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ESTIMATION OF DIASTOLIC INTRAVENTRICULAR PRESSURE GRADIENTS
USING COLOR DOPPLER M-MODE ECHOCARDIOGRAPHIC
SPATIOTEMPORAL VELOCITY DISTRIBUTIONS AND
THE ONE DIMENSIONAL EULER EQUATION

DISSERTATION

Presented in Partial Fulfillment of the Requirements for

the Degree Doctor of Philosophy in the

Graduate School of the Ohio State University

By

Neil Louis Greenberg, M.S.

* * * * *

The Ohio State University

1997

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ABSTRACT

The diagnosis of left ventricular diastolic dysfunction remains a real challenge in clinical practice. While complete information on left ventricular relaxation and compliance can be obtained from intracardiac pressure measurements and simultaneous volume measurements allowing reconstruction of pressure-volume loops, these invasive measures are not clinically feasible. The most commonly used technique to assess left ventricular diastolic function in clinical practice is the pulsed Doppler measurement of the left ventricular inflow velocities at the level of the mitral valve. Although a few characteristic inflow patterns have been described, this method is limited since the transmitral velocity profile is also affected by several parameters other than left ventricular diastolic function. The use of color Doppler M-mode echocardiography to assess left ventricular inflow has been shown to provide additional information on left ventricular diastolic function. The importance of intraventricular gradients during early diastole to assure efficient left ventricular diastolic filling has also been investigated.

The research presented in this dissertation demonstrates the application of fluid dynamics principles to the color Doppler M-mode spatiotemporal velocity distribution. This approach allows the noninvasive reconstruction of intracardiac pressure gradients present between left atrium and left ventricular apex during diastole. The local spatial and
temporal velocity distribution measured by color Doppler M-mode echocardiography can be used to calculate local pressure gradients using the Euler equation. Integration of the local pressure gradients allows us to calculate a pressure difference between two points along the inflow tract. In two series of animal investigations, the noninvasive estimates of the transmitral and intraventricular pressure differences were compared against direct catheter measurements for validation of this approach. Estimation of the intraventricular pressure difference using the noninvasive color M-mode data and the one dimensional Euler equation demonstrated no significant difference in comparison with the direct catheter measurement using the repeated measures analysis. The average difference between invasive measurement and noninvasive estimate of the intraventricular pressure difference was 0.03±0.29 mmHg. This study is the first to apply complex image processing (calculation of partial derivative) and fundamental fluid dynamics (Euler equation) to the analysis of diastolic filling using color Doppler M-mode echocardiography.
To my family
ACKNOWLEDGMENTS

I would like to thank Dr. Jim Thomas for giving me the opportunity to study in the Cardiovascular Imaging Center at the Cleveland Clinic Foundation. I have greatly enjoyed working with him and look forward to our continued research collaboration. I would like to thank Dr. J. Fredrick Cornhill for his role in developing the relationship between the Cleveland Clinic Foundation and the Ohio State University that allowed the possibility to conduct research alongside the clinical activities in Cleveland. I would like to thank my dissertation committee, and especially Geoff Lockwood, for their critical review of my research and thesis document.

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CHAPTER 1

INTRODUCTION

1.1 Importance of Diastolic Dysfunction

Diastolic function of the left ventricle is defined as the ability of the ventricle to adequately fill under low filling pressures. Diastolic dysfunction, or the inability of the ventricle to adequately fill, often precedes systolic dysfunction in a number of cardiac pathologies and can lead to symptoms of heart failure in patients with preserved systolic left ventricular function. Heart failure effects 5-10% of the population. The prevalence of diastolic dysfunction among patients with heart failure is 35-50%.

1.2 Cardiac Anatomy

Figure 1.1 and Figure 1.2 show diagrams of the anatomical structures of the ventricle involved in ventricular filling.
Figure 1.1: External diagram of the heart

Figure 1.2: Cross-sectional diagram of the heart showing the four cardiac chambers and valvular structures
1.3 Physiology of Diastole and Ventricular Filling

The ventricular cardiac cycle can be represented and described using a pressure-volume loop as shown in Figure 1.3. Ventricular systole begins with the closing of the mitral valve and at point labeled A on the loop. Ventricular pressure increases during isovolumic contraction until the aortic valve opens (point B). The ejection phase of systole begins at point B with ventricular volume decreasing until ventricular pressure decreases below aortic pressure. The aortic valve closes at point C and isovolumic relaxation begins. The mitral valve opens at point D when left ventricular pressure falls below left atrial pressure. Ventricular filling occurs between points D and A and a second cardiac cycle begins with mitral valve closure.

Figure 1.3: Left ventricular pressure-volume relationship throughout a cardiac cycle
Diastole is comprised of four hemodynamic phases: ventricular isovolumic relaxation, early ventricular filling period, diastasis, and atrial contraction. Figure 1.4 shows a schematic representation of left ventricular pressure and volume for a single cardiac cycle in which these four phases are indicated. Ventricular filling occurs during both the early ventricular filling phase and the atrial contraction period, resulting in two filling waves under normal circumstances. The early filling phase, E-wave, results from the pressure difference created by the active process of ventricular relaxation and the opening of the mitral valve. The second filling phase, A-wave, results from atrial contraction. Diastasis is the period between these two filling components where the pressure difference between the left atrium and ventricle is minimal.
Figure 1.4: Time course of left ventricular pressure (P) and volume (V) during a cardiac cycle. Systole (S) has been divided into isovolumic contraction (IC) and ejection. Diastole (D) is divided into isovolumic relaxation (IR), rapid filling period (RFP), diastasis, and atrial contraction.

Variables that impact ventricular filling include ventricular relaxation, ventricular compliance, the atroventricular pressure difference, and the intraventricular pressure gradient.

1.3.1 Ventricular Relaxation

The maximum negative rate of change of ventricular pressure and the time constant of relaxation are invasive measures ventricular diastolic function. An intracardiac ventricular pressure recording made by an micromanometer-tipped catheter is required to
make these measurements accurately. An example of the first derivative of the left ventricular pressure waveform \((dp/dt)\) is shown in Figure 1.5. The point of the maximum negative rate of change of left ventricular pressure occurs at approximately the time of aortic valve closure. This parameter has been shown to decrease with impaired relaxation resulting from myocardial ischemia and increase during sympathetic activation.\(^1\) Normal values should exceed 1,000 mmHg\(\cdot\)s\(^{-1}\), with severe left ventricular dysfunction associated with values below 500 mmHg\(\cdot\)s\(^{-1}\). However, the value of maximum pressure change occurs at a single point in time and cannot represent the entire relaxation period. Moreover, the value is not independent of the maximum ventricular pressure. The relaxation time constant does not demonstrate this load dependence.
The relaxation time constant ($\tau$) was first described by Weiss et al. in 1976 as a global measure of ventricular relaxation obtained from an exponential curve fit of the ventricular pressure waveform as it decays during the isovolumic relaxation period between aortic valve closure and mitral valve opening. The time course of the fall in left ventricular pressure was modelled using an exponential decay as shown in Equation 1.1,
\[ p(t) = P_0 e^{(-\tau t)} + p_\infty \] (1.1)

where \( p(t) \) is the left ventricular pressure curve, \( t \) is time, \( P_0 \) is the pressure at time \( t=0 \), \( \tau \) is the rate of exponential decay, and \( p_\infty \) is the pressure asymptote at time \( t=\infty \). Weiss calculated \( \tau \) assuming that \( p_\infty = 0 \). This assumption allows Equation 1.1 to be linearized by taking the natural logarithm of both sides and rearranging to obtain Equation 1.2.

\[ \ln p(t) = (-1/\tau)t + \ln P_0 \] (1.2)

Linear regression analysis is used to determine the least mean squared error solution for \( \tau \) and \( P_0 \).

Nonlinear estimation techniques have also been employed to compute the relaxation time constant without the required assumption of a zero ventricular asymptote.\(^3\) The nonlinear Levenburg-Marquart technique\(^4\) allows for the estimation of the pressure asymptote, \( p_\infty \), in addition to \( P_0 \) and \( \tau \). While the mean squared error is reduced with the introduction of the non-zero asymptote, this alone does not show that the estimate of \( \tau \) is more accurate. The improved fit to the actual pressure data is partially due to the additional degree of freedom introduced with the extra variable. While a monoexponential form of pressure decay is generally accepted as an accurate model, the specific technique can vary; and investigators have examined both polynomial and more complex exponential
models for the decline in left ventricular pressure.

The portion of the left ventricular pressure curve used in the estimation of $\tau$ is important. The region used usually begins at the time of the peak negative pressure change \((-\text{dp/dt}_{\text{max}}\)). However, the end point for curve fitting is less defined. Weiss used a pressure crossover 5 mmHg above end-diastolic pressure to define the extent of data for parameter estimation. Other investigators have used the left atrial pressure crossover point to define the time period.

1.3.2 Ventricular Compliance

Left ventricular compliance ($C_v$) is defined as the change in pressure ($p_v$) with volume ($V_v$) as shown in Equation 1.3.

$$C_v = \frac{dV_v}{dp_v} \quad (1.3)$$

In late diastole, the slope of the left ventricular pressure-volume curve provides a measure of the operating stiffness of the ventricle. Left ventricular stiffness is the reciprocal of compliance and is governed by a complex interplay of myocardial stiffness, ventricular geometry, and myocardial relaxation. An increase in chamber stiffness can result from (1) a rise in filling pressure, (2) an increase in myocardial stiffness, and / or (3) a decrease in ventricular distensibility. Left ventricular stiffness is difficult to measure even with invasive techniques, requiring high fidelity pressure measurements and volume assessment with high temporal resolution.
1.3.3 Atrioventricular Pressure Difference

The true driving force of ventricular filling is pressure difference between the left atrium and left ventricle. The intracardiac pressures required to observe the transmitral pressure difference are rarely measured in humans for clinical purposes. The requirement of simultaneous pressure recordings from both the left atrium and ventricle is generally not possible. Catheterization procedures generally do not allow measurement of the left atrial pressure. While retrograde measurements of LV pressure can be made by passing the catheter across the aortic valve, retrograde passage of the catheter across the mitral valve is very difficult.
Figure 1.6: Diastolic portion of left atrial (LAP) ventricular (LVP) pressure waveforms from a single cardiac cycle.

The diastolic filling period is computed using the zero crossings of the pressure waveforms and typically divided into three regions corresponding to early filling (E), diastasis (D), and atrial contraction (A). Diastolic parameters that can be computed include peak and mean left ventricular and atrial pressures during the entire diastolic filling period and each portion (E,D,A), the minimum left ventricular pressure, the left atrial pressure at mitral valve opening and at end-diastole, the duration of each filling region and
the times from mitral valve opening to the minimum left ventricular pressure and the maximum pressure difference.

1.3.4 Intraventricular Pressure Differences

While regional pressure differences between the left ventricle and aorta during ejection have been recognized for some time,\(^9\) the presence of diastolic intraventricular pressure differences was first reported by Ling\(^10\) \textit{et al.} in 1979 and Falsetti\(^11\) \textit{et al.} in 1980. Ling observed a 2-5 mmHg pressure difference during early diastolic filling between the mid ventricular level and the apex in a series of chronically instrumented animal experiments. Falsetti also found a 2.1 mmHg base-to-apex peak pressure difference between the ventricular apex and base during early filling under baseline conditions. In addition, Falsetti also examined the magnitude of the peak intraventricular pressure difference under various hemodynamic conditions using isoproterenol and propanolol, two pharmacologic agents that increase and decrease ventricular contractility, respectively. Falsetti observed increases to 4.9, 7.7 and 15.7 mmHg with graded infusions of isoproterenol at 4, 10 and 20 \(\mu\)g/min and a decrease in the magnitude of the intraventricular pressure difference with propanolol.

In 1988, Courtois\(^12\) \textit{et al.} systematically studied the regional diastolic pressure differences during left ventricular filling in a canine model and demonstrated a 3.1 mmHg difference between the apex and a ventricular location 6 cm away. Courtois used simultaneous pulsed Doppler echocardiographic velocity measurements to show basic
pressure-velocity relationships characterized by timing differences between the pressure crossovers and peak early filling velocity. In a subsequent investigation, Courtois found that these intraventricular pressure differences disappeared rapidly during ischemia induced by coronary occlusion, suggesting that quantitation of these gradients might be useful in the diagnosis of coronary artery disease in patients.

Nikolic et al. have examined the origin of regional pressure gradients in the left ventricle during early diastole. In an animal model where controlled ventricular filling was achieved by a mitral valve occluder, they observed diastolic intraventricular pressure differences in both filling and nonfilling beats. Ultrasonic crystal measurements of lateral and longitudinal ventricular dimensions also demonstrated no significant difference in ventricular geometry between filling and nonfilling beats. Their results support a hypothesis that intraventricular pressure gradients are related to the intrinsic relaxation of the myocardium, and not simply the fluid dynamics of filling. However, the recent work of Verdonck contradicts this hypothesis, suggesting that the pressure gradient during early diastole is due to early filling wave propagation towards the ventricular apex.

While these findings suggest the critical importance of the diastolic intraventricular pressure gradients in assuring adequate left ventricular filling, this information can only be obtained currently during invasive left heart catheterization with careful pressure measurements in the left atrium and multiple points in the left ventricle, an impractical procedure for diagnosis and follow up of patients in the clinical setting. The difficulty of
this approach is underscored by the fact that these animal observations\textsuperscript{10,11,12,13} have never been extended to humans. The validation of a technique allowing quantify of these pressure gradients noninvasively using Doppler echocardiographic data would allow this index of ventricular function to be obtained on a routine and serial basis in patients undergoing clinical echocardiographic examinations.

1.4 Pathophysiology of Diastolic Dysfunction

Diastolic dysfunction, or an elevation in filling pressure, can be increased by an increase in passive chamber stiffness or by impairment of ventricular relaxation. Chamber stiffness can be increased due to fibrosis, cellular disarray, and hypertrophy. Relaxation can be impaired due to hypertrophy, asynchrony, abnormal loading, ischemia, and abnormal calcium flux.

1.4.1 Cellular Mechanism of Contraction and Relaxation

Ventricular myocytes (100 μm in length, 20 μm in diameter) are composed of myofibrils which in turn are composed of sarcomeres (1.6-2.2 μm in length). Each sarcomere is composed of several thick myosin filaments, each surrounded by six thin actin filaments. The interaction between these filaments produces force and shortening of the myocardium. Myocardial fibers also contain a network of collagen fibers and microfibrils of glycoproteins and elastin which are important for cell orientation and diastolic tissue compliance. The myocytes also contain a large number of mitochondria.
(20% by volume) which are responsible for the production of adenosine triphosphate (ATP). The myocyte is surrounded by a surface membrane called the sarcolemma. Ionic gradients are maintained across the sarcolemma such that there is greater concentration of intracellular potassium (K⁺) and greater concentration extracellular sodium (Na⁺) and calcium (Ca²⁺). These ionic gradients are maintained by a Na⁺-K⁺ pump and an ATP dependent calcium pump. Troponin and tropomyosin are regulatory proteins associated with the thin actin filament. Troponin contains a component (troponin C) that binds Ca²⁺. The binding of Ca²⁺ to troponin causes a conformational change in tropomyosin allowing cross-bridge formation between the thick and thin filaments. Removal of Ca²⁺ from troponin results in relaxation. The sarcoplasmic reticulum (SR) is a network of intracellular tubules. Ca²⁺ is transported into the SR through a membrane bound protein, phospholamban, which has a very high affinity for Ca²⁺. The rate of tension decline during relaxation is related to the rate of Ca²⁺ detachment from troponin.

