteriosclerosis,
7 (O.G.L)	22.46	80	6.42	0.09	51.97	36.7	1.79	1.42	17654.1	Borderline stiff myocardium, good contractility, arteriosclerosis, arteriosclerosis,
8 (S.K.S)	6.05	96.42	1.72	0.11	23.17	24.1	2.28	2.71	3593.3	Borderline stiff myocardium, Poor contractility, arteriosclerosis and arteriosclerosis
9 (S.H.C)	13.22	135.14	2.93	-0.10	33.8	23.3	1.55	0.98	2002.46	Stiff myocardium, poor contractility, borderline arteriosclerosis; physiologic abnormal geometry.
10 (L.K.J)	12	238.26	4.63	0.18	31.51	31	1.78	1.97	2705.21	Stiff myocardium, poor contractility, borderline arteriosclerosis, arteriosclerosis,
11 (S.S)	21.04	60	9.21	0.10	45	40.4	1.26	0.71	21488.8	Borderline stiff myocardium, good contractility, borderline arteriosclerosis

12(B.C)	18.27	63	5.67	0.02	45.15	39.3	1.64	1.43	21402.7	Borderline stiff myocardium, low contractility, arteriosclerosis, atherosclerosis
13 (W.S.T)	13.25	87.39	4.81	0.26	55.36	22.6	2.73	2.39	11466	Borderline stiff myocardium, low contractility, arteriosclerosis, atherosclerosis
14 (T.T.L)	13.11	143.33	5.05	0.09	25.84	28.1	1.21	1.00	10972.2	Stiff myocardium, low contractility, borderline atherosclerosis
15 (H.B.O)	15.06	141.88	5.47	0.06	56.67	33.46	1.72	0.97	11604.1	Stiff myocardium, low contractility, atherosclerosis
16 (A.C.H)	14.67	26.67	11.8	0.21	107.5	34.22	1.44	1.19	22224.9	Normal myocardium, good contractility, borderline arteriosclerosis, borderline atherosclerosis
17 (T.B.A)	8.89	15	4.7	0.15	40.86	49.7	1.44	1.75	11093	Normal myocardium, low contractility, arteriosclerosis, borderline atherosclerosis
18(A.R.A.R)	16.35	105	6.58	0.10	63.4	46.21	2.14	1.39	11179.5	Stiff myocardium, low contractility, arteriosclerosis, atherosclerosis
19(A.B.K.T)	19.04	179.29	5.81	0.16	92.96	27.7	1.19	0.99	5727.16	Stiff myocardium, low contractility
20 (H.E.L)	10.9	64.44	3.84	0.21	43.89	34.17	1.58	1.04	9565.4	Borderline stiff myocardium, poor contractility, borderline atherosclerosis
21 (C.J.P)	25.76	184.09	7.96	0.21	45.87	46.1	1.59	0.90	16765.8	Stiff myocardium, good contractility, borderline atherosclerosis
22 (D.D.M)	21.06	34.17	6.9	0.06	100.58	31.57	1.61	1.03	21865.3	Normal myocardium, good contractility, borderline atherosclerosis
23 (T.P.S)	21.9	85	7.28	0.05	106	25.97	1.52	0.92	9401.5	Borderline stiff myocardium, good contractility, borderline atherosclerosis
24 (C.C.Y)	19.36	28.46	10.96	0.01	173.43	27.44	1.11	1.08	12741	Normal myocardium, good contractility, borderline arteriosclerosis
25 (L.C.P)	19.21	43.85	5.85	0.004	106.99	25	1.44	1.67	15165	Normal myocardium, good contractility, arteriosclerosis, borderline atherosclerosis
26 (S.T.S)	34.73	39.44	7.79	0.025	103.2	23.6	1.20	0.64	17296.45	Normal myocardium, good contractility, borderline atherosclerosis
27 (J.C)	11.71	100	5.23	0.16	6.15	23.9	0.93	0.33	12689.1	Borderline stiff myocardium, low contractility,

