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CONTINUOUS LEFT VENTRICULAR EJECTION FRACTION MONITORING BY CENTRAL AORTIC PRESSURE WAVEFORM ANALYSIS

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CONTINUOUS LEFT VENTRICULAR EJECTION FRACTION MONITORING BY CENTRAL AORTIC PRESSURE WAVEFORM ANALYSIS

By

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ABSTRACT

CONTINUOUS LEFT VENTRICULAR EJECTION FRACTION MONITORING BY CENTRAL AORTIC PRESSURE WAVEFORM ANALYSIS

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Left ventricular ejection fraction is one of the most significant measures of heart health used in medical practice today. Unfortunately, measuring left ventricular ejection fraction through imaging (e.g. echocardiography), the method used most commonly in clinical practice, requires heavy machinery and a skilled operator. Thus, measurements can only be taken periodically. To combat these disadvantages, we have developed an algorithm that uses central aortic blood pressure waveform analysis to continuously (i.e. automatically) determine left ventricular ejection fraction. To validate this technique, we have used hemodynamic data collected from nine dogs placed under a variety of hemodynamic stresses and instrumented to provide the data necessary for analysis. The results of this data analysis show a strong agreement between the measured left ventricular ejection fraction and that estimated by the algorithm. With additional testing, this algorithm could be used to continuously and automatically measure left ventricular ejection fraction in situations where an aortic catheter is already used. Future efforts to adapt the algorithm to routinely measured peripheral artery pressure waveforms are warranted.

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1. Introduction

1.1 Significance

Left Ventricular Ejection Fraction (LVEF), the ratio of stroke volume (SV) to end-diastolic volume (EDV), is one of the most powerful clinical measures of cardiovascular function [Katz 1992]. For instance, if a patient being monitored has been shown to have low cardiac output (CO), the rate of blood being pumped out of the heart, then the ejection fraction can be used to help determine what kind of problem the heart is having. If LVEF is low, then there is a problem with the left ventricles ability to pump blood out (systolic failure); however, if the LVEF is normal or high, then the problem is somewhere within the filling mechanism of the ventricle (diastolic failure). In addition, epidemiological data has shown a strong relationship between LVEF and outcome in outpatients with heart failure [Curtis et al. 2003]. Moreover, LVEF is being considered as a means to determine what type of treatment patients should receive. It has been recommended that an implantable device, the internal defibrillator, which is very expensive but potentially life-saving, should be used in cases where LVEF is less than or equal to thirty percent [Moss et al. 2002]. These, along with other applications, make the measurement of LVEF an important part of hemodynamic monitoring.

1.2 Current Methods

LVEF is currently measured in clinical settings through a variety of methods. The most common clinical techniques for measuring LVEF are

radionuclide angiography, echocardiography, and magnetic resonance imaging (MRI). Radionuclide angiography, the most invasive of the three methods, is done by injecting a small amount of radioactive material into the blood stream and using cameras designed to detect the radioactively marked blood as it travels through the body. A specialist will then review the recordings of this camera and use them to determine what problems may exist with the heart and circulatory system, as well as LVEF. Radionuclide angiography is considered the most accurate of the commonly used clinical techniques for measuring LVEF. Echocardiography, also known as trans-thoracic echocardiography, is the most commonly used method for determining LVEF in the clinical setting [Rumberger et al. 1997]. LVEF is measured through echocardiography by placing a person under a machine which records images through the use of sound waves. These images are then reviewed by an expert and LVEF is determined based on the volume of the left ventricle at the end of diastole and at the end of ejection. An illustration of this method can be seen in Figure 1. Echocardiography has been shown to compare closely with radionuclide angiography but the measurements do not match exactly [Habash-Bseiso et al. 2005]. MRI and other imaging techniques are also sometimes used following a similar method to that of echocardiography. These methods are less common than echocardiography because they come at a higher cost.

There are also several methods for measuring LVEF that have been suggested or proven in research settings but have not been put in to clinical

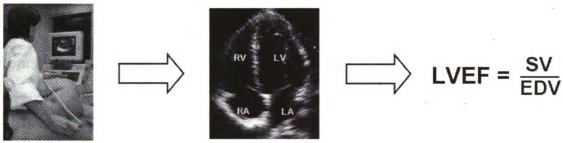

Figure 1. Illustration of LVEF measurement through echocardiography

practice due to the invasiveness or other difficulties of the procedures. The first of these methods is the non-imaging nuclear monitoring method [Dellegrottaglie et al. 2002]. This method relies on the same principles as radionuclide angiography but uses an automated nuclear probe which must be placed on the body in lieu of the imaging camera and professional analysis. Additionally, a conductance catheter method has been developed to automatically and continuously monitor LVEF [Burkhoff 1990]. This method requires the insertion of a catheter into the body to measure left ventricular volume and from that ejection fraction is calculated. Implanted sonomicrometry crystals can also be used to measure left ventricular volume and LVEF [Rushmer et al. 1956]. This method requires open heart surgery to implant sonomicrometry crystals at certain locations on the heart. These crystals then continuously measure certain dimensions of the heart which can be used to calculate the volume of the heart based on the known geometry of the heart. A summary of the available methods for measuring LVEF along with their advantages and disadvantages can be found in Table 1.

METHOD	ADVANTAGES	DISADVANTAGES
Conductance catheter	continuous	invasive, inaccurate
continuous thermodilution	continuous	right ventricular EF only
Imaging (e.g., echo)	non-invasive	expert operator, expensive
non-imaging nuclear monitor	non-invasive, continuous	too difficult to position
Ultrasonic crystals	continuous	thoracotomy

Table 1. A summary of the current methods for measuring left ventricular ejection fraction and their advantages and disadvantages

1.3 Limitations of Current Methods

All of the current methods have limitations which keep them from being an optimal solution for patient care. The imaging methods (e.g. echocardiography) generally share the downfall of being operator and equipment intensive. This causes two major problems. First, there is a high cost to do imaging based measurements of LVEF. This high cost results from the high cost of equipment and the high cost of skilled operators for a long period of time per measurement. This high cost may be one factor that prohibits there being enough measurements of LVEF to properly track the progress of the patient. It is uncommon in clinical settings to have LVEF measured more than one or two times a day and that is only done when there is reason to believe that there has been a significant change in hemodynamic state. The fact that LVEF measurement through imaging techniques is so operator intensive also prevents the measurements from being continuous. A continuous measurement of LVEF

would be advantageous because it would allow the physicians caring for the patient to immediately see the effects of any treatments they may be administering.

The continuous and automatic methods mentioned in the previous section (e.g. sonomicrometry crystals) allow for continuous measurement of LVEF but also have their own limitations. Although the specifics of these limitations vary, the basic reasons these methods are not used clinically are generally the same. First, these measurements require highly invasive procedures which add a large amount of risk to the measurement of LVEF. Since this risk can be avoided by using imaging methods, imaging methods are much more commonly used at the cost of continuous measurement. These methods also do not alleviate the limitations caused by high cost. Since these methods require highly invasive procedures, they also require highly skilled medical professionals to administer them. These limitations prevent the current continuous and automatic methods from being used in practice.

1.4 Proposed Solution

In order to measure LVEF continuously, automatically, and non-invasively (or minimally invasively), we propose, as our overall hypothesis, using mathematical analysis of routinely measured blood pressure waveforms to estimate LVEF. Specifically, the ultimate goal of this research is to use peripheral blood pressure waveforms, along with a model of the hearts functionality, to calculate LVEF continuously. In this thesis, I present a method

for calculating LVEF from the central aortic blood pressure (CAP) waveform. Although this waveform is not commonly measured in clinical practice due to the invasive nature of its measurement, analysis of these waveforms is simpler than analysis of peripheral blood pressure waveforms as will be described later. Thus, this thesis may be viewed as a first step towards proving our overall hypothesis and monitoring LVEF from routinely measured peripheral blood pressure waveforms.

1.5 Similar Work

There have been related attempts in the past to use a modeling based technique estimate hemodynamic parameters from blood pressure. First, a method presented by Guarini et al. uses a model based approach to measure many different hemodynamic parameters including EDV (from which LVEF can be calculated since CO is also measured in this case) from arterial blood pressure waveforms and a cardiac output measurement [Guarini et al. 1996]. This methodology yielded good results using computer generated data but was not verified against a gold standard in experimentally collected data. This lack of accuracy with actual data suggests although some assumptions about some of the parameters were made, the method was not able to predict this many parameters. The other downfall of this method is that it requires the continuous measurement of CO which requires an operator and invasive procedures to measure. For this reason, the method has little advantage over currently available methods for measuring LVEF.

In addition, a method developed by Xiao et al. attempts to use certain non-invasive blood pressure measurements and a hemodynamic model to calculate certain parameters of heart functionality. The method showed promise in calculating total systemic resistance and some promise in calculating other parameters such as EDV and maximum left ventricular elastance (E_{max}). This method, however, did not show promise in accurately estimating LVEF or SV (from which LVEF could be calculated given the estimation of EDV).

2. Method

2.1 Introduction to the Method

Our model based method for estimating LVEF from the CAP waveform is based off of two previously developed models. The first model used in our method, a lumped parameter model using the Windkessel model to represent the arterial branches, is a model of the arteries. The second model used is a model of left ventricular elastance (E_{lv}) over time which reduces the elastance over a heart beat to a function of several parameters. These two models will allow us to do a minimum square error parameter fitting which will allow for estimation of LVEF.

2.2 The Lumped Parameter Model of the Circulatory System

A lumped parameter model of the circulatory system allows for the physiology of the system to be represented by only a few values which summarize the effects of all of the blood vessels throughout the body and the heart. The cardiovascular system can be viewed as a hydraulic system for the purpose of these models. Hydraulic systems parallel electrical systems in many ways. A summary of the analogous terms used in hydraulic systems versus electrical systems can be seen in Table 2. All relationships found in electrical systems between the values summarized are maintained in hydraulic systems. This terminology will be used in order to treat the analysis of the cardiovascular system as circuit analysis to derive the necessary equations to accomplish our goal.

Hydraulic Variable	Electrical Variable
Pressure	Voltage
Flow	Current
Volume	Charge
Resistance	Resistance
Capacitance	Capacitance

Table 2. A summary of the parallels between hydraulic systems and electrical systems

Both of the lumped parameter models I will discuss in this thesis involve the Windkessel model. The Windkessel model is a model of the body's blood vessels which assumes that they can be modeled by a parallel combination of resistance, which represents the smallest blood vessels, and capacitance, which represents the large arteries that store blood. The heart can then be modeled in one of two ways to complete the cardiovascular picture. First, the heart can be modeled as a current source where the current represents cardiac output, the blood flowing out of the heart. Figure 2 shows a lumped parameter model of the circulatory system using a current source to represent the heart.