1.4.2 Hypertrophic Cardiomyopathy

Hypertrophy is a compensating mechanism in which the diameter of cardiac muscle fibers increase by synthesis of new myofibrils. This process helps to sustain systolic function with pressure or volume overload. However, the increase in cardiac mass and wall thickness greatly reduces the size of the left ventricular cavity thereby producing negative effects on diastolic properties and creating ventricular filling impairment. Gross pathologic findings demonstrate that hypertrophy can be concentric
or concentrated towards the upper portion of the intraventricular septum. From histologic examination, cardiac myocytes show marked hypertrophy and a loss of the normal parallel arrangement. Interstitial fibrosis is also seen with this pattern of fiber disarray. Patterns of muscle cell disorganization have been described for hypertrophic cardiomyopathy. Type I-A is the most common variety consisting of small groups of lesions in which adjacent myocytes are aligned perpendicular or obliquely to each other. Type I-B differs in that broad bundles of cells are observed with nonparallel alignment while cells within these bundles are normally arranged. Type II disorganization differs from Type I in that sections contain both longitudinally and transversely cut cells. With greater hypertrophy, fibrosis increases potentially due to vascular insufficiency.

1.4.3 **Restrictive Cardiomyopathy and Constrictive Pericarditis**

In contrast to hypertrophic cardiomyopathy, restrictive cardiomyopathy usually does not include significant ventricular hypertrophy, but rather an abnormal stiffness of the muscle that impedes relaxation and diastolic filling. An amyloid intracellular infiltrate is the most common cause of this restriction. The intrinsic myocardial stiffness can be increased by amyloid infiltration, fibrosis, or myocardial ischemia. This change corresponds to a shift to a steeper pressure-volume relationship. Extrinsic compression of the ventricle is an additional mechanism which results in diastolic dysfunction producing an upward displacement of the pressure-volume relation. Constrictive
pericarditis is an encapsulation of the heart by the pericardium that has become fibrous (2-10 mm thick) and often calcified.

Another cause of diastolic dysfunction is asynchrony in ventricular function. Variations in the onset, rate and extent of myocardial segmental lengthening effect ventricular heterogeneity. Delayed inactivation of contraction can also decrease the rate of relaxation. The rate of cross-bridge inactivation depends on the rate of calcium uptake by the sarcoplasmic reticulum. This reuptake process is energy dependent and therefore is impaired by a reduction in intracellular ATP. This mechanism is likely to be responsible for delayed relaxation with ischemia.

1.5 Doppler Echocardiographic Instrumentation

Clinical ultrasound instrumentation can combine a high resolution two-dimensional structural image with blood flow information obtained using the Doppler principle. While the Doppler frequency shift of backscattered ultrasound was described as a noninvasive means to evaluate blood flow in the late 1950's, the clinical usefulness was not exploited until the following decade. During this period, continuous and pulsed wave Doppler interrogation allowed for the localization of heart murmurs and investigations of valvular stenosis and regurgitation. These investigations provide not only a qualitative assessment, but also the ability to estimate pressure differences and flow rates across these lesions.

Doppler echocardiography has developed into an immensely valuable modality in clinical and research cardiology and now is the most commonly applied cardiac imaging
modality.\textsuperscript{16} It provides safe, noninvasive assessment of cardiac structure and function with a portability and cost-effectiveness unrivaled by competing methodologies such as nuclear or magnetic resonance imaging. Furthermore, despite the dramatic technical improvements in echocardiography and exponential growth in its clinical utility over the past 15 years, there is no evidence that this technology is plateauing. On the contrary, current improvements in phased array transducer design and parallel computer processing ensure that the quality of echo Doppler information will improve dramatically over the next several years, emphasizing the continuing need for research into the quantitative interpretation of echocardiographic data.

1.5.1 Continuous Wave Doppler

Continuous wave Doppler systems utilize a pair of piezoelectric elements to transmit and receive ultrasonic energy waves simultaneously. When a transmitted wave with frequency, $f_0$, interacts with a moving target with velocity, $v$, the frequency of the received signal will be shifted by $f_d$ according to Equation 1.4. However, note that the frequency shift is effected by two additional variables, the speed of sound, $c$, through the interrogation medium and the angle, $\theta$, between the direction of flow and the ultrasound beam.

$$v = f_d c / 2 f_0 \cos \theta$$

(1.4)
Cardiovascular devices usually assume a constant value for the speed of sound through tissue and blood (c=1560 m/s) and assume that the ultrasound beam has been positioned in parallel with the direction of flow. The maximum frequency shift will occur when the beam is aligned in parallel with flow (cos 0° = 1). The echocardiographic user can apply an angle correction for the cosθ term that will decrease the velocity estimate when the ultrasound beam is misaligned with the direction of flow. However, uncorrected misalignment of the ultrasound beam less than 20° from the flow direction results in less than a 6% velocity error (cos 20° = 0.94).

Several techniques can be used to compute the Doppler shift frequency from the received signal during continuous wave interrogation. The quadrature detection process is most common and allows the direction of the frequency shift, and therefore the direction of blood flow, to be determined.17 This demodulating scheme, shown in Figure 1.7, consists of multiplying the received echo [cos (ω₀ + ωₜ)t] by a pair of sinusoids at the transmit frequency (ω₀) that are 90 degrees out of phase with each other (cos ωₜ and sin ωₜ). The resulting signals are low-pass filtered to obtain I(t)=cos ωₜ and Q(t)= sin ωₜ. The additional high pass filtering block in Figure 1.7, is performed to remove low frequency information due to myocardial wall velocities. The magnitude and phase of the Doppler shift can be determined from the quadrature components, I(t) and Q(t).
These demodulated components can be combined to form a complex Doppler signal ($z$) as shown in Equation 1.5.

$$z(t) = I(t) + jQ(t) \quad (1.5)$$

A time-frequency analysis of the complex Doppler signal is performed to examine changes in the flow velocity as a function of time. A short-time Fourier transform (STFT) is generally employed to create a spectral Doppler image. This approach, shown diagramatically in Figure 1.8, divides the complex signal into segments of length ($L$) which overlap each other by length ($L'$). The complex Fourier transform of each segment results
in a spectrum of signal amplitude vs. frequency. Each spectrum is transformed into a bar representation where amplitude is encoded as intensity. Each bar is stacked vertically to form the spectral image showing the variations in frequency as a function of time. The frequency and temporal resolutions are controlled by the choice of L and L', respectively.

Figure 1.8: Time-frequency analysis using the short-time Fourier transform
An example of a CW spectral Doppler image is shown in Figure 1.9. This image was obtained using an Acuson echocardiograph with a 2.5 MHz probe. The image is divided into several regions which include patient information, instrument settings, and the time-velocity spectrogram of the Doppler shift with the amplitude of the spectrum encoded as pixel brightness. The scanline has been positioned through the aortic valve. With systolic blood flow away from the transducer, a negative spectral signal is observed during ventricular ejection.

Figure 1.9: Continuous wave Doppler image of aortic flow velocities
1.4.2 Pulsed Doppler

While continuous wave Doppler has several strengths, including the ability to examine high velocity flows and determine the maximum velocity along the ultrasonic beam, its major weakness is the inability to localize velocities along this same path. This weakness can be partially overcome by pulsed-wave systems described in the late 1960s by Peronneau, Wells, and Baker. Transmission of a series of ultrasonic pulses, as opposed to a continuous wave, allows the user to define a range or depth of interrogation as shown diagramatically in Figure 1.10. The range specification allows the system to calculate the time required for each pulse to reach the desired depth and the reflected signal to return to the receiver. Although generally called a Doppler system, the pulse-wave system does not measure a frequency shift. The system detects the displacement in the reflected signal that is acquired for a set of transmitted pulses. This displacement is due to the movement of the ultrasound scatters, such as red blood cells, and allows estimation of blood velocity. The returning echo, or backscattered signal, is analyzed for a specific interval following the time-of-flight for each pulse. The finite duration of the pulse, typically three to six cycles of the transmit frequency, results in a measurement derived from a range interval as opposed to an idealized point location. The duration of a 3 cycle pulse at $f_0=2$ MHz is 1.5 $\mu$s which corresponds to an axial measurement length of approximately 1.2 mm.
The maximum rate of pulse transmission, known as the pulse repetition frequency (PRF), is limited by the range of the target, $R$, and the speed of sound, $c$, as shown in Equation 1.6. For example, the examination of a target at 10 cm requires a time-of-flight equal to $2R / c$, or approximately 130 $\mu$s. The corresponding maximum pulse repetition frequency (PRF) is approximately 7.7 kHz.

$$\text{PRF} = \frac{c}{2R}$$  \hspace{1cm} (1.6)

The number of pulses that can be transmitted to make a velocity estimate from a single sample volume, or range gate, is limited by the duration in which the flow through the sample volume is considered stationary. If the flow velocity is assumed stationary over...
an interval of 10 ms, then the maximum number of pulses is approximately \( 77 \times (10^3 \times PRF) \).

The demodulated signals, \( I(t) \) and \( Q(t) \), resulting from each pulse are multiplied by a time window function that is generally the same length as the pulse to obtain \( I_k(t) \) and \( Q_k(t) \), where \( k \) is the pulse index. These signals are integrated to obtain a single sample from each pulse, \( I_k \) and \( Q_k \), as shown in Figure 1.11. The frequency spectrum of the set of samples obtained from a series of pulses is computed by the Fourier transform. The frequency components \( f \) are related to velocity \( v \) by Equation 1.7. Note that while this equation is similar to the standard Doppler equation, the Doppler principle has not been utilized by the pulsed-wave system.

\[
v = f \left( \frac{c}{2f_0} \right)
\]  

(1.7)

![Figure 1.11: Block diagram of the pulsed-wave Doppler system](image)
The tradeoff between temporal and velocity resolution is similar to the case for continuous wave Doppler analysis. Continuing the earlier example of velocity estimation at 10 cm, a series of 64 pulses can be transmitted and received in approximately 8.8 ms. This results in a temporal resolution of approximately 10 ms and a frequency resolution of approximately 120 Hz (PRF / k). This frequency resolution is equivalent to a velocity resolution of approximately 4.7 cm/s \( (v = fc / 2f_0) \). The temporal resolution can be increased to approximately 5 ms using a series of 32 pulses, however, the velocity resolution decreases to approximately 9.4 cm/s.

From Shannon's sampling theorem, the pulse repetition frequency (PRF) must be twice as much as the maximum frequency shift to be detected, or Nyquist frequency \( f_N \). If the frequency shift is greater than half the PRF, then aliasing occurs and the resulting velocity estimate is in error. The Nyquist velocity, \( v_N \), is the maximum velocity that can be detected without aliasing. In the example, \( f_N \) and \( v_N \) are approximately 3.85 kHz and 1.5 m/s. The additional tradeoff imposed by a pulsed-wave system is between velocity and spatial resolution.

An example of a PW spectral Doppler image is shown in Figure 1.12. This image was obtained using a 3.7 MHz transesophageal imaging probe and divided into a similar fashion as the CW example shown previously. The sample volume, indicated in the sector display by the circular icon along the selected ultrasound scanline, has been positioned at the tips of the mitral valve leaflets. With diastolic blood flow towards the
transducer, a positive spectral signal is observed with two filling components (E and A-waves) as previously discussed. The small ticks marks along the x-dimension at the top of the spectrum indicate temporal intervals of 200 ms. Therefore, the duration of ventricular filling is approximately 300 ms in this example. The vertical tick marks indicate velocity intervals of 20 cm/s. Therefore, the peak E and A-wave velocities are approximately 75 and 25 cm/s.

Figure 1.12: Pulsed wave spectral Doppler image of transmitral flow
The pulsed wave system can be easily extended to obtain velocity estimates at multiple range gates as described by Baker. This process does not increase acquisition time. The PRF is determined for the furthest range selected and the backscattered signal from each pulse transmission is sampled at various times corresponding to the ranges of interest. The desire to extend the processing over two dimensions requires the adjustment of the pulse transmission direction and significantly increases acquisition time. The techniques developed to obtain real-time 2D velocity maps are discussed in the following section.

1.5.3 Color Doppler Echocardiography

Color Doppler echocardiography provides spatial map of the blood velocity component directed towards the transducer throughout a region of interrogation within the heart or blood vessels. The ability to measure multiple velocities along the ultrasound beam path is possible if the PRF is set for the maximum depth desired and the reflected echo signal is gated into multiple intervals representing a set of spatial locations. The extension of this approach to estimate a two dimensional velocity map requires repositioning of the ultrasound beam and repeated interrogation along adjacent paths (N) through the region of interest. This region is either a sector (usually between 30 and 60°) with phased array transducers or a rectangular segment with linear array probes. The additional desire to display this velocity map as a function of time requires repetition of the entire process to achieve an acceptable temporal resolution. The temporal resolution
is generally described as the number of 2D velocity maps, or frames that are displayed per second (F). The tradeoff in the allocation of pulses (k) is shown in Equation 1.8 and Equation 1.9.

\[ kTNF = 1 \quad (1.8) \]
\[ kNF = 1/T = PRF \quad (1.9) \]

The total number of pulses available, the PRF, can be divided among the frame rate (F), the number of scan lines (N), and the number of pulses per scanline (k). Each of these variables effect the temporal, spatial, and velocity resolution. For example, a higher temporal resolution can be achieved by increasing the frame rate, but only at the expense of spatial resolution and/or the accuracy of the velocity estimate. From the previous example with a maximum range of 10 cm, the 7700 pulses per second can theoretically be allocated to obtain a sector map using 64 scanlines per frame (N) and a packet size of 8 pulses per scanline (k). This would permit the interrogation of 15 frames per second (F). With only eight samples, the classical Fourier approach used in pulsed and continuous-wave Doppler would result in poor estimate of the mean velocity. While various techniques have been investigated to provide a velocity estimate from the available data, the two methods for signal analysis that are employed in contemporary 2D velocity mapping systems are the autocorrelator and cross-correlation estimator.
The autocorrelation algorithm is a frequency domain estimation approach and was implemented for cardiac application by Kasai et al. in 1985. The technique was used as early as 1965 in other fields and identified as the optimal unbiased estimator for meteorological radar applications. The estimated mean velocity is proportional to the mean frequency of the complex Doppler signal, $z_k = I_k + jQ_k$. The mean frequency ($\bar{\omega}$) is defined as the first moment of the power spectrum, $P(\omega)$, of the Doppler signal as shown in Equation 1.10. The variance of the velocity estimate ($\sigma^2$), is given as the second moment of $P(\omega)$ around the mean frequency as defined in Equation 1.11.

$$\bar{\omega} = \frac{\int \omega P(\omega)d\omega}{\int P(\omega)d\omega}$$  \hspace{1cm} (1.10)

$$\sigma^2 = \frac{\int (\omega - \bar{\omega})^2 P(\omega)d\omega}{\int P(\omega)d\omega}$$  \hspace{1cm} (1.11)

An expression for the autocorrelation function, $R(\tau)$, can be derived using the Wiener-Khinchine theorem. The result is that $R(\tau)$ is the inverse Fourier transform of the power spectrum as shown in Equation 1.12.

$$R(\tau) = \frac{1}{2\pi} \int P(\omega)e^{j\omega\tau}d\omega$$  \hspace{1cm} (1.12)
Expressions for mean frequency and variance can be derived using the autocorrelation function. The first derivative of $R(\tau)$ with respect to $\tau$, $dR(\tau)/d\tau$, is shown in Equation 1.13.

$$\hat{R}(\tau) = \frac{dR(\tau)}{d\tau} = \int j\omega P(\omega)e^{j\omega \tau} d\omega$$ (1.13)

The mean frequency, defined in Equation 1.10, can be expressed using the autocorrelation function and its first derivative at $\tau=0$ as shown in Equation 1.14.

$$\bar{\omega} = \frac{1}{j} \int j\omega P(\omega) d\omega / \int P(\omega) d\omega = \frac{1}{j} \frac{\hat{R}(0)}{R(0)}$$ (1.14)

The second derivative of $R(\tau)$ with respect to $\tau$, $d^2R(\tau)/d\tau^2$, is shown in Equation 1.15.

$$\ddot{R}(\tau) = \frac{d^2R(\tau)}{d\tau^2} = \int (j\omega)^2 P(\omega)e^{j\omega \tau} d\omega = -\int \omega^2 P(\omega)e^{j\omega \tau} d\omega$$ (1.15)

The variance, defined in Equation 1.11, can be expressed using the autocorrelation function...
and its first and second derivatives at $t=0$ as shown in Equation 1.16.