28 (P.B)	6.263	100	6.26	0.23	58.6	27.8	1.27	1.13	13550.6	Borderline stiff myocardium, low contractility, borderline arteriosclerosis, borderline atherosclerosis
29 (M.L)	5.23	170	5.5	0.87	22.47	30.28	1.00	0.63	13118.2	Stiff myocardium, poor contractility,
30 (V.B)	4.15	83.33	2.87	0.37	80.9	29.4	0.86	0.46	10574.9	Borderline stiff myocardium, poor contractility,

Myocardial stiffness is based on $E_{p, \max} / P_{ed}$, contractility based on $((E_a / P)_{\max})$, $CONT1$, $CONT2$, $EBFA$ & $MSPI$, arteriosclerosis based on m_a and atherosclerosis based on R_p .

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7.6 Discussion and Conclusion

Cardiologists have been continually looking for better and more pertinent cardiac indices. In this chapter, we have applied our developed indices in earlier chapter into 30 subjects. We have designated the ‘state of health’ of the cardiac muscle and LV contractility on the basis of the matrix values of passive and active elastances ($E_{p,\max} / P_{ed}$ & $(E_a / P)_{\max}$), shape-based indices ($CONT1$ & $CONT2$), normalized power generated by sarcomere (CE) ($MSPI$) and maximal volume acceleration into the aorta ($EBFA$). Our diagnoses have correlated quite closely with the clinical data and indices, of the subjects studied.

CHAPTER 8

CONCLUSIONS AND FUTURE DIRECTIONS

The literature on the cardiovascular system offers a wealth of information on the cardiac functional indices as well as on the properties of the myocardium, based on LV models characterizing cardiac function. Yet, no satisfactory model describing the behavior and the performance of the LV diastolic filling, systolic ejection, aortic pressure has emerged. An acceptable model should hold promise for application in the clinical environment, and therefore be defined by parameters endowed with physiological meaning.

We have addressed this lacuna. Our work has involved biomechanics and biomathematical methods to analyze and determine (i) nonlinear passive and active elastance (Zhong et al., 2003a; 2004b; Ng et al., 2004a), (ii) shape factor based contractility (Zhong et al., 2004a; 2004c), (iii) aortic pressure determination, along with the aortic stiffness and peripheral resistance (Zhong et al., 2003b; 2004g), and (iv) systolic modeling of the left ventricle as a mechatronical excitation-contraction system (Zhong et al., 2004d; 2004e; 2004f).

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8.1 Conclusions

8.1.1 Nonlinear Volume-dependent Passive and Active Elastance

Time-varying elastance (or compliance) has been popularly used to describe the performance of left ventricle. However, different elastance definitions, while consistent in their dimension, have led to widely different results. In our study, we have redefined the elastance as: $dP = d(EV) = d(V/C) = VdE + EdV$, where E includes passive and active elastance. The incremental pressure corresponds to incremental elastance and incremental volume. During the isovolumic contraction phase, the pressure increases just because of increase of active elastance. Furthermore, the decreasing active elastance during the early phase of filling can explain the phenomenon of decreasing LV pressure during early stage of filling.

For active elastance, a simple formula is developed as: $E_a = E_{a0} (1 - e^{-\left(\frac{t}{\tau_c}\right)^{z_c}}) (e^{-\left(\frac{t-d}{\tau_R}\right)^{z_R}})$ as a function of time. When applying it into clinical data, the results showed that our elastance index $(E_a / P)_{\max}$ decreased with poor contracting LV. The passive elastance results represents myocardial property, a stiff myocardium prevents a more complete filling. Hence it can be deemed as resistance-to-filling index.

8.1.2 Left Ventricular Shape-based Contractility Indices

Based on clinical observations, it is concluded that a healthy LV shape factor is more akin to the optimal-ellipsoidal shape factor, but transforms towards a more spherical shape in a poorly contracting LV as well as in LV failure (Zhong et al., 2004i; 2004k). Since the LV wall stress depends on its shape, hence the LV contractile capacity also depends on the LV shape. This is the rationale behind the LV shape-based contractility index.