This version of the lumped parameter model has been shown to work in a method to estimate proportional SV from the CAP waveform [Bourgeois et al. 1976]. Bourgeois et al. used a CAP waveform measured through aortic catheterization and this model to estimate proportional SV. The test animals were also instrumented with a highly invasive aortic flow probe which gave the experimenters the exact value of SV to compare to their results. The

experimental animals were also subjected to a number of pharmacological interventions which allowed the experimenters to verify the method over a wide range of hemodynamic states. When the estimated SV was compared to the actual value of SV there was a linear relationship with a slope equal to the arterial compliance (C_a). This was the result that was expected based on there equations derived from the lumped parameter model above and the CAP waveform.

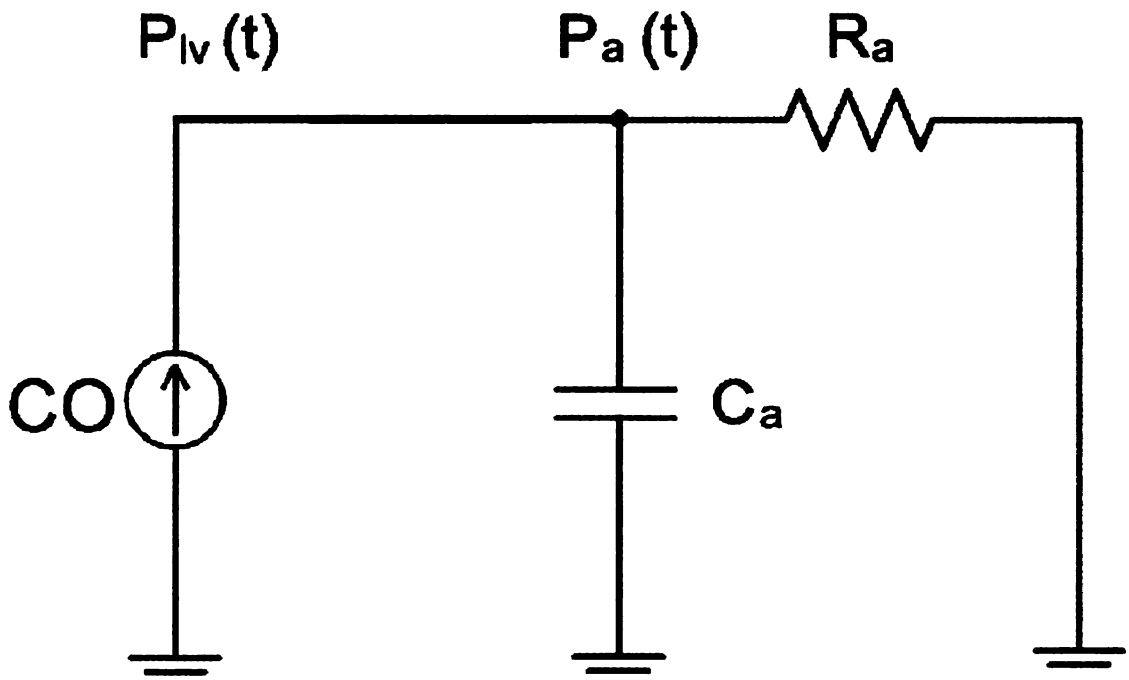

Figure 2. A lumped parameter model of the circulatory system which uses a current source with the value of cardiac output to represent the left ventricle

The successful implementation of this method proves two key facts about the lumped parameter model and the cardiovascular system. First, it proves that the Windkessel model of the arterial system along with a current source representing the heart is a reasonably accurate model of central aortic pressure.

Second, it proves that C_a does not vary significantly over a monitoring period even under highly varying hemodynamic conditions. If C_a did vary, the results would not have shown a linear relationship between estimated proportional SV and measured SV, because estimated proportional SV is multiplied by a factor of C_a. Based on those results, we will later assume that C_a is constant over a monitoring period to measure proportional SV or a single beat to measure LVEF.

The second version of the lumped parameter model using the Windkessel model of the blood vessels is the version that is used in our algorithm. This model replaces the current source as the model of the heart with a time variant capacitor [Sagawa et al. 1977]. This model of the heart is based on the fact that the heart acts like a capacitor for blood that varies in capacity as the heart squeezes during systole. This model for the circulatory system can be seen in Figure 3.

We choose to use the model of the circulatory system which models the left ventricle as time varying capacitance as opposed to a current source with the value of cardiac output for two reasons. First, we have a model for elastance, which is equal to one divided by the capacitance, which reduces the problem of determining elastance to the estimation of only a few parameters of the elastance function. This model will be introduced in the next section. The second reason is that this elastance model provides the framework necessary to estimate ejection fraction from a central aortic blood pressure waveform. The model using a current source to represent the left ventricle does not take advantage of enough information to accurately estimate ejection fraction.

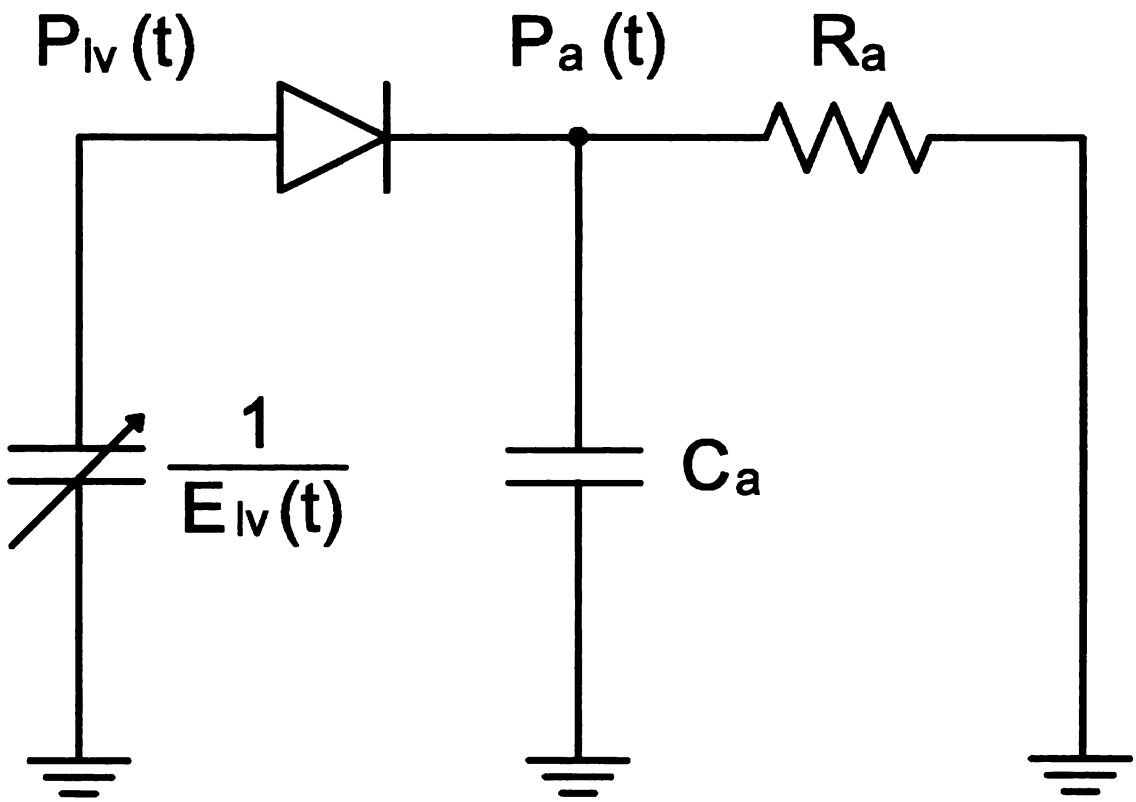

Figure 3. A lumped parameter model of the circulatory system which uses a time varying capacitor to represent the left ventricle

Notice that in both models of the circulatory system shown here, there is an ideal diode between the portion of model representing the left ventricle and the portion representing the arterial system. This diode represents the heart valve that allows blood to flow out of the heart into the aorta but does not allow blood to flow back into the heart. We model this as an ideal diode with no resistance. There is some resistance in the true cardiovascular system in series with the valve but this resistance is assumed to be negligible which has been shown to be valid when the heart valve does not show significant signs of stenosis. The result of this is that during systole, when the valve is open, $P_{lv}(t)$ is equal to $P_a(t)$.

2.3 The Raised Cosine Model of Time-Varying Elastance

Using only the lumped parameter model of the heart suggested in the last section and making no assumptions about the elastance curve, we find that knowledge of CAP yields less equations than the unknowns provided by the system. In that case the system is underdetermined and cannot be used to find any additional data about the hemodynamic state of the subject.

For this reason, we make an additional assumption about the form of the elastance curve. Empirical data has shown that when the elastance curve is normalized over maximum left ventricular elastance (E_{max}), minimum left ventricular elastance (E_{min}), and duration of systole (T_s, the time over which elastance is increasing) it will always have the same form even for a wide variety of patients [Heldt et al. 2002]. A summary of this data is shown in Figure 4.

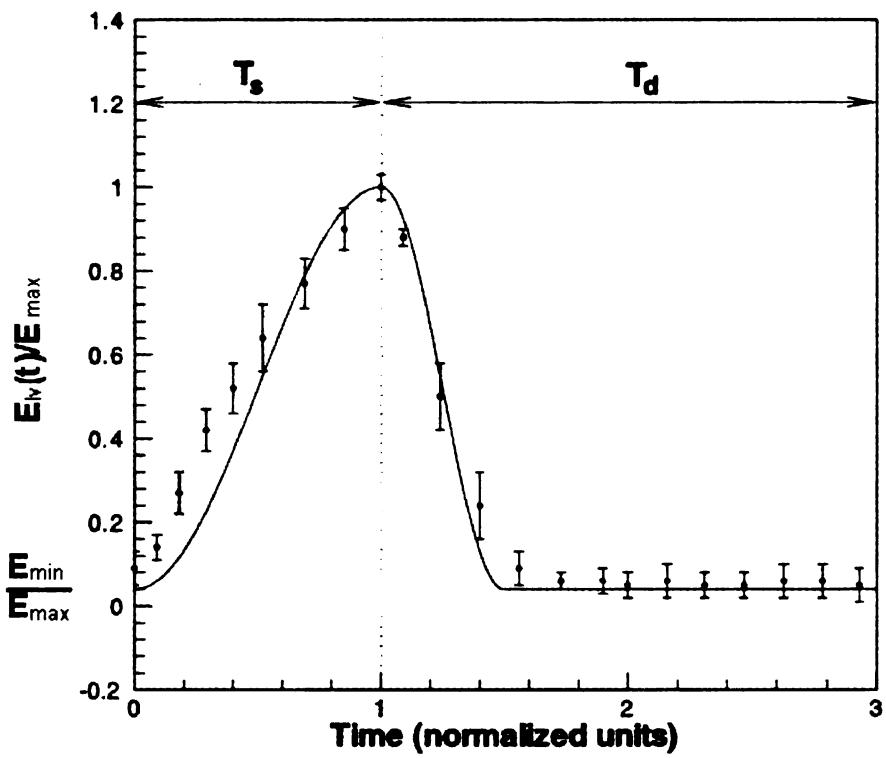

Figure 4. A summary of empirical data normalized to E_{max}, E_{min}, and T_s

This empirical data was then analyzed and found to closely match the form of a raised cosine that is a function of E_{max}, E_{min}, T_s, and time. This cosine curve can also be seen in Figure 4. Note that the area of closest agreement between the empirical data and the raised cosine is near the peak of the raised cosine. This close approximation at the top of the elastance curve is what is most important for our method as our method will concentrate on the period of ejection which is found to be around the top of the elastance curve. The equation of the raised cosine function used to parameterize elastance is:

$$\frac{E_{lv}(t)}{E_{\max}} = \begin{cases} \frac{E_{\min}}{E_{\max}} + \frac{E_{\max} - E_{\min}}{2E_{\max}}\left\{1 - \cos\left(\frac{\pi t}{T_s}\right)\right\}, & 0 \le t < T_s \\ \frac{E_{\min}}{E_{\max}} + \frac{E_{\max} - E_{\min}}{2E_{\max}}\left\{1 + \cos\left(\frac{2\pi(t - T_s)}{T_s}\right)\right\}, & T_s \le t < \frac{3}{2}T_s \\ \frac{E_{\min}}{E_{\max}}, & \frac{3}{2}T_s \le t, \end{cases}$$

