

THESIS

NEW FRANK-STARLING BASED CONTRACTILITY AND VENTRICULAR STIFFNESS

INDICES: CLINICALLY APPLICABLE ALTERNATIVE TO EMAX

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ABSTRACT

NEW FRANK-STARLING BASED CONTRACTILITY AND VENTRICULAR STIFFNESS INDICES: CLINICALLY APPLICABLE ALTERNATIVE TO EMAX.

Heart disease is the #1 cause of death in the United States with congestive heart failure (CHF) being a leading component. Load induced CHF, i.e. CHF in response to chronic pressure or volume overload, may be classified either as systolic failure or diastolic failure, depending on the failure mode of the pumping chamber. To assess the severity of systolic failure, there exist clinical indices that quantify chamber contractility, namely: ejection fraction, $(dP/dt)_{max}$ (related to the rate of pressure rise in the pumping chamber), and E_{max} (related to the time-dependent elastance property of the ventricle). Unfortunately, these indices are plagued with limitations due to inherent load dependence or difficulty in clinical implementation. Indices to assess severity of diastolic failure are also limited due to load dependence. The goal of this research is to present (1) a new framework that defines a new contractility index, T_{max} , and ventricular compliance ‘ a ’, based on Frank-Starling concepts that can be easily applied to human catheterization data, and (2) discusses preliminary findings in patients at various stages of valve disease.

A lumped parameter model of the pumping ventricle was constructed utilizing the basic principles of the Frank-Starling law. The systemic circulation was modeled as a three element windkessel block for the arterial and venous elements. Based on the Frank-Starling curve, the new contractility index, T_{max} and ventricular compliance ‘ a ’ were defined. Simulations were conducted to validate the load independence of T_{max} and a computed from a novel technique based on measurements corresponding to the iso-volumetric contraction phase. Recovered T_{max}

and ‘ a ’ depicted load independence and deviated only a few % points from their true values. The new technique was implemented to establish the baseline T_{max} and ‘ a ’ in normal human subjects from a retrospective meta-data analysis of published cardiac catheterization data. In addition, T_{max} and ‘ a ’ was quantified in 12 patients with a prognosis of a mix of systolic and diastolic ventricular failure. Statistical analysis showed that T_{max} was significantly different between the normal subjects group and systolic failure group ($p < 0.019$) which implies that a decrease in T_{max} indeed predicts impending systolic dysfunction. Analysis of human data also shows that the ventricular compliance index ‘ a ’ is significantly different between the normal subjects and concentric hypertrophy ($p < 0.001$). This research has presented a novel technique to recover load independent measures of contractility and ventricular compliance from standard cardiac catheterization data.

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LIST OF SYMBOLS

Symbo	meaning of symbol
T_{max}	The maximum active tension that can be achieved by myocardial
a	The quadratic coefficient to determine the curvature of the passive tension
T_{max} prime or indexed T_{max}	The T_{max} normalize with the BSA
a prime or indexed a	The 'a' value normalize with the BSA
SL	sarcomere length
f_{total}	myocardial total force tension
$f_{passive}(SL)$	myocardial passive force tension as the function of SL
$f_{active}(SL)$	myocardial active force tension as the function of SL
$e(t)$	sinuous function as time-varying pulse function
$T1$	systolic period 1
$T2$	systolic period 2
$T3$	systolic period 3
$T4$	diastolic period
R	vessel resistance
C	vessel compliance
L	vessel inductance
Rr	ratio of all the vessel resistance
Cr	ratio of all the vessel compliance
Lr	ratio of all the vessel inductance
IV	initial volume
ST	systolic duration
V_{lv}	left ventricular volume
Q_{mi}	mitral valve flow
Q_{ao}	aortic valve flow
P_{ao}	pressure across the aortic valve
P_{lv}	left ventricular pressure
P_{sas}	systemic aortic sinus pressure
CQ_{ao}	aortic valve area coefficient
CQ_{mi}	mitral valve area coefficient
L_{ao}	aortic valve inductance
L_{mi}	mitral valve inductance
P_{load}	simple load model pressure
CO	cardiac output
HR	heart rate
EDT	end diastolic time
EDV	end diastolic volume

<i>LVEDP</i>	left ventricular end diastolic pressure
<i>EICT</i>	end of isovolumetric contraction time
<i>LVEICP</i>	left ventricular end of isometric contraction pressure
<i>ICT(n)</i>	isovolumetric contraction time(normalize with systolic duration)
<i>EICT</i>	end of isovolumetric contraction volume
<i>d_P</i>	delta_pressure (ΔP)= LVEICP-LVEDP
<i>LVPW</i>	left ventricular posterior wall
<i>BSA</i>	body surface area

code for Table 3	meaning of code
Mi	Mild
Mm	mild to moderate
Mo	Moderate
Ms	moderate to severe
S	Severe
H	concentric hypertrophy
LV	left ventricle
MIS	mitral valve stenosis
AOS	aortic valve stenosis
MIR	mitral valve regurgitation
AOR	aortic valve regurgitation
AOC	aortic valve calcification
MIC	mitral valve calcification

CHAPTER 1 INTRODUCTION

Heart disease is the #1 cause of death worldwide, especially in the low income countries. The percent death rate due to heart disease increased 4% in high-income countries and 42% in low-income countries¹. In the USA, heart disease continues to kill more people than cancer. In 2008 alone, over 600,000 people died of heart disease, accounting for one in four of all human deaths. Untreated heart disease that are not related to coronary artery disease (e.g. heart valve disease) lead to load induced congestive heart failure. Load induced congestive heart failure occurs as a consequence of the overworking of the heart, when the heart can no longer pump enough blood to the systemic circulation. Right now, 7% of those living with heart disease have heart failure.

The main function of the heart is to pump adequate blood that carries oxygen and nutrients to all the parts of the body. The mean volumetric flow rate of the blood through any of the chambers of the heart is referred to as the cardiac output. There are two broad ways that the heart can fail to pump enough cardiac output: (1) due to abnormalities in cardiac contraction - i.e. systolic dysfunction; and (2) abnormalities of myocardial relaxation and heart filling - i.e. diastolic dysfunction. In order for the heart to generate a physiological level of cardiac output, both systolic and diastolic functions of the heart must occur in an efficient manner. The systolic function directly relates to the volume of blood ejected by the ventricle during contraction phase (systole). This broadly depends on afterload, contractility and myocardial mass, with contractility being the major pump characteristic that can impact the systolic function of the heart. Afterload refers to the force that the muscle is working against during contraction. Diastolic function directly relates to the volume of blood that the ventricle can re-fill during relaxation phase (diastole). Diastolic function broadly depends on myocardial relaxation, restoring forces within

the chamber (suction pressure), and passive ventricular filling. During the early diastole, the myofilament relaxation and suction dominate the relationship between pressure and ventricular volume. Late in the diastole, the ventricle fills passively and is often aided by pressure developed in the atrium to push blood through the atrio-ventricular valves into the ventricle.

Clinical evaluation and or diagnosis of heart failure involve quantifying systolic function as well as diastolic function. To quantify the ability of the left ventricle to eject blood, it is important to first quantify the inherent contractility of the myocardial cells. Contractility may be defined as the strength of ventricular contraction (for the purpose of this thesis – always the left ventricle) at a given end diastolic volume². This is an important parameter as it describes the ability of the myocardium to develop force independent of loading conditions³. Evaluation of the heart contractility is therefore critical when diagnosing congestive heart failure and manages the patients with congestive heart failure as it helps determine the timing of intervention. An ideal index of heart contractility for clinical use should be independent of preload, afterload and myocardial mass. In clinical practice, ejection-fraction (EF), circumferential shortening velocity of the chamber, $(dP/dt)_{max}$, etc. are used as the various indices of contractility⁴. However, these indexes are plagued with limitations. For example, $(dP/dt)_{max}$, which is a measure of the maximum rate of pressure rise in the ventricle, appears to depend on preload. EF appears to depend on afterload. Currently, one of most efficient way to estimate heart contractility is the maximum elastance at end systole (E_{max}). E_{max} from time-varying elastance model^{4, 5}. E_{max} corresponds to the slope of line that bounds the end-of-systole point of the P-V diagram of the ventricle over different heart rates (see Figure 1 in reference H. Suga / Journal of Biomechanics 36 (2003) 713–720 for illustration). However, this method to quantify E_{max} is limited with

respect to clinical cardiology because E_{max} as contractility index is based on total pressure and may not detect a decline in contractility function when diastolic pressure increase⁶.

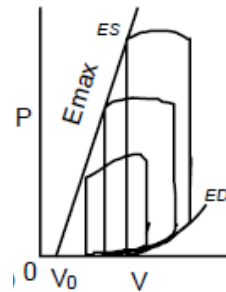


Figure 1: E_{max} (from H. Suga / Journal of Biomechanics 36 (2003) 713–720)

The diastolic dysfunction may be further differentiated as that which occurs during particular phases of diastole: (1) isovolumic relaxation period, and (2) the diastolic filling period. The isovolumic and filling indices of relaxation are influenced by the complex interactions between deactivation rate⁷, myocardial length etc.. This makes it difficult to define one mathematical index to capture the severity. Another approach is to examine the slope, dP/dV , of the pressure-volume (P-V) loop during diastole which quantifies ventricular chamber stiffness which in-turn is directly impacted by myocardial stiffness and ventricular geometry⁸.

As stated above, there exists a weakness with respect to the lack of a solid contractility index as well as an index to define the stiffness of the ventricle particularly from the stand-point of clinical implementation. The most severe drawback is that indices that are considered the best require P-V loop measurements and multiple heart rates which is rarely measured in humans.

Hypothesis and Specific Aims

The overarching hypothesis of this MS Thesis is that a new load independent index of contractility and ventricular stiffness may be engineered without the need for P-V loop

measurement. To test the hypotheses stated, specific aims have been constructed. The specific aims are:

Specific aim I: Develop a lumped parameter model of the left ventricle that can simulate physiological and pathophysiological hemodynamics governed by prescribed length-force dependent curve defined by Frank-Starling law and prescribed load characteristics.

Specific aim II: Define new contractility index T_{max} and ventricular compliance index- a , based on the length-force Frank-Starling curve, and verify load independence on simulated catheterization data.

Specific aim III: Examine T_{max} and a as defined in this thesis in normal human subjects and patients progressing to systolic and diastolic left ventricular failure.

Innovation: This MS thesis, presents a novel approach at two levels. First a zero-dimensional computational model (or lumped parameter model) of the left ventricle is developed by utilizing the Frank-Starling concepts at the individual muscle scale integrated into a physiological pumping chamber. The model proves to satisfy basic physiological properties not represented in the more well established simple time-varying elastance approach^{4, 5}. To our knowledge, only one other group has attempted modeling the ventricle using Frank-Starling model^{9, 10}. Secondly, using the computational model we engineered an analysis technique, that may be easy to implement clinically, to extract the two important indices T_{max} and a only requiring standard hemodynamic pressure waveforms from cardiac catheterization and echocardiography report. T_{max} , mentioned in the books as the maximum active tension, represents the internal contractility

parameter that sets the maximum possible pressure¹¹. During the isovolumetric contraction or iso-volumetric relaxation, the ventricular pressure is only related with the time because the ventricular volume is a constant at these two phases of the cardiac cycle. In these special time points which occur during start of systole or end of systole, T_{max} and 'a' can be recovered based on the pressure changes over the duration of the isovolumetric contraction phase, if the end diastolic ventricular volume (EDV) or end systolic ventricular volume (ESV) is known. From a practical clinical implementation stand-point, the recovery of T_{max} and a is better defined during the iso-volumetric contraction phase because the valve opening time is easier to obtain from the first crossover point between the pressure tracings of the left ventricle (P_{lv}) and aortic pressure (P_{ao}). To the best of our knowledge, the significance of the above approach may be important particularly because the current alternative index E_{max} , is difficult to implement clinically in humans.

Background of circulation system

Whole Cardiovascular System

The cardiovascular system forms a circle, pumping out the blood from heart through artery vessels and returning the blood to heart via veins, to perform ultimate function that maintain living: supplying the nutrient and removing the metabolic end products in all the organs and tissues. Its already have two circles: the pulmonary circulations and systemic circulation. Each one originates from chamber called ventricle and terminates in the chamber named as atrium in the heart. The physiological function of the atrium is to empty the blood to the corresponding ventricle, however, no directly communication existed between the two atriums or two ventricles.²

The pulmonary circulation is a path to pump the blood from right ventricle through lungs and finally to left atrium and systemic circulation works for pumping blood from left ventricle through all the organs except lungs and then to the right atrium. Generally, the blood vessels connecting with ventricle that carry blood away from heart are called arteries, while the blood vessels linking with atriums that carry blood backwards to heart are called veins. Some blood vessels have specific name because their locations and functions. The single large artery attaching with the left ventricle called aorta. The smallest artery named as arterioles, which branches into huge number of the capillaries (the smallest vessel). Like the arterioles, the smallest veins unite by capillaries are termed the venules. All of arterioles, capillaries and venules formed microcirculation among the tissues and organs.²

By the pulmonary circulation, they carry the oxygen from lung air sacs by breath, when the blood flows through lung capillaries. Therefore, the blood has high oxygen content in the pulmonary vein, left heart, and systemic arteries. During the systemic circulation, the blood flow leave left ventricle via aorta, then it goes with artery that branch off the aorta, dividing into progressively small vessels. As the blood go through the capillaries via microcirculation, some of oxygen leaves the blood to enter and be used by cell, causing in the lower oxygen content of venous blood. This venous blood return to the right atrium through two large veins: the inferior vena cava which collects blood from lower half of body and the superior vena cava which collects blood from higher portion of the body.²

In the summary, the blood that being pumped into systemic circulation must first being pumped through lungs. Thus, the blood returning from the body's tissue and organs must be oxygenated again in the pulmonary circulation, when it pumped again to them.²

Basic physics of blood flow in the vessels

In people's daily live, their metabolic rates and blood flow requirements in different organs and systems change with time. Thus, the cardiovascular system must have function to continuously adjust both magnitude of cardiac output and how the blood pumped by heart distributed to different parts of body. The physical factors that determine the rate of blood flow through a vessel is an import key to comprehend how the cardiovascular system operating.¹²

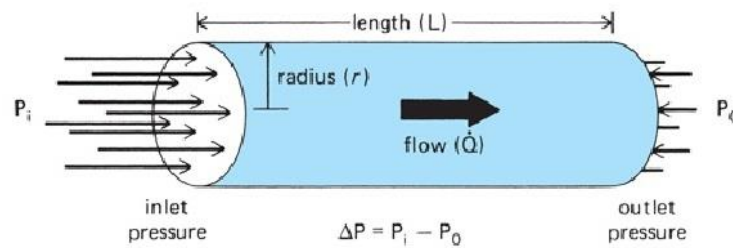


Figure 2: Factors influence fluid flow through a tube¹²

The tube depicted in Figure-2 is simulate how blood flow in a segment of vessel in human's body. The tube has certain radius (r) and certain length (L) and pressure difference exist between the inlet and outlet. This pressure difference provides the driving force for the fluid flow through the tube. The friction developed between the moving fluid and stationary tube wall will resist the fluid movement. To quantify the flow, pressure difference and resistance, the basic flow equation describe as follows:

$$\text{Flow} = \frac{\text{pressure difference}}{\text{resistance}} \quad (1)$$

$$Q = \frac{dP}{R} \quad (2)$$

The Q is the flow rate and has unit as volume/time, dP is the pressure difference and has unit as mmHg, R is the resistance created by friction to slow the flow and has unit as mmHg \times

time/volume. The equation above will tell the fluid rate in the tube is determined by the pressure difference and the tube resistance.¹²

This basic flow equation may be applied both single tube and complex networks of tubes. It tells blood flow could be only changed by two ways: 1 changing the pressure difference, or 2 changing vascular resistance. Normally, the blood flow is measured in L/min, and the blood pressure is measured in mmHg. Resistance of the blood vessel can be calculated from equation derived by French Physician Jean Leonard Marie Poiseuille:

$$R = \frac{8vL}{\pi r^4} \quad (3)$$

Where r represents the inside radius of the tube, L is the tube length and v equals the fluid viscosity. Examining the resistance formula of the blood vessel; a small change in the radius of vessel can greatly impact the vessel resistance and make a great influence in the coming flow.

Blood always flow through the vessel by following the path from a region of higher pressure (such as the arteries supplying the organ) to lower one (such as veins draining the organ). Pressures exert by the heart supply the driving force to move blood in cardiovascular system. Normally, the average pressure in systemic arteries is near 100 mmHg, and the average pressure in systemic veins is near 0 mmHg.¹²

Because the pressure differences exist in all systemic organs, cardiac output is distributed among these organs relying on their individual resistances. From the basis flow equation, organs with low resistance will receive high flow.¹²

Heart

The heart is hollow organ that lies in the center of thoracic cavity attaching to the great vessels to pump the blood to pulmonary circulation and systemic circulation. The fact that arterial pressure is higher than venous pressure by the pumping action of heart creates the drive force to keep blood flow through all organs. The right heart pump obtains the Oxygen and nutrient necessary to move blood through the pulmonary vessels and left heart pump gives the Oxygen and nutrient to move blood through the systemic circulation.²

The amount of blood that pumped by left ventricle in a certain time (normally in one minute) is called cardiac output (CO). The CO depends on the volume of blood eject in each heart beat (Stroke Volume or SV) and numbers of heart beat per minute (Heart rate or HR).²

$$CO = SV \times HR \quad (4)$$

Where the CO has unit volume/minute, SV has unit volume/beat, and HR has unit beats/minutes. By following the cardiac output equation, all influences on cardiac output must act by changing stroke volume or heart rate.