\[
\sigma^2 = \frac{\int \omega^2 P(\omega) d\omega}{\int P(\omega) d\omega} = \frac{\int (\omega - \bar{\omega})^2 P(\omega) d\omega}{\int P(\omega) d\omega} - \bar{\omega}^2
\]

The velocity estimate can be made using these equations. However, this technique can be further simplified to a less computationally demanding algorithm. Kasai described the simplification using a phasor description of the autocorrelation function as shown in Equation 1.17.²³

\[
R(\tau) = |R(\tau)| e^{j\phi}
\]

The relationships he derived for the mean frequency and variance are shown in Equations 1.18 and 1.19.

\[
\bar{\omega} = \phi(0) \equiv \phi(T)/T
\]

\[
\sigma^2 \equiv \frac{2}{T^2} \left( 1 - \frac{|R(T)|}{R(0)} \right)
\]
The complex multiplier shown in Figure 1.13 performs the computation shown in Equation 1.20.

\[ z(t) = (x(t) + jy(t))(x(t-T) - jy(t-T)) \]  \hspace{1cm} (1.20)

The real and imaginary components of \( z(t) \) are summed separately as shown in Equations 1.21 and 1.22.

\[ R_x(T, t) = \sum_{t=0}^{T} \text{Re}[z(t)] \]  \hspace{1cm} (1.21)

\[ R_y(T, t) = \sum_{t=0}^{T} \text{Im}[z(t)] \]  \hspace{1cm} (1.22)
Equations 1.18 and 1.19 are solved using the relationships shown in Equations 1.23, 1.24, and 1.25.

\[
\phi(T, t) = \tan^{-1} \frac{R_x(T, t)}{R_y(T, t)} \tag{1.23}
\]

\[
|R(T, t)| = \left[ R_x^2(T, t) + R_y^2(T, t) \right]^{\frac{1}{2}} \tag{1.24}
\]

\[
R(0, t) = \sum_{t=-\infty}^{\infty} x^2(t) + y^2(t) \tag{1.25}
\]

In the time domain, **cross-correlation** can be used to compute velocity estimates as first described by Embree\textsuperscript{24} and by Bonnefous\textsuperscript{25} in 1986. This technique has the potential advantage of providing a larger range of velocity estimates over the previously discussed approach. However, this benefit is balanced by the greater potential for velocity errors and the computational demands imposed by the technique. Cross-correlation of the received signals from two consecutive pulses provides the ability to estimate the time shift between the two waveforms. If data is obtained at times \(t_1\) and \(t_2 = t_1 + t_{prf}\), the received signals \(r_1\) and \(r_2\) are related by Equation 1.26 where \(t_s\) is the time shift and \(t_{prf}\) is the time between pulses.

\[
r_2(t_2) = r_1(t_2 - t_{prf} - t_s) = r_1(t_1 - t_s) \tag{1.26}
\]
The discrete crosscorrelation ($R_{12}$) is calculated as shown in Equation 1.27,

$$R_{12}(i,j) = \frac{1}{N} \sum_{k=0}^{N-1} n(k + jN)n(k + jN + i)$$ (1.27)

where $i$ is the time index, $j$ denotes the range gate, and $N$ is the number of samples in each range gate. The index, $i$, of the maximum value of $R_{12}$ provides $t_s$ and the velocity estimate is computed using Equation 1.28.

$$v = \frac{c}{2}\left(\frac{t_s}{t_{prf}}\right)$$ (1.28)

This velocity estimate can be improved by averaging several estimates of the crosscorrelation function obtained using a series of pulses. The sampling frequency, $f_s$, is required to be at least 4 times greater than the maximum transducer frequency (or the center frequency plus one-half the bandwidth). The factor of four is a result of the multiplication of the signals in the crosscorrelation. The maximum velocity that can be measured is a function of the number of samples used in the crosscorrelation calculation as shown by Equation 1.29.

$$v_{\text{max}} = \frac{c}{2}\left(\frac{t_{\text{max}}}{t_{prf}}\right) = \frac{c}{2}\left(\frac{N}{f_s}\right)/t_{prf} = \frac{c}{2}(N)(PRF/f_s)$$ (1.29)
One technique proposed to reduce the number of the required operations is to use the sign of the signals to construct one bit representations. This procedure greatly reduces the computational complexity and provides an estimate that has the same positions of the maximum values found in the complete crosscorrelation function provided that the sample size is not greatly limited. Expressions for the standard deviation of the velocity estimate have been derived by Bonnefous (1989) and Foster (1990). These expressions demonstrate that the variance is inversely related to the signal-to-noise ratio and the bandwidth of the pulse. The variance is also dependent on the decorrelation of received signals. Signals from sources where velocities are high and the angle of flow is large result in the most significant decorrelation. The greatest problem with the time-domain crosscorrelation approach to velocity estimation is the probability of correct detection. The notion of a variance estimate is not as meaningful with low SNR because the velocity estimate depends on the location of the maximum peak in the crosscorrelation function. The magnitudes of the peaks in $R_{12}$, which occur at intervals corresponding to the inverse of the transmit frequency ($f_0$), are more dependent on nonlinear variables with a low signal-to-noise ratio. Therefore, the correct peak may not be detected and result in an erroneous velocity estimate. The only commercial system that utilized the crosscorrelation technique is the Philips CVI device.

While tradeoffs of velocity and spatial resolution are similar to pulsed Doppler interrogation, color Doppler mapping is further complicated by the desire for resolution
in both spatial directions as well as in time. The problem is made even more difficult due to the desire to obtain structural information simultaneously, requiring resource allocation (time) to be spent collecting the "tissue" image. The color image is formed using the sparse "polar" data set obtained in a sector scan. The data must be 'scan converted,' or reformatted to an evenly spaced grid, for display. Interpolation in space and time allows commercial devices the ability to display 2D flow images. If the phase detected is negative, the velocity is away from the transducer and color coded with blue with increasing brightness as the velocity increases. If the detected phase is positive then velocity is towards the transducer and coded in red. Green can be mixed to indicate the variance of the velocity estimates or to increase the contrast for higher velocities.

Figure 1.14 shows an example of a 2D color Doppler image of blood velocities during early ventricular filling recorded using a 2.5 MHz transthoracic probe with the Hewlett Parkard 1500 echocardiograph. Note that the color information in this image has been translated into a grayscale representation. The color Doppler display is overlayed on a portion of the structural apical four chamber B-mode image showing the left ventricle (LV), left atrium (LA), right ventricle (RV) and right atrium (RA). Echocardiographic images are presented to the user in real-time, with a specific frame rate (12 frames/s) that is dependent on the selected imaging depth (16 cm) and size of the color Doppler region (approximately 1/3 of the 90 sector). The electrocardiogram at the bottom of the image indicates the time period during which data was obtained. The velocities are color-
encoded using the color bar shown in the upper right-hand portion of the image. Velocities towards the transducer are color coded from black (0 cm/s) to yellow (58 cm/s) (Note that this is the upper half of the color bar which is shown in a grayscale representation). Velocities away from the transducer are coded from black to blue (lower half of color bar).

Figure 1.14: Two dimensional color Doppler image showing blood velocities across a normal mitral valve during early ventricular filling.
1.5.4 Color Doppler M-mode Echocardiography

M-mode echocardiography allows visualization of cardiac structures along a selected scanline. The combination of this imaging modality and Doppler processing was introduced in 1981 by Eyer. The temporal resolution of velocity estimates can be greatly increased (by 10 fold over 2D systems) to 150 samples per second when the scan line is fixed (N=1). An additional increase in the packet size (k), or number of pulses per sample, is also possible from approximately 8 to greater than 50, greatly increasing velocity resolution.

By placing a scanline from the mid-left atrium through the mitral valve to the mid-left ventricle, a spatiotemporal velocity map, v[s,t], of diastolic filling can be obtained. In the color Doppler M-mode image shown in Figure 1.15, the x-dimension is time (t) increasing to the right and the y dimension is depth (s) from the transducer increasing down the image. In epicardial or transthoracic Doppler images, blood flow across the mitral valve is towards the transducer, from the left atrium into the left ventricle.
1.5.5 Accuracy of Doppler Velocity Estimates

Factors that influence the Doppler estimate of blood velocity include the speed of sound through tissue and blood, refraction of ultrasound waves, the angle of interrogation, ultrasound transmission frequency, the number of samples per mean velocity estimate (packet size), the axial resolution (pulse length), the lateral resolution (beam characteristics and number of lines per degree), temporal resolution, and wall filter characteristics.
Theoretical and experimental experiments that have examined the potential errors in Doppler velocity estimation by generally focusing on individual factors, such as Doppler angle misalignment due to refraction and the use of a single assumed speed of sound in all tissues. The first factor, refraction, is assumed not to occur in current ultrasound equipment and has only been previously examined in relation to the blood vessel boundary, and not before in a more complicated model where several tissue layers are involved. The second factor, a single speed of sound, is also assumed constant in Doppler systems despite the known differences in ultrasound speed through various biological materials as shown in Table 1.1.

<table>
<thead>
<tr>
<th>Material</th>
<th>Attenuation (dB/[MHz·cm])</th>
<th>Speed of ultrasound (m/s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>blood</td>
<td>0.17-0.24</td>
<td>1566</td>
</tr>
<tr>
<td>muscle</td>
<td>1.5</td>
<td>1542-1626</td>
</tr>
<tr>
<td>water</td>
<td>0.002</td>
<td>1480</td>
</tr>
<tr>
<td>bone</td>
<td>16.0-23.0</td>
<td>2070-5350</td>
</tr>
</tbody>
</table>

Table 1.1 Properties of biologic materials

Researchers have concluded that a 3% velocity error may result when these factors are examined individually. One device used to evaluate the accuracy of a pulsed Doppler
system is known as the string phantom. This device, introduced by Walker et al. (1982), uses a moving string with constant velocity to create a Doppler shift that is used to quantify sample volume size (spatial resolution for pulsed velocity measurements) and velocity accuracy.

Christopher et al. recently examined the combined effects of three basic factors, the refraction of ultrasound beams by tissue layers, the single speed of sound which is assumed by Doppler systems for all tissues, and the speed of sound which is assumed when calculating blood velocities with the Doppler equation. Theoretically, they derive an expression (Equation 1.30) for the net velocity measurement error \( \frac{v'}{v} \) due to the combined effects of these three factors:

\[
\frac{v'}{v} = \frac{1}{\sqrt{\left(\frac{c_1}{c_b'}\right)^2 \cos^2 \theta' + \left(\frac{c'}{c_b'}\right)^2 \sin^2 \theta'}}
\]  

(1.30)

where \( \theta' \) is the measured Doppler angle, \( c_b' \) is the assumed speed of sound in blood, \( c_1 \) is the speed of sound in the first layer, and \( c' \) is the assumed speed of sound in all tissues. A modified string phantom was employed with separate layers allowing refraction and a pair of liquid baths to allow \( c_1 \) and \( c_b \) to be varied independently. Their experimental results matched the theoretical predications and are important for calibration of ultrasound devices. However, the standard calibration solution, water \( (c_1 = 1494 \text{ m/s}) \),
caused only a 2% overestimation and was (more importantly for calibration purposes) nearly angle independent. In their discussion, the authors make the strong point that the string phantom is a great simplification of the actual task of clinical significance. The clinical situation would involve a spectrum of frequencies, a spread of Doppler angles, and a layer(s) of fat and/or muscle were the ultrasound times-of-flight may be unequal.

The axial resolution of an ultrasonic beam is related to length of the ultrasound pulse, which is equal to the product of the wavelength ($\lambda$) (Equation 1.31) and duration of the transmitted pulse.

$$\lambda = \frac{c}{f_o}$$  

(1.31)

The wavelength for a 2.5 MHz probe is 0.6 mm. Attenuation and absorption are additional factors which also effect system design choices. A general rule used is that sound attenuation is about 1 dB/cm/MHz, or 50 dB using the same 2.5 MHz probe to interrogate at 10 cm. While this echo signal is still detectable, an increase in frequency (10 MHz) to improve resolution would not provide enough returning signal strength (200 dB) at this depth.

In addition to the low amplitude ‘velocity’ information received during interrogation, the data from each sample may also contain high amplitude, low frequency information resulting from the effects of sampling tissue boundaries, or ‘walls’.
Therefore, additional processing is required to determine and remove the undesired content of the signal. This component, the "wall filter" is a special type of high pass filter designed for short data lengths and is also known as a moving target indicator (MTI) filter. Vandervoort et al. examined the impact of wall filtration on quantitative color Doppler velocity measurements using numerical simulations and *in vitro* experimentation. Using published filter characteristics, a computer simulation was performed to evaluate the error in the estimated mean frequency. Simplified spectral inputs that consisted of a rectangular pulse (constant magnitude) with mean frequency, $\mu$, and a fractional bandwidth between 0.1 and 0.5 were subjected to the various wall filters. This showed that while spectra with mean frequencies near the Nyquist limit were estimated accurately, those with mean frequencies between 20 and 50% of the Nyquist limit produced significant overestimation (20-70%). A stronger wall filter (higher frequency cutoff) or a wider spectra bandwidth resulted in larger mean velocity errors. *In vitro* data also demonstrated the effects of wall filtering on the measurement of peak velocity in a laser Doppler calibrated phantom. While accuracy with the low filter setting was excellent (error = 0.9±5.4%, $r = 0.99$), the high wall filter setting produced significant errors (15.3±29.0%, $r = 0.57$). Due to the high pass nature of the wall filter, considerable bias in velocity estimation has been shown. Rajaonah et al. recently described a technique to compensate for mean frequency bias caused by wall filtration. The estimation of mean frequency will be effected by noise if the autocorrelation function of
the noise at lag 1 ($R_n[1]$) is nonzero. If the noise is white ($R_n[1]=0$), the estimator will be unbiased. However, if a wall filter is used, then the autocorrelation function (or the inverse Fourier transform of the power spectral density) is generally nonzero, because the power spectrum of the noise is based on the frequency response of the filter. The compensation technique is based on estimating the autocorrelation function of the noise, which provides "calibration" prior to mean frequency estimation.

In 1991, Tamura et al. used a color Doppler flow mapping system to examine steady flow fields quantitatively and the accuracy of the velocity estimates was calculated in relation to theoretical models of the steady parabolic pipe flow fields. The authors derive a formula (Equation 1.32) for the velocity resolution, $\Delta v$, where $v_N$ is the Nyquist velocity and $n$ is the number of samples (or packet size).

$$\Delta v = \frac{v_N}{2(n-1)}$$

(1.32)

This simple formula predicts a velocity resolution of $v_N/14$ with $n=8$. In the case described earlier for a 10 cm depth of field, the Nyquist velocity is approximately 60 cm/s and the velocity resolution, $\Delta v$, is approximately 4 cm/s. This equation supports the commercial product of Hewlett-Packard, whose machines provide 2D color velocity resolution with 5 bits of accuracy (or $16^2$) velocity increments over ($-v_N, +v_N$). However, Equation 1.32 also predicts that this velocity resolution can be improved with
increased sampling (larger packet size) as possible with color Doppler M-mode imaging, which as described earlier would have $n = 50$ and therefore decrease the velocity resolution to near 1 cm/s, or fractionally to only 4% of $V_N$. This additional velocity resolution is not available in the digital storage of color Doppler M-mode images by Hewlett - Parkard. Tamura et al. found experimentally that the observed accuracy (6% of $V_N$) was better than that predicted by Equation 1.32 (20%).