We have also chosen to further reduce the parameters being searched over by assuming E_{min} to be .05*E_{max}. This assumption is based off of empirical data as well as the fact that the effect of E_{min} on the fitting of the curve should be minimal since the fitting will be done during the ejection interval which is near the top of the elastance curve. With this equation and the lumped parameter model described in section 2.2, we are now able to develop a system of equations which will allow us to estimate some unknown hemodynamic parameters in order to estimate LVEF. The derivation of this method will be shown in the next section.

2.4 Derivation of the Mathematical Method

Our model for the circulatory system and our model for the function of the heart can be combined in order to estimate some of the hemodynamic parameters of the system. The combination of the two models requires doing a circuit analysis of the circuit using all that is known about the parameters of the circuit. The derivation is started based on the fact that the blood flowing out of the heart must equal the blood flowing into the peripheral blood vessels. The equation for blood flowing out of the heart is:

$$i_{out} = \frac{d(C_{lv}(t) * P(t))}{dt}, \tag{1}$$

where i_{out} is the blood flow leaving the left ventricle, P(t) is the left ventricular pressure and the aortic pressure which are assumed to be equal, and:

$$C_{lv}(t) = \frac{1}{E_{lv}(t)}. \tag{2}$$

The equation for the blood entering the blood vessels is:

$$i_{in} = \frac{-C_a * dP(t)}{dt} - \frac{P(t)}{R_a}, \tag{3}$$

where i_{in} is the blood flow entering the aorta and C_a and R_a are the arterial capacitance and resistance respectively. The fact that blood flowing into the heart must equal blood flowing out of the heart is summarized as:

$$i_{out} = i_{in}. \tag{4}$$

By combing equations 1, 2, 3, and 4 we arrive at:

$$\frac{d\dfrac{P(t)}{E_{lv}(t)}}{dt} = \frac{-C_a * dP(t)}{dt} - \frac{P(t)}{R_a} \quad (5)$$

Then the equation is divided by C_a on both sides and integrated to yield the following:

$$\frac{P(t)}{C_a * E_{lv}(t)} = -P(t) - \frac{\int_0^t P(t)dt}{\tau} + C, \quad (6)$$

where τ is equal to the product of total peripheral resistance, R_a, and arterial capacitance, C_a, and C is the constant of integration. Time 0 is defined to be at the start of ejection. By observing the system at the start of ejection, C can be defined as:

$$C = \frac{P(0)}{C_a * E_{lv}(0)} + P(0). \quad (7)$$

The combination of equations 6 and 7 is:

$$\frac{P(t)}{C_a * E_{lv}(t)} = -P(t) - \frac{\int_0^t P(t)dt}{\tau} + \frac{P(0)}{C_a * E_{lv}(0)} + P(0). \quad (8)$$

The left side of equation 7 can easily be recognized as the volume of the left ventricle divided by C_a. The right side of the equation is the total blood flow through the aorta plus the volume of the heart at time 0 divided by C_a.

From equation 7 it is easy to derive the equation for proportional SV, SV divided by C_a, developed by Bourgeois et al. To do this, simply subtract proportional left ventricular volume at the end of ejection from the proportional volume at the beginning of ejection. This yields:

$$\frac{SV}{C_a} = P(eej) - P(0) + \frac{SA}{\tau}, \tag{9}$$

where SA is the integral of CAP over the period of ejection and P(eej) is CAP at the end of ejection. This is simply a function of CAP which is assumed to be a known waveform in this research; therefore, proportional stroke volume can simply be calculated by CAP waveform analysis.

The most difficult parts of calculating proportional stroke volume from CAP is properly identifying the beginning and end of ejection on the CAP waveform and calculating τ. The morphology of a CAP waveform containing little corruption due to reflections can be seen in Figure 5. As shown on the figure, when ejection starts there is a large spike in CAP as a result of the large increase in volume which is being pumped from the heart. The end of ejection is also recognizable on the waveform as a slight bump, called the dicrotic notch, in the decreasing side of the blood pressure waveform which occurs as a result of the valve closure and a small amount of blood flow back into the heart during the valve closure. To detect these points on the blood pressure waveform we used a

previously developed method for detecting the beginning of ejection and the maximum point of the blood pressure waveform for each beat. This algorithm searches the waveform for a local maximum over a window of about half of the size of the period of the waveform. The period of the waveform is assumed to be one divided by the heart rate although there is some beat to beat variation in this. Once the location of the maximum value of CAP for this beat is detected, the algorithm steps backwards in time through the data looking for the point at which the slope goes from positive to negative. This point is marked as the start of the upslope of blood pressure, which is also the start of ejection for that beat. After the operation of this algorithm, it is still necessary to detect the dicrotic notch signifying the end of ejection. In order to do this, we use a similar method as that used to detect the beginning of ejection. The algorithm steps forward in time from the maximum looking for the point at which the slope goes from negative to positive. This point is marked as the end of ejection.

Calculating τ from the CAP waveform requires some additional understanding of the waveform. During the diastolic portion of the waveform, when ejection is not occurring, the heart portion of the lumped parameter model has no effect on the CAP waveform. For this reason, the pressure is simply decaying across a parallel combination of a resistive load and a capacitive load. From circuit theory, it is known that the pressure will decay exponentially with a rate of speed based on the time constant, τ, which is the product of the capacitance and the resistance. Therefore, if the diastolic decay of the CAP

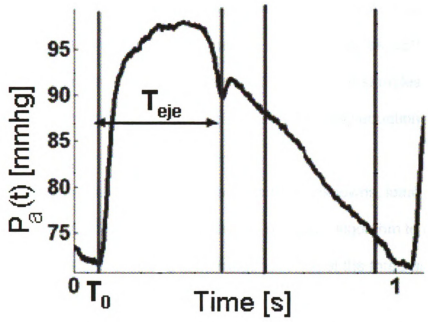

Figure 5. A single heart beat taken from a CAP waveform with little to no effects from wave reflections

waveform is plotted on a semi-logarithmic scale it will become a line with slope τ. This methodology is used to calculate τ in both the calculation of proportional stroke volume and the estimation of LVEF.

LVEF is somewhat more difficult to estimate than proportional SV is to calculate since it relies on more than just the difference between the pre-ejection and post-ejection volumes. LVEF also relies on the pre-ejection volume itself which does not allow it to be derived from equation 8 without the appearance of E_{lv}. For this reason the raised cosine model of E_{lv} is now used to make both sides of equation 8 a function of four parameters. Each side is a function of C_aE_{max}, the maximum left ventricular elastance multiplied by the aortic capacitance, T_s, the duration of time the elastance of the left ventricle is increasing, T_{begin}, the time at which ejection begins relative to the beginning of

systole, and time. Note that both sides would also be a function of C_aE_{min} if we did not previously assume that C_aE_{min} could be approximated as $.05*C_aE_{max}$ for this application. Since digitized measurements of CAP have samples at many different points in time during ejection, we are left with many equations and three unknowns.

To estimate the values of our three remaining unknowns, least square error fitting is implemented. Initially, we use a very basic algorithm to do least square error fitting. First, an acceptable range for each of the three unknowns is selected. The acceptable values for C_aE_{max} are based on previously collected hemodynamic data and are left at a very wide range as this is the most difficult variable to parameterize. The values of C_aE_{max} searched over in order to produce the results shown later in this thesis are .5 to 20.5. Values for T_s and T_{begin} are based on the definitions of these values and the morphology of the pressure waveform. The value of T_s is limited to being a fraction of the period of the blood pressure waveform since the systolic interval cannot be greater than the entire period of the heart. The range of T_s considered acceptable is also based on previously analyzed data. T_s is limited to values between one fifth and one half of the period. The range of acceptable values for T_{begin} range from 0, which means that ejection starts as soon as the heart starts to squeeze, to T_s, which means that the heart begins to eject at the last moments of systole. We then search over a set of equally spaced combinations of these values to find the value with the minimum squared error. The values of the three unknown

parameters which result in the minimum value of square error are considered the estimated hemodynamic state of the subject.

These values are then plugged in to the left hand side of equation 8 to calculate proportional stroke volume and end diastolic volume. The last step in calculating LVEF is to make an assumption about the unstressed volume of the heart. The unstressed volume of the heart is the volume at which there will be a blood pressure of zero. This volume cannot be determined from central aortic blood pressure and therefore must be accounted for now. An assumption of this value divided by C_a is made based on the size of the dog and previously analyzed hemodynamic data, and this value is then added to the previously estimated value of end diastolic volume. The final equation for left ventricular ejection fraction is:

$$LVEF = \frac{\frac{P_a(0)}{C_a * E_{lv}(0)} - \frac{P_a(es)}{C_a * E_{lv}(es)}}{\frac{P_a(0)}{C_a * E_{lv}(0)} + \frac{V_{lv0}}{C_a}}, \qquad (10)$$

where es is the time at which systole ends and V_{lv0} is the unstressed volume of the left ventricle.

2.5 Faster Execution of the Method

As stated in the previous chapter, the purpose of this method is to obtain a continuous and automatic measure of LVEF from CAP waveform analysis. In order to have a truly continuous measure it is necessary that the algorithm be able to operate on a real time basis. This means that the time the algorithm

requires to execute the least square error parameter fitting for a single beat must be less than the period of the CAP waveform. The execution time of the algorithm also includes all waveform morphology detections and all other calculations needed to execute the method. A three parameter search method as described in the previous section has an operational time proportional to the product of the number of sample points used for each parameter. Therefore, reducing the number of parameters which are estimated via a search method will reduce the execution time of the method by a factor of the number of sample points used for each parameter reduced. Since the three parameter search method described in the previous section was found to need a longer execution time per beat then the period of the waveform, we have developed an alteration to the algorithm which reduces the number of parameters to be searched over.