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The study of LV shape-based contractility indices is important, because of its relevance to cardiac contraction properties. Our new index of *CONT1* ($=dP / dt_{\max}$, maximum normalized wall-stress change-rate) incorporates B/A, V and MV. *CONT1* has a good correlation of $r=0.7300$ with the traditional invasive contractility index $dP / dt_{\max}$ as: $CONT1 = 0.0096 \times dP / dt_{\max} - 5.1$, ($r=0.7300$, $p<0.0001$), while *CONT2* has a fair correlation with $dP / dt_{\max}$: $CONT2 = -0.00033 \times dP / dt_{\max} + 0.54$, ($r=-0.6029$, $p<0.05$).

8.1.3 Noninvasive Determine Aortic Pressure and Pressure Drop Across the Aortic Valve

In this work, we develop an analysis of the pressure variation in the aorta during ventricular diastole and systole noninvasively. The systolic aortic pressure is dependent on the aortic stiffness and peripheral resistance, the diastolic and systolic phase intervals and the flow rate. The corresponding parameters m_a and R_p are indicators of arteriosclerosis and atherosclerosis, respectively.

For the subjects analyzed in this study, the relation between *EBFA* (equation 5.24) and $dP / dt_{\max}$ ($EBFA = 26 \times dP / dt_{\max} - 190000$) has a good correlation of $r=0.8779$. Further, *EBFA* can be determined noninvasively.

We also determined the expression for aortic pressure drop across the aortic valve noninvasively. Together, the aortic pressure and the pressure-drop across the aortic valve can contribute to the determination of LV pressure during the ejection. Since accurate measurement of blood pressure waveform requires catheterization of the aorta, this noninvasive determination of aortic as well as LV blood pressure is thus very useful in cardiology.

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8.1.4 Systolic Modeling of the Left Ventricle as a Mechatronical Excitation-Contraction System

Historically, the performance of the heart has been considered to be determined by four major factors: preload, afterload, heart rate, and the ever-elusive contractility. How to measure contractility has been a problem throughout the past century. Actually, contractility embodies the force-length relation during pre-ejection as well as the force-velocity relation during ejection. Prior investigations have not demonstrated the property of the contractile element based on the P - V data. The present study has provided the dynamics of the LV myocardial-sarcomere, contained with wall of the LV cylindrical model. The stress and displacement of the LV myocardial fiber unit are related to the LV pressure and volume data in terms of the sarcomere elements parameters (k , m , B_v). By fitting the clinical data, we have determined the in vivo characteristics of the LV sarcomere CE, in terms of ' σ_{CE} vs. $\dot{x}_2$ '. Thereafter, the power generated by the sarcomere CE is calculated as: $Power = 4(F_{CE} \times \dot{x}_2)$, and another new index $MSPI$ (normalized power) to characterize contractility is also defined as: $MSPI = Power_{max} / MV$.

8.2 Future Directions

Although there is much work to be done to validate the LV model, it has a bright future in the bioengineering field. A few future directions are outline here.

1. Sensitivity assessment of these indices

We have evaluated our bioengineering indices, namely: maximal active elastance per unit pressure $(E_a / P)_{max}$ passive elastance per unit P_{ed} , $E_{p,max} / P_{ed}$, shape-based indices $CONT1$ and $CONT2$, aortic stiffness (m_a), peripheral resistance (R_p), ejection blood-flow acceleration ($EBFA$), myocardial sarcomeric power index

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(*MSPI*) and efficiency (η), for our select patient population. The sensitivity of these parameters will be assessed when adequate data has been collected.