Rickey, Rankin and Fenster developed a flow phantom to evaluate the accuracy, linearity, and precision of color Doppler instruments. The key features of the desired phantom are outlined as “(1) produce a single uniform velocity which is spatially invariant; (2) have a volume of scattering material large enough to encompass the entire measurement volume; and (3) be accurate and precise.” Their phantom consists of a wide rubber belt rotated on smooth pulleys by a DC servomotor. The belt is covered by a thick layer (2 cm) of “cell foam” which provides a strong backscattered signal and feedback circuitry ensures accurate belt speed with an accuracy of 0.14%. They tested three color instruments (C1, C2, C3) which differed in their frequency estimator, achieved respectively by autocorrelation, FFT, and time domain correlation. While a linear probe was used with each instrument, the instrument settings (probe frequency, wall filter, gain, and PRF, etc.) were not constant. A region of interest within the color image was evaluated, computing the mean and standard deviation of the velocity estimate. The slope of the relationship between computed velocity and belt velocity was nearly unity for C1.
and C3, but only 0.86 for C2. All three devices demonstrated a larger error near zero velocity due to the effects of the wall filter.

Shandas et al. recently investigated flow acceleration in steady and pulsatile flow models using simultaneous color Doppler flow mapping (CDFM) and laser Doppler velocimetry (LDV). This is the first paper to compare ultrasound Doppler flow mapping to the reference standard velocimetry technique, establishing the accuracy of color Doppler. Aligned with the centerline of flow acceleration, the measured color Doppler velocities are in parallel with flow and therefore eliminate the need for angle correction. For steady flow, 4 seconds of color M-mode data were averaged. This method allows for maximum temporal resolution (5 ms) and efficient averaging (N=800 samples) to remove noise from the Doppler velocity estimates due to random flow variations. For pulsatile flow, 3 beats of centerline Doppler velocity information were averaged. Laser velocimetry measures were repeated 3 times (each with N=2000) at 10 evenly spaced locations along the centerline from 0.3 to 2.1 cm proximal to the orifice. Shandras et al. compare a theoretical model with both LDV and CDFM and conclude that there is remarkable agreement. The flow rate (Q) was computed for both LDV and CDFM techniques at each sample location, r, along the centerline using the proximal isovelocity surface area (PISA) equation (Q = 2πr²v_{r}) and normalized by the actual flow rate determined using a digital flowmeter calibrated using a graduated cylinder and stopwatch. They compare the velocity estimates by LDV and CDFM at a single point along the
centerline during pulsatile flow. The results indicate that the automated unaliasing algorithm used in the study was inaccurate beyond three times the Nyquist velocity (48 cm/s) and point out that the two techniques “agreed well” for velocities below 150 cm/s.

David Sahn examined the instrumentation and physical factors related to visualization of stenotic and regurgitant jets using color Doppler. The following conclusions were made: (1) A poor choice of the focusing point of the ultrasound beam (in the near field for a far field tube location) could create as much as 300% overestimation of the known tube diameter, (2) The “tissue priority algorithm,” which removes velocity information in favor of structural display tends to improve the definition of tube diameter, unless the tissue specific gain was increased to dominate causing vessel diameter underestimation, (3) The dependence of the angle (between the ultrasound beam and the flow direction) on color velocity visualization is important and can be observed as regions of greater velocity when flow is more parallel with the beam during these steady flow (constant velocity) imaging experiments, (4) While angle correction is possible for pulsed Doppler interrogation, the 2D color imaging systems do not make this correction, and (5) The wall filter will remove low flow signals and effect the minimal velocity observed.

1.6 Doppler Assessment of Ventricular Filling and Diastolic Function

Doppler echocardiography provides noninvasive characterization of diastolic filling patterns, estimation of ventricular compliance and relaxation, and quantitative
analysis of pressure drops across restrictive orifices, cardiac output, and most recently myocardial wall velocities.

1.6.1 Spectral Doppler Indices of Ventricular Filling

Characteristic transmitral flow patterns have been described in diseases such as hypertrophic cardiomyopathy,\textsuperscript{34,35} dilated cardiomyopathy,\textsuperscript{36,37} hypertension,\textsuperscript{38} myocardial ischemia,\textsuperscript{39} and coronary artery disease.\textsuperscript{40} However, transmitral flow is influenced by a complex interaction of factors other than diastolic function, such as preload, afterload, heart rate and atrioventricular conduction interval.\textsuperscript{41,42,43,44,45,46} Figure 1.16 shows spectral Doppler patterns obtained for transmitral and pulmonary venous flow in the same patient and subsequently aligned based on the electrocardiographic data. These spectra were obtained from a transesophageal imaging window and show negative (flow away from the transducer) ventricular filling E and A-waves, positive systolic flow (S) in the pulmonary vein during left atrial filling, positive early diastolic flow as the pulmonary vein acts as a conduit for ventricular filling, and negative diastolic flow reversal (AR) during atrial contraction.
Figure 1.16: Pulsed Doppler assessment of transmitral flow velocities with early (E) and late (A) filling waves (top) and pulmonary venous flow with systolic (S) and diastolic (D) flow into the left atrium and atrial reversal (AR) of flow due to atrial contraction (bottom). Note that these spectral images were not recorded simultaneously and have been aligned using the electrocardiographic waveform.
Parameters that can be extracted from pulsed Doppler recordings of transmitral flow include the peak velocity of the early (E) filling wave, the peak velocity of the atrial contraction wave (A), the time velocity integrals of these waves, and the ratio of both the peak velocities and time velocity integrals. The mitral deceleration time is a sensitive index of ventricular compliance, and the duration of the A wave has been reported to be of value in conjunction with the pulmonary venous A wave. These transmitral velocity parameters allow differentiation of several classes of diastolic function based on the physical factors that determine acceleration and deceleration of flow inside the heart.\textsuperscript{47}

\textit{Acceleration} of flow across the mitral valve is caused by the establishment of a pressure gradient between the atrium and ventricle for the early mitral filling wave, produced by active relaxation of the left ventricle. This acceleration is directly proportional to left atrial pressure and inversely proportional to the left ventricular relaxation time constant, $\tau$. \textit{Deceleration} reflects the rise in ventricular pressure as flow enters the ventricle, and so relates critically to ventricular compliance. A reduction in ventricular compliance will significantly shorten mitral deceleration time. It is important to recall that ventricular compliance may be reduced either by primary diseases of the myocardium (amyloidosis), disorders of ventricular geometry (hypertrophy), or simply by forcing the ventricle to fill on a steep proportion of its pressure-volume curve (dilated cardiomyopathy).

The \textit{normal pattern} is seen in young people up to middle aged adults and is characterized by an E wave greater than the A wave. With aging or the development of
mild diastolic dysfunction, a pattern of delayed relaxation ensues, whereby the E wave is smaller than the A wave and the deceleration time of the E wave is prolonged. This may be an entirely normal pattern in the elderly, but likely does reflect some fundamental change in relaxation parameters of the ventricle with age. The restrictive pattern is characterized by a very tall E wave with very rapid deceleration and a small A wave. The rapid acceleration is indicative of elevated left atrial pressure, whereas the rapid deceleration indicates decreased ventricular compliance, and so this pattern is fairly specific for a condition of reduced ventricular compliance with compensatory left atrial hypertension. The restricted pattern is typically seen as an end stage pattern in patients with restrictive or dilated cardiomyopathies. In between the delayed relaxation and the restrictive pattern, patients often evolve through a pattern similar to the normal pattern, termed the pseudonormal pattern, since it is actually indicative of rather advanced diastolic dysfunction. Distinguishing normal from pseudonormal is one of the challenges of assessing diastolic function and can be aided by evidence of left atrial enlargement (dilated atria are more commonly seen with pseudonormal pattern) or left ventricular hypertrophy (again suggestive of a pseudonormal filling pattern). In addition, pulmonary venous flow patterns are very useful in assessing diastolic function and in particular distinguishing normal from pseudonormal.

Parameters obtained from pulmonary venous spectra include the ratio of systolic (S) to diastolic (D) flow velocity, and the magnitude and duration of the atrial reversal
(AR) wave of the pulmonary veins. With the development of delayed relaxation, the S wave becomes greater than the D wave and atrial reversal begins to become more prominent. As the diastolic dysfunction progresses into a pseudonormal transmitral pattern, the S wave becomes blunted and the atrial reversal becomes very prominent, particularly its duration which typically exceeds that of the forward A wave through the mitral valve. Finally, with an end stage restrictive cardiomyopathy, the systolic filling fraction is extremely reduced and the atrial reversal wave far exceeds the forward A wave, unless atrial systolic failure has also ensued, in which case both are quite small. Investigators also utilize transmitral and pulmonary venous flow parameters to predict filling pressures.1,2

1.6.2 Ventricular Relaxation and Compliance

Several parameters of ventricular filling have been proposed as surrogates for ventricular relaxation and compliance,7,8,9 as information from cardiac catheterization involves much greater risk, expense, and inconvenience.

The isovolumic relaxation time can be measured noninvasively using a dual channel device allowing continuous wave Doppler recordings of both aortic valve closure as well as mitral valve opening. This can also be achieved using transmitral pulsed Doppler data and a phonocardiographic signal (a representation of the heart sounds recorded simultaneously and displayed on the echocardiographic image) to provide the timing of the aortic valve closure. The isovolumic relaxation time has been related quantitatively to
\( \tau \) and atrial and aortic pressure.\(^{53}\) A formula has recently been proposed to derive \( \tau \) from IVRT using systolic blood pressure and an assumed left atrial pressure.\(^{54}\)

The rate of the systolic left ventricular pressure increase, maximal dp/dt, can be made by applying the Bernoulli equation to the mitral regurgitant spectrum.\(^{55}\) By measuring the time interval (\( \Delta t \)) between a velocity of 1 m/sec (representing a transvalvular pressure difference of 4 mmHg) and 3 m/sec (corresponding to 36 mmHg pressure difference), we can approximate dp/dt as (36-4)/\( \Delta T \). It is also possible to calculate the peak dp/dt on an instantaneous basis by calculating the change in pressure continuously from the regurgitant spectrum.\(^{56}\) It is similarly possible to estimate negative dp/dt and the left ventricular relaxation time constant, \( \tau \), from the descending portion of the mitral regurgitant velocity tracing.\(^{57,58}\)

The deceleration time of the early mitral filling wave (\( E_{\text{dec}} \)) is one of the most useful qualitative indices of ventricular stiffness. Shortened deceleration times have been associated with reduced ventricular compliance,\(^{59,60}\) restrictive cardiomyopathy,\(^{61}\) and poor survival in congestive heart failure.\(^{62}\) These observations have been of great value in identifying patients with reduced ventricular compliance. Recently, Ohno et al. have validated in a canine model an analytical expression relating \( E_{\text{dec}} \) to ventricular stiffness.\(^{63}\) Modelling the atrium, ventricle, and valvular apparatus as a harmonic oscillator, they showed that \( E_{\text{dec}} \) is inversely proportional to the square root of ventricular stiffness \( K_{LV} \),
or \( E_{dec} \propto 1/\sqrt{K_{LV}} \). With the development of congestive heart failure over a four week period of rapid atrial pacing (with LV end-diastolic pressure rising from 9.8 to 34.3 mmHg), deceleration time fell from 88 to 51 ms with close correlation to \( 1/\sqrt{K_{LV}} \) \((r = 0.94)\). A follow-up paper\(^6\) has refined this approach utilizing more sophisticated mathematical modelling. Left ventricular compliance can be ascertained noninvasively by modelling left heart filling as a simple harmonic oscillator (equivalent in our mathematical model of having inertance dominate over convective impedance); in chronically instrumented dogs, ventricular compliance (varied by afterload changes) was shown to be proportional to the square of the E-wave deceleration time.

1.6.3 Assessment of Valvular Stenosis

Clinically, continuous-wave Doppler echocardiography is used to evaluate blood flow across stenotic valves and estimate the pressure drop and across regurgitant orifices to assess the severity of a lesion. Using Doppler echocardiography, Hatle\(^6\) and Holen have shown the ability to calculate transvalvular pressure gradients in a clinical situation across stenotic mitral and aortic valves noninvasively from the Doppler velocity profiles using the simplified Bernoulli equation as shown in Equation 1.33, where \( \rho \) is the blood density (1.05 g/ml), \( v \) is the maximum blood velocity, and \( \Delta p \) is the pressure difference across the valve.
\[ \Delta p = \frac{\rho v^2}{2} \]

This technique has been well validated for use in the assessment of aortic stenosis, mitral stenosis, and prosthetic valve function, although several limitations have been reported.

One assumption made in applying the simplified Bernoulli equation is that any pressure lost through the increase in kinetic energy as blood velocity rises passing through a stenotic orifice is lost irretrievably. However, for certain valve morphologies, the pressure can actually rise once it has fallen at the narrowest portion of the valve. For example, the St. Jude bileaflet mechanical prosthesis has a very slight flare between the two leaflets allowing flow to decelerate gradually as it goes through the central orifice. This gradual deceleration allows the conversion of kinetic energy back into pressure energy and thus recovery of pressure. Application of the simplified Bernoulli equation to the high velocity central orifice would yield overestimation of the net pressure drop.\(^6^6\)

A second case where the simplified Bernoulli equation does not work is for flow through non-restrictive orifices. One term of the complete Bernoulli equation which is usually neglected in clinical practice is the inertial component, related to the acceleration of blood across the valve. For restrictive orifices, this mass of blood is actually quite small and the inertial component is negligible in comparison to the convective component. For flow through a non-restrictive orifice, such as the normal mitral valve, the inertial component may actually be more than half of the total pressure drop. Thus calculating
the pressure difference on the basis of the simplified Bernoulli equation would underestimate the true pressure difference by more than 50%.67

Finally, for flow through long tunnel like stenoses (or through blood vessels, such as the coronary arteries), the viscous component of the Bernoulli equation becomes dominant. In the extreme form, for steady flow through a vessel of constant diameter, the pressure drop is given exclusively by this viscous component and is given by Poiseuille’s equation. Despite these exceptions, however, for the vast majority of high velocity flow of clinical interest, the simplified Bernoulli equation works surprisingly well.

1.6.4 Valvular Regurgitation

Regurgitant jets are characterized by highly turbulent chaotic flow with velocities beyond the Nyquist limit, greatly limiting their potential for quantitative analysis. In contrast, the region proximal to the regurgitant orifice displays smoothly accelerating flow. Figure 1.17 is a 2-dimensional color Doppler image showing blood velocities across a regurgitant mitral valve. This image was obtained from a transesophageal window allowing visualization of the left atrium at the top and a portion of the left ventricle below the plane of the mitral valve.
Figure 1.17: Two dimensional color Doppler image showing blood velocities across a regurgitant mitral valve.

For a small orifice lying in a flat structure, hemispherically shaped isovelocity contours of decreasing surface area and increasing velocity are formed. Flow can be approximated by measuring the radial distance from the regurgitant orifice (r) and calculating the area of a hemispheric proximal convergence zone (2\(\pi r^2\)). Multiplying this by the velocity of that contour will yield the instantaneous flow rate, \(Q=2\pi r^2v\). In routine application, this contour is most easily identified as the one where Doppler velocity aliases. As shown in Figure 1.17, the blood is aliasing at a velocity of 53 cm/s at approximately 1 cm from the orifice. This yields an instantaneous flow rate of approximately 333 ml/sec. Dividing this flow rate by the peak velocity through the regurgitant orifice (obtained by continuous-wave Doppler) yields an estimation of the
regurgitant orifice area, the size of the actual hole in the valve. Although geometric distortions can occur near the regurgitant orifice or in the presence of impingement by surrounding walls, in general the proximal convergence method is applicable in most patients. In some cases, particularly mitral valve prolapse and dilated cardiomyopathy, the regurgitant orifice area may vary throughout the cardiac cycle, and use of the color M-mode may allow accurate tracking of these changes.

1.6.5 Cardiac Output Quantification

Recently, the ability to quantitate volume flow rate, or cardiac output, has been described by Tsujino et al. Color Doppler velocities within the left ventricular outflow tract can be used to calculate ventricular stroke volume. Spatiotemporal integration of flow throughout systole across the left ventricular outflow tract provides an estimation of stroke volume is obtained from which cardiac output can be calculated by multiplying by heart rate. Although this method has limitations (such as gain, angle dependency, and the assumption that the flow is axially symmetric), it has shown to be quite accurate in comparison with thermodilution and pulsed wave Doppler cardiac output methods.