Linear algebra theory states that the value of a parameter which results in the least square error between two sides of a function can be calculated through a series of matrix multiplications if the function can be expressed as a linear function of the unknown parameter. This means that if a function is of the form:

$$\mathbf{A} = X\mathbf{B}, \tag{11}$$

then if the vectors **A** and **B** are known, the unknown value, X, can be calculated through a series of matrix functions rather than requiring that all possible values of X be searched over as done in the previous section. Therefore, we have modified the equations from the previous section to derive a linear function of C_aE_{max} so that C_aE_{max} can be calculated through a series of matrix calculations,

and the algorithm can be executed in a much shorter time as it does not require searching over a very wide range of possible values for C_aE_{max}.

In order to make these equations more easily read, we will first define C(t), the part of our model equation for $E_{lv}(t)$ not dependant on E_{max} as:

$$C(t) = 1 - \cos\left(\frac{\pi * t}{T_s}\right), \qquad 0 \le t < T_s$$

$$= 1 + \cos\left(\frac{2\pi(t - T_s)}{T_s}\right), \qquad T_s \le t < \frac{3}{2}T_s$$

$$= 0 \qquad otherwise. \qquad (12)$$

Using this equation, we represent left ventricular elastance as:

$$E_{lv}(t) = E_{\min} + \frac{E_{\max} - E_{\min}}{2} C(t). \qquad (13)$$

This equation can be further reduced because we have assumed that E_{min} is equal to $.05*E_{max}$. We therefore rewrite equation 13 as:

$$E_{lv}(t) = .05 * E_{\max} + .475 * E_{\max} * C(t). \qquad (14)$$

Using this equation for E_{Iv} we can rewrite equation 8 as:

$$\frac{P(t)}{.05 * C_a E_{\max} + .475 * C_a E_{\max} * C(t)} =$$

$$-P(t) - \frac{\int_0^t P(t)dt}{\tau} + P(0) + \frac{P(0)}{.05 * C_a E_{\max} + .475 * C_a E_{\max} * C(0)} \cdot$$

(15)

This equation can be adjusted as follows:

$$.05 * C_a E_{\max} + .475 * C_a E_{\max} * C(t) =$$

$$\frac{P(t)}{-P(t) - \frac{\int_0^t P(t)dt}{\tau} + P(0) + \frac{P(0)}{.05 * C_a E_{\max} + .475 * C_a E_{\max} * C(0)}} \cdot$$

(16)

Multiplying both sides by one over C_aE_{max} and rearranging terms results in:

$$\left(-P(t) - \frac{\int_0^t P(t)dt}{\tau} + P(0) \right) * C_a E_{\max} =$$

$$\frac{P(t)}{.05 + .475 * C(t)} - \frac{P(0)}{.05 + .475 * C(0)}. \quad (17)$$

This equation is now a linear equation of C_aE_{max} with all of the other values being known for a give pair of T_s and T_{begin}. The method can now achieve the same results as before by searching over only two parameters and calculating the value C_aE_{max} which minimizes square error.

3. Experiments

3.1 Introduction to Experiments

In order to verify that the mathematically developed method presented in chapter two can work on real data it is necessary to collect such real data in a manner that allows for the verification of the method. This is best done when the most information about the state of the subject is available. Collection of information such as stroke volume, left ventricular volume, central aortic blood pressure, and left ventricular ejection fraction is desired in such an experiment. The measurement of peripheral blood pressure is also desired as it will allow us to validate are overall hypothesis in the future. It is also important that the method be verified over as many different hemodynamic states as possible. This means that the hemodynamic data should be collected while the subject of the experiment is put under a number of experiments which affect the waveforms being measured. Since the collection of some of these waveforms requires very invasive procedures and the hemodynamic state of the subject must be varied, collection of this type of data in humans is too dangerous. For that reason, varying experiments on nine dogs have been done which collect some data which can be analyzed to verify this method. Specifics of the experiments and the data gathered will be covered in the sections that follow.

3.2 Sonomicrometry Crystals and Chronic Pacing Experiments

The first set of experiments used in order to verify the functionality of the method presented in chapter two were performed on five dogs. The purpose of

these experiments was to test the method under conditions of reduced cardiac function in order to verify that the method can detect this state.

These experiments measured all of the important hemodynamic waveforms to verify the method. First, they measured left ventricular volume through a two-dimensional sonomicrometry crystal method. This method requires the implantation of four sonomicrometry crystals in to the walls of the heart such that two dimensions of the heart are accurately measured. These dimensions of the heart are then used in conjunction with the known geometry of the heart to calculate left ventricular volume. In addition, CO and SV were measured using an aortic flow probe which is placed around the aorta and measures the rate at which blood leaves the heart. LVEF is then calculated as the ratio of stroke volume from the aortic flow probe to end diastolic volume measured by the sonomichrometry crystals. The last needed parameter for the verification of the technique is central aortic blood pressure. The dogs in these experiments were also instrumented with an aortic catheter which was used to measure central aortic blood pressure.

The experiments also used a technique known as chronic pacing to reduce the functionality of the heart as measured by LVEF. In chronic pacing, electrical pacing wires are attached to the heart to cause it to beat at a much faster rate than the heart would normally pace itself. This pacing is continued over a long period of time, in this case, several weeks. After the pacing wires are removed and the heart is allowed to return to a self regulated state, the heart stills shows semi-permanent effects of the pacing. SV and LVEF are both greatly

reduced and end diastolic volume has been shown to increase. Since LVEF is reduced by this process, these experiments mimic a heart which is performing at reduced capacity due to chronic heart failure or other similar heart diseases. A summary of the instrumentation of the dogs in these experiments can be found in Figure 6.

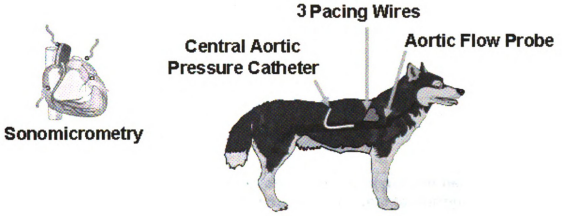

Figure 6. A summary of the instrumentation of the subjects used in the first set of experiments which concentrate on reduced cardiac function

The values of many key hemodynamic parameters vary greatly over the many subjects in these experiments. LVEF, SV, mean CAP, and several other parameters show a great deviation between the control measurements taken before chronic pacing and the heart failure measurements take after chronic pacing. A summary of the range of hemodynamic parameters found in the control measurements of these experiments can be found in Table 3 and a summary for the range of hemodynamic parameters found in heart failure can be found in Table 4.

These experiments provide all of the necessary measurements needed to verify the functionality of the method presented in this thesis. LVEF is measured

through the use of sonomicrometry crystals and an aortic flow probe, and CAP is measured through central aortic catheterization. Chronic pacing allows the same subject to have measurements taken for a heart functioning normally and a heart functioning at a reduced level.

	Minimum	Maximum	Average
Mean Heart Rate (beats/min)	94.7	122.1	112.0
Mean CAP (mmHg)	97.89	130.13	115.84
Mean LVEF (%)	50.45	69.74	61.56
Mean SV (ml)	32.75	49.12	39.01

Table 3. A summary of the mean values of certain important hemodynamic parameters measured in the chronic pacing experiments during control experiments. This table shows the wide range of hemodynamic parameters seen between dogs in their control states.

	Minimum	Maximum	Average
Mean Heart Rate (beats/min)	111.2	177.0	137.6
Mean CAP (mmHg)	74.62	115.56	92.92
Mean LVEF (%)	26.33	37.62	30.79
Mean SV (ml)	20.87	29.32	25.07

Table 4. A summary of the mean values of certain important hemodynamic parameters measured in the chronic pacing experiments during heart failure experiments. This table shows the wide range of hemodynamic parameters seen between dogs in their heart failure states as well as the large contrast between the hemodynamic state of the dogs in their control and heart failure states.

3.3 Dobutamine

Another set of experiments used to verify this technique were done on three dogs. These experiments were performed to test the effectiveness of the method under drug induced improved hemodynamic state.

These experiments provide only limited knowledge of the hemodynamic state. In these experiments there is no direct measure of LVEF, CO, or SV, so the results of implementing the method can not be verified against exact numbers. The results are instead verified only qualitatively against the known increase in LVEF seen with the administration of a commonly experimentally used drug, dobutamine. Like the dogs in the first set of experiments, the dogs in these experiments were also instrumented with an aortic catheter which was used to measure central aortic blood pressure. The instrumentation of the subjects of these experiments can be seen in Figure 7.

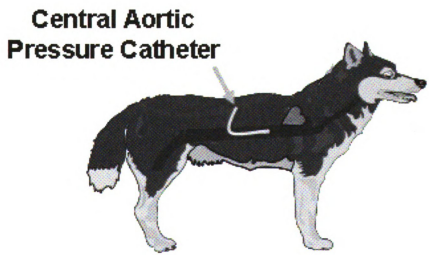

Figure 7. A summary of the instrumentation of the subjects used in the second set of experiments which concentrate on drug induced increased cardiac function

In order to vary the hemodynamic state during these experiments pharmacological intervention was used. Dobutamine, a drug used to temporarily increase the functionality of the heart was administered to each of the dogs in varying amounts. Measurements of central aortic blood pressure were made at a control state when no drugs were being administered and at states where varying levels of dobutamine were administered. It is known that LVEF increases with increasing dosages of dobutamine so the results of our method can be verified qualitatively without a direct measure of LVEF. Table 5 provides a summary of the variations in hemodynamic data in the dogs during control and Table 6 provides the same data for the dogs under the effects of dobutamine.

These experiments provide a measure of CAP and a qualitatively known variation in LVEF through which the method can be verified. This data allows for the verification of the method in control subjects as well as in those same subjects with increased heart functionality due to the administration of drugs. This is a good compliment to the first data set which verifies the method in subjects with reduced heart functionality.

	Minimum	Maximum	Average
Mean Heart Rate (beats/min)	104.0	111.8	108.9
Mean CAP (mmHg)	70.63	87.66	76.70

Table 5. A summary of the mean values of certain important hemodynamic parameters measured in the dobutmaine experiments during control experiments. This table shows the wide range of hemodynamic parameters seen between dogs in their control states.

	Minimum	Maximum	Average
Mean Heart Rate (beats/min)	134.0	198.0	156.1
Mean CAP (mmHg)	71.50	92.73	80.90

Table 6. A summary of the mean values of certain important hemodynamic parameters measured in the dobutamine experiments during dobutamine administration. This table shows the wide range of hemodynamic parameters seen between dogs during dobutamine administration as well as the large contrast between the hemodynamic state of the dogs during control and dobutamine administration experiments.

3.4 Echocardiography and Pharmacological Interventions

The last experiment used in this study included only one dog. The purpose of this experiment was to test the method under conditions of both reduced cardiac function and increased cardiac function based on the effects of different pharmacological interventions.