2. Mechanism of LV twisting and pressure increase during isovolumic contraction

To reproduce the ventricular cavity pressure increase during the isovolumic contraction phase of the cardiac cycle, we need take into the fiber angle and twist effect consideration. We will determine the principal stresses and their orientations for a number of clinical cases. Since the tensile principal stress and its orientation are associated with LV myocardial fiber contractile stress and orientation, it provides a measure of the intrinsic capacity of the LV to contract and raise the pressure. In other words, LVs with different fiber orientations would have different capacities to generate the LV pressure increase and would also twist differently. Perhaps, based on our clinical applications, we could end up employing the amount and rate-of-twist of LV to designate the intrinsic contractile capacity of the LV and its reduction in an impaired LV. This insight can only be obtained by studying a number of patients' LVs with a range of cardiac diseases.

3. Sarcomere model

We have determined the profile of CE “contractile stress vs shortening velocity” (CE-CSSV) for all the patients studied. We considered CE-CSSV as a measure of LV sarcomeric capacity to contract strongly with a high shortening velocity. At this time, since this constitutes pioneering work to determine the in-vivo sarcomere characteristics of a LV, we examined a number of such CSSV profiles, to interpret them and give us insight into how we can employ them to characterize the inherent contractile capacity of the LV. For instance, we computed the cyclic variation of the

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sarcomere contractile $[\sigma_{CE} \times (\text{shortening} - \text{velocity})]$, representing a measure of LV sarcomere power as well as its maximal value, and investigate its relevance as an intrinsic LV performance index.

In the next stage, we also plan to incorporate this sarcomere model into helically wound myocardial fibers, activate the model, and demonstrate LV twisting phenomenon and pressure generation. By simulating this model with the monitored LV pressure and deformation, we can determine the sarcomeric activation parameters and the helical angle. This could give us even more insight into the LV contractile phenomenon and capacity.

4. Pulse shape analysis

We will determine the aortic pressure profiles for our patient group, determine their Fourier components, and compare their amplitudes. It is our expectation that the shape of the aortic pressure profile contains a lot of useful hitherto-unraveled information concerning cardiac-vascular interaction and coupling. In Chinese Medicine and Ayurveda, the physician feels the pressure pulse with three figures, and is able to indicate the malfunction organ disease of the patient. We intend to develop a bioengineering model for this medical practice.

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Appendix A.

Appendix A: Derivation of Equation (3.1)

Figure A-1: Dynamic equilibrium of a myocardial element. Element mass $m_e = \rho dx dy h = (\rho h) dx dy = \rho h A_e = m_s A_e$, $d\sigma = (dP_{el})R/(2h)$, dP_{el} is the incremental elastic-recoil pressure. For dynamic equilibrium of the myocardial element, $A_e(dP_{LV} - dP_{el}) + m_e \ddot{u} = 0$, or $A_e(dP_{LV} - d(2\sigma h/R)) + m_e \ddot{u} = 0$

Dynamic equilibrium of the LV myocardial element gives:

$$m_e \ddot{u} + dP_{el} A_e - dP_{LV} A_e = 0$$

$$\text{or } m_s \ddot{u} + dP_{el} - dP_{LV} = 0 \quad (\text{A-1})$$

where the myocardial element mass, $m_e = m_s A_e$, m_s (the myocardial surface-density or mass per unit surface area) $= \rho h$, ρ is the myocardial density, and u is the radial displacement, dP_{el} and dP_{LV} are the incremental elastic-recoil and left ventricular pressures (as depicted in Figure A-1).

Now since,

$$m_s = \frac{m_e(\text{element mass})}{A_e(\text{element surface area})} = \rho h \quad (\text{A-2})$$

$$\Delta V = 4\pi R^2 \Delta u = \dot{V} \Delta t$$

Appendix A.

$$\therefore \dot{V} = 4\pi R^2 \dot{u}, \text{ and } \ddot{V} = 4\pi R^2 \ddot{u} \quad (\text{A-3})$$

we can write:

$$m_s \ddot{u} = \frac{(\rho h) \ddot{V}}{4\pi R^2} = \left(\frac{\rho}{4\pi R^2}\right) h \ddot{V} = \rho_s h \ddot{V} = M \ddot{V} \quad (\text{A-4})$$

where ρ_s is the surface density, $M = \rho_s h$, and V is the LV volume.