1.6.6 Tissue Doppler Imaging

Doppler methodology can also be utilized to investigate myocardial tissue velocities and ventricular wall motion. Miyatake et al. described a new method for the evaluation of wall motion using Color-code tissue Doppler imaging (TDI). Using the
principles that (1) cardiac wall velocities are much slower than blood velocities and (2) that Doppler signal intensities are much stronger for tissue than blood, the conventional wall filter step is eliminated and replaced by a low pass filtering operation that enhances tissue velocities. Recently pulsed Doppler recordings of myocardial and annular velocity have been used to differentiate restrictive cardiomyopathy from constrictive pericarditis. Diastolic annular velocity is quite low in restriction and elevated in constriction, even though their transmirtal inflow patterns may be quite similar.

1.6.7 Diastolic Flow Propagation

Color Doppler M-mode echocardiography has recently been proposed as a promising new technique to evaluate left ventricular diastolic filling and function. Color Doppler M-mode imaging provides velocity information along an entire ultrasound scanline. A spatiotemporal map of blood velocity along the left ventricular inflow tract throughout diastole can be obtained quite easily in routine clinical transthoracic or transesophageal studies using any contemporary echocardiographic instrument (Figure 1.15). By placing the M-mode cursor through the mitral valve from the mid left atrium to the left ventricular apex, the spatiotemporal pattern of structural changes along this cursor can be observed such as the opening and closing of the mitral valve (MV). When color Doppler processing is activated, a second spatiotemporal display, representing the velocity distribution, is superimposed on the structural information using a standard color map where velocities towards the transducer are color-coded in red and those away from
the transducer are shown in blue. Several clinical studies have shown the potential of color M-mode echocardiography for characterizing ventricular diastolic function.

Brun et al. defined left ventricular flow propagation velocity as the slope of the black-to-color transition during early left ventricular filling. His measurements were made manually by drawing a line tangent to the leading edge of early filling (E-wave) as shown in Figure 1.18.

![Figure 1.18: Propagation velocity of early ventricular filling](image)

Note that this propagation velocity is distinct from the velocities within the propagating wave (the component velocities recorded by a pulsed Doppler sample volume between the mitral leaflets). Brun observed that the propagation velocity was only 20% of the peak E-wave (component) velocity in patients with dilated cardiomyopathy, but these were nearly equal in normal controls. He further demonstrated an inverse relationship between flow propagation velocity and ventricular relaxation time constant, τ.
Staugaard et al. proposed an alternative parameter of flow propagation. She used digital color Doppler M-mode images to evaluate left ventricular filling by examining the time delay between the maximal velocity at the tip of the mitral leaflets and the maximal velocity near the left ventricular apex. This index was shown to be a sensitive measure of changes in ventricular filling induced by balloon angioplasty of the left anterior descending coronary artery. She found that the time delay markedly increases during ischemia induced by occlusion of the coronary artery in an animal model and during balloon angioplasty in patients. She also observed that the color Doppler filling pattern returned back to normal within minutes after the procedure. These findings are reminiscent of Courtois' observations that the left ventricular base-to-apex pressure difference disappears during ischemia induced by coronary occlusion, and suggests that color M-mode data may relate fundamentally to intraventricular pressure gradients. Staugaard also demonstrated delay of flow propagation in patients with dilated cardiomyopathy, changes which were examined in an in vitro flow model from the same laboratory.

A third parameter of flow propagation has been proposed by Takatsuji et al. Instead of measuring the slope of the leading edge of the color, they have instead chosen the slope of a velocity components greater than 70% of the maximum velocity. This technique is perhaps more robust than Brun's method because low velocity information is ignored. Their clinical study examined three groups of patients using both standard pulsed Doppler techniques and color M-mode imaging: the first had normal systolic
(EF>60%) and diastolic (E/A>1) function; the second had systolic dysfunction with a mitral filling pattern of delayed relaxation (E/A<1); and the third group had systolic dysfunction and a pseudonormal filling pattern (E/A>1). They found that the propagation velocity was decreased in both diastolic dysfunction groups, although the E/A ratio for the pseudonormal group was not different than the control group. They further showed moderate correlations at catheterization between propagation velocity and standard invasive indices such as relaxation time constant (r=0.82, p<0.001), peak negative dp/dt (r=0.72, p<0.001), and minimal left ventricular pressure (r=0.61, p<0.001). This study demonstrates that color Doppler M-mode measures of diastolic function are superior to the pulsed Doppler transmitral flow pattern parameters by showing less dependence on loading conditions.

These studies have indicated that while color M-mode echocardiography is closely related to abnormalities of ventricular filling, there is no agreement as to how best to characterize these patterns objectively and reproducibly.

1.7 Research Objectives

The diagnosis of left ventricular diastolic dysfunction remains a real challenge in clinical practice. While complete information on left ventricular relaxation and compliance can be obtained from intracardiac pressure measurements and simultaneous volume measurements allowing reconstruction of pressure-volume loops, these invasive measures are not clinically feasible. The most commonly used technique to assess left ventricular
diastolic function in clinical practice is the pulsed Doppler measurement of the left ventricular inflow velocities at the level of the mitral valve. Although a few characteristic inflow patterns have been described, this method is limited since the transmitral velocity profile is also affected by several parameters other than left ventricular diastolic function. The use of color Doppler M-mode echocardiography to assess left ventricular inflow has been shown to provide additional information on left ventricular diastolic function. The observations by Stugaard and Courtois suggest the critical importance of intraventricular gradients during early diastole to assure efficient left ventricular diastolic filling.

The research presented in this dissertation demonstrates the application of fluid dynamics principles to the color Doppler M-mode spatiotemporal velocity distribution. This approach allows the noninvasive reconstruction of intracardiac pressure gradients present between left atrium and left ventricular apex during diastole. The local spatial and temporal velocity distribution measured by color Doppler M-mode echocardiography can be used to calculate local pressure gradients using the Euler equation. Integration of the local pressure gradients allows us to calculate a pressure difference between two points along the inflow tract. This noninvasive pressure difference is compared to direct catheter measurements for validation. The following section outlines the chapters describing the methodology and experimental results.
1.8 Thesis Outline

A description of the methodology that allows noninvasive estimation of intracardiac pressure gradients is presented in Chapter 2. This chapter includes a description of the methodology used to obtain and analyze simultaneous invasive intracardiac pressure recordings and color Doppler M-mode echocardiographic images. Chapter 3 describes a simplified finite element model of ventricular filling which is used to numerically examine the fundamental assumptions made in applying fluid dynamics principles to the color Doppler M-mode echocardiographic data. Chapter 4 covers the in vivo experiments performed in an animal model to evaluate the ability to noninvasively estimate the transmural pressure difference. Chapter 5 presents the in vivo experiments also performed in an animal model to examine the accuracy of noninvasive quantification of intraventricular pressure gradients. Chapter 6 discusses the implications of the technique and future research directions.
2.1 Fluid Mechanics of Ventricular Filling

Three-dimensional flow across a normal mitral valve (from the left atrium to the left ventricular apex) is governed by the Navier-Stokes equations for incompressible fluid, shown in Equation 2.1,

\[ \nabla \cdot \mathbf{v} = 0 \]
\[ -\nabla p + B + \mu \nabla^2 \mathbf{v} = \rho \left[ \frac{\partial \mathbf{v}}{\partial t} + (\mathbf{v} \cdot \nabla) \mathbf{v} \right] \]  

(2.1)

where \( \mathbf{v} \) is a three component vector of local blood velocity, \( p \) is the local pressure, \( B \) represents body forces (such as gravity) acting on the fluid, and \( \rho \) and \( \mu \) are blood density and viscosity, respectively. Note that the first equation is the differential form of the continuity equation guaranteeing conservation of mass, while the second is actually three equations governing conservation of momentum, compressed into one equation by the vector notation. This complex set of coupled differential equations can be simplified by the following assumptions: the viscous term, \( \mu \nabla^2 \mathbf{v} \), is very small and can be neglected,\(^82,83\) the gravitational force is balanced by hydrostatic buoyancy, and therefore \( B = 0 \).
Considering flow along a streamline, this becomes the one dimensional Euler equation as shown in Equation 2.2.

\[
\frac{\partial p}{\partial s} = -\rho \left[ \frac{\partial v}{\partial t} + v \frac{\partial v}{\partial s} \right]
\]  

(2.2)

This equation is now directly applicable to color M-mode data as follows: Assuming that the Doppler M-mode cursor closely approximates an inflow streamline, the color coded Doppler velocity map provides the spatiotemporal velocity distribution, \( v[s,t] \), along an inflow streamline from the left ventricular base to apex.

Integrating the Euler equation along an inflow streamline, from the left atrium to the left ventricle, yields an estimate of the transmitral pressure difference \( (\Delta p_{c+I}) \) as shown in Equation 2.3.

\[
\Delta p_{c+I} = \frac{1}{2} \rho t \left( v_{LV}^2[t] - v_{LA}^2[t] \right) + \rho \int_{s_{LA}}^{s_{LV}} \frac{\partial v[s,t]}{\partial t} ds
\]  

(2.3)

The transmitral pressure drop \( (\Delta p_{c+I}) \) is expressed as a sum of convective (C) and inertial (I) forces. The convective term can be evaluated using velocity estimates in the left atrium and ventricle, \( v_{LA} \) and \( v_{LV} \). The inertial term requires integration of acceleration \( (\partial v[s,t]/\partial t) \) over the distance \( (s) \) between the velocity estimate locations, corresponding to the pressure difference of interest. For flow through restrictive orifices such as stenotic
or regurgitant valves, the inertial term is quite small, and $\Delta p$ can be given solely by the convective term. If $v_{LA}$ is much smaller than $v_{LV}$, the Bernoulli equation reduces to the simple expression (for $\Delta p$ in mmHg and $v$ in m/sec): $\Delta p = 4v^2$. Formulas based on the simplified Bernoulli equation for valvular area and Doppler based measurement of transvalvular pressure gradients are therefore most accurate with a stenotic orifice. Unfortunately, for flow through nonrestrictive orifices (such as the normal mitral valve), the inertial term is not negligible and is of similar magnitude to the convective term. The importance of the convective and inertial components has also been described in relation to left ventricular regional pressure differences in dogs and patients. Pasipoularides used volume flow velocity and intraventricular pressure measurements to determine that 85% of the total peak pressure drop across the left ventricular outflow tract was due to the local acceleration or inertial component. Although previous authors have noted the significance of the inertial term in the complete Bernoulli equation, experimental data in patients is quite limited. In particular, there is essentially no data characterizing mitral impedance in various disease states. Nishimura and others have shown that inertance is small in stenotic mitral valves, while our own data indicate that normal mitral valves which open fully have an inertial component at least as large as the convective component. It can be anticipated that pressure gradients within the ventricle will be dominated by inertia even more than nonrestrictive orifices, since there is essentially no change in the cross-sectional area of the flow volume as it propagates into the ventricle.
2.2 Invasive Hemodynamic Measurements

2.2.1 Pressure Acquisition

Pressure waveforms were obtained using Millar micromanometer catheters (Millar Instruments, Houston, TX). For the investigations of transmitral filling pressures, both animal and human, a dual sensor catheter model was selected (model SPC-771). This catheter has a diameter of 1.70 mm (often referred to as 5 French) and a length of 120 cm. This dual sensor model contains two pressure transducers located 5 cm apart from each other on center. The distal transducer is located at the tip of the catheter with the second, proximal, sensor positioned 5 cm away. Each transducer has a separate connection terminal. Each connector is connected to a Millar control box (Model TC-510) which provides controls for adjusting the zero pressure reference voltage as well as generation of 0 and 100 mmHg signals to calibrate the recording device.

To obtain intraventricular pressures, a customized Millar catheter was designed and manufactured. The catheter consists of 6 pressure transducers is 2.67 mm in diameter (8 French), and 120 cm long. The position of the six sensors was designed such that the most distal 5 sensors are separated by 1.5 cm on center from the tip of the catheter to obtain regional left ventricular pressure waveforms. The most proximal sensor was designed to obtain left atrial pressure and is positioned 3 cm from the most basal ventricular pressure sensor, or 9 cm from the most distal sensor at the tip of the
transducer. Due to the stiffness of the distal portion of this catheter, it was introduced into the left atrium through the left atrial appendage.

**Amplification and Filtering:** The pressure signals were amplified using a Gould universal amplifier (Gould, Valley View, OH). The data was filtered using the universal amplifier with the high pass filter set at DC and the low pass filter set at 500 Hz. The balance control was adjusted to produce a zero volt signal when the Millar Control Box was set to 0 mmHg. The gain was adjusted such that a 2.5 volt signal was produced for a 100 mmHg input provided by the Millar Control Box. The electrocardiogram (ECG) was also amplified using a Gould ECG Amplifier. The standard lead I representation was selected with electrodes placed on the left arm, right arm and right leg. The amplified signals, available from the rear of the amplifier case, were connected to an interface box for signal acquisition.

**Sampling (Analog-to-Digital Conversion):** Hemodynamic waveforms were digitized at 1,000 Hz using a AT-MIO-16 multifunction data acquisition card (National Instruments, Austin, TX) and a Gateway 486/50 MHz personal computer (Gateway, North Sioux City, SD) using a custom acquisition program developed in the LabVIEW (National Instruments, Austin, TX) environment. The multifunction data acquisition card was configured to sample up to eight channels using a differential amplifier. The device was also configured to sample a possible input range of ±5 Volts with 12 bits of resolution. Therefore, a sampling resolution of 0.00244 V (or 10V/4096) was achieved.
Recalling that the pressure waveforms were amplified such that 100 mmHg produced a 2.5 V signal, the resolution of the sampled pressure signals was 0.0977 mmHg (or \(100 \text{ mmHg} / 2.5 \text{ V}\)\(\times(10 \text{ V} / 4096)\)).

**Calibration:** The pressure channels were calibrated by the following process. First the electrical "zero" of the Gould universal amplifier was set by varying the balance control such that the 0 mmHg calibration signal from the Millar control box produced a 0 mmHg signal on the acquisition display. The gain of the universal amplifier was set using the calibration control knob to display 100 mmHg for the corresponding signal from the Millar control box. Prior to introduction, the catheters were immersed in a saline solution for one hour to minimize 'drift.' As recommended by the manufacturer, the catheter was positioned just below the surface level of the fluid and the balance control on the Millar control box was adjusted to produce 0 mmHg on the acquisition display. The transducers at the distal portion of the catheter were introduced into a pressurized chamber. The pressure was varied from 0 to 100 mmHg in 20 mmHg steps to insure proper calibration of the amplifier and recording system.

**Data Storage:** The hemodynamic data were stored as a binary file with a header defined in the LabVIEW acquisition program. The header included the patients name, date and time of the recording, a list of the signals recorded and the programmable gains associated with each channel, the sampling frequency selected, and any addition comments entered by the user. The list of signals recorded contains the type of signal
(pressure, ECG, voltage, velocity), the sampling location of the signal (left ventricle, left ventricular apex, left atrium, etc.) as well as the hardware used for collection (Fluid-filled catheter, Millar catheter, Marquette amplifier, Gould universal amplifier, etc.). This signal information is used to scale the data, which is stored in its original 12 bit representation as a 16 bit integer, for analysis. The acquisition software allows the user to specify a local path for data storage. Following an experimental session, the group of files are transferred to a file server for easy access throughout the department as well as routine archival.

2.2.2 Computation of Diastolic Pressure Gradients

EchoVIEW is capable of retrieving specific pressure waveforms by name using the header information stored with the raw data. The left atrial and ventricular pressures can be referenced using “LA Pressure” and “LV Pressure.” The hemodynamic data can be reviewed using stacked waveform displays or an overlaid graph. Prior to analysis, the pressure waveforms are generally filtered using a modified version of the digital Butterworth filter that removes the temporal delay normally caused by this type of digital filter. The low pass frequency cutoff can be specified by the user.