Like the first set of experiments, this experiment measured all of the important hemodynamic parameters to verify the method. In this experiment, LVEF was measured periodically through the most common clinical measurement technique, echocardiography. To do this, echocardiograms were taken and analyzed by specialists to determine the volume of the heart at the beginning and end of ejection. Also like the first set of experiments, CO and SV were measured using an aortic flow probe. LVEF is then calculated as the ratio of stroke volume from the aortic flow probe or echocardiography (both values are the same) to end diastolic volume measured by echocardiography. An aortic catheter was used to measure central aortic blood pressure as in the first two

sets of experiments. A summary of the instrumentation of the dogs in these experiments can be found in Figure 8.

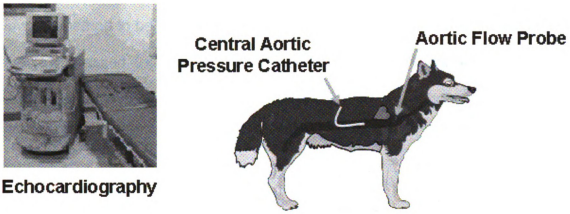

Figure 8. A summary of the instrumentation of the subject used in the last experiment which analyzes the dog in states of both increased and decreased heart function

In order to vary the functionality of the heart to provide a range of hemodynamic states to test the method, two different pharmacological interventions, dobutamine and phenylepherine, were used at different dosages. The result of these pharmacological interventions is that the data set includes a wide range of values for both SV and LVEF. This data simulates a subject with normal, decreased, and increased heart function, and will allow us to prove that the method described in chapter two works in all cases. A summary of the range of hemodynamic values found in this data set can be found in Table 7.

All of the necessary measurements to verify the functionality of our method are provided by this experiment. LVEF is measured through echocardiography, the most common clinical way to measure LVEF, and CAP is

measured through central aortic catheterization. This experiment also is done continuously so that the change in LVEF during the times where echocardiography measurements are not being taken can still be estimated by our method. The pharmacological interventions done during this experiment allow the method to be tested on the same subject in a control state, and in states of increased and reduced heart function. This experiment is excellent to show the effectiveness of this technique while highlighting its benefits.

	Minimum	Maximum	Average
Heart Rate (beats/min)	93.0	131.0	114.7
Mean CAP (mmHg)	59.47	160.13	105.91
LVEF (%)	48.0	90.0	71.9
SV (ml)	18.85	32.75	25.03

Table 7. A summary of the mean values of certain important hemodynamic parameters measured in the echocardiography experiment.

4. Results

4.1 Verifying our Assumptions

The first step in verifying our new technique is to verify that the algorithms used to detect waveform morphology are working acceptably well, and to verify that our assumptions are founded. In order to do this, we used data from the chronic pacing experiments to verify that the method for estimating proportional stroke volume from central aortic blood pressure presented by Bourgeois et al. By verifying his results using this data, we prove that most of our assumptions are accurate and that are detection schemes are working. We also can verify that the effects of chronic pacing do not invalidate any of the assumptions proven by the technique of Bourgeois et al, while the data collected in their original paper shows that drug intervention does not invalidate these assumptions. Figure 9 shows examples of the use of this technique on a dog in control state as well as dog in chronic pacing induced heart failure.

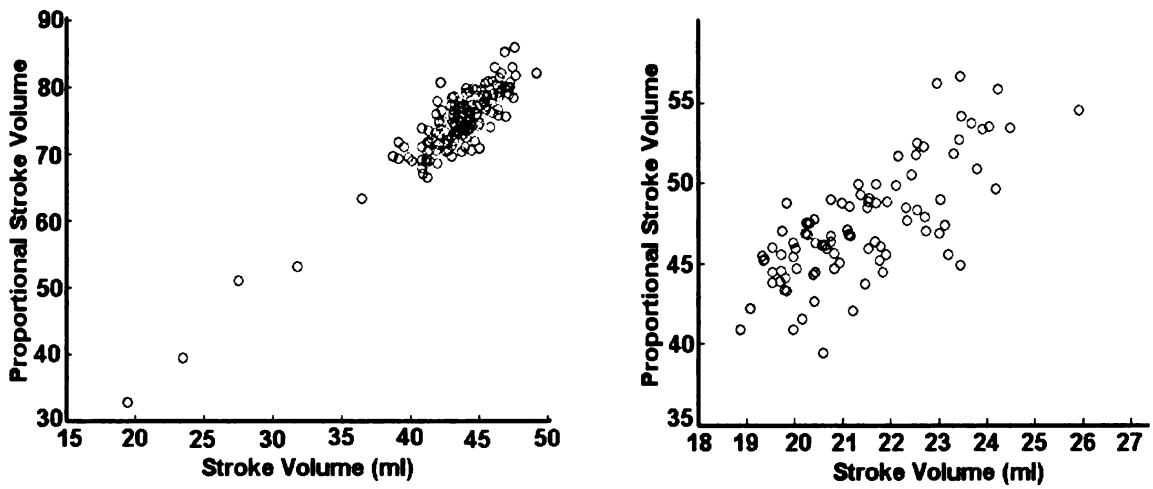

Figure 9. Examples of the effectiveness of the technique of Bourgeois et al. The graph on the left is of a dog in control state while the graph on the left shows the technique on the same dog in chronic pacing induced heart failure.

Much like the results shown by earlier research, this figure shows a strong linear correlation between proportional stroke volume as estimated by the previously developed technique and stroke volume as measured by an aortic flow probe. Since it is shown by the derivation of the equations used in this technique that the scale factor between the proportional stroke volume shown here and actual stroke volume is one divided by the arterial compliance, the strong linear correlation between these values proves that arterial compliance is constant over minutes to hours. Our assumption that arterial compliance is constant throughout one heart beat is a simple consequence of that fact. The successful implementation of the method of Bourgeois et al. verifies that our waveform feature detection schemes are working and that most of the assumptions used in deriving our algorithm are accurate.

4.2 Curve Fitting Examples

The second step in verifying that the methodology was working correctly was to verify that for an appropriate elastance curve, the result of both sides of equation 8 is a proportional volume curve. In order to do this, we found the elastance curve that yields the best fit between the two sides of the equation. After calculating each side of the equation based on the optimal elastance curve and the portion of the blood pressure waveform corresponding to ejection, we plotted these curves and verified that there morphology matched that of the ejection portion of the left ventricular volume waveform. Figure 10 shows examples of the plot of the left and right side of the equation from the heart failure experiments.

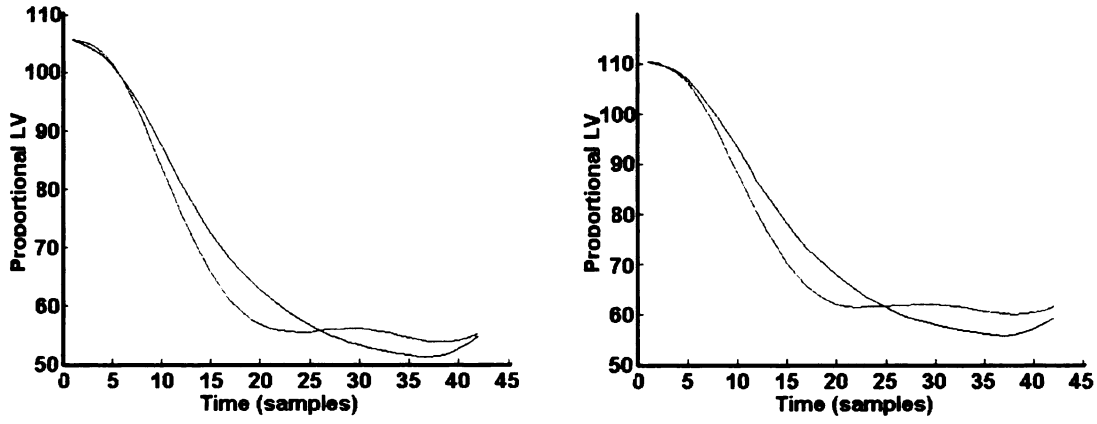

Figure 10. Examples of the results of the left and right sides of equation 8 for the optimal elastance curve for two different beats.

These proportional left ventricular volume curves show very close correspondence to each other as is expected since the elastance curve was parameterized to minimize the difference between the two curves. It is also quite clear that both sides of the curve match closely to the morphology of a left ventricular volume waveform during ejection. The blood volume drops rapidly at the beginning of ejection while the heart continues to squeeze and then the amount of blood leaving the heart tails off as the systolic interval ends. The close correspondence of the estimated proportional volume curves shown in Figure 10 and real left ventricular volume waveforms helps to verify that our method is producing the predicted results.

4.3 Results during Chronic Pacing Induced Heart Failure

The last step in verifying our method for estimating left ventricular ejection fraction is to verify that the estimated ejection fraction yielded by the method matches the expected values. As discussed in the previous chapter, the first data set used to verify our method used chronic pacing to induce heart failure

which allows us to verify that the method works on subjects in both normal hemodynamic conditions and in those with hearts functioning at a lower level. This data set supplied beat by beat measurement of left ventricular ejection fraction through the measurement of left ventricular volume by a two dimensional sonomicrometry crystal method. The sonomicrometry crystal data verified that after chronic pacing, both stroke volume and ejection fraction are greatly reduced. Figure 11 shows a comparison of the estimated ejection fraction and the measured ejection fraction in all five of the dogs used in this experiment.

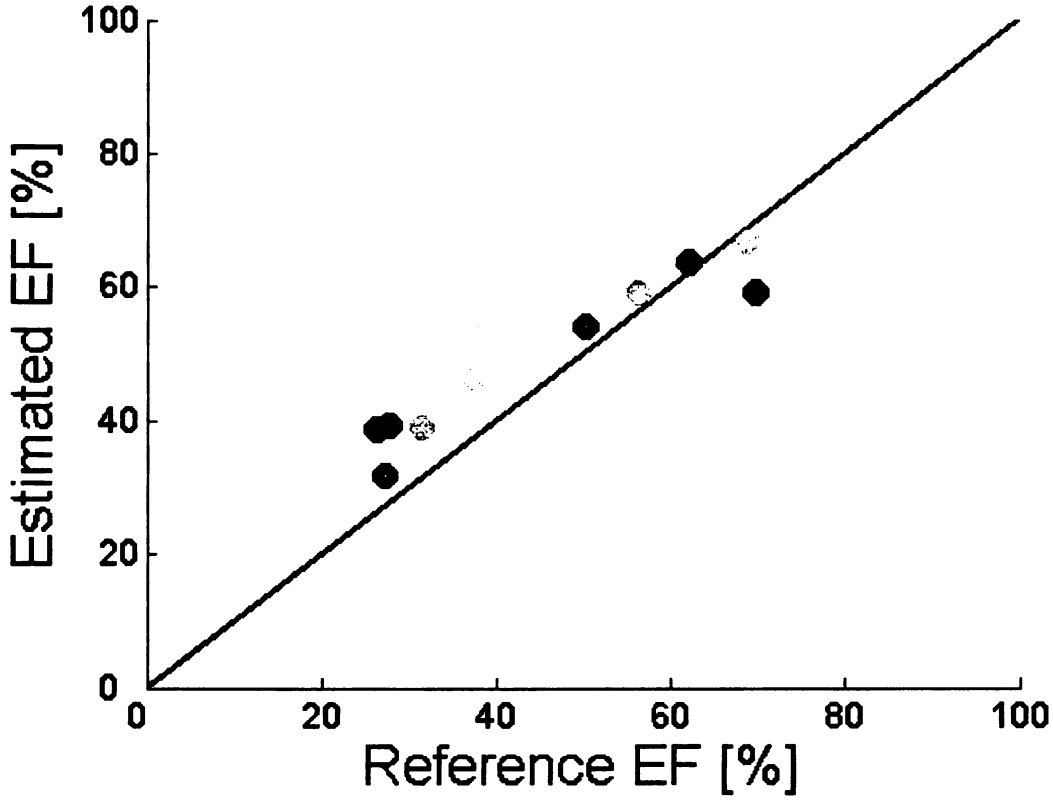

Figure 11. Summary of the results of all five dogs used in the chronic pacing induced heart failure experiments