Now, refer to Figure A-1,

$$d(P_{LA} - P_2) = d(P_1 - P_2) = R_e \dot{V} \quad (\text{A-5})$$

and

$$dP_2 = dP_{LV} - \frac{\rho_f v^2}{2} \quad (\text{A-6})$$

where R_e is the resistance to LV filling (through the open mitral-valve), ρ_f is the blood density and v is the blood velocity at site 2.

$$\therefore dP_{LV} = dP_{LA} - R_e \dot{V} + \frac{\rho_f v^2}{2} \quad (\text{A-7})$$

Then, let us define incremental elastic recoil pressure (in response to incremental LV pressure dP_{LV}) as:

$$dP_{el}(\text{elastic recoil pressure}) = d\left(\frac{V}{C}\right) = d(EV) = EdV + VdE \quad (\text{A-8})$$

Hence, from equations (A-1, A-4, A-7 & A-8), we have

$$M \ddot{V} + d(V/C) = dP_{LV} = dP_{LA} - R_e \dot{V} + \frac{\rho_f v^2}{2} \quad (\text{A-9})$$

$$\text{or, } M \ddot{V} + R_e \dot{V} + d(V/C) = dP_{LA} + \frac{\rho_f v^2}{2} \quad (\text{A-10})$$

Introducing the term elastance ($=1/C$), we can put down

$$M \ddot{V} + d(VE) = dP_{LA} - R_e \dot{V} + \frac{\rho_f v^2}{2} = dP_{LV} \quad (\text{A-11})$$

Appendix B.

Appendix B: Patient Medical Histories

15 June 2004

TPS

History:

Mr. TPS has a complicated medical history.

He has background medical history of hypertension, dyslipidemia, and history of kidney stone. He also had family history of premature coronary disease. He previously smoked cigarette, but had since stopped after his coronary bypass surgery.

His coronary artery disease dated back to 1989 when he suffered an inferior myocardial infarction. Following a strongly positive stress test, he was found to have triple-vessel disease, for which he underwent a coronary bypass surgery (CABG) in 1993. He had a LIMA grafted to LAD, and saphenous vein grafts (SVGs) grafted to OM1 and RCA. He remained largely asymptomatic after the CABG till late 2003 when there was recurrence of exertional angina. Nuclear stress test then reviewed a large area of ischemia in anterior territory.

Cardiac catheterization performed on 11 Feb 2004 revealed the followings:

- ❖ Left main coronary artery – minor disease;
- ❖ Left anterior descending artery – total occlusion at ostial LAD. A patent LIMA was grafted to mid LAD, with long 80% stenosis in native LAD distal to the anastomosis.
- ❖ Left circumflex artery – OM1 occluded. SVG to OM1 was occluded. OM2 had 70-80% stenosis.
- ❖ Right coronary artery – dominant vessel. Mid RCA was totally occluded. Hypertrophied right ventricular branch supplied collaterals to distal RCA and distal left circumflex artery. SVG to distal RCA was totally occluded.

Left ventriculography showed normal LVEF of 60%, with 1+ mitral regurgitation. Basal inferior wall was hypokinetic.

Appendix B.

15 June 2004

DDM

History:

Mr. DDM, a 55 year-old Eurasian gentleman, had the history of hypertension for 10 years, dyslipidemia, and was a chronic smoker for more than 30 years. He was admitted to another institution in Oct 2003 for unstable angina. Since discharge, he continued to have daily exertional angina. Physical examination was unremarkable, with a well-controlled blood pressure. ECG showed non-specific ST-T wave changes. (No echocardiography was done).

Cardiac catheterization performed on 6 Feb 2004 showed severe double-vessel disease, with a totally occluded mid left circumflex artery, and 80% stenosis in proximal RCA, and 90% stenosis in distal RCA. The left main coronary artery and left anterior descending artery had no severe narrowing. Left ventriculography showed normal left ventricular systolic ejection, with visually estimated LVEF of 60%. The LVEDP was 18 mmHg.