ANATOMY

In anatomy structure, the heart is divided into two parts: the right half and left half, each one consisting of an atrium and a ventricle. The atrium on each side empties blood into the ventricle on that side, and the ventricle pump the blood received from atrium into the systemic circulation (from left ventricle) or pulmonary circulation (from right ventricle). These atrial and ventricular pumping actions occur because the volume of cardiac chamber is changed by individual cardiac muscle's rhythmic and synchronized contraction and relaxation.²

Between the atrium and ventricle in each half, locate atrioventricular valves (AV valve), which only permit blood to flow from atrium to ventricle not in other direction. The left AV valve is called mitral valve, and the right AV valve is called the tricuspid valve. The semilunar valves locate in the opening of left ventricle into the aorta and right ventricle into the pulmonary trunk. The semilunar valves are contained in the left half is called aortic valves and in the right half is called pulmonary valves. These valves allow blood to flow from ventricle into the arteries during ventricular contraction but prevent blood moving back during ventricular relaxation. Both the AV valves and semilunar valves are act in passive manners: The valves' opening and closing states are controlled by the pressure differences across them. When the heart valve is opened, they offer tiny resistance to prevent blood flow across the valve. That means very small blood pressure gradient can generate large amount of blood flow. In some specific valve disease state, a narrowed valve will offer a high resistance to blood flow during the valve opening; this would cause the heart chamber to create an unusual high blood pressure to pump sufficient blood flow across the valve.²

There are no valves locating at the entrances of superior and inferior venae cava into right atrium and of the pulmonary veins into the left atrium. A very little blood is moved back into the veins because the atrial contraction compresses the vein entrances to create an increasing resistance to back flow.²

CARDIAC CELLS

The cells existing in the cardiac muscle are called myocardium, and these myocytes are arranged in layers that are tightly bound together and encircle to create the blood-filling chamber. Similar with the skeletal muscle, myocytes are formed with arrangement with the thick myosin and thin actin filaments. The thick myosin and thin actin filaments arranged in repeating

structure along the myofibril, and one of this structure is termed sarcomere. When the force generated from myocardium shortening, the overlapped myosin and actin in each sarcomere will move to each other. This muscle contraction mechanism is known as sliding-filament mechanism. The length of sarcomere in each myocyte can influence the force generated from myocardium. This is called the Frank-Starling law.²

Cardiac circle

Cardiac circle is an order that contraction and relaxation happened in atrial and ventricle. Mainly, the cardiac circle can be divided by two major phase by the event occur in ventricles: the period of ventricular contraction and blood ejection, systole, and the period of ventricular relaxation and blood filling in ventricles, diastole. In one adult human, the average heart rate is 72 beat per minutes, each cardiac circle lasts 0.8 seconds, with nearly 0.3s in systolic period and 0.5s in diastolic period.²

In the systole and diastole, each one could be subdivided into 2 periods. During the first period of the systole, the ventricle contract without any heart valve opening, the blood can't be eject into arteries, and the ventricular volume is constant. This period is named as isovolumetric ventricular contraction. In this stage, the ventricular pressure increased tremendously because the ventricular walls are developing tension to squeeze the blood they enclose and volume of blood in the ventricle is not change.²

The second period of the systole started when the rising pressure in the ventricles exceeds the pressure in the pulmonary trunk or aorta and the pulmonary or aortic valve begin to open to eject blood into arteries from ventricles. This period is termed ventricular ejection period. During

this period, the volume of blood ejected from ventricles is called the Stroke Volume (SV). This value usually utilize for cardiac output calculation.²

During the first period of the diastole, the ventricle start to relax, the pulmonary and aortic valve close to prevent the blood entering into arteries, and the volume of ventricle still remain constant. The period is termed isovolumetric ventricular relaxation, according to no change in ventricular volume. After isovolumetric relaxation, the AV valves open to fill the ventricles with blood flow from the atria. This second period in the diastole is called ventricular filling. After ventricular filling has taken place, the atria contract to pump more blood into ventricular at the end of diastole. One important point should be notice: The ventricle receives blood not only in atrial contraction but also throughout the all diastole. When the adult person is at rest, and only 20% blood entering into ventricles directly contributed by atrial contraction, the rest of them are filled in the early stage in ventricular filling.²

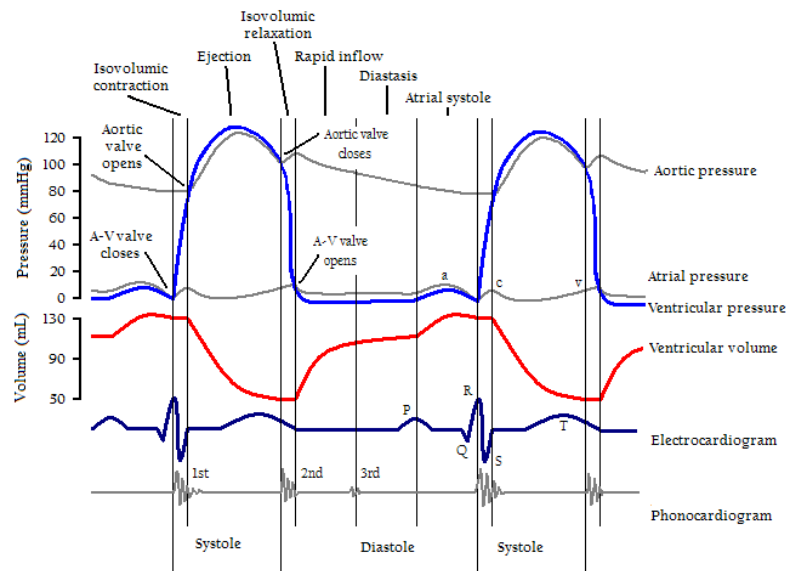


Figure 3: Cardiac cycle in left heart²

The total cardiac circle could be seen in Figure 3. It describes the changes of pressure and volume in ventricles, atria, and aorta at each stage. The blood volume in the ventricle at the end of diastole is named the end-diastolic volume (*EDV*) and the amount of blood remaining after ventricular ejection is called the end-systolic volume (*ESV*). The discrepancy between the *EDV* and *ESV* is the stroke volume that mentioned in previous paragraph.

Heart Failure

Heart Failure is defined as inadequate cardiac function to pump enough blood for body's peripheral requirements in oxygen and nutrients. Underlying this definition, two important concepts should be noticed. First, heart failure can involves in the pumping function of ventricle without the state of myocardium. That means the structure and function of myocardium could be normal in the patient with heart failure. Second, heart failure also relates to the notion of time. The heart failure may occur in patient with severe hypertension or valvular disease, after years the patient suffering the acute heart disease, despite use of drugs to prevent myocardial hypertrophy and cardiac remodeling. In the early stage of heart disease, the heart of patients can compensate perfectly by increase of heart contraction force. In the late stage, the deteriorated cardiac function will result from alteration of the myocytes phenotype and function in myocardial. Finally cardiac remodeling will lead heart overworking and cause the congestive heart failure at the end of stage.¹³

The deteriorated cardiac function can be classified into three catalogs by dysfunction in different cardiac circle: Systolic Dysfunction, the abnormalities in cardiac contraction, Diastolic Dysfunction, the abnormalities in myocardial relaxation and ventricular filling and arrhythmia, the abnormalities in cardiac circle generations.

Four basic properties, determining the stroke volume, are very important in evaluate the systolic dysfunction. They are preload, afterload, contractility and myocardial mass. Preload linked with the Frank-Starling concepts and do not have a universe accepted definition. It have been defined as the sarcomere length stretch at end of diastole or the force that caused by this sarcomere stretch. The definition of afterload is the force that myocardium need to overcome when in shorten in ventricles. If the afterload increases, the ventricles have to contract hard to generate more force to overcome it. Contractility is the ability that myocyte can develop force independent of loading conditions. However, there is no precise way to measure the contractility in cardiac muscle. Some authorities use indices, such as dp/dt , EF , ESV and $ESPVR$, to represent the cardiac contractility. The stroke volume is direct proportional to the preload and contractility and inverse ratio with the afterload. Last, the myocardium mass is very easy to understand; it describe the innate size of muscle in the ventricles that is another important factor to influence the stroke volume.¹³

The Diastolic dysfunction contributes heart failure when they result in abnormally high ventricular pressure in the heart chamber during diastole. The variables in ventricular pressure and volume relation, which determined diastolic dysfunction, can be classified into three categories: factors impact deactivation of the myofilament; factors impact filling of fully relaxed; and restoring force that response for diastolic suction. The results of filling patterns and relation between the ventricular pressure and volume have dynamic interaction with these three factors.¹³

CHAPTER 2 METHODOLOGY

Overview:

To test the overarching hypothesis, the following methodology is adopted. We first develop a computational model of the ventricle that captures the most physiological characteristics compared to existing models (reviewed below in the background section). This computational model consists of a Frank-Starling based ventricle which is connected to a lumped parameter model of the systemic circuit. To be comprehensive, we developed a simple systemic circuit as well as a more complex systemic circuit with increasing physiological aspects of the systemic circuit. Following this, we introduce our novel technique to extract both T_{max} , as well as ventricular stiffness parameter “ a ” based on measurements related to the iso-volumetric contraction phase. The validity of this approach is tested by connecting the pump model to both simple and complex systemic circuits representing “synthetic” cardiac catheterization data. Finally we present methodology for implementation of T_{max} and ‘ a ’ in clinical human catheterization data. See the figure 4.

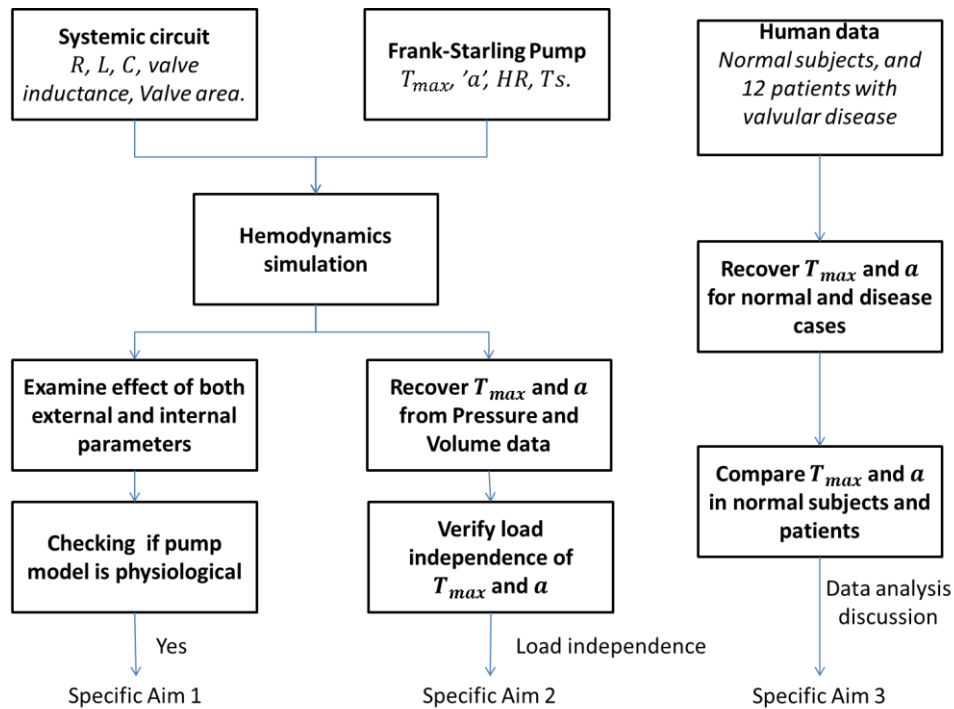


Figure 4: The whole research flow chart

BACKGROUND

Computational models of the ventricle help study physiological properties in normal and disease state. One approach to model the ventricle is the time-varying elastance approach^{14, 15}. This model of ventricular contraction is an analogy of a variable capacitance, termed ventricular elastance⁴. Ventricular elastance E_v is defined as the time varying ratio of instantaneous ventricular pressure and ventricular volume to mimic the heart filling as well as contractile properties. Now, many modelers use this approach to measure the total energy of ventricular contraction⁵, or to numerically construct the whole cardiovascular system^{16, 17}. One important drawback of this approach is that E_v is a fixed parameter, failing to capture the true physiological observation that the heart muscle contraction process is dynamic following a length-force relation and force-velocity relation in the system¹⁰. Also, ventricular pressure is altered with ventricular outflow, named as ejection effect, consisting of pressure deactivation (which means

measured pressure within the ventricle is less than that predicted by the isovolumic pressure model in early ejection) and hyper-activation (which means measured pressure being above the predicted value in later ejection)¹⁸. A correction to fixed E_v approach was proposed by Palladino et al. by adding the ventricular outflow dependent function to the time-varying elastance model to modify the ventricular pressure waveform⁹. The output flow is consequently adjusted to account for the pressure deactivation and hyper-activation effect during the ejecting process.

Another alternative approach is to build the computational ventricle model based on individual myocardial muscle properties and take into account their geometric arrangement¹⁹. Given the muscle fiber arrangement and the geometrical complexity of the whole heart, this approach is cumbersome to implement and relies on accurate finite-element schemes for numerical implementation. While such finite-element modeling techniques perfectly capture the ventricular stiffness, challenges exist with respect to the nonlinear active myocardial arrangement.

In all the above approaches to computationally model the ventricle, key physiological facts such as the existence of a passive and an active tension in the muscle are over simplified. Particularly, active muscle tension which is defined as the component tension developed by the stimulated muscle, and forms the basis of heart contraction.

To test the overarching hypothesis of this thesis, one of the intermediate objectives is to describe the left ventricle based on the single myocardial muscle length-force model. Length-force relationships of cardiac muscles are well characterized. Forces from all the muscles may be collectively related to the pressure developed in the ventricle through the Laplace law. While,

this greatly simplifies the effects of the complex geometry of the left ventricular chamber, it captures the essential dynamic properties. As described below our approach to model the length-force relationship of the muscle directly utilizes the frank starling concept at the individual muscle scale which is later integrated into a physiological pumping chamber that satisfies the basic physiological properties not captured in a simple time-varying elastance approach. The frank starling law builds the required relationship between muscle length and force. The length can be expressed with respect to ventricular volume, while the force can be directly related to ventricular pressure. A physiological time function is introduced based on literature²⁰ to model the smooth transition of the muscle force from a passive state to the active state.

PARAMETRIC MODEL OF THE FRANK-STARLING MECHANISM

The pump model is created based on the frank-starling law to generate blood pressure which in turn drives blood flow through the systemic circuit. As described below in the frank-starling pump model, the waveform of ventricular pressure can be derived from the waveform of end-diastolic volume. The lumped parameter simulation of the systemic circuit then solves for the time variations of pressure and flow in the different blocks namely, the aortic valve, and the various compliance and inductance elements representing the various portions of the systemic circuit (i.e. arteries, arterioles, capillaries, and veins). Cardiac output is calculated as the average blood flow rate, and it is possible to derive the characteristic variation of cardiac output as a function of heart rate. Ventricular power output is computed from the P-V loop integration. The influence of changing heart rate in both cardiac output and power is observed for different initial conditions. To ensure the frank-starling heart model is physiological, the simple lump parameter model is created to observe waveform of the ventricle pressure and aortic flow. The more complex systemic circuit model is utilized to accurately analyze the impact of pressure and flow

with respect to changes in internal (pump) and external (load) parameters in a physiological setting.

THE FRANK-STARLING PUMP MODEL

Frank-Starling law describes the relationship of the strength of contraction to the ventricular filling. To be precise, the strength of ventricular contraction increases in response to an increase in the volume of blood filling the heart (the end diastolic volume). This implies the more the blood return to the ventricle, the more powerful the ventricle would contract.

To develop a mathematical model of the Frank-Starling law, a functional relationship between peak systolic ventricle pressures must be established with respect to end-diastolic volume. Note that the left ventricle volume is related to the sarcomere length (SL) by simply relating the ventricular volume to the perimeter of the chamber cross-section, which in turn relates to SL . At the muscle scale, the muscle tension could be calculated from the length-force relationship as shown in the Fig 5A (derived from Vahl, C. F et al, 1997). As shown in the figure, the force in the muscle may be passive force (during diastole) or active force (during systole). Curves for passive and active forces are shown as a function of SL . The calculate force from this relationship is then translated into left ventricular pressure using the Laplace equation.

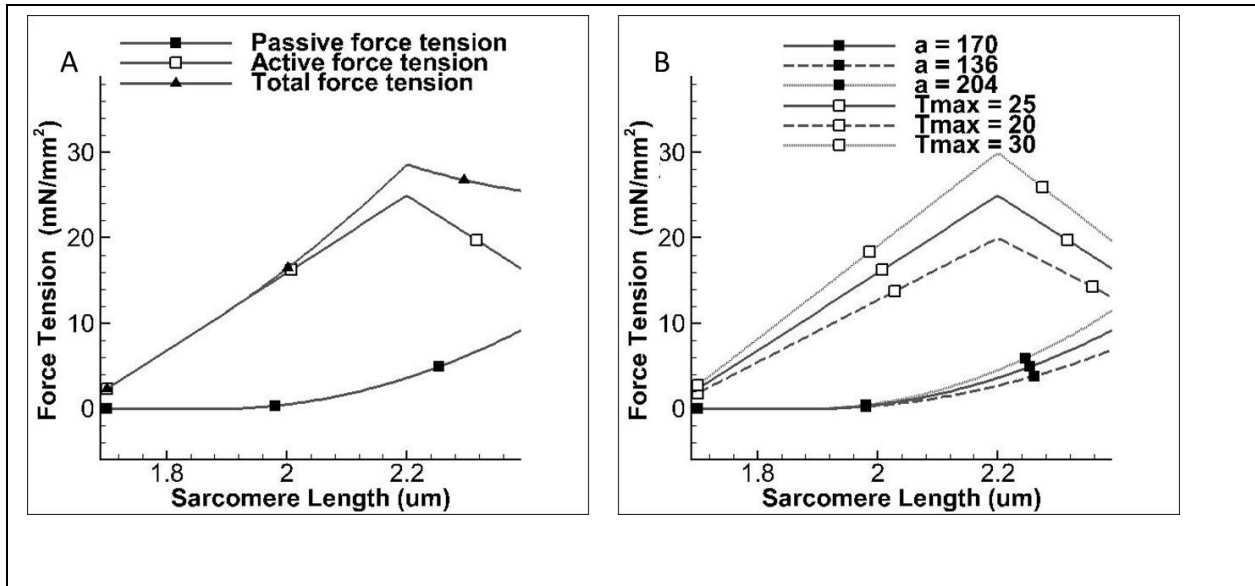


Figure 5: the length-force relationship in myocardial

To calculate SL from ventricular volume an ellipsoidal assumption is made with the strand length of muscle fiber proportional to the radius. Although the average sarcomere length increasing with every stretch, sometimes the change percentage of average SL is smaller than resulting change in muscle fiber length²¹. The normal range of SL in human is from 1.7 µm to 2.3 µm²². To project the length of radius with unit of mm deriving from the end-diastolic volume into sarcomere length with unit of µm a simple conversion formula is created by following experience equations reference in book²³.

$$SL = \frac{\frac{ventricular\ radius}{3.52} + 1.22}{1000} \quad (5)$$

When the sarcomere length (in microns) is calculated from the end-diastolic volume (in ml), the total muscle force tension (combination of active and passive components) is then to obtain from the length-force relationship in Fig-5A. The following equation describes the time dependent total muscle force:

$$f_{total}(t) = f_{passive}(SL) + f_{active}(SL) \times e(t) \quad (6)$$

Where $f_{passive}(SL)$ is passive force tension relationship, $f_{active}(SL)$ is active force tension relationship, and $e(t)$ is the time-varying function to model the contraction as the sum of the active and passive forces in a smooth manner. While $f_{passive}(SL)$ and $f_{active}(SL)$ are two functions only related to sarcomere length, $e(t)$ is simply modeled by the summation of sinuous functions ranging from 0 to 1 during the whole cardiac cycle based on the single muscle fiber model²⁰. Following equation describes $e(t)$:

$$e(t) = \begin{cases} 1 - \cos\left(\pi\left(1 + \frac{T1-T2}{(T3-T1)} + \frac{(t-T1)(T3-T2)}{(T3-T1)T1}\right)\right) & 0 \leq t < T1 \\ 1 - \cos\left(\pi\left(1 + \frac{t-T2}{(T3-T1)}\right)\right) & T1 \leq t < T2 \\ 1 - \cos\left(\pi\left(\frac{t-T3}{T2-T3}\right)\right) & T2 \leq t < T3 \\ 0 & T3 \leq t < T4 \end{cases} \quad (7)$$

The $T1$, $T2$, $T3$ and $T4$ indicate different time period in the cardiac cycle in Figure 6.