This figure shows that there is a strong correlation between the estimated ejection fraction and the reference ejection fraction taken from the

sonomicrometry crystal data. The five data points with both reference and estimated ejection fraction above fifty percent correspond to each of the five dogs in its control state. The remaining five data points, which have reference and estimated ejection fraction of below fifty percent, correspond to each of the five dogs after chronic pacing induced heart failure. The stark contrast in the estimated ejection fraction of a healthy dog and that of one in heart failure shows the strong ability of the method to detect a subject with reduced heart functionality. This ability of the method is the most important thing that the method can do as the primary clinical use of the method would be to monitor a patient with possible reduced heart functionality and to detect changes in that patient's clinical state.

The only notable negative feature shown in Figure 11 is that the method appears to be very accurate in control while tending to always overestimate ejection fraction in heart failure. We believe this to be the result of a change in unstressed left ventricular volume resulting from chronic pacing. Proportional unstressed volume is assumed to be a value (10 mmHg) based on normal experimental values seen in other data sets. Since unstressed volume is assumed to be the same for all of these experiments, the change in unstressed volume results in the incorrect estimation of ejection fraction in the heart failure state. This problem would be alleviated in clinical settings by using an initial measurement of left ventricular ejection fraction taken via a current non-invasive method to calibrate our method. If necessary, the method could then be recalibrated any time there is a noticeable change in ejection fraction.

Using sonomicrometry crystals for continuous measurement of left ventricular volume also allows for the validation of the method on a beat by beat basis which will not be possible in the other experiments where we do not have a gold standard measurement of ejection fraction or only have instantaneous measurements of ejection fraction for a few beats.

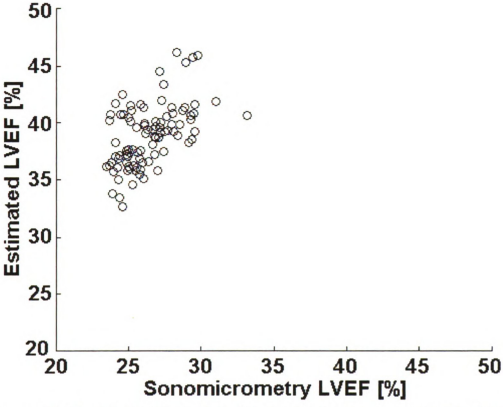

Figure 12. Beat by beat scatter plot comparing sonomicrometry LVEF to LVEF estimated by our method on a dog in chronic pacing induced heart failure

Figure 12 shows a beat by beat comparison of LVEF estimated by our method to the reference LVEF obtained from the volume waveform measured via sonomicrometry crystals. The linear nature of this plot indicates that method is working correctly since beats with higher reference ejection fraction correspond to the beats with higher estimated ejection fraction.

4.4 Results during Dobutamine Infusion

As stated in the previous chapter, our second data set used dobutamine infusion both to vary the hemodynamic state of the subject and to estimate the expected result of the experiments. The three dogs used in this second set of experiments were given varying amounts of dobutamine to raise stroke volume and ejection fraction while instrumented with central aortic catheters to measure central aortic blood pressure. The results of using our method on these central aortic blood pressure waveforms are shown in Figures 13 through 15.

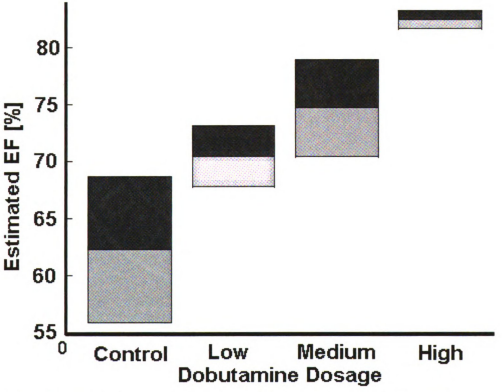

Figure 13. Results of our method on dog one of the dobutamine experiments. The middle of each bar is the mean of the results under the conditions listed on the x axis and the bottom and top halves represent the standard deviation of the measurements.

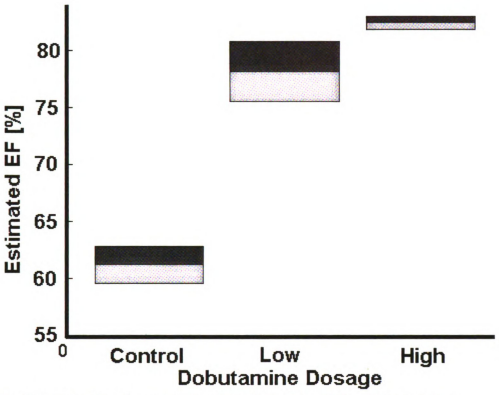

Figure 14. Results of our method on dog two of the dobutamine experiments.

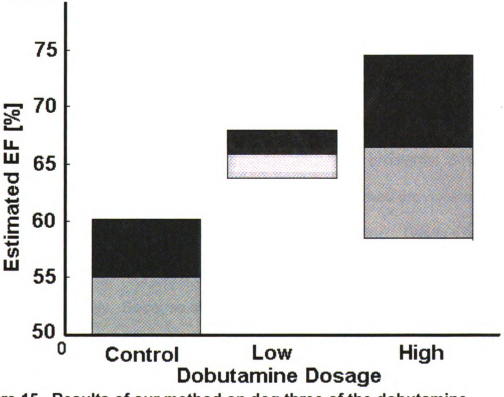

Figure 15. Results of our method on dog three of the dobutamine experiments.

All three dogs show that there is a significant increase in left ventricular ejection fraction from the control state to the dobutamine states as expected based on previous experiments. In all of the experiments there is a less notable but still significant increase in ejection fraction with increase in dobutamine dosage. The reduced effect of increasing the dosage of dobutamine is to be expected since there is a limit to the amount of increase in ejection fraction that can be caused by dobutamine infusion. These experiments show the ability of our method to detect increase in cardiac function to drug infusion. This is another important test for the method as drug infusion may be used in clinical settings to increase ejection fraction in unhealthy patients.

4.5 Results during Drug Infusion Compared to Echocardiography

The last experiment used for testing our method shows all of the method's benefits over echocardiography in a range of hemodynamic states. In this data set, continuous central aortic blood pressure waveforms were taken while periodic measurements of ejection fraction were taken via echocardiography. The periodic echocardiography measurements mimic standard practice for a patient being monitored for heart problems. Since central aortic blood pressure is measured continuously, our method provides a continuous measurement of left ventricular ejection fraction. This is a huge advantage over echocardiography because changes in heart function can be noticed immediately. Because of this, medical personnel could respond to a failing heart immediately where in the past they would not be aware of the condition.

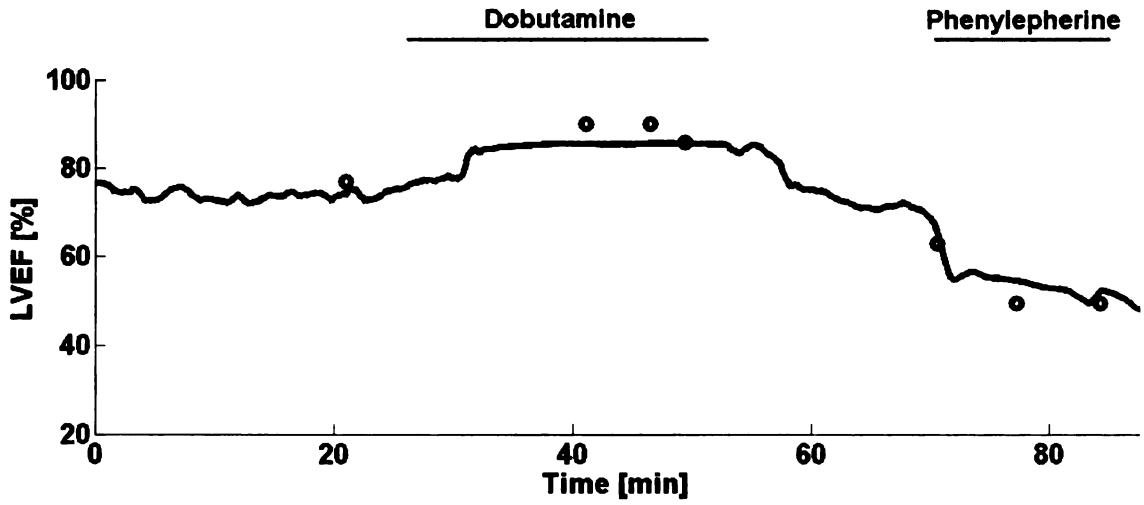

Figure 16. Results of our method on our last experiment. The line corresponds to the estimated LVEF based on our method while the circles correspond to actual LVEF based on echocardiography measurements.

Figure 16 shows the results from this last experiment. The effects of dobutamine and phenylepherine on LVEF in this experiment are clear. Dobutamine infusion raises LVEF by slightly over ten percent while phenylepherine lowers LVEF by about twenty percent from its baseline value. Due to these two effects, there is a range of LVEF in this data set of over forty percent. Despite this wide range of LVEF values, it is clear that our method corresponds very closely with the values measured by echocardiography. It is also quite clear that the method shows a change in LVEF as a direct response to drug infusion. Estimated LVEF rises upon dobutamine infusion and again upon increased dosage of dobutamine (not labeled), while it decreases upon cessation of dobutamine infusion and again upon administration of phenylepherine. To additionally highlight the advantage of our method, it can be seen that our method detects the effect of dobutamine at least ten minutes earlier than does

the echocardiography measurement. In an intensive care unit where measurements of LVEF are only taken every several hours or days, the advantage of our method would be even more distinct.