**Calculation of Invasive Transmitral Pressure Differences:** The instantaneous transmitral pressure difference was computed from the direct measurements of left ventricular and left atrial pressures ($\Delta p_{\text{cath}}[t] = p_{\text{LA}}[t] - p_{\text{LV}}[t]$). The zero-crossings at the onset and completion of left ventricular filling were determined to separate the diastolic
intervals. The peak pressure difference ($[\Delta_p]_{\text{cath}}^{\text{max}}$) during early filling, the time to the peak filling pressure difference ($t_{[\Delta_p]_{\text{cath}}^{\text{max}}}$) and the mean pressure difference ($\overline{\Delta_p}$) were measured from the instantaneous transmitral pressure differences ($\Delta_p_{\text{cath}}[t]$).

**Calculation of Invasive Intraventricular Pressure Differences:** Instantaneous transmitral ($\Delta_p_{\text{MV}}$) pressure differences were computed from the direct measurements of the left atrial and basal left ventricular pressures ($\Delta_p_{\text{MV}}[t] = p_{\text{LA}}[t] - p_{\text{base}}[t]$). The intraventricular pressure difference ($\Delta_p_{\text{IV}}$) was computed from the direct measurements of left ventricular apical and basal pressures ($\Delta_p_{\text{IV}}[t] = p_{\text{base}}[t] - p_{\text{apex}}[t]$) in the same cardiac cycles. The total pressure difference ($\Delta_p_T$) is the sum of the transmitral and intraventricular pressure gradients ($\Delta_p_T[t] = \Delta_p_{\text{MV}}[t] + \Delta_p_{\text{IV}}[t]$). The zero-crossings at the onset and completion of left ventricular filling were again determined to separate the diastolic intervals. The peak pressure differences ($[\Delta_p_T]_{\text{max}}$; $[\Delta_p_{\text{IV}}]_{\text{max}}$) during early filling and the time from mitral valve opening (pressure crossover) to the peak filling pressure differences ($t_{[\Delta_p_T]_{\text{max}}}$; $t_{[\Delta_p_{\text{IV}}]_{\text{max}}}$) were measured from these instantaneous pressure differences. The mitral and intraventricular pressure differences were also measured when the total pressure difference was maximum ($[\Delta_p_{\text{MV}}]_{[\Delta_p_T]_{\text{max}}}$; $[\Delta_p_{\text{IV}}]_{[\Delta_p_T]_{\text{max}}}$).
$[ΔpTV][ΔpT_{max}]$) to calculate the relative contribution of the transmitral and intraventricular pressure differences to the total pressure difference.

**Maximum rate of Pressure Change, (-dp/dt)$_{max}$:** The first derivative of the left ventricular pressure waveform (dp/dt) can be computed using two approaches. The first, more simplistic, approach computes the derivative using the LabVIEW derivative routine "derivative x(t).vi" which evaluates the instantaneous derivative of pressure as the difference in pressure between two consecutive samples divided by the time difference. This method results in a noisy pressure derivative.

The second approach utilizes a digital filter (Equation 2.4) which provides both a filtered version of the pressure waveform (y[t]) as well as the first derivative (y'[t]). The sampling interval ($Δ$) and the cutoff frequency ($α$) in radians/s are used to compute the filter coefficients.

$$
\begin{align*}
\begin{bmatrix} y[t+1] \\ \dot{y}[t+1] \end{bmatrix} &= e^{-αΔ} \begin{bmatrix} 1 + αΔ \\ -α^2Δ \end{bmatrix} \Delta \begin{bmatrix} y[t] \\ \dot{y}[t] \end{bmatrix} + \begin{bmatrix} 1-(1+αΔ)e^{-αΔ} \\ α^2Δe^{-αΔ} \end{bmatrix} x[t] \\
\end{align*}
(2.4)
$$

For each cardiac cycle, the peak positive and negative derivative values are reported and presented graphically to the user.

**Relaxation Time Constant, τ:** The relaxation time constant ($τ$) is computed using three methods. The first two methods differ in the curve fitting technique used, linear vs.
nonlinear approaches, and the second two methods differ in the equation that represents the model for pressure decay. This model is shown in Equation 1.1 where \( p(t) \) is the left ventricular pressure curve, \( t \) is time, \( p_0 \) is the pressure at time \( t=0 \), \( \tau \) is the rate of exponential decay, and \( p_\infty \) is the pressure asymptote at time \( t=\infty \). The region of the left ventricular pressure curve used in the estimation of \( \tau \) is important and several user defined options are available to automate this process. The region used begins in all cases at the time of the peak negative pressure change (\(-dp/dt_{\text{max}}\)). However, the end of the region is set according to the users choice of either the left atrial crossing, a user-defined pressure crossover, or a pressure crossover above the minimal left ventricular pressure for each individual beat. With the appropriate region identified each of the following estimates of the relaxation time constant are computed.

**Linear Exponential Zero Asymptote \( (\tau_{\text{exp}}) \):** In this approach, the pressure asymptote, \( p_\infty \) is fixed at zero. The remaining equation is linearized by taking the natural logarithm of both sides of Equation 1.1. This equation can be rearranged to show the standard linear form \( y=mx+b \), where \( y = \ln p(t) \) and \( x = t \). In this form, a linear regression can be performed to calculate \( m \), or \((-1/\tau)\), and \( b \), or \( \ln p_0 \).

**Nonlinear Exponential Zero Asymptote \( (\tau_{\text{LM},p_\infty=0}) \):** Assuming a zero pressure asymptote, Equation 1.1 can be solved using the nonlinear Levenburg-Marquart technique.

**Nonlinear Exponential Non-Zero Asymptote \( (\tau_{\text{LM}}) \):** Using the nonlinear
Levenburg-Marquart technique, the assumption of a zero asymptote can be eliminated and the extra variable, \( p_\infty \), can be estimated along with \( p_0 \) and \( \tau \).

In each case, the mean squared error (mse) is computed as a parameter of the goodness of fit. While the mse is reduced with the introduction of the non-zero asymptote, this alone does not show that the estimate of \( \tau \) is more accurate.

2.2.3 Calculation of Diastolic Function Parameters

The diastolic filling period is computed using the zero crossings of the pressure waveforms and typically divided into three regions corresponding to early filling (E), diastasis (D), and atrial contraction (A). Diastolic parameters that can be computed include peak and mean left ventricular and atrial pressures during the entire diastolic filling period and each portion (E, D, A), the minimum left ventricular pressure, the left atrial pressure at mitral valve opening and at end-diastole, the duration of each filling region and the times from mitral valve opening to the minimum left ventricular pressure and the maximum pressure difference.

2.3 Noninvasive Doppler Measurements

Simultaneous Doppler M-mode velocity distributions were collected with the hemodynamic waveforms described previously. The velocity distributions were stored digitally following a six second acquisition period. The echocardiograph also recorded the electrocardiographic signal (ECG) and an additional timing signal for synchronization of
velocity and pressure data as described below.

2.3.1 Echocardiographic Instrumentation

A Sonos 1500 echocardiograph (Hewlett-Packard, Andover, MA) equipped with digital storage and retrieval (DSR) capabilities was used to obtain color Doppler M-mode images. In the animal investigations, a 3.5 MHz epicardial imaging probe was positioned at the ventricular apex. From this apical scanning window, the Doppler cursor was positioned across the mitral valve and aligned in parallel with mitral inflow using two-dimensional color Doppler flow imaging. Color Doppler velocity images were obtained using a M-mode format providing the spatial velocity distribution along the Doppler scanline from the left ventricular apex to the left atrium (Y-axis) and its temporal changes during the cardiac cycle (X-axis). In the human investigation, a 5.0/3.7 MHz transesophageal probe provided similar data with the exception that the probe was located behind the left atrium, resulting in a Doppler path from the left atrium to the left ventricular apex.

The raw image is composed of two bytes of data for each pixel; one byte contains the grayscale structural M-mode data, the other contains velocity (5 bits) and variance (3 bits) information. This velocity distribution across the mitral valve has a spatial resolution of approximately 0.5 mm, a temporal resolution of 5 milliseconds and a velocity resolution of 6.5 percent of the Nyquist velocity, $v_N$ (or approximately 2.6 cm/s when $v_N = 42$ cm/s). The color Doppler velocity maps were stored on optical disk using the DSR capabilities of
the Sonos 1500, allowing digital processing of the color Doppler velocity information.

2.3.2 Simultaneous Hemodynamic Acquisition

A digital timing marker signal was generated within the data acquisition program. Initially, a square wave with variable duty cycle was used. To assist in the storage of digital image files, the current version of the timing marker consists of a series of pulses as shown in Figure 2.1.

![Timing marker signal](image)

Figure 2.1: Timing marker signal

Using this version, the user could more easily identify the portion of the echocardiographic data buffer to select for storage on optical disc. One of two digital-to-analogue converters on the multifunction data acquisition card was used to transform the timing marker signal to an analog form for acquisition with the Doppler velocity data via the physiologic input channel on the HP Sonos 1500. The physiologic input channel zero

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and gain were adjusted to display the timing signal at the bottom of the echocardiographic sweep display. The analog timing signal was also digitized along with the pressure data and stored in the hemodynamic data file. Following a six second acquisition of hemodynamic data, including digitization of the timing signal, a series of images from the Sonos 1500's memory buffer were digitally stored to optical disc. The timing marker can be easily extracted from the digital image file and cross correlated with the signal acquired with the pressure data to compute the temporal alignment of the Doppler and hemodynamic data for direct comparison. The alignment is confirmed by the cross correlation of electrocardiographic signals acquired in a similar fashion.

2.3.3 Data Storage

The spatiotemporal velocity distributions are stored to an optical disk using the Digital Storage and Retrieval (DSR) capability of the Sonos 1500. This system allows echocardiographic images to be stored digitally, an option that was not offered by other vendors several years ago. While newer echocardiographic devices, such as the Sequoia (Acuson, Mountain View, CA) and HDI 3000 (Advanced Technology Laboratory, Bethel, WA) now have digital image storage capabilities, the image acquisition stage and file format are more prohibitive for quantitative analysis of color Doppler data because echocardiographic images are frame-grabbed using a 24-bit color image acquisition board. Using this approach, the investigator would have to estimate the velocity using a color lookup table created from the color bar. One potential problem with this approach would
be interference in the velocity data caused by tissue, or structural, data and compression algorithms used to decrease file storage requirements.\textsuperscript{90} Hewlett Packard has chosen to preserve 5 bit velocity resolution, using two 8 bit values for each pixel to separate structural and velocity data.

2.4 Color Doppler M-mode Image Processing

The color Doppler M-mode image was preprocessed to extract and calibrate the velocity information. The velocities were extracted from the raw image file using EchoVIEW, the customized analysis program developed in LabVIEW (National Instruments, Austin, TX). The program allows the user to identify regions within the image where the flow velocities have aliased, or wrapped, beyond the Nyquist velocity. With these regions identified, an unaliasing algorithm is used to convert the color scale into true velocities, given the Nyquist limit stored with the image. Final calibration of the velocity distribution requires the spatial and temporal resolutions that are also coded in the header of the raw image file.

2.4.1 Retrieval of Digital Doppler Data

The echocardiographic images stored on optical disk have a file format similar to the TIFF standard. The data is organized using tags, some of which are identical to those found in the TIFF standard and some which are considered proprietary. Hewlett Packard provided documentation of their file structure to allow the tag information to be read and
interpreted correctly. This information was used to develop a routine to read the tags which provide header information and compressed image data.

An image header structure was created that included information from many of the tags, including the image type (spectral Doppler, M-mode, 2D), imaging depth, time resolution, image height and width, spatial resolution, velocity range, and the comment stored by the user during the storing process. One important piece of header information that is not stored as a particular tag is the Nyquist velocity. This parameter is identified using a character recognition approach. Using a set of standard values, a crosscorrelation is performed on the particular image region that identifies the Nyquist velocity. If the value is not found, the user can manually select the nyquist velocity and add the new information to the library of possible values.

The data for each frame of the echocardiographic data is compressed using the PackBits algorithm. This lossless compression scheme greatly reduces the file size by encoding multiple common pixel values with a value and length. For example if the background pixel value “0” occurs 250 times in sequence, 250 bytes would be required for storage. This same information could be encoded as two bytes “250” “0”.

The additional processing step performed before using the digital velocity distribution is the removal of timing marks that occur at 1 cm intervals in vertical bands at 1 second intervals. These timing marks are coded with a distinct value that can be
identified. The velocity data for each of these pixel location is missing and is replaced as the average of the 8 neighboring pixels.

2.4.2 Temporal Alignment with Hemodynamic Data

Time-based echocardiographic images, included color Doppler M-mode images, are aligned with the hemodynamic data file by determining the maximum correlation of the timing marker and electrocardiographic signals from both data sources. The timing marker and ECG signals that are seen on the echocardiographic image are coded in the HP-TIF file using a small range of specific values. Using simple thresholding, a physiologic data image can be produced as shown in Figure 2.2.

Figure 2.2: Physiologic waveforms extracted from color Doppler M-mode image
Using the information that this image contains two non-touching waveforms, a search from both the top and bottom of the image results in the locations of the two waveforms at each point in time. For visualization purposes, the two waveforms are then scaled such that the minimum value is zero and the maximum value is one. This step is not critical for crosscorrelation, which is independent of signal magnitude.

2.4.3 Dealiasing Algorithm

The raw spatiotemporal velocity distribution that is extracted from the digital Color Doppler M-mode file may contain velocities that have aliased past the Nyquist velocity. Dealiasing is performed either automatically by shifting the positive/negative velocity assignment rollover to the nadir of the velocity bin histogram or with guided manual control using a region growing algorithm capable of separating aliased velocity regions. Figure 2.3 shows an example of the dealiasing procedure in which the region growing technique has been utilized to create a mask that defines the image regions which represent aliased flow velocities. Following the dealising procedure, the actual velocities for each pixel are calculated using the Nyquist velocity as shown in Equation 2.5, and the distribution is calibrated using the temporal and spatial image resolutions.

\[ v[s,t] = \left( \frac{V_N}{15} \right) p[s,t] \]  

(2.5)
Figure 2.3: Dealiasing Procedure - a) Original color Doppler M-mode image, b) Mask image defined by region growing algorithm, c) dealiased spatiotemporal velocity distribution.
2.4.4 Spatiotemporal Velocity Filtration

The spatiotemporal velocity distribution can be filtered using several approaches. A median filter, with variable kernel size, is one option. The alternative involves Fourier truncation to remove high frequency components in both spatial and temporal directions. The first step in this approach is to compute the 2D Fourier transform of the velocity distribution. This is currently implemented using the 1D Fourier transform VI that is a standard part of the LabVIEW analysis toolkit. This is accomplished by first applying the 1D Fourier transform to each row in the image and then to each column of the result. In future versions of the software, a direct 2D algorithm would reduce the computation time. The second step, following the 2D Fourier transform, is the removal of high frequency terms. This is accomplished using an ideal low pass filter that has either a constant radius (circular) or constant lengths in both dimensions (rectangular). The Fourier coefficients that fall outside the circular or rectangular region are set to zero. The final step is an inverse 2D Fourier transform, also performed using the same algorithm as in the forward case with two passes of the 1D version.

Figure 2.4 demonstrates the results of median and Fourier spatiotemporal velocity filtering. The original velocity distribution (Figure 2.4A) has been filtered using a 3x3 kernel where the original value is replaced by the median (Figure 2.4B) or by Fourier coefficient truncation above 10% of the maximum frequency in both the temporal and spatial dimensions.
Figure 2.4: Spatiotemporal velocity filtration; A) unaliased spatiotemporal velocity distribution showing diastolic filling patterns from three cardiac cycles, B) median filtered distribution using a 3x3 kernel, and C) fourier truncation of frequencies above 10% of the maximum in both the temporal and spatial dimensions.
2.5 Spatiotemporal Velocity Differentiation

Estimation of the pressure gradient distribution (\(\partial p/\partial s\)) requires differentiation of the velocity distribution in both space and time. Methodology exists to perform partial differentiation both directly as well as analytically. The analytic derivatives are obtained following a polynomial surface fit to the raw data. With estimates of these partial derivatives, the Euler equation provides a pressure gradient distribution, \(\partial p/\partial s\), that can be integrated over a specific region to compute an instantaneous pressure difference, \(\Delta p(t)\). For example, the transmitral pressure difference can be estimated with integration from the left atrium to left ventricle. The integration length from the atrium into the ventricle can be varied to compute the pressure difference to different locations within the ventricle.