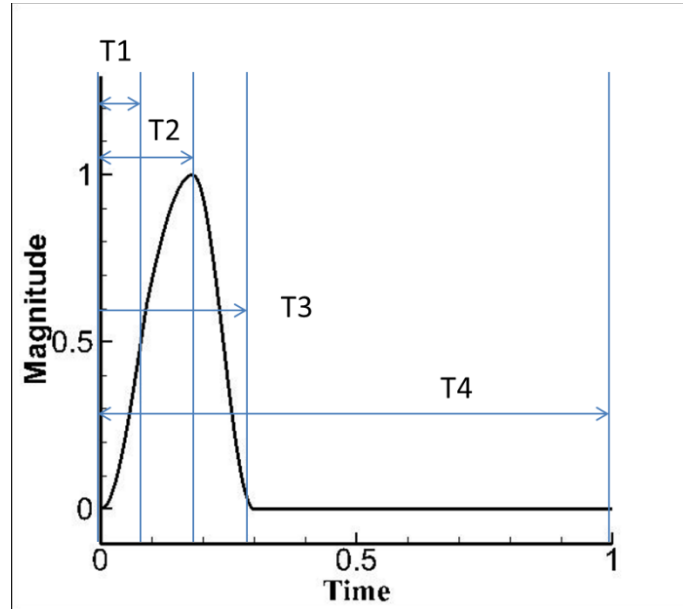


Figure 6: the time function $e(t)$ is simply modeled by the summation of sinuous functions

f_{active} is modeled as two linear lines while $f_{passive}$ is modeled as a parabolic relationship (see Figure 5A). The following equations for f_{active} and $f_{passive}$ are derived from paper²⁴:

$$f_{active} = \begin{cases} 100 \left(\frac{SL}{2.2} - 1 \right) + T_{max} & SL \leq 2.2 \mu m \\ -100 \left(\frac{SL}{2.2} - 1 \right) + T_{max} & SL > 2.2 \mu m \end{cases} \quad (8)$$

$$f_{passive} = \begin{cases} a \left(\frac{SL}{2.2} - 1.87 \right)^2 & SL > 1.87 \mu m \\ 0 & SL \leq 1.87 \mu m \end{cases} \quad (9)$$

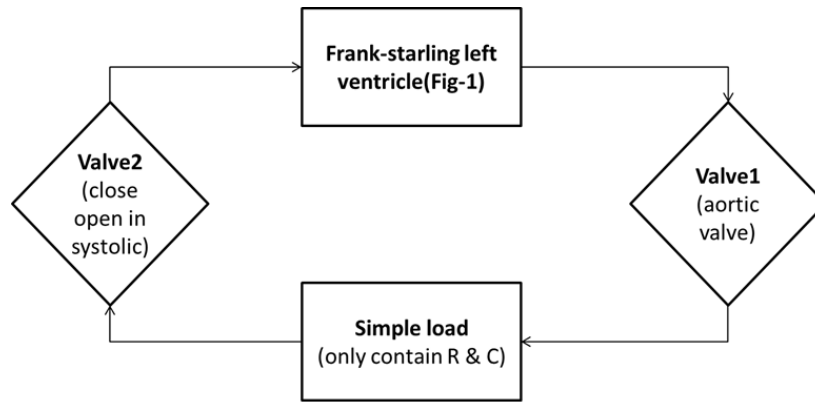
Where, T_{max} is the internal parameter related to the maximum possible active tension that a muscle can generate, and a is the internal pump parameter to determine the passive tension. For the human myocardium, the $T_{max} = 25 \text{ mN/mm}^2$ and ' a ' = $1.7 \times 10^8 \text{ mN/mm}^4$. In the above equations $2.2 \mu m$ corresponds to the critical SL where the active tension is maximum, i.e. equal to T_{max} . The significance of this critical SL is that if the muscle is stretched beyond $2.2 \mu m$ then it progressively loses the strength of active tension. Figure 5B shows the altered frank starling relationships corresponding to altered T_{max} and ' a '. Increasing or decreasing T_{max} corresponds to higher or lower contractility of each muscle and thus is an index that directly regulates the strength of contractility. Increasing or decreasing a corresponds to increasing or decreasing the stiffness (i.e reducing or increasing compliance respectively) of the ventricular chamber. It is hypothesized that evaluations of these pump parameters

THE LUMPED PARAMETER MODEL OF SYSTEMIC CIRCUIT

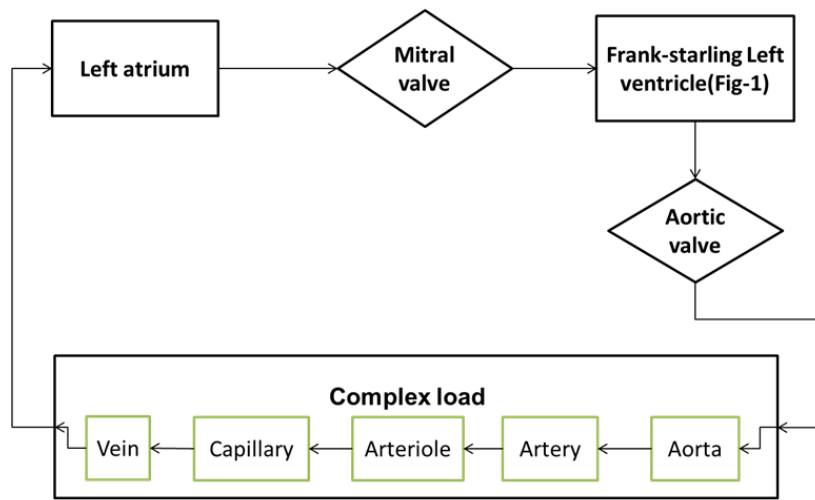
A lumped parameter model is a collection of differential equations that model a system. In this research, the system circuit is modeled as a zero-dimensional circuit; the components of the circuit each have governing differential equations with parameter values that define flow and pressure behavior. Consider the heart as a voltage time dependent voltage source (analogy to

pressure source) that drives “current” (analogy to flow) throughout the systemic circuit. The systemic circuit is like a wire with a sequence of inductors, capacitors, and resistors.

Figure 7 shows two circuits namely the simple model, and the complex model shown connected to the frank-starling based heart model. In the Simple model (Fig 7A), the heart is made up of only the left ventricle connected to the aortic valve followed by an idealized systemic load consisting of one resistance and one capacitance. Such a model is equivalent to a typical laboratory pulse-duplicator system. In the complex model (Fig 7B), the systemic load consists of elements representing the systemic aortic sinus (*sas*), systemic arteries (*sat*), systemic arteriole (*sar*), systemic capillary (*scp*) (and) and systemic vein (*svn*), with each of these elements representing a resistance R , capacitance C and inductance L respectively. Note that for the complex model the heart pump is now two chambered with two valves: i.e. left ventricle, left atrium, aortic valve and mitral valve. While our models bypass the right side of the heart and the pulmonary circuit, the results may be expected to be equivalent given that the return characteristics from the systemic venous to right atrium is nearly identical (in both pressure and flow characteristics) when compared to the pulmonary venous return to the left ventricle. This justifies the bypass of the right side without loss of generality given the specific hypothesis being tested.



A: Simple model



B: Complex model

Figure 7: frank-starling pump with simple and complex circulation system

The systems of governing equations for the both simple and complex circuits are outlined below.

$$\frac{dP_O}{dt} = \frac{Q_o - Q_i}{C} \quad (10)$$

$$\frac{dQ_o}{dt} = \frac{P_i - Q_o R - P_o}{L} \quad (11)$$

Where the P_O and P_i represent the output pressure and input pressure, the Q_O and Q_i represent the output flow and input flow.

The left ventricular volume, V_{lv} changes with time governed by the difference in the mitral flow Q_{mi} and aortic flow Q_{ao} :

$$\frac{dV_{lv}}{dt} = Q_{mi} - Q_{ao} \quad (12)$$

When the left ventricular volume V_{lv} is obtained, the systolic left ventricular pressure P_{lv} can be calculated from the V_{lv} and cardiac cycle time based on frank-starling law.

$$P_{lv} = F_{frank-starling}(V_{lv}, time) \quad (13)$$

The differential of aortic valve flow with time $\frac{dQ_{ao}}{dt}$ is determined based on the difference between the left ventricle pressure and systemic aortic sinus pressure, $P_{lv} - P_{sas}$, resistance of the aortic valve resistance governed by the valve area coefficient CQ_{ao}^2 and inductance of the mass of blood between the ventricle and the aortic sinus, L_{ao} by following equation:

$$\frac{dQ_{ao}}{dt} = \frac{P_{lv} - P_{sas} - \frac{|Q_{ao}|Q_{ao}}{CQ_{ao}^2}}{L_{ao}} \quad (14)$$

In the simple model, the simple valve is used to permit the load flow back to left ventricle in one direction only in diastole. The pressure of the simple load part P_{load} is such that:

$$P_{load} = \begin{cases} P_{lv}, & \text{in diastole} \\ P_{sas}, & \text{in systole} \end{cases} \quad (15)$$

The returning back flow Q_{mi} is calculated using the following equation:

$$Q_{mi} = \frac{P_{sas} - P_{load}}{R_{total}} \quad (16)$$

In the complex model, the mitral valve has very similar governing equation as the aortic valve by simply changing the L_{ao} to L_{mi} , CQ_{ao} to CQ_{mi} , $P_{lv} - P_{sas}$ to $P_{la} - P_{lv}$. (the difference between the left atrial pressure and left ventricular pressure)

The cardiac output is computed by heart rate multiplying with stroke volume.

$$CO = HR \times SV \quad (17)$$

Where, CO is the cardiac output, HR is the heart rate and SV is the stroke volume.

The above equations (10), (11), (12), (13) (14) are coupled to those that govern the circuit, pump and valves. In the complex model, the other parts of model are identical to that described in Ref.¹⁶ and is therefore not described. We also utilized the same parameter values as in Ref¹⁶ which provided excellent physiological waveforms for pressures and flow in complex model. In the simple model, the only difference is that we just ignore the inductance, combine all the resistance in the artery block into single value resistance R_{total} and acquire C_{total} in the similar way. Also, no left atrial and mitral valve exist in the simple model.

Aortic valve modeling

To obtain physiological aortic blood flow, the aortic valve was modeled as a transient process between the open and close states of valve. When the left ventricle pressure is equal or larger than the systemic aortic pressure, the aortic valve starts to open. The valve area coefficient CQ_{ao} increases linearly from the minimum closed area to maximum opening area during the valve opening time T_o . Valve closure begins only after the aortic flow changes sign during which the valve area coefficient transitions back to minimum area over a closing time T_c . Both T_o and

T_c are valve parameters to control the valve opening and closing time respectively. The modeling of mitral valve is the same as described for the aortic valve.

Dynamic tests in both simple model and complex model

The system response with respect to flow and pressure generated by the left ventricle was examined using four tests spanning different initial conditions, external load parameters, internal parameters, total blood volume in the circuit, and systolic fraction. Table 1 lists all the parameters corresponding to each “test”. In the table, T_{max} is the internal parameter that reflects the maximum active force tension. ‘ a ’ is internal parameter that determines the parabolic shape for passive force tension.

Moving to complex model, adjusting the percentage of parameters replaces directly changing the load parameters value because each block of the complex model has its own load parameters. Rr , Lr , Cr are the percentage changing in resistance, inductance and capacitance applying to the complex load parts. In the normal case, the general parameters are set as heart rate of 60bpm and systolic-duration is equal to 0.3s in both simple model and complex model. The internal parameters of frank starling pump are set as max active force tension of 25 mN/mm² and passive force tension parameter $a = 1.7 \times 10^8$ mN/mm⁴²⁴. External parameters in simple model are made up by Resistance $R = 1.5$ mmHg/ml and Compliance $C = 3.0$ ml/mmHg. The value of parameters in the complex model can be seen in Table 2.

Table 1: test in alternation internal and external parameter

	Simple model	Complex model
Test1: change the internal parameters	T_{max} change $\pm 20\%$	
	' α ' change $\pm 20\%$	
Test 2: change the external parameters	R change $\pm 20\%$	Rr change $\pm 20\%$
	C change $\pm 20\%$	Cr change $\pm 20\%$
		Lr change $\pm 20\%$
Test 3: change the initial volume	Initial volume = 0, 60, 120ml	
Test 4: change the systemic time	Systemic fraction = 0.4, 0.3, 0.2s	

Table 2: Parameters for the blood vessel (From Korakianitis et al, 2005)

Branch	Parameter	Value	Unit
Systemic circulation	C_{sas}	0.08	ml/mmHg
	R_{sas}	0.003	mmHgs/ml
	L_{sas}	0.000062	mmHgs ² /ml
	C_{sat}	1.6	ml/mmHg
	R_{sat}	0.05	mmHgs/ml
	L_{sat}	0.017	mmHgs ² /ml
	R_{sar}	0.5	mmHgs/ml
	R_{scp}	0.52	mmHgs/ml
	R_{svn}	0.075	mmHgs/ml
	C_{svn}	20.5	ml/mmHg

DEFINITION OF THE CONTRACTILITY INDEX T_{max} AND VENTRICULAR COMPLIANCE INDEX ‘ a ’

In this section we first describe the new framework or technique to recover the contractility index T_{max} and compliance index a from both simulated as well as real cardiac catheterization data.

Definition of the new indices

■ Contractility (E_{max} vs. T_{max})

T_{max} denotes the maximum active tension in the Frank-Starling length-force curve shown in figure 8A. Together with the passive force tension coefficient ‘ a ’, these two internal force tension parameters form the total force tension which make a determination of the whole ventricular pressure. Notice that to T_{max} may be calculated given hemodynamic data containing the pressure, volume and time information.

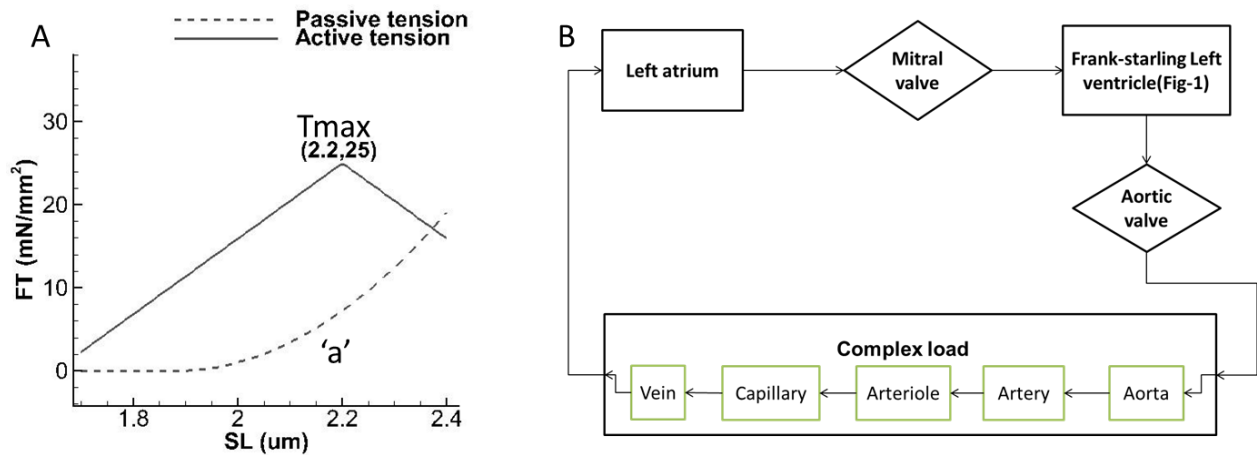


Figure 8: ventricular internal parameters T_{max} and ‘ a ’

E_{max} , developed by Suga et al, represents the maximum value of the ratio between the ventricular pressure and ventricular volume (normally defined as Elastance). It is widely accepted as a cardiac contractility index since E_{max} is major determinant of the left ventricle systolic performance^{25, 26}. This maximum elastance always occurs at end systolic^{4, 5, 25}, where the relation of pressure and volume is usually coincident with the upper left-hand corner of PV loop. Based on this specific position in PV loop, E_{max} can be approximately calculated from the diastolic notch pressure and end-ejection volume or from the full P-V loop measurement.

Comparing with the widely acceptable contractility index E_{max} , T_{max} pays more attention on representing an average measure of cardiac muscle contractility. From the fig 9A and 9B, E_{max} measurements points are illustrated from the end systolic period. Points are shown both on the P-V loop as well as on a simulated cardiac catheterization data. In contrast, T_{max} recovery process is based on the time point within the cardiac cycle when ventricular pressure catches up with aortic pressure (iso-volumetric contraction phase).

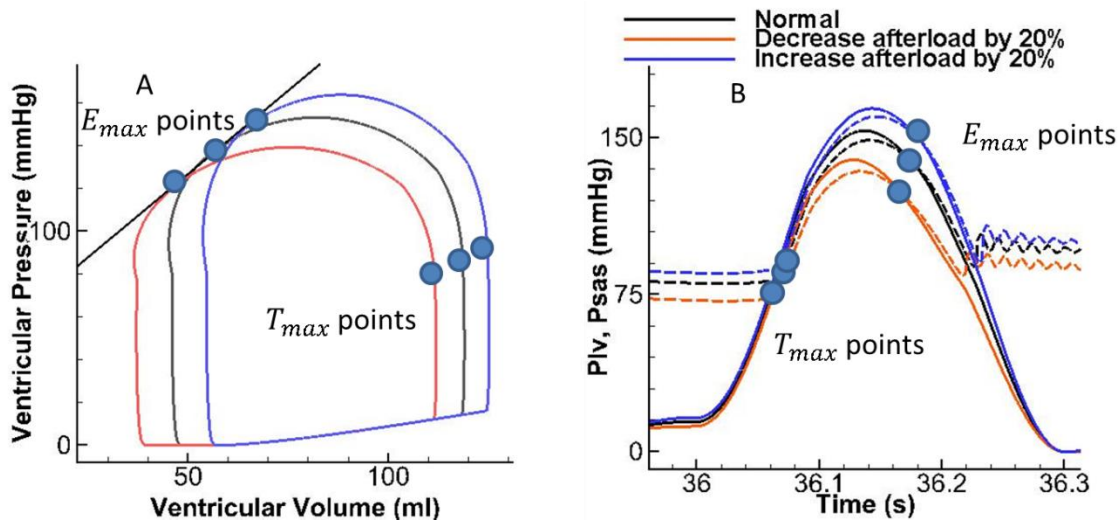


Figure 9: The measurement points in E_{max} and T_{max}

■ Ventricular Compliance

While, T_{max} is the internal pump parameter that characterizes the maximum active tension, ' a ' is the quadratic coefficient to determine the curvature of passive tension in fig 8A. This coefficient reflects the ventricular stiffness or compliance. Increased a means that the cardiac muscle can only stretch to the shorter length for the same preload. Thus a plays a critical role in influencing myocardial relaxation⁸.

For the normal human ventricle, the $T_{max} = 25 \text{ mN/mm}^2$ and ' a ' = $1.7 \times 10^8 \text{ mN/mm}^4$. In some dilated cardiomyopathy case, the T_{max} may decrease to around 18 mN/mm^2 and ' a ' could double the value comparing with the normal case²⁴.

Simulated Catherization Data

Hemodynamics simulated with the coupling of the frank-starling pump described earlier and the lumped parameter model of the systemic circuit (complex model only), provides the simulated catheterization data needed to test the hypothesis. Briefly, left ventricle volume is converted to the sarcomere length (SL) using the ellipsoidal assumption. The corresponding total muscle tension is calculated from the frank-starling length-force relationship and time. Lastly, the Laplace equation is used to compute left ventricular pressure from the total muscle tension force. The pressure calculated is then passed on to the lumped parameter model which then computes the flow based on the series of resistances, capacitances, and inductances in the complex model.

In above described model, we have several parameters including the active force tension, passive force tension, heart rate and systolic duration corresponding to the pump; and resistance, inductance, capacitance, and valve coefficient area corresponding to the systemic circuit (load).

The function of Frank-Starling ventricle is controlled by the internal parameters; the response of the systemic circuit is governed by the external parameters showed in Korakianitis model^{16,17}. A combination with the ventricular model and circuit model forms the simulation results of the hemodynamics as seen in Fig 10. The hemodynamics of the simulation results derived the above framework provides insight into the interaction among these parameters.