4.6 Real Time Evaluation

In order for our method to fully provide the advantages that have been described, it would be useful for the algorithm to function in real time. In this situation, real time functionality means that the data is processed at least as quickly as it is generated. This is useful because one of the biggest advantages of the algorithm is that it provides knowledge of changing heart condition as it happens. This advantage does not exist if the method takes several minutes or hours to find a solution for a small amount of data as is the case with echocardiography which requires a technician to analyze images from a single beat for several minutes to determine the ejection fraction. To verify that our method can indeed run in real time we simply ran the algorithm using a standard home personal computer processor and measured the run time of the process. We then compared this time to the length of the data set that it was being tested with and made sure that the run time was less than the duration of the data set. This verifies that the method can operate in real time, possibly requiring a short delay before the first beats are analyzed. For this experiment we used our last data set which had a duration of about one hour and thirty minutes. With our original version of the method, which did not take advantage of the linear equation of C_aE_{max} to reduce run time, the method required slightly less than an hour and a half to execute on a personal computer processor. Although this

would qualify for real time operation, because run time is slightly less than the duration of the data set, it may not function well in an actual integrated systems environment where there may be the desire to run more than one process on the system's microprocessor or to use a slower microprocessor to save on cost and energy. Our linear solution of C_aE_{max} provides a very good solution to these problems. When the linear version of our technique is used, the entire run time of the method, including the time taken for central aortic blood pressure waveform morphology detection, is slightly less than three minutes running in matlab on a personal computer. This duration suggests that doing real time analysis on a similar system would require only one thirtieth of the systems resources so that many other system functions could be executed. Alternatively, the method could be run on a system with reduced processing power to reduce cost and power consumption. In either case, the method has been shown to maintain its stated advantage of real time constant monitoring due to the fact that it can easily run in real time.

4.7 C_aE_{max} Estimation

In addition to left ventricular ejection fraction, E_{max} is considered a very powerful measurement of heart functionality [Sagawa et al. 1977]. The elastance curve is an exact measure of how the heart is functioning during systole which is largely unaffected by the amount of blood filling the heart or being pumped out. Unfortunately, E_{max} is almost never measured clinically due to the highly invasive procedures necessary for measurement. In order to measure elastance directly, it is necessary to have both a continuous measure of left ventricular volume and

a continuous measure of left ventricular pressure. Doing either of these measurements requires left ventricular catheterization or another highly invasive procedure which is both dangerous and expensive due to the highly skilled operators required. In addition, to accurately measure E_{max} it is necessary to change the loading conditions on the heart which is also difficult and dangerous. This is one of the reasons that left ventricular ejection fraction is much more common clinically. Our method, however, estimates proportional elastance as a necessary step in estimating ejection fraction. C_aE_{max} as estimated by our method could be used clinically to provide more specific information as to the systolic functionality of the heart. Figure 17 shows the changes in C_aE_{max} due to the drug infusions in our last experiment.

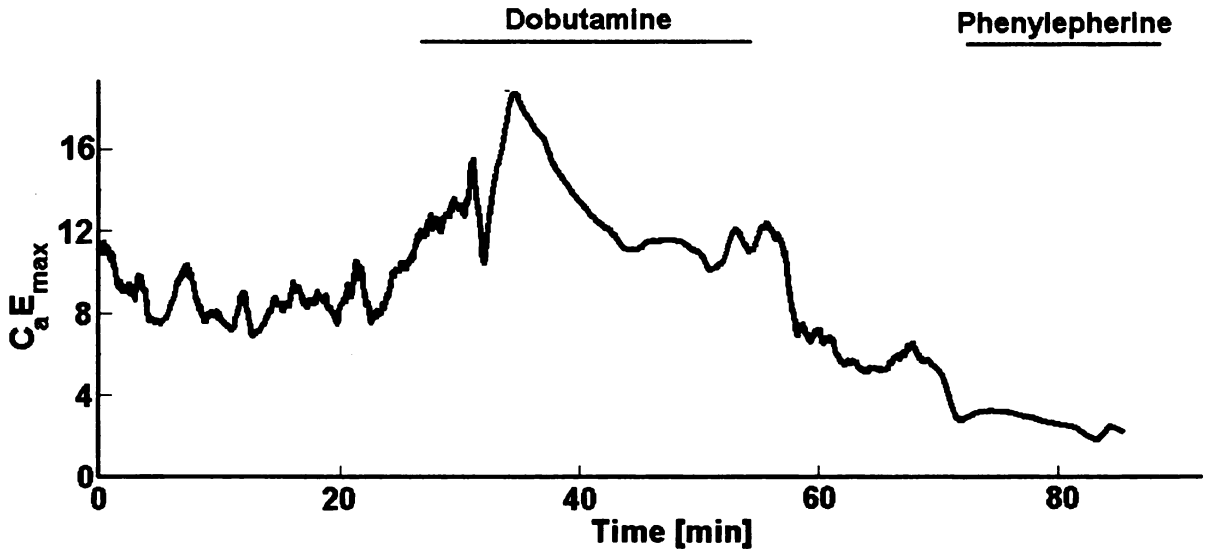

Figure 17. C_aE_{max} results of our method on our last experiment.

It is quite clear in the figure that C_aE_{max} rises with dobutamine infusion and decreases with phenylepherine similarly to left ventricular ejection fraction. The estimation of C_aE_{max} could be used clinically to provide more specific information

than is currently available. Our method provides a far less invasive and more cost effective way to measure both left ventricular ejection fraction and proportional maximum elastance than current techniques.

5. Discussion

5.1 Parameters Being Estimated

In chapter two it was shown how the method was formulated using assumptions and facts found in previous research. The lumped parameter model used to represent the cardiovascular system was presented and the research of Bourgeois et al. was used to support its validity. In addition, we presented a model for the elastance curve which would be used to define the functionality of the heart in only a few parameters. This model, which uses a raised cosine elastance curve to model the heart as a time varying capacitor, is verified using empirical data. The model, as it has been used, makes several assumptions about the form of the elastance curve which are vital to our method as they reduce the number of parameters to be estimated by the method to a number which can be solved for. In this section, we will discuss these assumptions and the possible effects of relaxing these assumptions or adding additional assumptions.

C_aE_{max} and C_aE_{min} are the two parameters of the elastance model which determine its magnitude. In the model as it is presented in previous research, there is no assumption regarding the relationship between C_aE_{max} and C_aE_{min} other than that C_aE_{min} must be less than C_aE_{max}. For this reason, the initial form of our algorithm included C_aE_{min} as a parameter to be estimated. There were three reasons that were factors in deciding to make an additional assumption regarding C_aE_{min}. The first reason was that any estimation of C_aE_{min} would be inaccurate given the data provided. The main source of data for this method, the

central aortic blood pressure waveform, contains no information about C_aE_{min} because the valve between the left ventricle and the aorta is closed when the left ventricle is fully relaxed. This makes any estimation of C_aE_{min} by our algorithm an extrapolation which cannot be expected to be accurate. The remaining reasons for making an additional assumption about C_aE_{min} result from the algorithmic downsides of estimating the parameter. Both downsides of estimating C_aE_{min} result from the fact that it is an additional parameter to estimate. First, since the measured data contains some error and the general assumptions about the hemodynamic system are known to be imperfect, less parameters can be estimated accurately than the number of equations provided by the data. Therefore, reducing parameters through valid assumptions should provide more accurate estimations of the remaining parameters and a better estimation of left ventricular ejection fraction. The second downside of estimating additional parameters is that it significantly adds to the time required for the method to work. The run time of the method is proportional to the product of the range of the parameter multiplied by the accuracy to which the parameter is estimated of all of the parameters estimated through non-linear means. Since the accuracy of the method and its execution speed could be greatly improved by doing so, we made the assumption discussed earlier that C_aE_{min} was equal to $.05*C_aE_{max}$. This assumption was assumed to be valid based on empirical data that suggested this to be relatively accurate and the fact that small differences between assumed C_aE_{min} and the actual value of C_aE_{min} will not result in large differences in the estimated value of left ventricular ejection fraction. For this reason, the amplitude

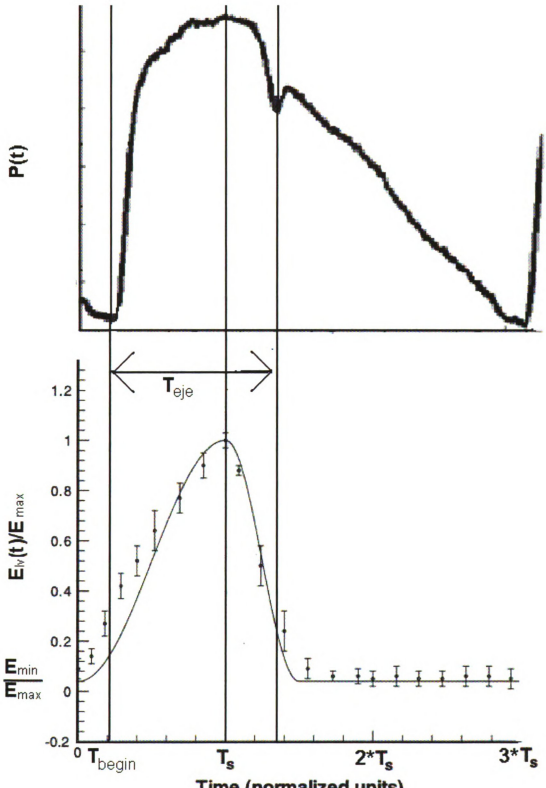

Figure 18. Graphs of the normalized elastance curve used to model the left ventricle in our method and a central aortic blood pressure waveform with important timing parameters noted

of our estimated elastance curve is estimated completely through the estimation of C_aE_{max}; however, the method could be adapted to estimate both C_aE_{max} and C_aE_{min} with the risk of losing accuracy and a guaranteed increase in execution time.

Another parameter that is being estimated by our current method is T_{begin}. T_{begin} is defined as the time between when the heart begins to squeeze and the beginning of ejection. The beginning of ejection is clearly visible in the central aortic blood pressure waveform as a sharp spike in blood pressure directly after the valve between the left ventricle and the aorta opens. Figure 18 depicts both a central aortic blood pressure waveform and the normalized elastance curve and denotes T_{begin} as well as some of the other timing parameters which will be discussed during this section. T_{begin} is a parameter that must be estimated by our method and cannot be assumed based on previously obtained data. In order to estimate this parameter it must be determined what range of values are physically realistic for it. It is clear that T_{begin} must be greater than zero because ejection will not begin until the heart begins to squeeze. It is also clear that T_{begin} must be less than T_s because the ejection will begin before the left ventricle reaches its maximum squeezing point or it will not be reached at all. Using this as the acceptable range of values for T_{begin} it is one of the parameters estimated with our method.