2.5.1 Direct Differentiation

The partial derivatives of velocity (\(\partial v/\partial t\) and \(\partial v/\partial s\)) can be computed by convolving a differential operator, like the Sobel kernel, with the raw spatiotemporal velocity pattern. The 3x3 kernel shown below in Equation 2.6 examines velocity differences between velocity samples 10 ms apart. This kernel also smoothes the derivative calculation by the weighting matrix [1 2 1]. A transposed version of the Sobel kernel can be used to compute \(\partial v/\partial s\) as shown in Equation 2.7.
Figure 2.5: A) Color Doppler M-mode spatiotemporal velocity pattern \( v[s,t] \) showing two diastolic filling periods and B) partial derivative of velocity with respect to time \( \frac{\partial v}{\partial t} \) using the direct approach.

### 2.5.2 Analytical Differentiation

An analytic expression of velocity as a function of depth and time, \( v[s,t] \), during the early diastolic filling phase is computed using a polynomial surface fitting algorithm. A 8th order bivariate polynomial (Equation 2.8) was selected to obtain accurate velocity fitting to the early E-wave filling pattern.
\[ v(s,t) = \sum_{m=0}^{8} \sum_{n=0}^{8} a_{n,m} s^n t^m \] (2.8)

Figure 2.6b shows the 8th order polynomial surface fit of the typical raw early filling (E-wave) spatiotemporal velocity distribution shown in Figure 2.6a.

Figure 2.6: A) Early filling spatiotemporal velocity distribution; B) corresponding 8th order polynomial representation

The fitted spatiotemporal velocity distribution equation, \( v(s,t) \), was differentiated with respect to both time and depth as shown in Equations 2.9 and 2.10.
\[
\frac{\partial v[s,t]}{\partial t} = \sum_{n=0}^{t+1} \sum_{m=0}^{s} m a_n m s^n t^{m-1} 
\]  
(2.9)

\[
\frac{\partial v[s,t]}{\partial s} = \sum_{n=0}^{t+1} \sum_{m=0}^{s} n a_n m s^n t^{m-1} 
\]  
(2.10)

Image representations of the partial derivations of velocity with respect to temporal and spatial changes were constructed using a color map in which positive velocity derivatives are red and negative velocity derivatives are blue. Image representations of the partial derivatives, \(\partial v/\partial t\) and \(\partial v/\partial s\), were examined and used to compute the partial derivative of pressure with respect to depth, \(\partial p/\partial s\), using the Euler equation. From the resulting pressure gradient distribution, \(\partial p/\partial s\), it is apparent that positive transmitral pressure gradients occur early near the apex of the ventricle. The E-wave deceleration begins within the atrium progressing with time into the ventricle as shown by the black region.
Figure 2.7: Diagramatic calculation of the pressure gradient distribution using the surface fitted results for the velocity distribution and the corresponding partial derivatives with respect to time (t) and distance (s).

One problem using the analytic differentiation approach is the accuracy of the surface fit. The choice of a polynomial equation for a description of the raw spatiotemporal velocity distribution may not allow the degree of accuracy required to obtain a parameterization of the velocity space. Chebyshev polynomials would allow control of boundary conditions which may allow for a better fitted representation. A spline surface also has distinct advantages over the simple polynomial approach.
2.6 Computation of Pressure Gradients

**Estimation of Transmitral Pressure Differences:**

*Calculation of the convective contribution to the transmitral pressure difference:* The velocity profiles in the left atrium (approximately 1 cm above the level of the mitral valve) \((v_{LA}[t])\) and 5 cm downstream in the left ventricle \((v_{LV}[t])\) approximating the pressure transducer locations \((s_{LA} \text{ and } s_{LV})\) were extracted from the spatiotemporal color Doppler velocity distribution and used to compute the convective component of the pressure difference, \(\Delta p_c[t]\), using the simplified Bernoulli equation.

*Calculation of the inertial contribution to the transmitral pressure difference:* The instantaneous value of the inertial component, \(\Delta p_i[t]\), was calculated by the product of blood density, \(\rho\), and the integral of the temporal acceleration term \((\partial v / \partial t)\) along the ultrasound scanline from \(s_{LA}\) to \(s_{LV}\). The temporal acceleration term was evaluated by convolving the velocity distribution, \(v[s,t]\), with the Sobel operator as shown in Equation 2.11.

\[
\Delta p_i[t] = \rho \int_{s_{LA}}^{s_{LV}} \frac{\partial v[s,t]}{\partial t} \, ds = \rho \sum_{n} v[s,t] \otimes \begin{bmatrix} -1 & 0 & 1 \\ -2 & 0 & 2 \\ -1 & 0 & 1 \end{bmatrix}
\]  

(2.11)

The class of Sobel operators contains the kernel shown above which is specific in its size (3x3) and direction. In calculating the temporal derivative of the velocity distribution, it is
important to normalize the result with the sum of the absolute weights used within the Sobel kernel as well as incorporate the correct spatial and temporal resolutions (ds and dt).

**Calculation of the transmitral pressure gradient:** The noninvasive Doppler derived diastolic transmitral pressure difference, $\Delta p_{c+i}[t]$, was computed as the sum of convective and inertial components using the unsteady form of the Bernoulli equation.

The Doppler derived pressure differences from both the simplified Bernoulli equation ($\Delta p_c[t]$) and unsteady Bernoulli equations ($\Delta p_{c+i}[t]$) were compared with the invasively measured pressure differences ($\Delta p_{cath}[t]$) using linear regression analysis. The correlations between instantaneous catheter and Doppler pressure waveforms were computed over the time interval defined by the catheter-based zero-pressure crossovers at the beginning and end of diastole and compared after Fisher z-transformation by a paired $t$-test. The error in the peak pressure differences during early filling were computed:

$$\varepsilon_c = [\Delta p_c]_{\text{max}} - [\Delta p_{cath}]_{\text{max}} \quad \text{and} \quad \varepsilon_{c+i} = [\Delta p_{c+i}]_{\text{max}} - [\Delta p_{cath}]_{\text{max}}.$$  

Also the temporal delay between the Doppler-derived peak pressure differences and the peak catheter pressure difference ($\Delta t_c = t[\Delta p_c]_{\text{max}} - t[\Delta p_{cath}]_{\text{max}}$; $\Delta t_{c+i} = t[\Delta p_{c+i}]_{\text{max}} - t[\Delta p_{cath}]_{\text{max}}$) were obtained to assess the degree of phase lag. The invasive and noninvasive peak pressure differences as well as the temporal delays between the Doppler-derived peak pressure differences and the peak catheter pressure difference were compared using the paired $t$-test.
Estimation of Intraventricular Pressure Differences: The instantaneous value of the intraventricular pressure difference ($\Delta p_{IV}[t]$) is calculated by integration of the pressure gradient ($\partial p/\partial s$) between the left ventricular base and apex. Pressure differences between the left atrium and left ventricular apex and base ($\Delta p_T$ and $\Delta p_{MV}$) are computed by varying the limits of integration. The pressure gradient is computed as the product of blood density ($\rho$) with the sum of the convective ($v \cdot \partial v/\partial s$) and inertial components ($\partial v/\partial t$). These partial derivatives of the velocity distribution with respect to space ($s$) and time ($t$) are evaluated by convolving the velocity distribution, $v[s,t]$, with Sobel operators.
Figure 2.8: Pressure gradient distribution ($\frac{\partial p}{\partial s}$)

Figure 2.9: Pressure distribution ($p(s,t)$) resulting from integration of pressure gradient

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Figure 2.10: Pressure difference waveforms extracted from pressure distribution. The total pressure difference \((p_{LA} - p_{LV_{apex}})\) is shown as the sum of the transmitral pressure difference \((p_{LA} - p_{LV_{base}})\) and the intraventricular pressure difference \((p_{LV_{base}} - p_{LV_{apex}})\).

Figure 2.11: Pressure difference waveforms extracted from pressure distribution. The intraventricular pressure difference \((p_{LV_{base}} - p_{LV_{apex}})\) is shown as the sum of the basal pressure difference \((p_{LV_{base}} - p_{LV_{mid}})\) and the apical pressure difference \((p_{LV_{mid}} - p_{LV_{apex}})\).
CHAPTER 3

NUMERICAL MODELLING: VALIDATION OF ANGLE DEPENDENCY

3.1 Introduction

The application of the Euler equation to the color Doppler M-mode (CMM) diastolic spatiotemporal velocity distribution can provide noninvasive estimates of transmitral and intraventricular pressure differences. A critical assumption made in applying this fluid dynamics principle is that the ultrasound scanline approximates an inflow streamline. A numerical model of ventricular filling can be used to examine the importance of scanline alignment with inflow velocities. The properties of an ideal numerical model would include three dimensional deformable boundaries with spatiotemporal changes derived from actual anatomic data. The inclusion of dynamical boundary conditions in a model of ventricular relaxation would produce three dimensional pressure and velocity distributions during the early filling phase for subsequent analysis without the requirement of imposed flow waveforms. However, current commercial modelling packages are not capable of modelling this interaction between the motion of boundary conditions and the fluid dynamics solution. A much simplified model of ventricular filling is described in this chapter. This two dimensional model has fixed boundaries, an imposed velocity profile within the left atrium, and an outlet for flow
within the left ventricle. Given the inability to model the dynamic interaction between the wall boundaries and the fluid mechanics, the volume injected into the left ventricle must leave this chamber during diastole. Given these limitations, this model is expected to provide an initial examination of the importance of scanline placement. The errors described and assessed by this technique may be influenced by the limitations of the model and therefore further research in the development of a more realistic model is desired.

3.2 Finite Element Model of Ventricular Filling

To evaluate the impact of scanline misalignment, simplified axisymmetric finite element models of pulsatile flow were created using cross-sectional geometry derived from echocardiographic data. Figure 3.1 shows an example of this approach, whereby a transesophageal echocardiogram was traced to define the borders of the left atrium, mitral valve, and left ventricle. From these borders, an axisymmetric representation of the ventricle was formed and translated into a finite element model in ANSYS / FLOTRAN v.5.1 (Ansys Inc., Houston, Pennsylvania).
Axisymmetric models were generated for both normal and dilated ventricular cardiac morphologies. The solutions resulting from a pulsatile input provides velocity and pressure data in a series of 2D images with 5 ms resolution. Figure 3.2 shows a velocity distribution from this model when a pulsatile input (with a temporal profile of half a sinusoid, a peak flow rate of 100 ml/s and a flow duration of 300 ms) was imposed at the left atrial entrance.
Figure 3.2: Velocity and pressure distribution resulting from the numerical simulation 150 ms after a pulsatile input (with a temporal profile of half a sinusoid, a peak flow rate of 100 ml/s and a flow duration of 300 ms) was imposed at the left atrial entrance.

From the series of temporal frames simulated (at 5 ms intervals), a spatiotemporal display of the velocity distribution along the centerline was generated, shown in Figure 3.3, similar to a color Doppler M-mode display.
Figure 3.3: Spatiotemporal display of the velocity distribution along the centerline generated from the series of temporal frames simulated at 5 ms intervals, similar to a color Doppler M-mode display

3.3 Data Analysis

Streamline data was extracted from these data sets and used to compute the pressure gradient distributions as previously described using the Euler equation. These computed pressure distributions were compared with the pressure data along the streamline extracted from the modelled pressure distributions. The analysis was further perturbed by (1) rotating the echocardiographic scanline by 5 degree increments (5-30°) to
determine the effect on the pressure distribution calculations, and (2) shifting the echocardiographic scalene off-axis in steps of 0.15 cm.

To examine the effects of scanline misalignment on the accuracy of estimating the intraventricular pressure difference (pressure difference between the left ventricular base and apex), the maximum pressure difference was extracted for each perturbed condition (both angle and positional change).

3.4 Results and Discussion

Applying the Euler equation, the pressure distributions along the centerline (0°) and at rotated angles of 5, 10, 20, and 30 degrees were generated for qualitative comparison with the model results. Figure 3.4 shows both velocity (top) and pressure (bottom) distributions for each of the rotations. Note that while the strong correspondence at 0 degrees is generally preserved at 10 degrees, it is significantly poorer at 20 degrees. As shown in Figure 3.5, the overall velocity error between the theoretical computation and the results of the scanline perturbed by 10 degrees was 1.16±1.29 cm/s. This error increased to 3.58±4.13 cm/s with misalignment by 20 degrees. The magnitude of velocity error at 20 degrees is comparable to that found with color Doppler velocity estimation. The computed maximum pressure difference from each angular perturbation was also computed. Figure 3.6 demonstrates the increase in the error of the estimation of the intraventricular pressure difference associated with increased angular perturbation. Note that for a misalignment of less than 10 degrees, the pressure difference error is less
than 0.02 mmHg. At 20 degrees, the pressure difference error is approximately 0.1 mmHg.

Figure 3.4: Velocity (top) and pressure (bottom) distributions for each of the rotations (0, 5, 10, 20, and 30 degrees)
Figure 3.5: Velocity error with scanline misalignment by angle perturbation

Figure 3.6: Pressure difference error with scanline misalignment by angle perturbation
The Euler equation was also applied to the velocity data extracted along simulated ultrasound scanlines displaced at 0.15 cm increments from the flow centerline. The maximum intraventricular pressure difference was extracted for each perturbation and compared to the simulation results. The results shown in Figure 3.7 demonstrate that a shift in the position of the simulated ultrasound scanline by approximately 1 cm from the central axis results in pressure difference error less than 0.05 mmHg. The mitral orifice that was modelled was 3 cm in diameter, or 1.5 cm radially from the centerline. The pressure difference error in this simulation increased significantly in the lateral region, with the central 2/3 allowing pressure differences estimation with an error less than 0.1 mmHg.

![Figure 3.7: Pressure difference error with scanline misalignment by displacement](image)

Figure 3.7: Pressure difference error with scanline misalignment by displacement
The increase in the pressure difference error in the lateral portion of the flow results due to the curved streamline paths. However, the expected error would be less in this region with a more accurate approximation to the actual flow streamline. Although the ultrasound scanline represents a linear path, a choice of orientation allowing both an offset in displacement as well as an angular correction could improve the pressure difference error. To demonstrate the possible error in the technique when the scanline is aligned "best" with the flow streamline, the scanline was chosen through the 2D flow field to best fit the streamline at each displacement from the centerline of flow. The results shown in Figure 3.8 demonstrate the improvement that is most significant in the lateral portion of the simulation (beyond a radius of 1.0 cm).

![Graph](image)

**Figure 3.8:** Pressure difference error with scanline misalignment by displacement corrected by best linear fit with flow streamline
These simulations demonstrate that misalignment of the Doppler scanline by a specific degree of angular perturbation (less than 20 degrees) or lateral displacement (within the central 60 percent of the mitral orifice area) will provide an accuracy of less than 0.1 mmHg in the intraventricular pressure difference estimate obtained by numerical application of the Euler equation. These results, however, are specific for the numerical model investigated and future work is required to improve the finite element model and reduce the limitations imposed. I believe that these simulations do demonstrate that useful estimates of pressure differences can be derived from scanline velocity information provided that the misalignment between the scanline and inflow streamline are minimized.
CHAPTER 4

IN VIVO ESTIMATION OF THE TRANSMITRAL PRESSURE DIFFERENCE

4.1 Hypothesis

In vivo experimentation was selected to examine the following hypothesis: The instantaneous transmitral pressure difference during diastole can be estimated from the unsteady Bernoulli equation using the spatiotemporal velocity distribution obtained from color Doppler M-mode echocardiography.