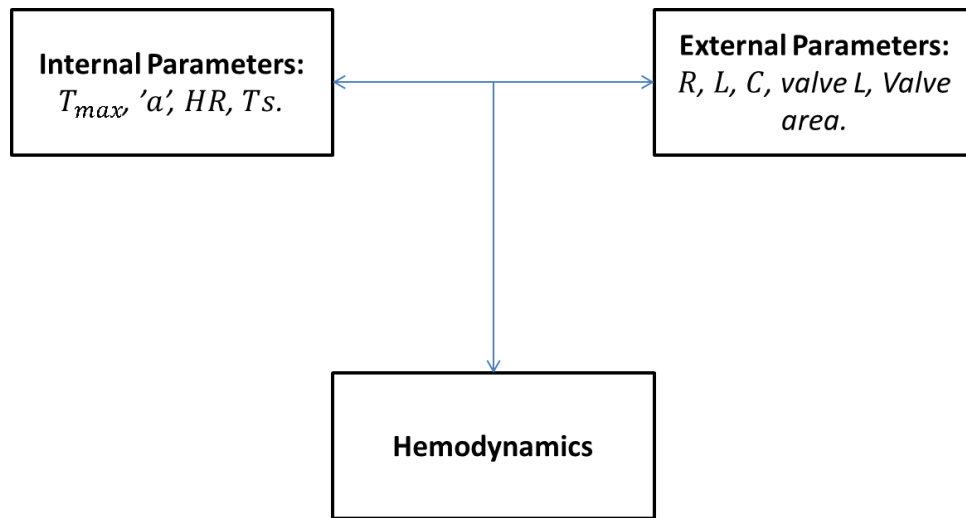


Figure 10: hemodynamics controlled by both internal and external parameters

Recovery of T_{max} and 'a' from catheterization data

The ventricular pressure is directly related to the total force tension which could be computed from ventricular volume and time through the equation (13) (Fig 11A). Thus in order to extract T_{max} and 'a', we need pressure, volume, and time information in the hemodynamics (Fig 11B). These required variables (with the exception of volume) are readily measured from catheterization data (Fig 12A).

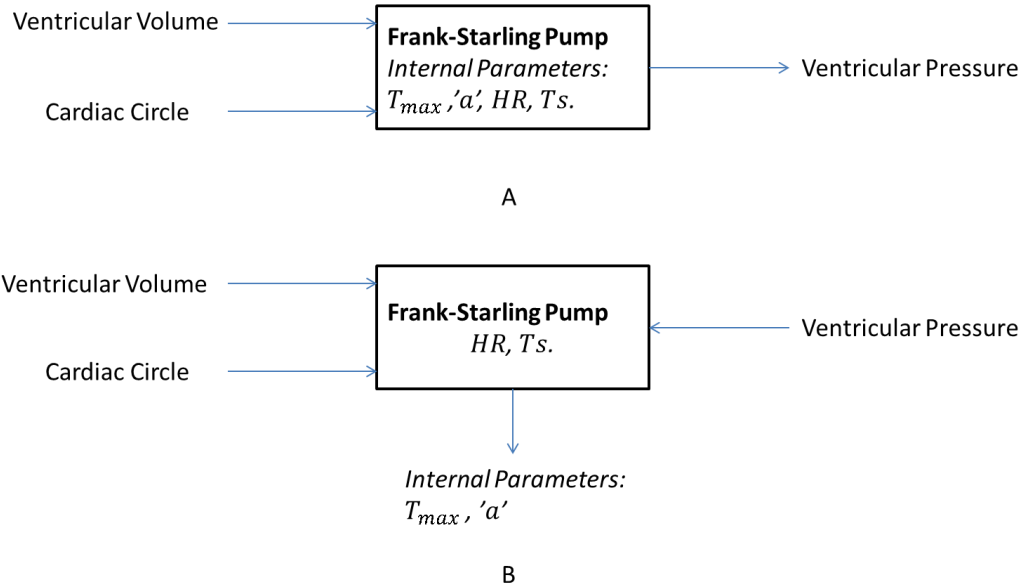


Figure 11: (A) how the Frank-Starling pump model generates the ventricular pressure. (B) the inverse calculation of internal parameters based on hemodynamics.

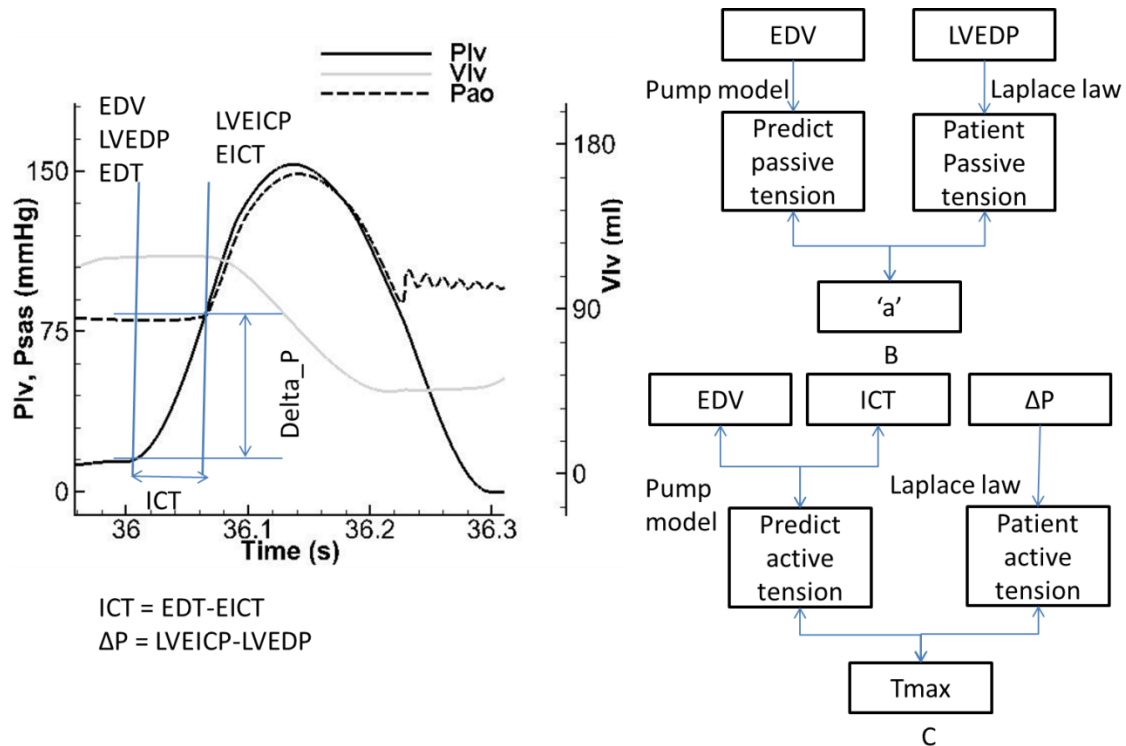


Figure 12: Recover the T_{max} and 'a' from the ventricular pressure, ventricular volume and aortic sinus pressure.

The quadratic coefficient ‘ a ’ only regulates the passive force tension throughout the cardiac cycle. Thus the gradual increase in pressure during filling provides a method to recover ‘ a ’ in a straightforward way.

T_{max} influences the level of developed force tension during myocardial contraction. During cardiac catheterization, the ventricular pressure and aortic sinus pressure are measured through minimally invasive catheterization of the patient. The heart dimensions such as the size and shape are typically evaluated using echocardiogram (ultrasound). Using variables measured in a standard cardiac echo, it is possible to evaluate the left ventricular end diastolic volume (EDV).

The Left Ventricular End Diastolic Volume (EDV) relies on the left ventricular internal diastolic dimension ($LVIDd$) from the echocardiographic equations summarized by Robert Donatiello and Daniel Shindler²⁷:

$$EDV = \frac{7.0}{2.4+LVIDd} \times LVIDd^3 \quad (18)$$

But, echo report only offers average value of several dimensions of heart, and cannot supply enough detail of these dimensions changing when the heart is pumping.

Without the instantaneous left ventricular volume coupling with catheter pressure in patient data, the Recovering process of the internal parameter - ‘ a ’ and T_{max} only can be performed at some special cardiac stage that given the known ventricular volume by echo report. The end diastolic period is a perfect cardiac stage to extract the coefficient ‘ a ’ from the pressure-volume relationship. The end diastolic volume (EDV) in echo report and left ventricular end diastolic pressure ($LVEDP$) measured from catheterization data can be utilized together to

inverse compute the ‘ a ’ by making comparison between the actual passive tension from clinic data and predicted passive tension from Frank-starling pump model like the figure 12B.

Considering the information of the ventricular volume (V_{lv}) extracted from the echo report, isometric contraction and isometric relaxation are two particular time phases when the force transitions between total force and passive force. To recover T_{max} , we use the point when ventricular pressure equals aortic pressure as the event marking the end of the iso-volumetric contraction phase. The pressure jump between end of diastole and the end of iso-volumetric contraction phase together with the duration of time between these two events is utilized to extract T_{max} . In the clinical catheterization data, the ventricular pressure (P_{lv}) at end of isometric contraction is featured by the abrupt change in the sign of rate of change of aortic sinus pressure (P_{ao}) just before positive flow through the aortic valve. When the P_{lv} exceed the P_{ao} , the aortic valve open its leaflets, the blood ejection from the heart begins and V_{lv} begins to decrease. The first cross point of the P_{lv} and P_{ao} is the ending point of the isometric contraction. The pressure difference between the one at cross point pressure and $LVEDP$ in patient data precisely dictates the active force tension. The isovolumetric contraction time (ICT) at cross point together with the systole duration determines a normalized position in the time function $e(t)$ (Equation (7)). With the combination of three hemodynamic variables: EDV and ICT , the predicted active tension relating T_{max} is calculated by the Frank-starling model in equation (6) The patient T_{max} can be obtained by comparing it with patient active tension computed from Laplace law. The whole recovery process is detailed in figure 12C.

The measurement of all above hemodynamical variables could be seen in the Fig 12A. The end diastolic time (EDT) and $LVEDP$ are measured at end diastolic period when left ventricle begins to contract. The corner point before the ventricular pressure tremendous

increasing is what we would like to find. The *ICT* is equal to end isovolumetric contraction time (*EICT*) minus *EDT* and is normalized by systolic duration to eliminate heart rate influence.

Load Independence test

For T_{max} and ‘ a ’ to be viable for clinical application, they must satisfy load independence. In order to estimate the independence T_{max} and ‘ a ’, test 1 is designed to extract T_{max} and ‘ a ’ from the hemodynamic data under different initial volumes and external parameters (load characteristics). The internal parameters in the frank-starling pump are set as $T_{max} = 25\text{mN/mm}^2$, ‘ a ’ = $1.7 \times 10^8\text{mN/mm}^4$ and systolic duration = 0.3s when coupling with different external load parts in Table 3.

Table 3: parameters changes in the independence test

Normal subject	Normal
Change with afterload	$Rr = 80\%$
	$Rr = 120\%$
	$Cr = 80\%$
	$Cr = 120\%$
Change with preload	Initial Volume (IV) =60 ml
	Initial Volume (IV) = 120 ml

EXAMING THE T_{max} AND 'a' IN HUMAN CATHETERIZATION DATA

Lastly, methods to extract contractility and stiffness from human catheterization data are described in this section.

Meta-Data

Before analyzing the patient catheter data, the normal range of the T_{max} and 'a' should be calculated for normal human subjects. In order to set the passive filling parameter 'a', the $LVEDP$ and EDV values are obtained from the 6 normal subjects presented in Rackley et al²⁸. The normal value for T_{max} is based on isovolumetric contraction time (ICT) and diastolic pressure reported in 20 normal subjects provide by Frank et al²⁹. In the recovery process, the baseline value assigned to the $LVEDP = 12\text{mmHg}$ and $EDV = 120\text{ml}$ in a health person.

Clinic Data

12 patient were recruited through Institutional Review Board Approval at both Colorado State University and Poudre Valley Health System ($PVHS$). Echocardiography data along with cardiac catheterization data was analyzed for the 12 patients who had these tests done due to valve disease or history of concentric hypertrophy. Each patient data package included three files: the real time left ventricular catheterization pressure data, the real time aortic sinus catheterization pressure data and the echocardiogram report. Test 2 ran through 12 patients to convert the numerical pressure data into the hemodynamic waveform as a graph and recover both T_{max} and the passive tension coefficient 'a' from these pressure waveforms as described in flow chart shown in Figure 4. The catheterization pressure data were sampled at frequency equaling to 250Hz with the pressure resolution at $\pm 0.02\text{ mmHg}$. The first order derivative of the real time pressure was available to help locate end diastole position.

Before analyzing the calculated internal parameters, 12 patients are classified into three groups by their different valvular diseases^{30, 31}: systolic failure candidate, diastolic failure candidate and normal patient. Determination of the classification of patient data is based on the diagnosis results recording in the echo report. Most of patients corresponded to different types of valvular disease. The combination of valvular diseases brings the difficulty to patient group classification. Identification of candidacy is determined by the severity of valvular disease which can represent the dominance of the systolic dysfunction or diastolic dysfunction. The patient treatment history also serves an important role as the additional reference materials to assist patient data analysis. The severity of the valvular disease could be judged by different treatment. Combining the diagnosis results from echo report and treatment files, the 12 patients are successfully sorted into three catalogs in Table 4.

Table 4 contains human cardiac physiological information such as sex, age, heart rate, body surface area (*BSA*) and the diagnosis summary from the echo reports. From the Table 4, we deduct the patient as the candidate of systolic failure or diastolic failure based on their diagnosis summary and use it to analysis the results in the Table 7.

Table 4: The information and diagnosis results of 12 patients

I.D.	AGE	SEX	BSA	ECHO-DATE	CATHER DATE	Peak Pre candidate	diagnosis results
1	76	F	1.6	8/29/2010	9/1/2010	165 diastolic	mo LV H. s MIS. s AOS.
2	61	F	1.9	6/9/2011	5/26/2011	150 systolic	mi LV H, mi MIR. mm AOR.
3	40	M	2.2	5/31/2011	5/30/2011	120 Normal	mi LV H.
4	57	M	1.9	5/5/2011	6/1/2011	100 Normal	borderline LVH, mi AOC.
5	71	F	1.7	4/6/2011	5/3/2011	120 diastolic	mi MC. mo AOC, ms AOS.
6	82	M	1.8	6/1/2011	10/31/2011	140 diastolic	mi LV H, mo MIC, s AOS. mm AOR.
7	63	M	1.9	5/13/2010	9/7/2010	110 systolic	mi LV H, ms MIG, mi AOC, mo AOR.
8	79	F	1.4	11/18/2010	1/20/2011	200 diastolic	mo LV H, mi MIR, mo AOR, ms AOS.
9	60	F	1.9	9/15/2010	9/15/2010	140 diastolic	mi LV H, ms AOR, an eccentric jet of aortic insufficiency.
10	43	F	1.8	3/24/2011	5/10/2011	90 systolic	ms AOR, mi AOC
11	47	M	1.8	9/30/2010	10/4/2010	90 systolic	s MIS.mo MIR
12	47	M	2	10/6/2010	10/22/2010	120 systolic	mi LV H, ms MIR

CHAPTER 3 RESULTS

Hemodynamic simulation results

Normal Baseline Case

To test computational framework with the novel frank-starling pump coupled to the simple lumped parameter model is used to observe the waveform of pressure and flow in left ventricle in Fig 13A. The simple model was used to examine hemodynamics for a variety parameter combination. Fig 13A depicts the hemodynamics representing physiological level of left ventricular volume, normal aortic flow, left ventricular and aortic pressure waveforms. With the 140mmHg highest magnitude, the impulse of ventricular pressure appears regularly every one second. The aortic pressure follows the ventricle pressure in the systolic period ranging from 75mmHg to 130mmHg. The dynamic physiological features like dicrotic notch are also captured by the model just after the aortic valve closes. The peak magnitude of aortic flow equals to 900ml/s, while the shape of the aortic flow also mimics the conditions in real heart at physiological levels comparing with the aortic flow result in Korakianitis' model.

For the complex model simulation, the loading conditions in normal case are similar to that in the simple model. Waveforms of left ventricle and aortic flow are displayed in Fig 13B show no difference comparing with the simple model in Fig 13A. The rate of left ventricle volume filling during diastolic time has “fast-slow-fast” feature owing to the addition of the left atrium and mitral valve in the complex model. The oscillation behind the dicrotic notch also could be observed because the vessel inductance added now plays a dynamic role in complex model.

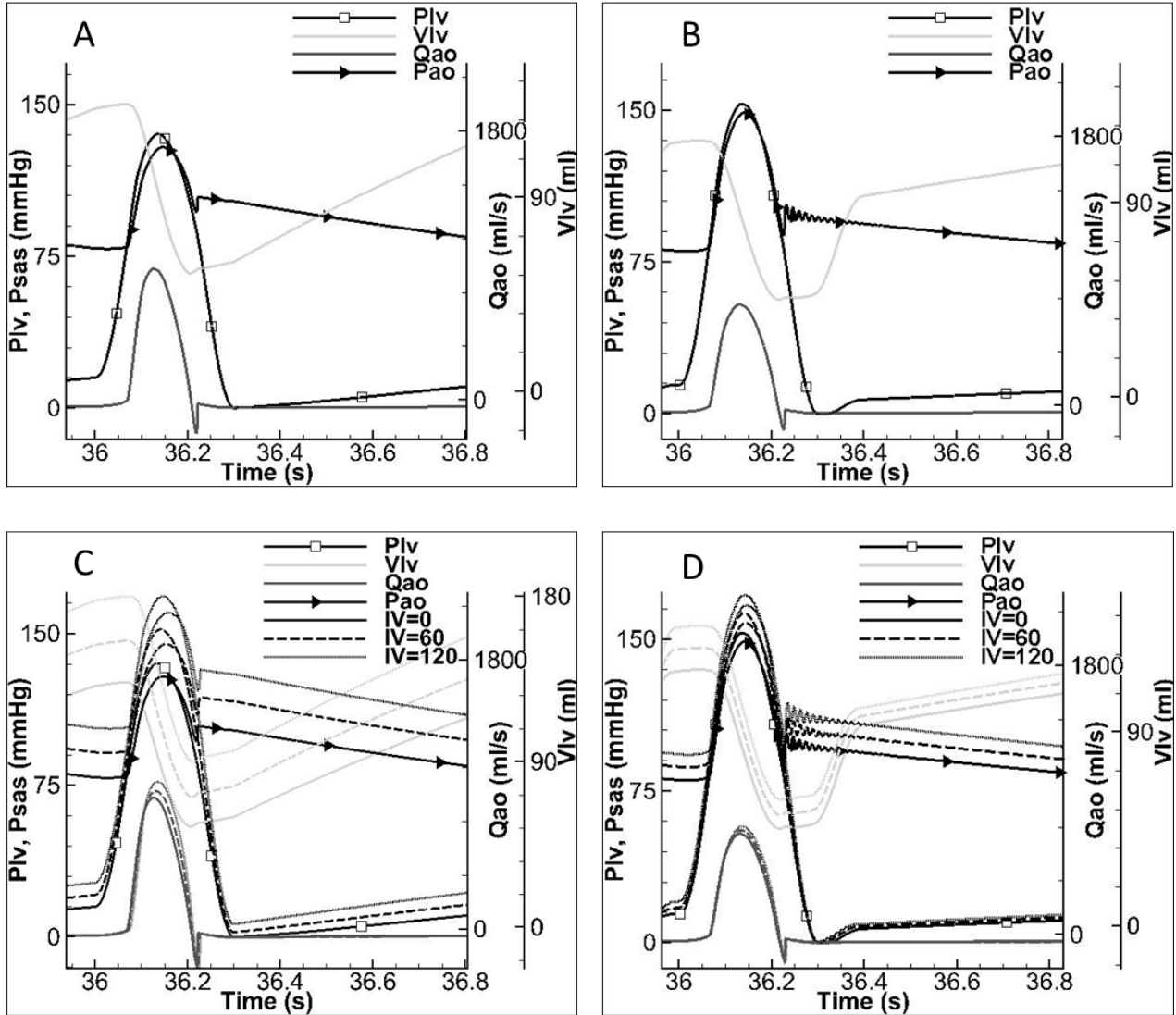


Figure 13: baseline case hemodynamic waveform and preload influence in hemodynamics.