During the previous research that resulted in the elastance curve used in modeling the left ventricle in our method, it was found that empirical data supported the assumption that T_s is about twice the duration of the time that it

takes for the heart to relax to the point where the elastance is once again equal to C_aE_{min}. This assumption, however, could be relaxed and the ratio of the duration of these parameters could be estimated as part of the method. The result of relaxing this assumption would be a modification of equation twelve, which defined the raised cosine curve used in our model of the elastance curve without including the scaling of C_aE_{max}. If the assumption that T_s is twice the duration of the relaxing of the left ventricle is removed, the equation for this part of the equation would be:

$$C(t) = 1 - \cos\left(\frac{\pi * t}{T_s}\right), \qquad 0 \le t < T_s$$

$$= 1 + \cos\left(\frac{\alpha\pi(t - T_s)}{T_s}\right), \qquad T_s \le t < T_s + \frac{1}{\alpha}T_s$$

$$= 0 \qquad otherwise, \qquad (18)$$

where α is the scale factor by which T_s is greater than the duration of the relaxation time of the left ventricle. All other parts of our method would remain the same so C_aE_{max} could still be estimated through a linear method and all other parameters, including α would be estimated through a non linear method of least square error fitting. Including this additional parameter for estimation would have the same downsides as were explained in the discussion of C_aE_{min} but would be necessary if it was found that the assumption that α is equal to two is not a good one. Through our testing it has been found that assuming our α parameter is

equal to two appears to be valid and does not result in significantly different results for left ventricular ejection fraction then does allowing it to vary. For this reason, and the fact that empirical data also supports this assumption, we use this assumption and do not include α as an additional estimated parameter of our method.

The last parameter to be considered in this section is T_s. Much like T_{begin} and C_aE_{max}, T_s must be determined in order to estimate left ventricular ejection fraction. T_s can clearly be constrained to being a fraction of the duration of the cardiac cycle, where the duration of the cardiac cycle is the time between two consecutive heart beats. Using that as a constraint, T_s can be an estimated parameter of the technique as described in chapter two. An alternative to estimating T_s is to measure it based on the electrocardiogram and some basic assumptions.

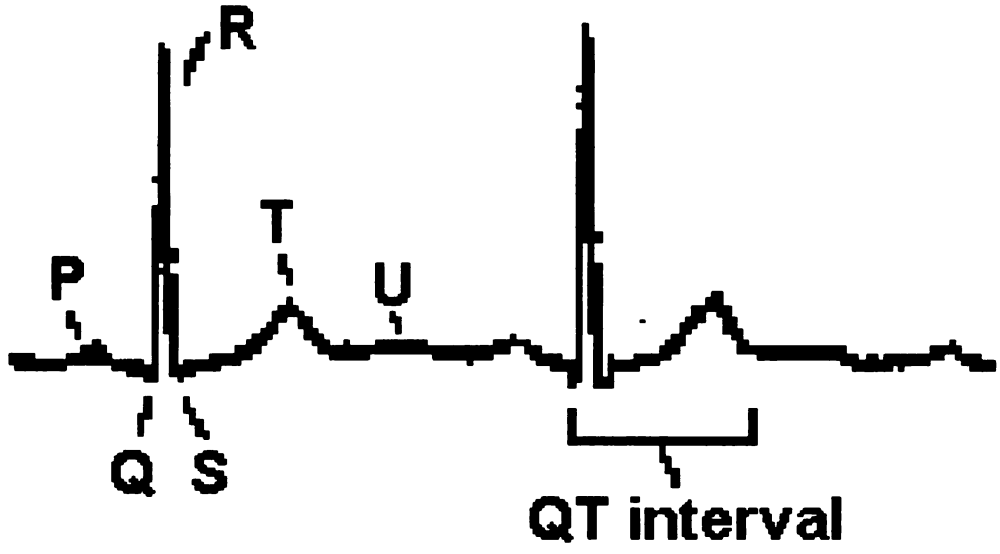

Figure 19. A standard ECG waveform with important characteristics labeled

Electrocardiograms are one of the most common measurements taken in a clinical setting because they are completely noninvasive and provide important information about electrical activity of the heart. Electrocardiograms are taken by attaching electrodes to certain places on the body which then measure the potential difference between these places. When systole begins, the SA node of the heart starts an electrical signal which travels around the heart causing it to squeeze. The Q wave denotes the beginning of the left ventricle receiving the electrical signal, while the T wave denotes the electrical relaxation of the left ventricle. Therefore, assuming cancellations of electromechanical delays, the QT interval would be the duration of both the rise in elastance and the subsequent fall in elastance. T_s is therefore simply a function of the QT interval and α. Using this knowledge we can avoid estimating a non-linear parameter, T_s, and measure it instead. The added difficulty of doing this is that it is necessary to automatically detect the Q and T waves to measure the QT interval. We have developed an algorithm to do so based on the same methodology used to detect features of the blood pressure waveform. There are also several other methods becoming available for such detection that could also be used in place of this method which is currently unproved in all but a small amount of data. A version of our method which estimates α rather than assuming it to be two and uses the electrocardiogram waveform to measure T_s was applied to the second set of experiments where dobutamine was used to alter the hemodynamic state of the subjects. The results of this alteration of the method compared to the version of the method used in previous chapters can be found in Tables 8 through 10.

	Mean estimated ejection fraction using C_aE_{max}, T_s, T_{begin} estimation method	Mean estimated ejection fraction using C_aE_{max}, α, T_{begin} estimation method
Control	.6233	.6492
Low Dose dobutamine	.7051	.7042
Medium Dose dobutamine	.7476	.7527
High Dose dobutamine	.8251	.8281

Table 8. A summary of the results of two variations of our method in dog 1 of the dogs used in the dobutamine experiments

	Mean estimated ejection fraction using C_aE_{max}, T_s, T_{begin} estimation method	Mean estimated ejection fraction using C_aE_{max}, α, T_{begin} estimation method
Control	.6123	.6545
Low Dose dobutamine	.782	.7285
High Dose dobutamine	.8248	.8271

Table 9. A summary of the results of two variations of our method in dog 2 of the dogs used in the dobutamine experiments

	Mean estimated ejection fraction using C_aE_{max}, T_s, T_{begin} estimation method	Mean estimated ejection fraction using C_aE_{max}, α, T_{begin} estimation method
Control	.5507	.6714
Low Dose dobutamine	.6584	.717
High Dose dobutamine	.6648	.8247

Table 10. A summary of the results of two variations of our method in dog 3 of the dogs used in the dobutamine experiments

It can be seen from Tables 8 through 10 that ejection fraction is estimated to be similar using both variations of our method. Since the time required to use the linear method estimating T_s is less than the time required to do QT interval

detection and use the method with a measured value of T_s, the method currently estimates C_aE_{max}, T_s, and T_{begin} while using assumptions and measurements to complete the parameterization of each cardiac cycle.

5.2 Algorithm Speed

In chapter four the usefulness of having a real time algorithm was discussed. Using a linear estimation of C_aE_{max} and searching for T_s and T_{begin} over an acceptable range yields well better than real time run speed on a standard home PC processor. However, making an algorithm more optimized for speed would only improve the situation by allowing the designers of systems which would run this algorithm more flexibility in hardware choices. The key factor in optimizing our method for speed is to reduce the number of parameters requiring a non-linear minimization as it was discussed earlier that each parameter increases run time by a large factor. In the previous section it was shown that the algorithm could be optimally done by estimating three parameters; two of these parameters will require non-linear minimization while C_aE_{max} can be solved for using very quick linear minimization techniques for any given pair of T_{begin} and T_s. The method as described in previous chapters simply uses a grid over all the physiological possible values of the remaining parameters and finds the combination of the three estimated parameters which minimizes the difference between the sides of equation 8. To further increase the speed of the method it is possible to use improved non-linear minimization techniques. Since the functioning of the heart does not vary much from one beat to the next, it

would be possible to use the values of the parameters estimated for the last beat as an initial guess for the values of the current beat. This initial guess could then be used to form a much smaller grid than the one containing all of the physiologically possible values which would allow for finding the minimum point much more quickly. There are also several other techniques available for non-linear minimization which use an initial guess for a value to quickly arrive at the minimum point. The two dimensional golden search method or the simplex method are two examples of such methods which could be used to optimize the speed of our algorithm. Since the algorithm runs well within real time constraints in its current, robust form it could be used in this way or with more consideration to optimizing the speed at which it runs.

5.3 Unstressed Volume

In previous chapters, we have discussed the necessity of making a guess as to the value of unstressed volume. The unstressed volume, or dead volume, is the volume of blood the heart contains with zero blood pressure. This value cannot be estimated from aortic blood pressure. In addition, our method does not use just the unstressed volume of the heart, but actually needs this value divided by the arterial compliance. Since both of these values are unknown, the only way to use the method with no additional testing is to use normal values for each of these parameters to estimate the value in our method. Doing this would result in some inaccuracy but would not decrease the ability of the algorithm to detect a change in ejection fraction. As mentioned in chapter four, an alternative to simply using a normal value for this parameter is to take a single measurement

of left ventricular ejection fraction using another method, such as echocardiography, and calculating unstressed volume divided by arterial compliance based on that measurement. The method could then be recalibrated whenever there is a notable change in ejection fraction or any other reason to believe that unstressed volume may have changed. While this is a shortcoming of our method, the advantages of having a continuous measurement of left ventricular ejection fraction more than make up for the small inaccuracies that could be caused by misestimating unstressed volume or the need for periodic echocardiography measurements since echocardiography measurements are currently needed more often than would be the case with our method.

6. Conclusion

6.1 Summary

This thesis presents a novel, model based technique for measuring left ventricular ejection fraction, an important hemodynamic indicator, through central aortic blood pressure waveform analysis. This technique was tested using data collected from nine dogs and showed ejection fraction estimated using this technique showed a strong correlation with the expected value of ejection fraction and the ejection fraction monitored using common and accepted techniques.

6.2 Future Research

Chapter two describes the constraints on the cardiovascular system in terms of two models. The first model is a lumped parameter model of the cardiovascular system which is widely accepted and shown to be approximately accurate by many past researchers. The second model is the model the left ventricle as a time varying capacitor with elastance defined by a raised cosine which is a function of only a small number of parameters. The assumption made in forming our method is that since there are many equations corresponding to each time at which central aortic blood pressure is sampled and only three unknowns, there is a unique solution to these three variables. We have shown that by following this assumption and implementing the method as described that our results correlate very well with measured and expected results. In the future, we would like to prove mathematically that the solution to these three parameters is unique based on the factual constraints of the situation. This would be the

same as proving that our large number of equations are each unique and do not all contain some or all of the same data. This proof would give theoretical validity to our method.

Another area that will be addressed by future research is adapting our method to minimally invasive or non-invasive measurements. Our current method relies on a continuous, accurate measurement of central aortic blood pressure. Central aortic blood pressure is not commonly measured in clinical settings due to the highly invasive nature of inserting a catheter in to the aorta. For this reason our current method would not be usable in a standard clinical setting. In the future, we would like to adapt the method to work using blood pressure measurements from one or more locations where blood pressure can be measured minimally invasively or non-invasively. To do this we will investigate a technique which will reconstruct the central aortic blood pressure waveform via analysis of more readily available peripheral blood pressure waveforms. The algorithm presented in this thesis will then be used to estimate ejection fraction from this reconstructed central aortic blood pressure waveform.

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