(A) baseline case in simple model. (B) baseline case in complex model. (C) initial ventricular volume (preload) influence in simple model. (D) initial ventricular volume (preload) influence in complex model.

Fig 13C and Fig 13D illustrates the impacts of hemodynamics from initial volume (IV) of the blood for both simple and complex models respectively. Generally, higher blood volumes in the circuit lead to higher pressures in ventricular chamber and systemic aortic sinus. Due to this initial volume influence, all later simulations are conducted by letting the system bleed such that the EDV is fixed at 120ml as a control.

The relationship between the cardiac output (CO) and heart rate (HR) is another physiological characteristic and is presented in Fig 14A for the simple model and in Fig 14B for the complex model. The heart rate was varied from 30 beats/min to 180 beats/min for the simple model, while ranging 30 beats/min to 150 beats/min in the complex model. From Fig 14A, The HR-CO relation curve has a distinct peak equaling about 5.2 L/min around $HR = 50$ beats/min and it has long descend limb on the right side. The situation about the HR-CO curves in Fig 14B is different. The peak of HR-CO curve move to the point when heart rate equal to 135 bpm and the curve has an inflection point at $HR = 120$ bpm. As can be seen, the cardiac output is larger than 5L/min when complex model performing above 60 bpm heart rate and keep increasing until reach the peak of cardiac output 6.5L/min. This result is very close to the normal value of cardiac output of a healthy adult during exercise.

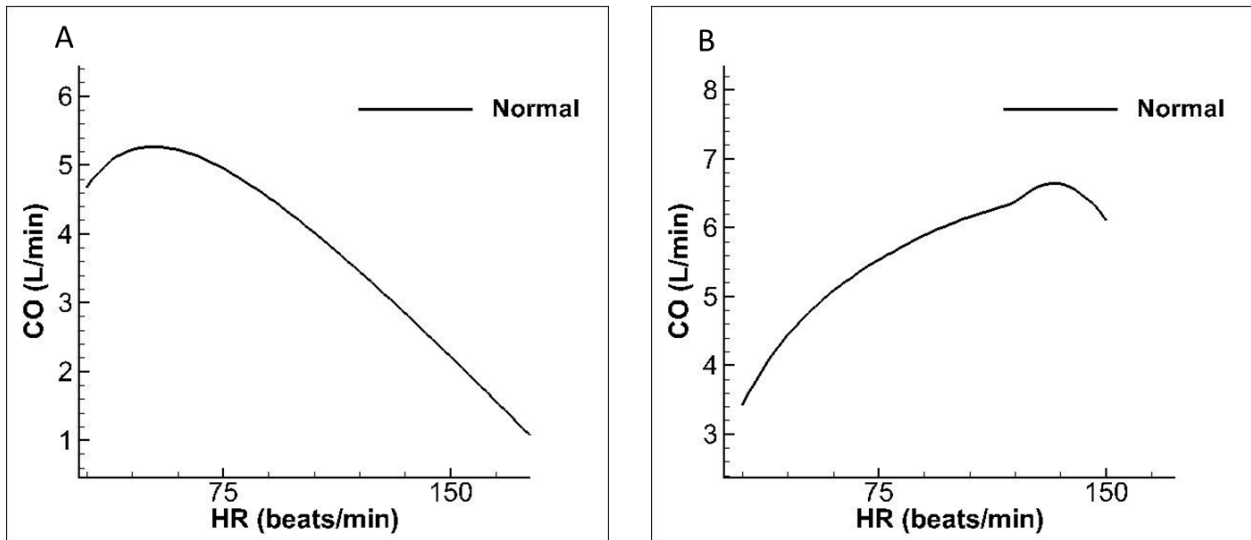


Figure 14: Cardiac output in both simple and complex model. (A) is for simple model and (B) is for complex model.

The results of Dynamic test with load variation

Beyond the normal case, both simple and complex models were tested for hemodynamics for different internal parameters, external parameters, and systolic fractions. In each simulation, the heart rate was fixed at 60 beats/min in all waveform tests. *EDV* is adjusted to 120ml during the blood priming process. In each single test, P_{lv} stands for the left ventricle pressure, P_{ao} indicates the pressure downstream of the aortic valve, V_{lv} stands for the left ventricle volume and Q_{ao} represents the aortic flow. Solid line is the representation of the normal baseline case in waveform test. The long dash and dash dot express the alternative simulation results for the parameter variation.

Six graphs in Fig 15 show waveforms changing in response to the perturbations of the external parameters (corresponding to the load). Fig 15A and Fig 15D depicts the peak magnitude of P_{lv} , P_{ao} increase and waveform of V_{lv} shift up with increasing resistance. Also note that higher resistance leads to lower flow in the simple and complex models. Waveforms in Fig 15B and Fig 15E also show that P_{lv} and Q_{ao} are negligibly changed with a capacitance perturbation. Notice that the dissimilar capacitances results in different decay rates of P_{ao} in diastole. We also tested the inductance difference in the complex model (no figure presented); it only causes the frequency of oscillation varying in P_{ao} just after the aortic valve closes.

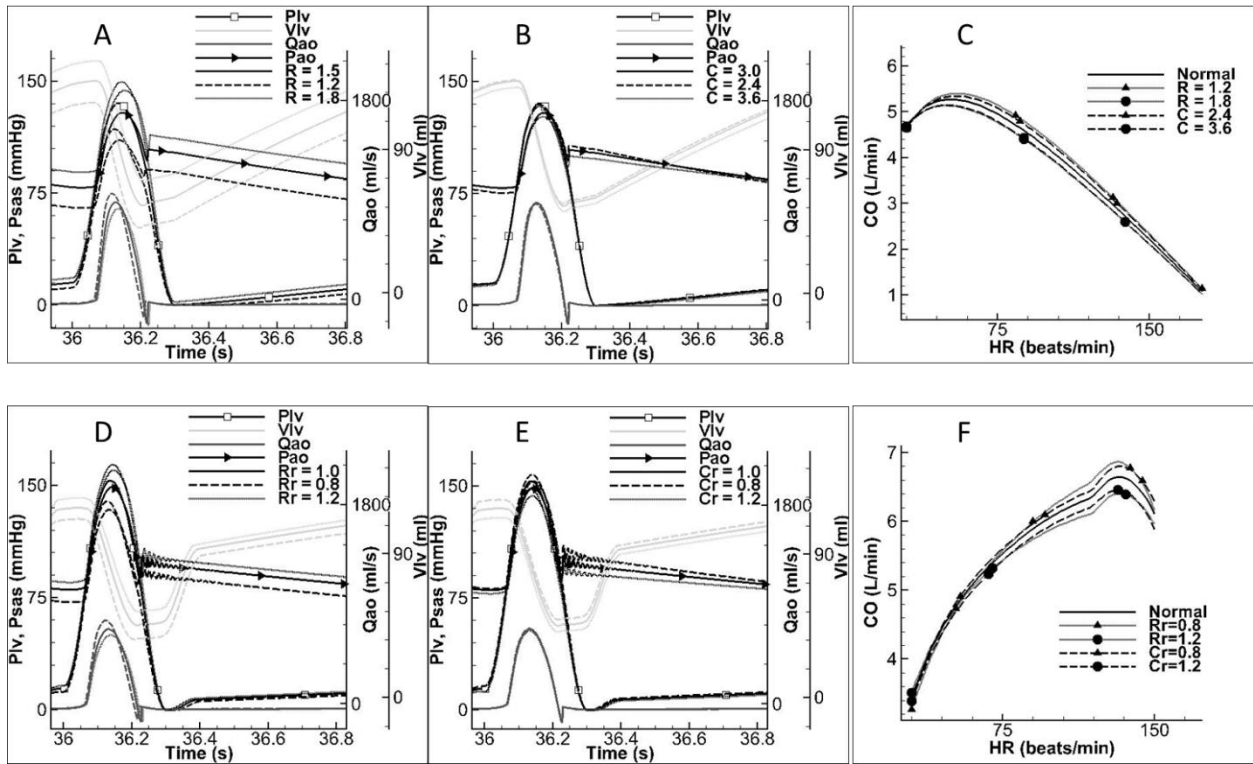


Figure 15: Dynamic tests on different external loads.

Fig 15C and Fig 15F shows heart rate vs. cardiac output curves for the different external parameter combinations. At a certain heart rate, lower resistance can lead to the higher CO , and the capacitance just causes the same effect as the resistance. The influence of the magnitude of CO is slightly greater by changing the same percentage in resistance than in capacitance. At the low heart rates and high heart rates, the five HR- CO curves are similar in magnitude for the simple model, while the largest variation in CO appears at the middle of the curve in the simple model. In contrast, for the complex model the maximum variation in CO , with respect to external parameters, occurs at the peak performance point.

Fig 16 illustrates variations in hemodynamics due to perturbations in the internal parameters. Both P_{lv} and Q_{ao} in Fig 16A and Fig 16D show significant changes with changes in T_{max} . These changes exist only during systole while they remain the same in diastole. Fig 16B

shows that P_{lv} increase during diastolic period when the passive tension parameter ‘ a ’ is increased. No change in Q_{ao} and V_{lv} is noticed during the whole test. In the Figure 16E, all the waveforms have visible difference, but the magnitude is insignificant comparing with the response to changes in resistance or T_{max} . In the Fig 16C and 16F, the higher T_{max} and lower ‘ a ’ induce the same result in plots: the higher CO in one heart rate; the active force parameter T_{max} has more impact on the CO and more sensitive with the heart rate than passive force parameter ‘ a ’.

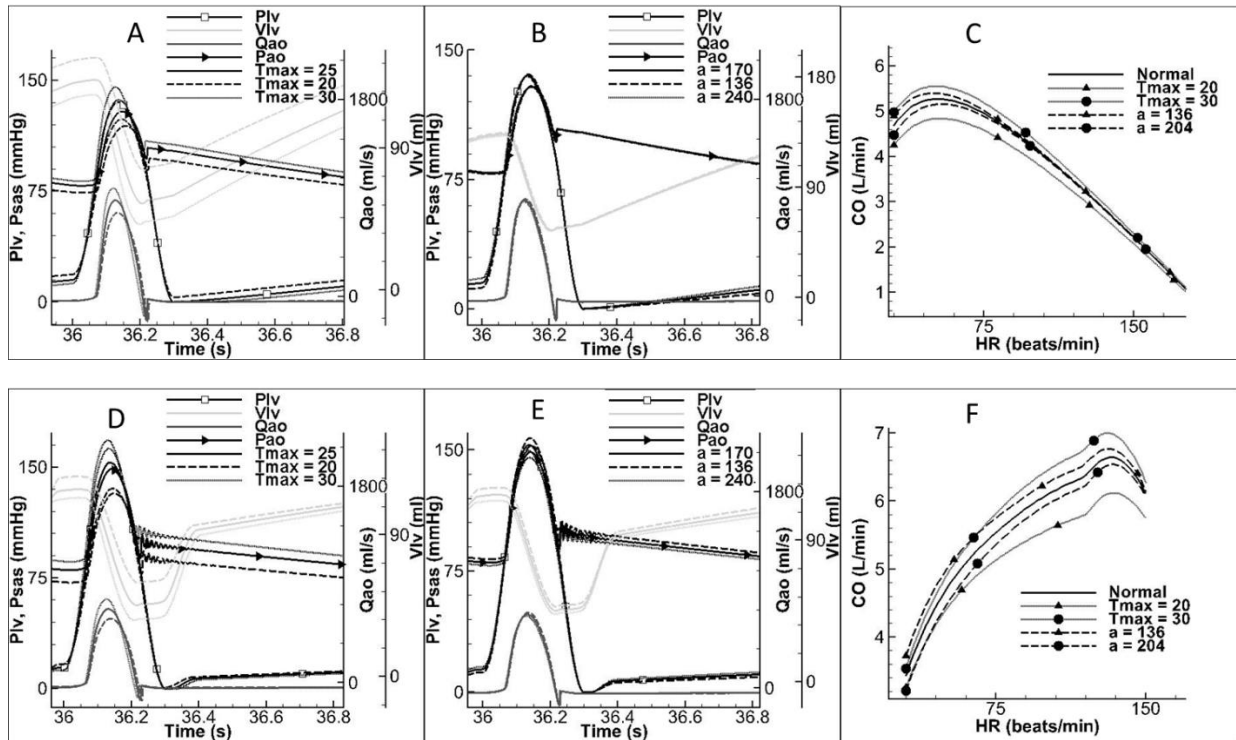


Figure 16: Dynamic tests on different internal loads.

The effect of systolic fraction on hemodynamics is illustrated in Figure 17 it is easy to see that the waveform of P_{lv} is narrower when systolic duration decreases. It clearly affects the peak magnitude of Q_{ao} and the opening and closing time position of the aortic valve. The peak P_{lv} has great difference in Fig 17A and in Fig 17C. The magnitude of cardiac output have considerably

reduction and HR-CO relation curves shift to right when the systolic duration time decreases from 0.4s to 0.2s.

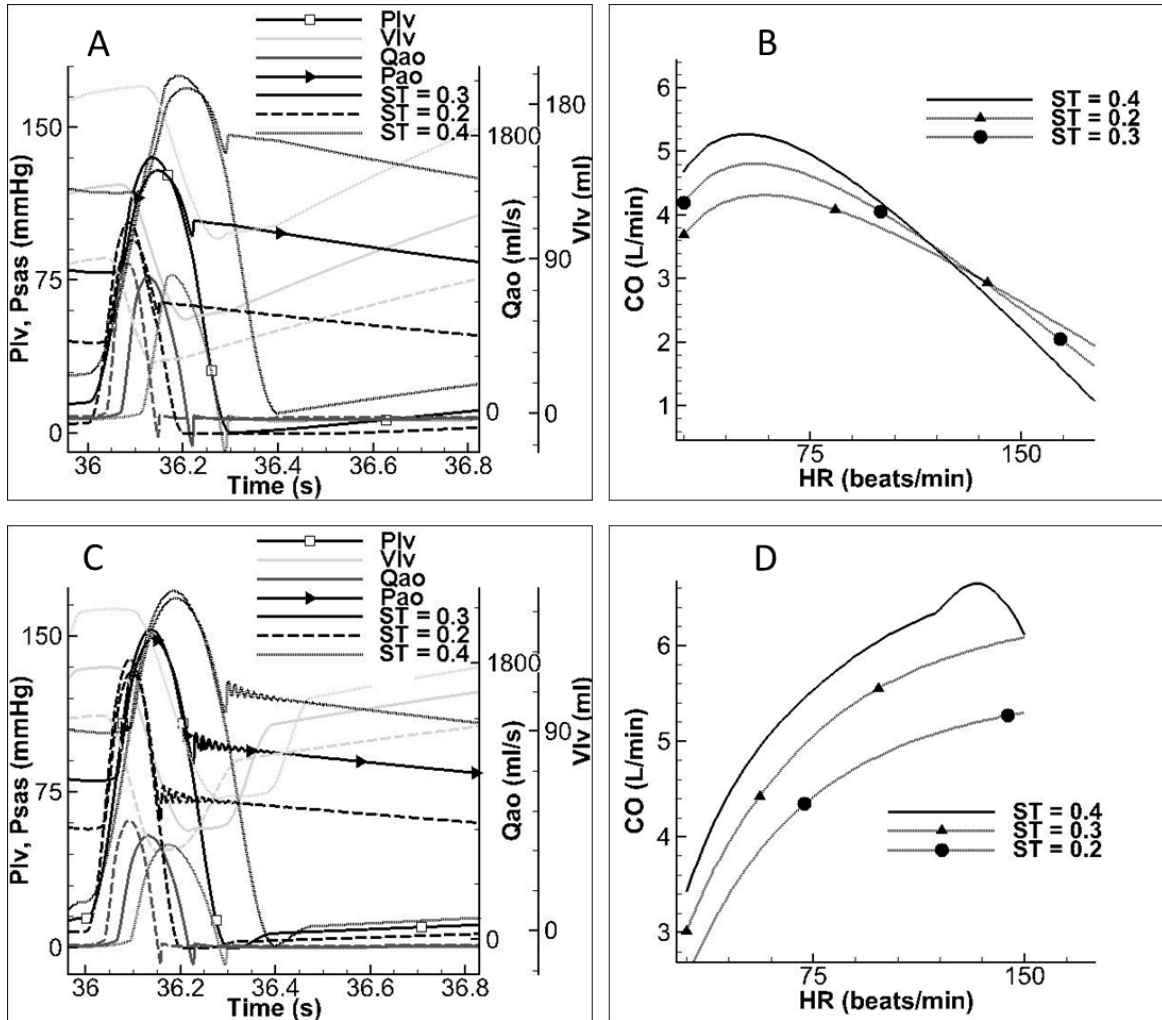


Figure 17: Dynamic test on different systolic duration.

Results of T_{max} and 'a' from model simulations to test independence

Table 5 lists the different combinations of the preload and afterload in this study. The load resistance and capacitance are adjusted to increase or decrease at 20% in order to see the influence on the “recovered” internal parameters: T_{max} and 'a' as calculated by the flow chart

shown in Figure 12B and 12C. Change of initial volume to mimic the alternation of preload also test the impact on the robustness of recovering T_{max} and ‘ a ’.

Table 5: the results of the independence tests

	EDT (s)	EDV (ml)	EDP (mmHg)	EICT (s)	EICP (mmHg)	EICV (ml)	Ratio Tmax	Ratio A
Normal	36.0005	126.70	13.95	36.0702	81.88	127.17	1.0220	1.000142
R = 80%	36.0005	117.43	11.62	36.0667	71.95	117.86	1.0172	1.000462
R = 120%	36.0005	134.52	15.95	36.0724	88.26	134.96	1.0169	1.000348
C = 80%	36.0005	130.7	14.97	36.0683	80.19	131.11	1.0204	1.000372
C = 120%	36.0005	121.3	12.59	36.0715	81.16	121.79	1.0170	1.000419
IV =60	36.0005	138.56	16.98	36.0714	88.18	138.97	1.0156	1.000340
IV = 120	36.0005	150.31	19.99	36.0723	94.43	150.68	1.0156	1.000302

The normal case works in the general parameter combination as shown in the dynamic tests. From the Table 3, T_{max} and ‘ a ’, recovering from the hemodynamic data for 7 tests, shows no significant difference to their respective true values. The ratio is presented, thus a value of 1 implies perfect recovery.

From the calculation, the average value of ratio of T_{max} for the five models is 1.0178 ± 0.0025 and the average ‘ a ’ is 1.00034 ± 0.000010 . This shows that recovery of T_{max} is robust to within 2% and ‘ a ’ is robust to within 0.3% much better than T_{max} . On the initial volume variation group, T_{max} ratio has mean equal to 1.0177 ± 0.0037 . The passive force tension parameter ‘ a ’

own the value 1.00035 ± 0.000012 in varying afterload and 1.00026 ± 0.000011 in varying preload. Overall these results show that the methodology to recover T_{max} is indeed robust.

Results of T_{max} and ‘ a ’ from human data

From Figure 12, the recovery process of T_{max} and a based on comparison between the predict value from model and calculate value from patient pressure data. Here the $T = 25$ mN /mm² and $A = 1.7 \times 10^8$ mN /mm⁴ defined as the basic unit for T_{max} and a .

Normal subjects

Table 6 shows the T_{max} and a calculated for normal subjects based on published data presented in Frank et al, 1962 and Rackley et al 1970. The ‘ a ’ value is 0.424 ± 0.125 A and the T_{max} is 1.831 ± 0.786 T. Considering the effect of body surface area, the two internal parameters are adjusted by normal body surface area (BSA). The final ‘ a ’ prime index of passive fill is 0.235 ± 0.070 A/m² while the value of T_{max} prime index is 1.193 ± 0.485 T/m².

Table 6: T_{max} and 'a' extract from the meta-data.

ID	Diastolic Pao(mmHG)	ICT(ms)	ICT 2 (ms)	Cycle Length(ms)	Cycle Length 2 (ms)	Tmax prime
1	70	40	42	819	9050.912	
2	75	38	35	915	7541.152	
3	80	48	54	801	8910.692	
4	80	41	37	917	9901.423	
5	70	46	50	849	8490.661	
6	90	42	48	1410	12352.296	
7	70	60	43	949	9790.731	
8	80	49	59	848	10160.743	
9	80	39	37	989	9311.515	
10	80	28	36	795	9061.701	
11	85	56	53	1014	9050.823	
12	80	41	37	815	7831.028	
13	85	39	50	905	8711.036	
14	80	44	44	971	9421.143	
15	80	56	82	926	10380.536	
16	80	50	62	1027	10810.877	
17	90	52	38	663	6800.658	
18	90	25	46	635	7481.107	
19	90	33	41	919	8201.490	
20	80	32	34	925	10402.080	

NO.	age(yr)	LVEDP(mmHg)	EDV(ml)	a' prime
1	31	6	109	0.236
2	54	11	126	0.306
3	21	14	153	0.265
4	17	16	162	0.273
5	30	7	119	0.226
6	32	7	174	0.106

B: 'a' prime from normal subjects

A: Tmax prime from normal subjects

Clinic patients data

Figure 18A shows an example of the ventricular pressure waveform and aortic sinus pressure waveform obtained for a single patient. The solid line ranging from 0mmHg to 120 mmHg represents left ventricular pressure over about ten heart beats. The dot-dash curve, which has smaller magnitude than solid line, states the changing trend of the aortic sinus pressure. Given that the aortic and ventricular pressure tracings are obtained by the same catheter while crossing the avel, the two waveforms are not acquired in a synchronized manner. Thus, to calculate End Iso-volumetric contraction pressure (*EICP*), the average of trough value from the aortic pressure waveform (Fig 18B) is taken as *EICP*. ; The *ICT* and ΔP have been are evaluated as shown in Fig 18C. Finally, internal parameter T_{max} and 'a' are extracted from these hemodynamic variables for each of the 12 patients in the Table 7.

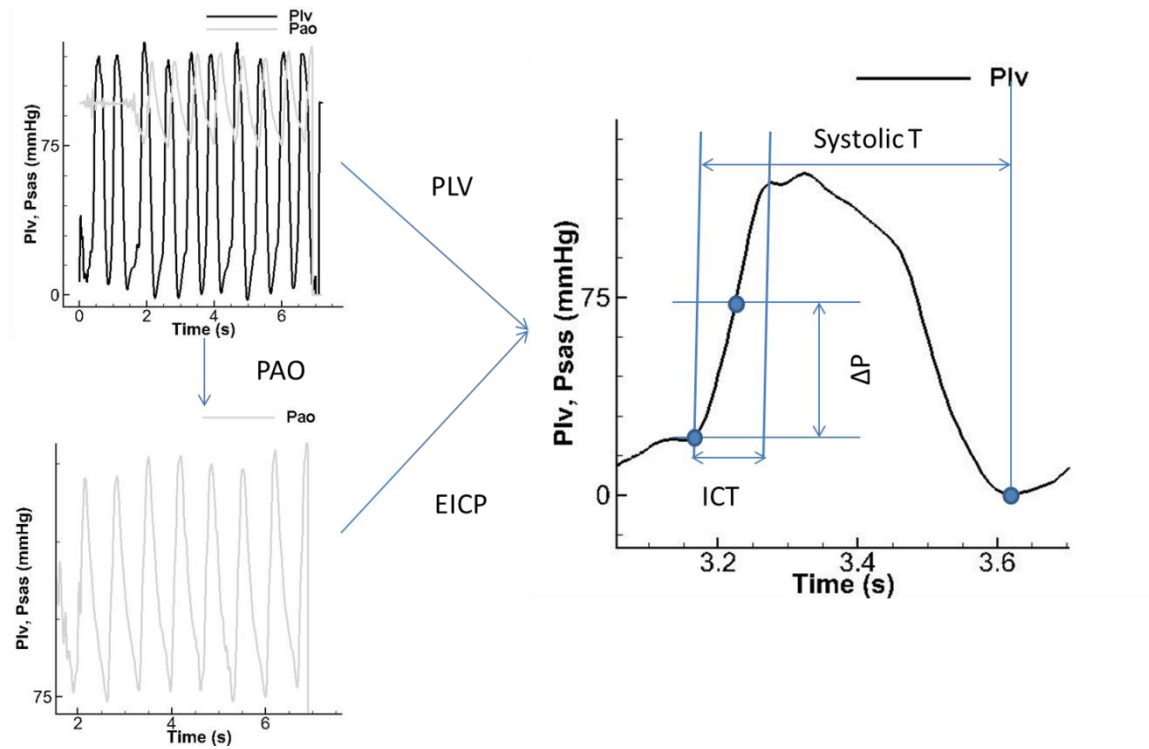


Figure 18: Variables stretch from patient catheter data.

Table 7: T_{max} and 'a' extract from the patient catheter data.

I.D.	EDV	EDP	EICP	d_p	ICT(n)	radius	LVPW	Tmax	a	BSA	Tmax'	a'
	ml	mmHg	mmHg	mmHg		cm	cm	T	A	m2	T/m ²	A/m ²
1	83.07	18.70	56.5	37.80	0.111	4.36	1.3	1.377	2.177	1.6	0.861	1.361
2	129.50	16.07	76.59	60.52	0.15	5.06	1	1.380	0.680	1.9	0.726	0.358
3	97.34	18.20	76.39	58.19	0.143	4.60	1.2	1.325	1.325	2.2	0.602	0.602
4	92.45	16.08	59.4	43.32	0.126	4.52	1	1.720	1.650	1.9	0.905	0.868
5	107.52	18.26	57.42	39.16	0.117	4.76	1	1.530	1.200	1.7	0.900	0.706
6	70.00	15.78	55	39.22	0.101	4.12	1.4	1.721	3.907	1.8	0.956	2.171
7	92.45	17.09	51.38	34.29	0.096	4.52	1	2.060	1.760	1.9	1.084	0.926
8	92.45	18.54	46.32	27.78	0.086	4.52	1.2	1.717	1.583	1.4	1.226	1.131
9	58.16	15.80	56.41	40.61	0.091	3.87	1.3	2.585	21.462	1.9	1.360	11.296
10	129.50	19.90	54.31	34.41	0.141	5.06	0.9	0.978	0.944	1.8	0.543	0.525
11	118.20	9.19	46.73	37.54	0.162	4.91	0.9	0.844	0.533	1.8	0.469	0.296
12	112.81	22.51	73.42	50.91	0.154	4.83	1.4	0.821	0.936	2	0.411	0.468

Table 7 includes all the hemodynamic parameters required to recover T_{max} and 'a'. Both T_{max} and a have been indexed to BSA . Indexed T_{max} value ranges from 0.411 T/m² to 1.360 T/m² for the 12 subjects. Most of patient show the 'a' prime near or below 1.0 A/m², with only

two exception: patient with ID 6 which has 'a' prime nearly equal to 2.2 A/m^2 and patient with ID 9 which has the largest 'a' prime 11.3 A/m^2 . Two patients who were considered relatively normal with only mild valve disease or borderline hypertrophy show an indexed T_{max} between 0.60 T/m^2 and 0.9 T/m^2 . The Figure 19, also deriving from Table 7, just display the statistical results of the two group of candidates with a theoretical prognosis of systolic dysfunction and diastolic dysfunction.

From the Table 4 and Table 7, all the patients who are candidates for diastolic dysfunction have T_{max} prime of $1.06 \pm 0.22 \text{ T/m}^2$, while another group of patients who are candidates for systolic dysfunction show T_{max} prime of $0.65 \pm 0.27 \text{ A/m}^2$. Mann-Whitney test have been performed between the diastolic candidate group-normal subjects and systolic candidate group-normal subjects to test existence of the significant difference. The p value = 0.019 show there is significant difference between the systolic dysfunction group and normal subjects, while diastolic dysfunction group and normal baseline subjects are not statistically significant (p value = 0.921).

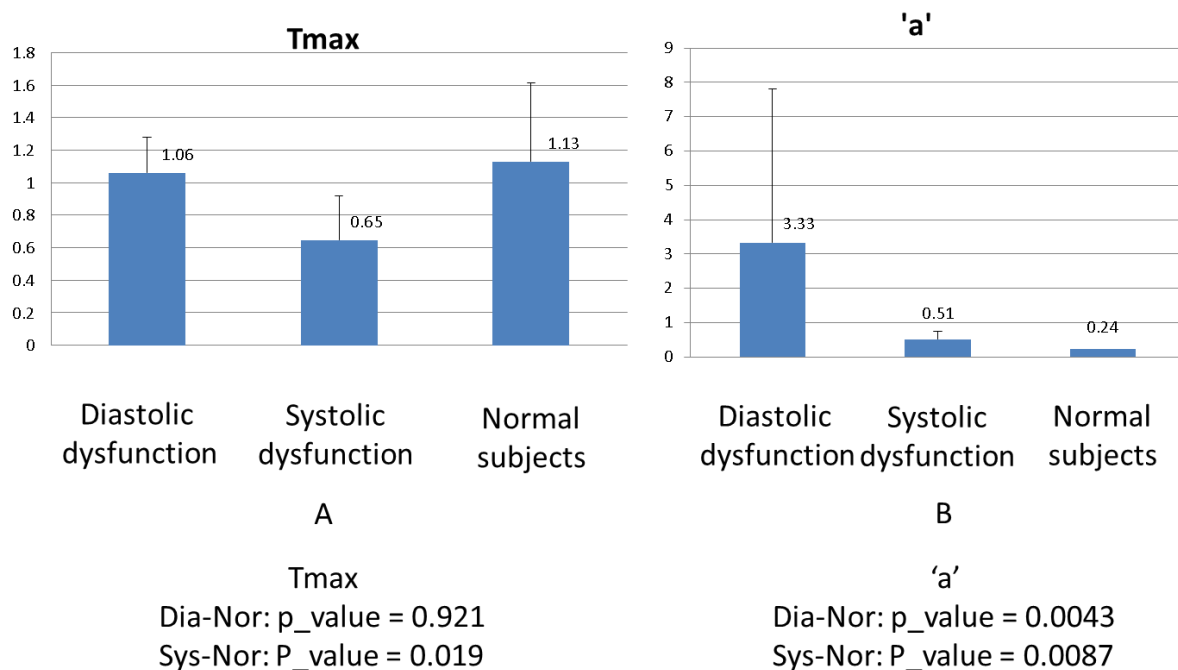


Figure 19: the statistical analyses perform among the normal subjects and different heart dysfunction groups.

The same statistical analysis in 'a' prime has been performed among 12 patient's data. The 'a' prime values are $3.33 \pm 4.48 \text{ A/m}^2$ in the diastolic dysfunction group and $0.52 \pm 0.25 \text{ A/m}^2$ in systolic dysfunction group. Due to the small sample size and large stand deviation, the non-parametric Mann Whitney rank test is performed to acquire the p value in column char 1B instead of the student t-test. The p value shows in the column chart 1B are equal to 0.0087 and 0.0043 which are much small than 0.05, this fact indicate the statistically significant existing between two types of the heart failure candidates and normal subjects. Another statistic test about 'a' prime value performed between the normal group and patient who have mild or above concentric hypertrophy in 12 patients group. The p value equaling to 0.0067 represent the statistical significance.

CHAPTER 4 DISCUSSION

Hemodynamic simulation

Specific aim 1 of this thesis deals with constructing a framework to couple the novel left ventricle model based on the Frank-Starling law with two types of systemic blood circulation (both simple and complex lumped parameter models). The waveforms from the baseline tests and dynamic test shown in Figure 13, 15 and 16 tell about the performance of this framework and depict the validity of the Frank-Starling pump model.

In the baseline case (Figure 13), all the essential mechanistic properties are captured in the simple model results. Here the left ventricle pressure is generated from the left ventricle volume using the Frank-Starling length-force relationship (Figure 5A) in conjunction with time. Both ventricular pressure and systemic aortic sinus pressure together create a pressure gradient across the aortic valve which determines the magnitude and direction of the aortic flow. The time-dependent flow rate in the systemic circuit along with the respective compliance sets the variation in P_{ao} . Finally, the return flow to the left ventricle is calculated based on the mean pressure drop across the resistance. In the complex model, the left atrium model along with the mitral valve greatly improves the physiological venous return characteristics to the ventricle. Addition of inductance elements in the systemic circuit further improves the dicrotic notch compared to that in the simple model (see Figure 13A and 13B).

Previous lumped parameter models such as that developed by Korakianitis, Shi et al^{16,17}, the characteristics are usually described with the direct pressure-volume relation based on the widely used time-dependent elastance theory proposed by Suga et al's^{4, 5, 14, 15}, in which the ventricle pressure is described as a function of the ventricle volume multiplied by the time-varying

elastance (i.e. there are no specific active and passive properties). Comparing the direct conversion from chamber volume to chamber pressure, our ventricle model builds the relationship between the ventricle pressure and ventricle volume based on the length-force dependent curve from the frank-starling law while separating the active contractile parameter with the passive stiffness parameter. It has more complexity in transforming the ventricle pressure from ventricle volume by adding two new variables as the sarcomere length of cardiac muscle and the force tension generating from the cardiac muscle contraction. The major advantage in our model is that we independently control both systolic and diastolic pump performance parameters. For example, the failing human heart with dilated cardiomyopathy²⁴ can be simply modeled as a decrease of the active force tension T_{max} and increase of the passive for tension coefficient 'a'.

The other advantage of our model is that we can obtain more physiological aortic flow characteristics in our simulation. Unlike the Korakianitis model, the blood flow doesn't have a very sharp peak that is 1.5 times higher than the normal case.

Upon closer examination of Fig 14, the shape and magnitude of the CO curves change tremendous from Fig 14A to 14B. The reason of changing shape of the curve is due to the addition of the left atrium and mitral valve along with the more distributed compliance in the systemic circuit. In the simple model, ventricular filling depends on the return flow back to the left ventricle passively by the pressure difference during the diastolic time. The longer the diastolic time, the more amounts of blood returns to ventricle, and more blood can be pumped by the ventricle. When the heart rate increases, the diastolic time would decrease for a fixed systolic duration. So, the descending limb occupies the largest part of the HR-CO characteristic curve shown in the simple model case (Figure 14A). In the complex model, the flow back to the

ventricle is controlled by the atrial contraction actively. So the diastolic time has a relatively much smaller effect on the blood return. It shows that flow output decreases more rapidly in the simple model than complex model with increasing heart rate increase. However, at higher heart rate close to 180bpm, the diastolic time is too short in the complex model. The average blood pumped by ventricle then quickly decends beyond a heart rate of 180bpm (see Figure 14B). The variation in average value of the *CO* is due to the net difference in impedance of the two models.

In the Fig 14B, there is a clear inflection point at $HR = 120$ beats/min in the HR-CO curve. This is due to the atrial pulse. This inflection point is a consequence of the merger of the early systolic filling with the A-wave produced by the atrium. When the heart rate is low, the two mitral flow pulses (E and A waves) are separated. Once the heart rate increases to about 180 bpm, the time period of one cardiac cycle is at 0.333 sec/beats. Thus, if the systolic time is fixed at 0.3s, the diastolic time is only 0.033s. So mitral flow is a single pulse with much greater magnitude instead of the two mitral flow pulses (E and A waves) at low heart rates. Heart rate equaled 120bpm may be considered as the transition point between two pulse mitral flow to a single pulse mitral flow scenario.

In the dynamics tests (Figures 15, 16 and 17), the relative influences on the waveforms seems not too different between external and internal parameters. In the systemic circuit, the resistance parameter has equivalent effect as the afterload since increased resistance leads to an increase in arterial pressure. This increased arterial pressure causes increased systolic pressures and a consequent reduction in myocardial shortening velocity which could be directly related with the heart ejection velocity and therefore the aortic flow. Consequently, this decreased aortic flow reduces the stroke volume and the Frank-Starling mechanism will partially compensate this reduction in the stroke volume. This variation of hemodynamics can be seen in the Fig 15A and

15D. The capacitance is another important external parameter that controls the pressure at the aortic sinus during the diastolic period. The 20% variation of capacitance brings the small difference in slope of the P_{ao} during diastolic period which could be inspected in the Fig 15B and 15E.

The T_{max} parameter regulates the active force tension. From Fig 16A and 16D, higher T_{max} applying results in large increase in the aortic flow or stroke volume. This increase in stroke volume would also compensate with the Frank-Starling principle. Notice that both increase of external resistance or internal T_{max} will cause the ventricular systolic pressure to increase.

Passive force tension dictated by the coefficient ' a '. Increasing ' a ' will increase the baseline ventricular pressure during diastole. The active tension however remains the same. This can be seen with the three aortic flow curves collapse as one curve displayed in Fig 16B. In Fig 16E however, aortic flow does not overlap and may be due to the differences in EDV .

The systolic time dictates the duration over which the ventricle contracts. Changes in it can greatly influence hemodynamics evidently. Fig 17B and Fig 17D notice that the HR-CO curves cross with changing systolic duration time. Decreasing the systolic time, means more time for the ventricle filling and therefore more blood pumped out in ventricular contraction. The cardiac output consequently increases in this situation. This effect is more dominated at the high heart rate. On the other hand, decreasing of the systolic time indicates the decrease of the opening time in aortic valve and less amount of blood can flow across the valve. It is more easily to see this phenomenon in the low heart rate. The compromise these two influences will form the crossed curves we see in the Fig 17B and 17D.

Load Independence of T_{max} and a

Perturbations in external parameters such as resistances and capacitance results in variations of the load characteristics. These reflect in the hemodynamics as changes in $LVEDP$, $EICT$ and $EICP$. The low resistance causes an obvious decrease in both EDP and $EICP$. On the contrary, low capacitance generates an increase in $LVEDP$ and an invariant in $EICP$. Adjustment of initial volume leads the more blood volume adding into whole system that increase base line both in ventricular volume and pressure.

Results show that the recovery procedure developed in this thesis to evaluate the pump internal parameters, T_{max} and a , for all of the 7 tests, showed tiny differences and highly robust values evident from the small standard deviations. The percentage change of the T_{max} is only about 0.246%, while passive filling ‘a’ has smaller value that equal to 0.01%. The little change of the T_{max} and ‘a’ shows that the procedure to recover internal parameters in Frank-Starling pump is independent of both internal and external loads in cardiovascular system. Results obtained from test 1 prove the independence between the internal parameters and external loads to ensure the validity of heart contractility recovery method. They also build a solid approach to extract T_{max} and ‘a’ from the clinical cardiac catheterization pressure data.

Despite the T_{max} and ‘a’, some information about Frank-Starling pump dynamics can be acquired from the Table 5. Comparing the EDV and $EICV$ in each external load, the $EICV$ is noted to be a little bit larger than EDV . During the isometric contraction process, the ventricular volume should remain constant when the ventricular pressure continues increasing. The tiny difference between the EDV and $EICV$ maybe attributed to the small regurgitant flow from the aortic valve. The average change of the ventricular volume during ICT was found to be about

0.25 percent only. Thus we can ignore this tiny difference and assume that the ventricular volume is indeed constant during *ICT*.

Patient data

In figure 19A, statistical result shows no significant difference of *BSA* indexed T_{max} between patients with a prognosis of diastolic failure vs. normal subjects. This conclusion is reasonable as diastolic dysfunction is attributed to the impairment of myocardial relaxation and inadequate heart filling. By definition it has no influence to the contractility of the myocardial muscles at least in the early stages. In this stage, the patient usually has normal ejection fraction and requires no clinical intervention. However, failure of the ventricular filling does result an increase in the *LVEDP*, and that leads the systolic dysfunction at the final stage. We can predict that the *BSA* indexed T_{max} to goes down, when diastolic dysfunction continue to progress. On the contrary, some of valve diseases such as regurgitation help the ventricular volume grow large through volume overload which ultimately leads to systolic dysfunction. Systolic dysfunction refers to the direct loss of contractility. A mechanism is from damage to myocardial cells from ischemia secondary to infarction with eventual scar formation. The scar tissue replaces the dead myocytes ultimately reduce the strength of contraction of the myocardium. So the patients, which belong to the category of systolic dysfunction, will have the lower T_{max} than normal subjects.

The variations observed in the *BSA* indexed ' a ' may be due to the various stages of ventricular structure remodeling secondary to valvular diseases. For instance, both hypertension and aortic valve stenosis lead to an increase in *LVEDP* which ultimately cause concentric hypertrophy of the left ventricle with a corresponding decrease in both *EDV* and *ESV*. The passive force tension parameter ' a ' is very sensitive to *EDV*. We hypothesis that the parameter

'a' can be used to quantify or assess the severity of concentric hypertrophy. In table 7, the patient '6' and '9', who have the maximum (11.3 A/m^2) and second maximum (2.2 A/m^2) highest 'a' value after indexing to *BSA*. They are the ones with the smallest *EDV* (only 58.2ml and 70.0ml) out of all patients. From both of their echo reports, the diagnosis states that the two patients had moderate concentric hypertrophy while the other patients did not have hypertrophy.

The high 'a' prime indicate the high stiffness of the heart muscle fiber structures which prevent the ventricular filling due to low trans-mitral pressure gradient. In the figure 19B, the Mann-Whitney non-parametrical test p values of the 'a' prime index equaling to and 0.0043 conclude the significant difference in diastolic dysfunction and normal subject. Here we can see the patient '9' have the largest 'a' prime value about 5 times large to the secondary ones, that lead to very large standard derivation in the diastolic group. If we just exclude this data and recalculate the 'a' prime in the diastolic dysfunction group, the result of 'a' prime is $1.34 \pm 0.62 \text{ A/m}^2$ which also significant larger than normal subject $0.23 \pm 0.07 \text{ A/m}^2$ (with p value 0.01) and systolic dysfunction group $0.52 \pm 0.25 \text{ A/m}^2$ (with p value 0.03). Considering most of patients have a least mild concentric hypertrophy in both systolic and diastolic heart failure candidate from Table 4, the value of 'a' prime equaling $0.99 \pm 0.58 \text{ A/m}^2$ with have been calculated in the patient with any severity of concentric hypertrophy excluding patient '9'. P value of 'a' prime is less than 0.001 representing the significance difference between normal subjects and concentric hypertrophy group.

There are a few cause affecting the results of *BSA* index T_{max} and 'a' recovering from normal subjects. First cause is the *EDV* and *LVEDP* are not provided by raw data which we used to recovery T_{max} in normal subjects. The assumption that the $LVEDP = 12 \text{ mmHg}$ and $EDV = 120 \text{ ml}$ for all the normal subjects will remove each individual difference that lead the results of

T_{max} more weighting on ICT . The second cause is the age difference. The age of normal subjects for recovering 'a' are ranging from 17 to 54, the average value is 31 with stand deviation 13. In the systolic group, most of patient around 50 years old, the average value is 52 with stand deviation 9. With the increasing of age, the patient have more chance to suffer from vascular sclerosis that finally lead to increasing of filling pressure. This factor will bring more uncertainty when comparison made between the normal subjects and 12 clinic patients data.

During the hemodynamic variables measurement, some difficulties are encountered in irregular patients' pressure waveform. Sometimes, the end diastolic point is easy to find by the platform feature in the ventricular pressure waveform. However, it becomes very difficult to identify the certain end diastolic point when the flat platform feature is not obvious. In this situation, this heart beat may be neglected or use the average of the previous EDP as EDP at this point to calculate the ICT during heart beat. The second problem in variables probing process is that pressure waveform is not smooth enough for some patient to have some type of the valve disease. It improves the difficulty to decide end systolic time for obtaining systolic during in this situation. Wrong systolic during will cause the miscalculation during pump internal parameters recovery process that can greatly influence the results of the T_{max} prime and 'a' prime.

SUMMARY

We have successfully shown how the new ventricle model based on the frank-starling law in conjunction with two difference kinds of systemic circuit model (simple and complex) can be used as a platform to develop clinically important indices. We defined the new contractility index T_{max} to represent the force generation capacity of the heart muscle for improving clinical management through better timing for intervention. We also defined a new passive filling index – ‘ a ’ to describe the diastolic function for evaluation of concentric hypertrophy or simply characterize the ventricular compliance. Our patient analysis has demonstrated a method to recover T_{max} and a from cardiac catheterization data and we explained the advantages of the use of these new indices as opposed to current indices that are not load independent .

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APPENDIX I: SOURCE CODE

Simple Model

```
#include "stdio.h"
#include <conio.h>
#include <math.h>

const double pi = 3.1415926;

double delta_t = 0.0001;
double heart_rate = 80;
double systolic_fraction = 0.3;

double function_nfmax(double r);
double function_nfmin(double r);
double function_nfmin2(double r);
double function_et(double t);
double ftime(double t);
double ftime2(double t);
void heart_pump(double t);
void new_heart_pump(double t);
void valve(double t);
void load(double t);
double heartbeat(double t, double time);
void reset();
void valve2(double t);
void change_volume(double time);
void aortic_flow(double t);
void testcontrol(int test);

double rad = 1.8;
double forcep = 0.0;
double forcea = 0.0;
double forcet = 0.0;
double et = 0.0;
double length;
double Vlv= 120;
double pressure;
double volume[10000];
double flow_array[5500];
double valve_pressure = 100, valve_flow = 0, dvalve_flow = 0, dvalve_pressure = 0;
double load_pressure = 0, load_flow= 0,dload_pressure= 0, dload_flow = 0;
double output1 = 0;
//double R = 1.073, L = 0.002, C = 168;
```

```

//double valve_R = 150, llao = 0.0003;
//normalize parameters
double V0 = 148.62;
double P0 = 1.0, T0 = 1;
double in_r1 = 1.0;
double in_r2 = 1.0;
double Q0;
double R, L, C;
double valve_R, llao;
double initial_close_area;
double subarea;
double vr;

double power;
int count = 0; double markt = 0.5;
double output=0;

int mark1=0,mark2=0, mark3=0, mark4=0;
int markv = 0;
int flow_count = 0;
double t_o, t_c;
double A,fn;
double delay_flow;
double Ft;
double Pao;
char name1[30];
char name2[30];

int main()

{

double data1, data2;
int k;
int i = 0;

FILE *fp;
FILE *input1;
FILE *CO;

Q0 = 1.0/T0;

```

```

valve_R = 300; lla0 = 0.0003;
initial_close_area=5.0;
subarea = 30;
printf("=%0lf\n", Q0);

input1 = fopen("U:\\commom\\Myocardialmodel\\724\\volume.dat","r");

while(!feof(input1)) {
k = fscanf(input1,"%0lf %0lf",&data1,&data2);
//volume[i] = (data2/Q0*59.0/67.0 + 8.0/67.0)*Q0;
volume[i] = (data2-50)*0.7+50;
i++;
}
volume[10000] = volume[0];

for(int test = 13; test<=13; test++) //perform 13 different tests
{

testcontrol(test);
fp = fopen(name1, "w");
CO = fopen(name2, "w");

for(heart_rate = 60; heart_rate <=60; heart_rate = heart_rate + 2 ){//run the model on different
heart rate
reset();
double time=0.0; double t=0.0;
for(time = 0.0,t=0.0;time<=50.0;time+=delta_t, t+=delta_t){//main loop. 50.0 is the total running
time

t = heartbeat(t, time);

if(time <= 10.0){//prime the whole system
aortic_flow(t);
}
if(time > 10.0){//after 10s the heart start to pump
Vlv = Vlv + (load_flow*delta_t - valve_flow*delta_t);
heart_pump(t);
valve(t);
// systolic_fraction = 0.3;

}

load(t); //simple load

```

```

    valve2(t);    //simple valve that controal the flow back to ventricle only in diastole
    power = pressure*valve_flow;
    output = output + valve_flow*delta_t;
    if(t<=0.3){
        output1 = output;
    }
//fprintf(fp,"%lf\t%lf\t%lf\t%lf\t%lf\t%lf\t%lf\t%lf\t%lf\n",time,pressure,Vlv,valve_flow,valve_press
ure,load_flow,rad, length);
//fprintf(fp,"%lf\t%lf\t%lf\t%lf\t%lf\t%lf\t%lf\t%lf\t%lf\n",time,pressure,Vlv/V0,valve_flow,val
ve_pressure,load_flow,power,output, length);
fprintf(fp,"%lf\t%lf\t%lf\t%lf\t%lf\t%lf\t%lf\t%lf\t%lf\t%d\t%d\t%d\n",time,pressure,Vlv,valve_flow,
valve_pressure,load_flow,load_pressure,Pao, mark1,mark2,mark3);
//fprintf(CO,"%lf\t%lf\t%lf\n", time, ftime(t), output);
if((time>45 && count == 0)&& t>=(60.0/heart_rate)-delta_t*5){

//      fprintf(CO,"%lf\t%lf\t%lf\n", heart_rate, output, heart_rate*output);
      fprintf(CO,"%lf\t%lf\t%lf\t%lf\t%lf\n",    heart_rate,    heart_rate*output/1000,
output,heart_rate*output/1000, output1);
      printf("heart_rate = %.1lf\n", heart_rate);
      count = 1;

    }
}

fclose(fp);
}

fclose(CO);
}
fclose(input1);

    return 0;
}

// heart pump modelling by the frank-starling law
//here pressure is governed by sarcomere length and et time function
void heart_pump(double t)
{
    double tt = t;
    if(Vlv < 0){
        Vlv = - Vlv;
        mark4 = 1;
    }
    length = pow(Vlv*0.75/pi, 1.0/3);
    if(mark4 == 1){
        length = - length;
    }
}

```

```

        mark4 = 0;
        Vlv = - Vlv;
    }

    rad = (length/3.52+1.22)/2.2;
    et = ftime(tt);
    forcep = function_nfmin(rad);
    forcea = function_nfmax(rad);
    forcet = forcep + forcea*et;
    pressure = forcet/length*3.05*200;
}

//aortic valve control the arotic flow by giving pressure gradient
void valve(double t)
{

    double Area;
    double T_open, T_close, T_fast_close;

    double Nf;
    Area = valve_R;

    T_open = (systolic_fraction) * (1.0/10.0); //0;// (systolic_fraction * T) * (0.5 / 6);
    T_close = (systolic_fraction) * (1.0/20.0);
    T_fast_close = T_close;
// calculate the absolute value of valve_flow

    if(valve_flow < 0)
        Nf = - valve_flow;
    else
        Nf = valve_flow;

// The whole valve opening process, valve start to open just when pump pressure greater than
valve pressure
    if(pressure >= valve_pressure) {
        mark3 = 1;
        mark2 = 0;
// record the valve initial open time
        if(mark1 == 0) {
            t_o = t;
            mark1 = 1;
        }
    }
}

```

```

// Valve is gradually opening during the T_open and totally open after T_open
    if((t - t_o) <= T_open){
        Area = subarea+ (valve_R-subarea)*(t-t_o)/T_open;}
//
        Area = 2.02+ (valve_R-2.02)*(t-t_o)/T_open;}
    else Area = valve_R;
// Calculate the valve flow base on pressure, valve_pressure, valve_flow, valve opening area, and
valve inductance.
//
    dvalve_flow = (pressure-valve_pressure-Nf*valve_flow/Area/Area)/(lao);
//
    valve_flow = valve_flow + dvalve_flow*delta_t;
}
/// The valve closing process
    else {
        mark1 = 0;
// valve start to close just when flow backtoward
        if(valve_flow < 0.0) {
// record the valve initial close time
            if(mark2 ==0) {
                t_c = t;
                mark2 =1;

            }
            if((t - t_c) <= T_close) {
                Area = initial_close_area + valve_R - (valve_R)*(t-
t_c)/T_fast_close;
            }

            else {
                mark3=0;
            }

        }
// update the valve flow

        if (mark3 == 0){

            Area = initial_close_area;

        }

    }

    if(valve_flow <= -500 ) {
        valve_flow = -500;
    }

```



```

//dvalve_flow = (pressure-valve_pressure-Nf*valve_flow/Area/Area)/(lao);
    dvalve_flow          =          (pressure-valve_pressure-Nf*valve_flow/Area/Area*3-
vr*valve_flow)/(lao);
valve_flow = valve_flow + dvalve_flow*delta_t;
A = Area;
fn = Nf;
Pao = valve_pressure+vr*valve_flow;;

flow_array[flow_count] = valve_flow;
if(flow_count<=5499)
{flow_count++;}

}

//simple load part
void load(double t)
{
/*    dload_pressure = (load_flow - valve_flow)/C;
    dload_flow = (valve_pressure - load_pressure - R*load_flow)/L;
    load_pressure = load_pressure + dload_pressure*delta_t;
    load_flow = load_flow + dload_flow*delta_t;
*/

    dvalve_pressure = (valve_flow - load_flow)/C;
    valve_pressure = valve_pressure + dvalve_pressure*delta_t;
    load_flow = (valve_pressure - load_pressure)/R;
}

// active force tension related with certain sarcomere length
double function_nfmax(double r)
{ double nmax = 1.0*in_r1;
    double fmax;
    if(r<=1)
    {
//        fmax = (100*(r-1)+25)/25;//here r must the length at EDV, and it do not change
        fmax = nmax/0.25*(r-1)+nmax;
    }
    if(r>1)
    {
//        fmax = (-100*(r-1)+25)/25;
        fmax = -nmax/0.25*(r-1)+nmax;
    }
    if(fmax <0)
    {
        fmax = 0;
    }
}

```

```

        return fmax;
    }

// passive force tension related with certain sarcomere length
double function_nfmin(double r)

{
    double a = 170*in_r2;

    double fmin;
//    fmin = (247.84-580.6*(r/2.2)*2.2+340*(r/2.2)*(r/2.2)*2.2*2.2)/25;// here r must change
with the ventricle filling
//    fmin = (247.84-580.6*r+340*r*r)/25;
    fmin = (a*(r-580.6/340/2)*(r-580.6/340/2)-340*580.6*580.6/680/680+247.84)/25;
    if (r <= 580.6/340/2)
    {
        fmin = 0;
    }
    if (fmin <=0)
    {
        fmin = 0;
    }
    return fmin;
}

```

```

double heartbeat(double t, double time)
{ double T;
  T = 60/heart_rate;
  if(time <= 10.0){
    if(t >= 1){
      t = delta_t;
      output = 0;
      mark1 = 0;
      t_o = 1.1;
      t_c = 1.1;
      flow_count = 0;

    }
  }
  else if(time <= 20.0){
    if(t >= T){
      t = delta_t;
      output = 0;
      mark1 = 0;
      t_c = 31;
    }
  }
}

```

```

        t_o = 31;
        flow_count = 0;
    }

}
else{
    if(t >= T){
        t = delta_t;
        output = 0;
        mark1 = 0;
        t_c = T+1;
        t_o = T+1;
        flow_count = 0;
//        R = 1.5*4;
    }
}
return t;
}

void reset()
{
rad = 1.8;
forcep = 0.0;
forcea = 0.0;
forcet = 0.0;
et = 0.0;
pressure = 0; //Vlv = 0;
valve_pressure = 0;valve_flow = 0;dvalve_flow = 0,dvalve_pressure = 0;
load_pressure = 0;load_flow= 0;dload_pressure= 0;dload_flow = 0;
count = 0; markt = 0.5;
output=0;
mark1=0;mark2=0;mark3=0;mark4=0;
markv = 0;
}

//simple valve that control the flow back to ventricle only in diastole
void valve2(double t)
{
    if(t > systolic_fraction)
        load_pressure = pressure;
    if(t <= systolic_fraction)
        load_pressure = valve_pressure;
}

```

```

// et time function
double ftime(double t)
{
    double e;
    double Ts1,Ts2,Ts3;

//T = 60/heart_rate;
Ts1 = (systolic_fraction) * (0.9/ 3);
Ts2 = (systolic_fraction) * (1.80 / 3);
Ts3 = systolic_fraction;

double cc = 1.0;
if (t <= Ts1) {
    e = 1 - cos(pi+pi*(Ts1-Ts2)/(cc*(Ts3-Ts1))+pi*(t-Ts1)*(cc*(Ts3-Ts1)-
Ts2+Ts1)/(cc*(Ts3-Ts1)*Ts1));
}
    if (t > Ts1 && t <= Ts2) {
        e = 1 - cos(pi+pi*(t-Ts2)/(cc*(Ts3-Ts1)));
    }
    if (t > Ts2 && t <= Ts3) {
        e = 1 - cos((t-Ts3)/(Ts2-Ts3)*pi);
    }
    if (t > Ts3) {
        e = 0;
    }

    return e/2;
}

//prime aortic flow
void aortic_flow(double t) {
    double T;
    T = 60.0/60;//defines the period of the heart
    if (t >= 0 && t <= systolic_fraction * T) { // this if loop defines the curve that primes the
circulatory system with a simusoidal blood flow
        valve_flow = 416.6 * sin(t * pi/(systolic_fraction * T));
    }
    else valve_flow = 0;
}

void testcontrol(int test)
{ R = 1.325; C = 2.75; in_r1 = 1.0; in_r2 = 1.0; systolic_fraction = 0.3;vr = 0.08;Vlv = 0;
    switch(test)
    {
        case 1:

```

```

    R = R*1.2;
    vr = vr*1.2;
    sprintf(name1,"waveform(Rr = 1.2).dat");
    sprintf(name2,"CO(Rr = 1.2).dat");
    break;
case 2:
    R = R*0.8;
    vr = vr*0.8;
    sprintf(name1,"waveform(Rr = 0.8).dat");
    sprintf(name2,"CO(Rr = 0.8).dat");
    break;
case 3:
    C = C*1.2;
    sprintf(name1,"waveform(Cr = 1.2).dat");
    sprintf(name2,"CO(Cr = 1.2).dat");
    break;
case 4:
    C = C*0.8;
    sprintf(name1,"waveform(Cr = 0.8).dat");
    sprintf(name2,"CO(Cr = 0.8).dat");
    break;
case 5:
in_r1 = 1.2;
    sprintf(name1,"waveform(T = 1.2).dat");
    sprintf(name2,"CO(T = 1.2).dat");
    break;
case 6:
    in_r1 = 0.8;
    sprintf(name1,"waveform(T = 0.8).dat");
    sprintf(name2,"CO(T = 0.8).dat");
    break;
case 7:
    in_r2 = 1.2;
    sprintf(name1,"waveform(a = 1.2).dat");
    sprintf(name2,"CO(a = 1.2).dat");
    break;
case 8:
    in_r2 = 0.8;
    sprintf(name1,"waveform(a = 0.8).dat");
    sprintf(name2,"CO(a = 0.8).dat");
    break;
case 12:
Vlv = 60;
    sprintf(name1,"waveform(Vlv=60).dat");
    sprintf(name2,"CO(Vlv=60).dat");
    break;

```

```

    case 13:
    Vlv = 120;
        sprintf(name1,"waveform(Vlv = 120).dat");
        sprintf(name2,"CO(Vlv = 120).dat");
        break;

    case 9:
        systolic_fraction = 0.4;
        sprintf(name1,"waveform(sf = 4.0).dat");
        sprintf(name2,"CO(sf = 4.0).dat");
        break;
    case 10:
        systolic_fraction = 0.2;
        sprintf(name1,"waveform(sf = 2.0).dat");
        sprintf(name2,"CO(sf = 2.0).dat");
        break;
    case 11:
    sprintf(name1,"waveform(normal).dat");
        sprintf(name2,"CO(normal).dat");
        break;

    }

}

```

Complex model

```

#include "stdio.h"
#include <conio.h>
#include <math.h>

const double pi = 3.1415926;

double delta_t = 0.0001;
double heart_rate = 80;
double systolic_fraction = 0.3;

double function_nfmax(double r);
double function_nfmin(double r);
double function_nfmin2(double r);
double function_et(double t);
void heart_pump(double t);
void valve(double t);
void load(double t);
double heartbeat(double t, double time);
void reset();
void valve2(double t);

```

```

void change_volume(double time);
void atrium(double t);
void valve3(double t);
void load_complex(double t);
void load_complex2(double t);
double ftime(double t);
void aortic_flow(double t);
void testcontrol(int test);
double rad = 1.8;
double forcep = 0.0;
double forcea = 0.0;
double forcet = 0.0;
double et = 0.0;
double length;
double Vlv=120;
double Plv;
double Vla, Pla, dVla;
double EDV, ESV;
double volume[10000];
char name1[30];
char name2[30];
double Psas = 100, Qao = 0, dQao = 0, dPsas = 0;
double Pao = 0.0;
double load_Plv = 0, Qsvn= 0,dload_Plv= 0, dQsvn = 0;
double output1;

//normailze parameters
double in_r1 = 1.0;
double in_r2 = 1.0;
double V0 = 1.0;

double P0 = 1.0, T0 = 1.0/1.0;
double Q0 = 1.0*1.0;

double CQao = 300, Lao = 0.0003;

double power;
int count = 0; double markt = 0.5;
double output=0;

int mark1=0,mark2=0, mark3=0, mark4=0;
int markv = 0;
double t_o, t_c, t_mc;
double A,fn;
double Qmi, dQmi, CQmi = 400*sqrt(P0)/Q0, Lmi = 0.0003*Q0/P0/T0;

```

```

double RR = 1.0, RL = 1, RC = 1.0;

// --- complex load constant
// the capitalized first letters of the systemic constants use the following naming system:
// C = capacitance, R = resistance, L = inductance

// aorta
double Csas = 0.08;
double Rsas = 0.003;
double Lsas = 0.000062;

// systemic artery
double Csat = 1.6;
double Rsat = 0.05;
double Lsat = 0.0017;

// systemic arteriole
double Rsar = 0.5;

// systemic capillary
double Rscp = 0.52;
// systemic vein

double Rsvn = 0.075;
double Csvn = 20.5;
// --- complex load constant
// construct above parameters into two blocks: artery and vein
double Ra = 2.5, Ca = 3.0, Rv = 0.075, Cv = 20.5;

// --- complex load variables
double dQsas=0.0, dPsat=0.0, dQsat=0.0, dPsvn=0.0, Qsas=0.0,Psat=0.0, Psvn=0.0, Qsat=0.0,
Pra=0.0;

int main()

{

double data1, data2;
int k;
int i = 0;

```



```

FILE *fp;
FILE *input1;
FILE *CO;

//P0 = 1.2;
sprintf(name1,"waveform(normal).dat");
sprintf(name2,"CO(normal).dat");

input1 = fopen("U:\\commom\\Myocardialmodel\\724\\volume.dat","r");

while(!feof(input1)) {
k = fscanf(input1,"%lf %lf",&data1,&data2);

volume[i] = (data2-50)*0.7+50;
i++;
}
volume[10000] = volume[0];
for(int test = 1; test <= 13; test++) //perform 13 different tests
{
testcontrol(test);
fp = fopen(name1, "w");
CO = fopen(name2, "w");
for(heart_rate = 60; heart_rate <= 60; heart_rate = heart_rate + 2 ){ //run the model on different
heart rate
reset();
double time =0.0; double t=0.0;
//systolic_fraction = 0.3;
for(time = 0.0,t=0.0;time<=40.0;time+=delta_t, t+=delta_t){ //main loop. 40.0 is the total
running time

t = heartbeat(t, time);
//loop the load flow back to the heart pump
if(time <= 10.0){ //prime the whole system with aortic flow
aortic_flow(t);
}
if(time > 10.0){ //after 10s the heart start to pump

atrium(t);
valve3(t);
Vlv = Vlv + (Qmi*delta_t - Qao*delta_t);
heart_pump(t);
valve(t);

}
}
}

```

```

//      change_volume(time);

//      load(t);
//      load_complex2(t);          //complex load

power = Plv*Qao;
output = output + Qao*delta_t;
if(t<= systolic_fraction)
{
    output1 = output;
}
if(t<= systolic_fraction*0.1){
EDV = Vlv;
}
if(t<=systolic_fraction*0.9){
ESV = Vlv;
}
//fprintf(fp,"%lf\t%lf\t%lf\t%lf\t%lf\t%lf\t%lf\t%lf\n",time,Plv,Vlv,Qao,Psas,Qsvn,rad, length);
//fprintf(fp,"%lf\t%lf\t%lf\t%lf\t%lf\t%lf\t%lf\t%lf\t%lf\n",time,Plv,Vlv/V0,Qao,Psas,Qsvn,pow
er,output, length);
fprintf(fp,"%lf\t%lf\t%lf\t%lf\t%lf\t%lf\t%lf\t%lf\t%lf\t%lf\n",time,Plv,Vlv,Qao,Psas,Qsvn,
load_Plv,Pla, Vla,Qmi,Pao);
    if((time>35 && count == 0)&& t>=(60.0/heart_rate)-delta_t*5){

//      fprintf(CO,"%lf\t%lf\t%lf\n", heart_rate, output, heart_rate*output);
//      fprintf(CO,"%lf\t%lf\t%lf\t%lf\t%lf\n",  heart_rate,  heart_rate*output1/1000,
output1,heart_rate*(EDV-ESV)/1000, EDV-ESV);
        printf("heart_rate = %.1lf\n", heart_rate);
        count = 1;

    }
}

fclose(fp);
}

fclose(CO);
}
fclose(input1);

    return 0;
}

// heart pump modelling by the frank-starling law

```

```
//here pressure is governed by sarcomere length and et time function
```

```
void heart_pump(double t)
{
    if(Vlv < 0){
        Vlv = - Vlv;
        mark4 = 1;
    }
    length = pow(Vlv*0.75/pi, 1.0/3);
    if(mark4 == 1){
        length = - length;
        mark4 = 0;
        Vlv = - Vlv;
    }
    rad = (length/3.52+1.22)/2.2;;

    et = ftime(t);

    forcep = function_nfmin(rad);
    forcea = function_nfmax(rad);

    forcet = forcep + forcea*et;
    Plv = forcet/length*3.05*200;
}
}
```

```
//aortic valve control the arotic flow by giving pressure gradient
```

```
void valve(double t)
{
    double Area, initial_close_area=5.0*sqrt(P0)/Q0;
    // double Area, initial_close_area=0.336;
    double T_open, T_close, T_fast_close;

    double Nf;
    Area = CQao;

    T_open = (systolic_fraction) * (1.0/10.0); //0;// (systolic_fraction * T) * (0.5 / 6);
    T_close = (systolic_fraction) * (1.0/30.0);
    T_fast_close = T_close;
    // calculate the absolute value of Qao

    if(Qao < 0)
        Nf = - Qao;
```

```

else
    Nf = Qao;

// The whole valve opening process, valve start to open just when pump Plv greater than valve
Plv
    if(Plv >= Pao) {
        mark3 = 1;
        mark2 = 0;
// record the valve initial open time
        if(mark1 == 0) {
            t_o = t;
            mark1 = 1;
        }

// Valve is gradually opening during the T_open and totally open after T_open
        if((t - t_o) <= T_open){
            Area = 30*sqrt(P0)/Q0+ (CQao-30*sqrt(P0)/Q0)*(t-t_o)/T_open;}
//
            Area = 2.02+ (CQao-2.02)*(t-t_o)/T_open;}
        else Area = CQao;
    }

// The valve closing process
    else if(Plv < Pao) {
        mark1 = 0;
// valve start to close just when flow backtoward
        if(Qao < 0.0) {
// record the valve initial close time
            if(mark2 ==0) {
                t_c = t;
                mark2 =1;

            }
            if((t - t_c) <= T_close) {
                Area = initial_close_area + CQao - (CQao)*(t-t_c)/T_fast_close;
            }

            else {
                mark3=0;
            }
        }

// update the valve flow
        if (mark3 == 0){

```

```

        Area = initial_close_area;
    }
}

if(Qao <= -500 ) {
    Qao = -500;
}

dQao = (Plv-Pao-Nf*Qao/Area/Area*1)/(Lao);
Qao = Qao + dQao*delta_t;
A = Area;
fn = Nf;
Pao = Psas + Qao*0.04*RR*Q0/P0;
}

// active force tension related with certain sarcomere length
double function_nfmax(double r)
{
    double nmax = 1.0*in_r1;
    double fmax;
    if(r<=1)
    {
        //          fmax = (100*(r-1)+25)/25;//here r must the length at EDV, and it do not change
        fmax = nmax/0.25*(r-1)+nmax;
    }
    if(r>1)
    {
        //          fmax = (-100*(r-1)+25)/25;
        fmax = -nmax/0.25*(r-1)+nmax;
    }
    if(fmax <0)
    {
        fmax = 0;
    }
    return fmax;
}

// passive force tension related with certain sarcomere length
double function_nfmin(double r)
{

```

```

double a = 170*in_r2;

double fmin;
// fmin = (247.84-580.6*(r/2.2)*2.2+340*(r/2.2)*(r/2.2)*2.2*2.2)/25;// here r must change
with the ventricle filling
// fmin = (247.84-580.6*r+340*r*r)/25;
fmin = (a*(r-580.6/340/2)*(r-580.6/340/2)-340*580.6*580.6/680/680+247.84)/25;
if (r <= 580.6/340/2)
{
    fmin = 0;
}
if (fmin <=0)
{
    fmin = 0;
}
return fmin;
}

```

```

double heartbeat(double t, double time)
{ double T;
  T = 60/heart_rate;
  if(time <= 10.0){
    if(t >= 1){
      t = delta_t;
      output = 0;
      mark1 = 0;
      t_o = 1.1;
      t_c = 1.1;
    }
  }
  else if(time <= 30.0){
    if(t >= T){
      t = delta_t;
      output = 0;
      mark1 = 0;
      t_c = 31;
      t_o = 31;
    }
  }
  else{
    if(t >= T){
      t = delta_t;
    }
  }
}

```

```

        output = 0;
        mark1 = 0;
        t_c = T+1;
        t_o = T+1;
    }
}
return t;
}

void reset()
{
rad = 1.8;
forcep = 0.0;
forcea = 0.0;
forcet = 0.0;
et = 0.0;
Plv = 0;Pla = 0;Vla = 0;
Psas = 0;Qao = 0;dQao = 0,dPsas = 0;
load_Plv = 0;Qsvn= 0;dload_Plv= 0;dQsvn = 0;
dQsas=0.0; dPsat=0.0; dQsat=0.0; dPsvn=0.0; Qsas=0.0;Psat=0.0; Psvn=0.0; Qsat=0.0;
EDV = 0; ESV = 0;
count = 0; markt = 0.5;
output=0;
mark1=0;mark2=0;mark3=0;mark4=0;
markv = 0;
}

void change_volume(double time)
{
    double target = 105;
    if(time > 15.0 && markv == 0){
        Vlv = target;
        markv = 1;
    }
    if(time > 16.0 && markv == 1){
        if((Vlv -target) > 0.05 || (Vlv -target) < -0.05){
            Vlv = target;
            markv = 2;
        }
    }
    if(time > 17.0 && markv == 2){
        if((Vlv -target) > 0.05 || (Vlv -target) < -0.05){
            Vlv = target;
            markv = 3;
        }
    }
}

```

```

    }
}

// model left atrium with the simple elstance model
void atrium(double t)
{
    double T;
    double ela, Elad = 0.1, Elas = 0.45;
    double e;
    double T1,T2;
    T = 60.0/heart_rate;
    T1 = 0.92 * T;
    T2 = 0.999 * T;

    dVla = Qsvn - Qmi;
    Vla += dVla*delta_t;

    if (t <= T1) {
        e = 0;
    }
    if (t > T1 && t <= T2) {
        e = 1 - cos((t - T1) / (T2 - T1) * 2 * pi);
    }
    if (t > T2) {
        e = 0;
    }
    ela = Elad + (Elas - Elad) * e / 2;
    Pla = 1.0 + ela * (Vla - 4.0/V0);
    Pla = Pla;
}

// mitrial valve controlling the mitrial flow
void valve3(double t)
{
double T;
    double NQmi = 0.0;
    int open;

    T = 60/heart_rate;
    if(Qmi < 0)
        NQmi = - Qmi;
    else
        NQmi = Qmi;
}

```



```

        if(Pla >= Plv) {
            open = 1;
//            mark4 = 1;
//            t_mc = t;
        }
        if(Pla < Plv) {
            if(Qmi>0){
                open = 1;
//                t_mc = t;
            }
        }
    else{
        open = 0;
//        mark4 = 0;

    }

}

```

```

if(open == 1){
dQmi = (Pla-Plv-Qmi*NQmi/CQmi/CQmi)/(Lmi);
Qmi = Qmi + dQmi*delta_t;
}
else{
dQmi = (Pla-Plv-Qmi*NQmi/CQmi/CQmi*8100)/(Lmi);
Qmi = Qmi + dQmi*delta_t;
}

```

```

}

```

```

//complex load parts

```

```

void load_complex(double t)

```

```

{

```

```

    // formulas below provide input and output values for the different vessels of the systemic
circuit

```

```

    dPsas = ((Qao - Qsas) / Csas);

```

```

    dQsas = (Psas - Psat - Rsas*Qsas)/Lsas;

```

```

// systemic artery

```

```

    dPsat = ((Qsas - Qsat) / Csat);

```

```

    dQsat = ((Psas - Psvn - (Rsat + Rsar + Rscp) * Qsat) / Lsat);

```

```

//systemic vein
dPsvn = ((Qsat - Qsvn) / Csvn);

// now advance in time
Psas = Psas + delta_t*dPsas;
Qsas = Qsas + delta_t*dQsas;
Psat = Psat + delta_t*dPsat;
Qsat = Qsat + delta_t*dQsat;
Psvn = Psvn + delta_t*dPsvn;
    Qsvn = (Psvn - Pla)/Rsvn; //important: I am looping the Qsvn back into the left atrium
}

//complex load parts constructing the at, ar, cp into artery block
void load_complex2(double t)
{
    // formulas below provide input and output values for the different vessels of the
systemic circuit
    dPsas = ((Qao - Qsas) / Csas);
    dQsas = (Psas - Psat - Rsas*Qsas)/Lsas;

    // systemic artery
    dPsat = ((Qsas - Qsat) / Ca);
    dQsat = ((Psas - Psvn - (Ra) * Qsat)/ Lsat);
//dPsat = ((Qao - Qsat) / Ca);
//dQsat = ((Pao - Psvn - (Ra) * Qsat)/ Lsat);
    //systemic vein
    dPsvn = ((Qsat - Qsvn) / Cv);

    // now advance in time
    Psas = Psas + delta_t*dPsas;
    Qsas = Qsas + delta_t*dQsas;
    Psat = Psat + delta_t*dPsat;
    Qsat = Qsat + delta_t*dQsat;
    Psvn = Psvn + delta_t*dPsvn;
        Qsvn = (Psvn - Pla)/Rv; //important: I am looping the Qsvn back into the left atrium
}

//et time function
double ftime(double t)
{
    double e;
double Ts1,Ts2,Ts3;

```

```

//T = 60/heart_rate;
Ts1 = (systolic_fraction) * (0.9 / 3);
Ts2 = (systolic_fraction) * (1.80 / 3);
Ts3 = systolic_fraction;

double cc = 1.0;
if (t <= Ts1) {
    e = 1 - cos(pi+pi*(Ts1-Ts2)/(cc*(Ts3-Ts1))+pi*(t-Ts1)*(cc*(Ts3-Ts1)-
Ts2+Ts1)/(cc*(Ts3-Ts1)*Ts1));
}
    if (t > Ts1 && t <= Ts2) {
        e = 1 - cos(pi+pi*(t-Ts2)/(cc*(Ts3-Ts1)));
    }
    if (t > Ts2 && t <= Ts3) {
        e = 1 - cos((t-Ts3)/(Ts2-Ts3)*pi);
    }
    if (t > Ts3) {
        e = 0;
    }

    return e/2;
}

//prime aortic flow
void aortic_flow(double t) {
    double T;
    T = 60.0/60;//defines the period of the heart
    if (t >= 0 && t <= systolic_fraction * T) { // this if loop defines the curve that primes the
circulatory system with a sinusoidal blood flow
        Qao = 416.6 * sin(t * pi/(systolic_fraction * T));
    }
    else Qao = 0;
}

void testcontrol(int test)
{ //R = 1.5; C = 3.0;
    RR = 1.0; RC = 1.0; in_r1 = 1.0; in_r2 = 1.0; systolic_fraction = 0.3; Vlv = 0;
    switch(test)
    {
    case 1:
        RR = 1.2;
        sprintf(name1,"waveform(Rr = 1.2).dat");
        sprintf(name2,"CO(Rr = 1.2).dat");
        break;
    case 2:

```

```

        RR = 0.8;
        sprintf(name1,"waveform(Rr = 0.8).dat");
        sprintf(name2,"CO(Rr = 0.8).dat");
        break;
    case 3:
        RC = 1.2;
        sprintf(name1,"waveform(Cr = 1.2).dat");
        sprintf(name2,"CO(Cr = 1.2).dat");
        break;
    case 4:
        RC = 0.8;
        sprintf(name1,"waveform(Cr = 0.8).dat");
        sprintf(name2,"CO(Cr = 0.8).dat");
        break;
    case 5:
    in_r1 = 1.2;
        sprintf(name1,"waveform(T = 1.2).dat");
        sprintf(name2,"CO(T = 1.2).dat");
        break;
    case 6:
        in_r1 = 0.8;
        sprintf(name1,"waveform(T = 0.8).dat");
        sprintf(name2,"CO(T = 0.8).dat");
        break;
    case 7:
        in_r2 = 1.2;
        sprintf(name1,"waveform(a = 1.2).dat");
        sprintf(name2,"CO(a = 1.2).dat");
        break;
    case 8:
        in_r2 = 0.8;
        sprintf(name1,"waveform(a = 0.8).dat");
        sprintf(name2,"CO(a = 0.8).dat");
        break;
    case 9:
    Vlv = 120;
        //systolic_fraction = 0.3;
        sprintf(name1,"waveform(Vlv = 120).dat");
        sprintf(name2,"CO(Vlv = 120).dat");
        break;
    case 10:
        Vlv = 60;
        //systolic_fraction = 0.2;
        sprintf(name1,"waveform(Vlv = 60).dat");
        sprintf(name2,"CO(Vlv = 60).dat");
        break;

```

```

    case 11:
//Vlv = 0;
        systolic_fraction = 0.4;
        sprintf(name1,"waveform(sf = 0.4).dat");
        sprintf(name2,"CO(sf = 0.4).dat");
        break;
    case 12:
//Vlv = 0;
        systolic_fraction = 0.2;
        sprintf(name1,"waveform(sf = 0.2).dat");
        sprintf(name2,"CO(sf = 0.2).dat");
        break;
    case 13:
//Vlv = 120;
        sprintf(name1,"waveform(normal).dat");
        sprintf(name2,"CO(normal).dat");
        break;
    }
Ra = 3.0*RR, Ca = 2.5*RC, Rv = 0.075*RR, Cv = 20.5*RC;Csas = RC*0.08;
Rsas = RR*0.003;
    printf("%lf\t%lf\t%lf\t%lf\n", Ra, Rv, Ca, Cv);
}

```