4.2 Experimental Protocol

Six adult mongrel dogs weighing 29.7 ± 7.4 kg [mean ± standard deviation] were anesthetized with intravenous sodium pentobarbital (25 mg/kg), intubated and ventilated using room air. A peripheral vein, the right internal jugular vein, and the right femoral artery were canulated for administration of medication and hemodynamic monitoring. Pulmonary artery pressure and arterial pressure were measured using fluid filled catheters and monitored throughout the experiments. Following a midline sternotomy, the sternum was split widely and the heart suspended in a pericardial cradle insuring an adequate echocardiographic imaging window.
4.3 Data Acquisition

The data acquisition setup is illustrated in Figure 4.1. High fidelity pressure data from the left atrium and left ventricle is recorded using a dual sensor Millar catheter.

Figure 4.1: Diagram of data acquisition setup

Figure 4.2 is an example of a 6 second hemodynamic data set showing the electrocardiogram (ECG) at the bottom, left atrial pressure ($p_{LA}$), left ventricular pressure ($P_{LV}$), and the timing marker signal (top).
Figure 4.2: Hemodynamic data set with left atrial and ventricular pressure, electrocardiogram, and timing marker signal.

Figure 4.3: Echocardiographic data collection
Figure 4.3 shows an example of the spatiotemporal velocity distribution from the left atrium to the left ventricle obtained by color Doppler M-mode echocardiography identifying the separate E-wave (early filling wave) and A-wave (atrial contraction). Notice the ECG and marker signals which are stored with the image file for temporal alignment.

![Graph showing diastolic left atrial and ventricular pressure waveforms and computed transmitral pressure difference.](image)

Figure 4.4: Diastolic left atrial and ventricular pressure waveforms and computed transmitral pressure difference

Figure 4.4 illustrates the physiologic tracings corresponding to the two cardiac cycles in the color Doppler M-mode display. The instantaneous invasive transmitral
pressure difference ($\Delta p_{\text{cat}}$) is calculated and also shown near the bottom of Figure 4.4. Note that there are three sections to the diastolic pressure difference waveform; an initial positive difference due to early filling during ventricular relaxation, a second region of pressure difference reversal that decelerates the early filling wave, and a third positive pressure difference during atrial contraction.

4.4 Data Analysis

Invasive transmitral pressure difference measurements were made on 15 cardiac cycles from each of the six animal investigations. Noninvasive estimates of the pressure difference were computed using color Doppler M-mode images from the corresponding cardiac cycles. These noninvasive estimates were computed from both the simplified and unsteady forms of the Bernoulli equation. A repeated measures analysis was utilized to statistically evaluate the noninvasive estimation techniques as compared to the reference catheter measurement. This analysis was performed to examine both the magnitude and timing of the peak transmitral pressure difference.
4.5 Results and Discussion

4.5.1 Invasive Pressure Differences

The invasive peak pressure difference ($\Delta p_{\text{cath}}$) during early filling for all cardiac cycles analyzed was $1.76 \pm 0.57$ mmHg and the time to the peak filling pressure difference ($t_{\Delta p_{\text{cath}}}$) was $39 \pm 14$ ms. The invasive mean pressure difference ($\overline{\Delta p_{\text{cath}}}$) throughout diastole was $0.68 \pm 0.38$ mmHg.

Table 4.1 summarizes these invasive measurements for each animal experiment.

<table>
<thead>
<tr>
<th>dog</th>
<th>$\Delta p$ [mmHg]</th>
<th>$\Delta p_{\text{max}}$ [mmHg]</th>
<th>$t_{\Delta p_{\text{max}}}$ [ms]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.73</td>
<td>2.50</td>
<td>38</td>
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<tr>
<td>2</td>
<td>0.91</td>
<td>1.68</td>
<td>36</td>
</tr>
<tr>
<td>3</td>
<td>0.92</td>
<td>2.16</td>
<td>28</td>
</tr>
<tr>
<td>4</td>
<td>0.86</td>
<td>1.48</td>
<td>57</td>
</tr>
<tr>
<td>5</td>
<td>0.40</td>
<td>1.82</td>
<td>48</td>
</tr>
<tr>
<td>6</td>
<td>0.28</td>
<td>0.93</td>
<td>27</td>
</tr>
</tbody>
</table>

mean ± std.dev. $0.68 \pm 0.38$ $1.76 \pm 0.57$ $39 \pm 14$

Table 4.1: Catheter measurements under baseline conditions
4.5.2 Doppler Derived Pressure Differences - Simplified Bernoulli Equation

Using the simplified Bernoulli equation (convective term only) the instantaneous pressure difference ($\Delta p_c(t)$) was calculated for all cardiac cycles ($N=90$). Figure 4.5 shows an example of a reconstructed pressure difference based on the convective forces only.

Figure 4.5: Comparison of Doppler derived instantaneous transmitral pressure difference with catheter-based measurement
Notice that the peak transmitral pressure differences ([ΔpC]_{max}) are lower (0.85±0.49 mmHg) and greatly underestimate the catheter measures ([ΔpC]_{max} = 0.70[Δp_{cath}]_{max} - 0.41, r = 0.86, p<0.001, ε_c = -0.91±0.32 mmHg, N= 90) as illustrated in Figure 4.6.

Figure 4.6: Comparison of the catheter-based peak transmitral pressure difference with estimate using the simplified Bernoulli equation
Similar results were observed when all cardiac cycles obtained in one animal where averaged ($[\Delta p_C]_{max} = 0.82[\Delta p_{cath}]_{max} - 0.60, r = 0.89, p<0.017, \varepsilon_C = -0.91\pm0.25 \text{ mmHg}, N=6$) as illustrated in Figure 4.7.

![Graph showing the comparison of catheter-based peak transmitral pressure difference with Doppler derived estimates using the simplified and unsteady forms of the Bernoulli equation.](image)

**Figure 4.7**: Comparison of the catheter-based peak transmitral pressure difference with Doppler derived estimates using the simplified and unsteady forms of the Bernoulli equation.
The pressure differences by the simplified Bernoulli equation also show a systematic time lag when compared with the invasive pressure differences. The time to peak pressure difference \( t_{\Delta p_c,\text{max}} \) is \( 75\pm24 \) ms and the time difference \( (t_{\Delta p_c,\text{max}} - t_{\Delta p_{\text{cath}},\text{max}}) \) between the peak catheter pressure measurement and peak pressure difference by the simplified Bernoulli equation was \( \Delta t_c = 36\pm17 \) ms (Figure 4.8).

Figure 4.8: Comparison of the catheter-based timing of the peak transmitral pressure difference with the timing determined using the simplified Bernoulli equation
The mean transmitral pressure difference ($\overline{\Delta p_c}$) is 0.44±0.18 mmHg. Using the simplified Bernoulli equation the mid-diastolic reversal of the pressure difference was never seen.

Table 4.2 summarizes the averaged data for each animal experiment.

<table>
<thead>
<tr>
<th>dog</th>
<th>$\delta$ [mmHg]</th>
<th>$\Delta t$ [ms]</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$C$</td>
<td>$C+I$</td>
</tr>
<tr>
<td>1</td>
<td>1.21</td>
<td>0.19</td>
</tr>
<tr>
<td>2</td>
<td>1.01</td>
<td>-0.03</td>
</tr>
<tr>
<td>3</td>
<td>0.56</td>
<td>-0.28</td>
</tr>
<tr>
<td>4</td>
<td>0.93</td>
<td>0.13</td>
</tr>
<tr>
<td>5</td>
<td>1.07</td>
<td>0.04</td>
</tr>
<tr>
<td>6</td>
<td>0.68</td>
<td>0.03</td>
</tr>
</tbody>
</table>

| mean ± std.dev. | $0.91 \pm 0.32$ | $0.01 \pm 0.24$ | $36 \pm 17$ | $2 \pm 10$ |

Table 4.2: Comparison of catheter pressure difference parameters to Doppler estimates using the simplified (C) and unsteady (C+I) Bernoulli equations
4.5.3 Doppler Derived Pressure Differences - Unsteady Bernoulli Equation

shows the color coded temporal acceleration image resulting from the convolution of the original velocity distribution in the color Doppler M-mode image (1) with the Sobel operator shown in Equation 6. The instantaneous value of the inertial component ($\Delta p_1[t]$) was computed from the integration of this temporal derivative and included in the unsteady Bernoulli equation (Equation 3) to compute the Doppler derived diastolic transmitral pressure difference ($\Delta p_{C+1}[t]$). illustrates the comparison between the invasive pressure difference and the two noninvasive Doppler derived pressure differences using the simplified and unsteady Bernoulli equations respectively. The peak transmitral pressure difference ($[\Delta p_{C+1}]_{max}$) closely approximates the invasive measurements ($[\Delta p_{cath}]_{max}$) for analysis of individual cardiac cycles (Figure 4.9) ($[\Delta p_{C+1}]_{max} = 0.95[\Delta p_{cath}]_{max} + 0.07$, $r = 0.92$, $p<0.001$, $\varepsilon_{C+1} = -0.02 \pm 0.24$ mmHg, $N=90$) as well as averaged data per animal ($[\Delta p_{C+1}]_{max} = 1.02[\Delta p_{cath}]_{max} - 0.05$, $r = 0.96$, $p<0.003$, $\varepsilon_{C+1} = -0.01 \pm 0.16$ mmHg, $N=6$) as illustrated in Figure 4.7.
Figure 4.9: Comparison of the catheter-based peak transmitial pressure difference with estimate using the unsteady Bernoulli equation

The timing of the peak pressure difference calculated by the unsteady Bernoulli equation closely coincides with the invasive peak pressure differences with a $\Delta t_{CH} (t[\Delta p_{cath}]_{max} - t[\Delta p_{cath}]_{max}) = 2 \pm 10 \text{ ms}$ (Figure 4.10).
4.6 Repeated Measures Analysis

Repeated measures analysis was performed to compare the noninvasive estimates of the peak transmitral pressure difference with the catheter-based reference measurement. Data consisting of 15 repeated measurements for both the magnitude and timing of the peak transmitral pressure difference was categorized by subject (6 animals) and method (catheter measurement, simplified Bernoulli estimate, and unsteady Bernoulli
estimate). The results of this analysis demonstrated a significant difference \((p<0.015)\) between the estimates of the peak transmitral pressure difference and no significant difference among the individual animals studied. A further analysis of the measurement method using a Bonferroni test of mean differences demonstrated a significant difference between the peak transmitral pressure difference by catheter and the simplified Bernoulli estimate \((p<0.01)\). The mean differences in magnitude and timing of the peak transmitral pressure difference between the catheter measurements and the unsteady Bernoulli estimate were not significant.

The results obtained in these animal investigations were encouraging and lead to an experimental protocol involving human subjects. In this investigation, 10 patients undergoing heart surgery were asked to participate in an approved study protocol to investigate diastolic function using simultaneous hemodynamic and Doppler ultrasound information. Data were obtained prior to cardiopulmonary bypass, following cannulation for safety considerations. Simultaneous Doppler and physiological data were obtained in a similar fashion as compared to the animal investigations using a dual sensor pressure catheter which was introduced by the cardiac surgeon through the right upper pulmonary vein. Using echo guidance and hemodynamic waveform monitoring, the catheter was positioned across the mitral valve to obtain both left atrial and ventricular pressure. Figure 4.11 demonstrates the relationship between the catheter based measurement of the peak transmitral pressure difference and the noninvasive Doppler-derived estimate. The
noninvasive estimate was computed using both the simplified and unsteady forms of the Bernoulli equation.

Figure 4.11: Comparison of catheter-based measurement of peak early transmitral pressure difference with noninvasive estimation using the unsteady and simplified forms of the Bernoulli equation

The estimation of the peak transmitral pressure difference was significantly improved in this series of human investigations when the inertial forces included in the unsteady Bernoulli equation were added to the convective forces.
CHAPTER 5

IN VIVO EXPERIMENTATION OF INTRAVENTRICULAR PRESSURE GRADIENTS

5.1 Hypotheses

In vivo animal experimentation was selected to investigate the following hypotheses:

I. The intraventricular pressure gradient can be estimated from the one-dimensional Euler equation using the spatiotemporal velocity distribution available from color Doppler M-mode echocardiography.

II. The intraventricular pressure gradient can be estimated accurately using this technique following a physiologic perturbation that alters the magnitude and distribution of the pressure distribution.

5.2 Experimental Protocols

Simultaneous pressure and velocity data were obtained from six adult mongrel dogs, anesthetized with intravenous sodium pentobarbital (25 mg/kg), intubated and ventilated using room air. A peripheral vein, the right internal jugular vein, and the right femoral artery were cannulated for administration of medication and hemodynamic monitoring. Pulmonary artery pressure and arterial pressure were measured using fluid
filled catheters and monitored throughout the experiments. Following a midline sternotomy, the sternum was split widely and the heart suspended in a pericardial cradle insuring an adequate echocardiographic imaging window.

Data was obtained from 10 cardiac cycles under baseline hemodynamic conditions in all six animals and from an additional 10 cardiac cycles in 4 animals following intravenous administration of isoproterenol (0.1 μg/kg/min).

5.3 Data Acquisition

An example of the simultaneous Doppler velocity and intracardiac pressure data acquired in this experiment is shown in Figure 5.1. Following positioning of the Doppler scanline (Figure 5.1, A), the spatiotemporal velocity distribution (Figure 5.1, B) was acquired with color-coded blood flow velocities on a 5 bit scale such that zero velocity is black, velocities towards the transducer are red/yellow, and velocities away from the transducer are blue/cyan. The maximum, or Nyquist, velocity was held constant in this experiment at ±81 cm/s. The simultaneous intraventricular and left atrial pressure measurements (Figure 5.1, C) are aligned using the timing marker and electrocardiogram waveforms.
Following extraction of the early filling wave, the pressure gradient ($\partial p/\partial s$) is calculated using the one dimensional Euler equation as shown graphically in Figure 5.3. A noninvasive Doppler estimate of the intraventricular pressure difference ($\Delta p_{IV}$) is computed by integration of the pressure gradient, $\partial p/\partial s$, over the range in depth
(\Delta s=5 \text{ cm})$ corresponding to the distance between the transducers located on the catheter at the left ventricular base and apex.

![Diagram](attachment:figure5.3.png)

**Figure 5.3**: Diagrammatic solution to the one-dimensional Euler equation

### 5.4 Data Analysis

Invasive intraventricular pressure difference measurements were made on 10 cardiac cycles from each of the six animal investigations under baseline conditions, and on an additional 10 cardiac cycles in 4 of these investigations following intravenous administration of isoproterenol (0.1 \( \mu \text{g/kg/min} \)). Noninvasive estimates of the pressure difference were computed by the one-dimensional Euler equation using color Doppler M-mode images from the corresponding cardiac cycles. A repeated measures analysis was
utilized to statistically evaluate the noninvasive estimation techniques as compared to the reference catheter measurement.

5.5 Results and Discussion

Under baseline conditions, the maximum intraventricular pressure difference ([Δp_{IV}]_{max}) by direct catheter measurement was 1.80±0.47 mmHg. This represented 71.1±12.6% of the total maximum pressure difference ([Δp_T]_{max}) which was 2.58±0.66 mmHg. The percentage of the intraventricular pressure difference at the time of peak total pressure difference ([Δp_{IV}]/[Δp_T]_{max}) was slightly less (68.1±12.1%). The average noninvasive estimate of the peak intraventricular pressure difference ([Δp_{IV}]_{max}) for the baseline data was 1.77±0.53 mmHg, representing 68.0±7.2% of the total maximum pressure difference ([Δp_T]_{max}). Again the percentage of the intraventricular pressure difference at the time of peak total pressure difference was slightly less (66.1±7.8%). Repeated measures analysis demonstrated that there was no significant difference between invasive and noninvasive estimates of both the intraventricular and total pressure differences. The average difference, or error (ε_{IV} = [Δp_{IV}]_{max} - [Δp_{IV}]_{max}^{n}), between invasive measurement and noninvasive estimate of the intraventricular pressure difference was 0.03±0.29 mmHg. The error (ε_T = [Δp_T]_{max} - [Δp_T]_{max}^{n}) between invasive measurement and noninvasive estimate of the total pressure difference was 0.04±0.23 mmHg.
Repeated measures analysis also demonstrated that there was no significant difference between the invasive measurement and noninvasive estimate of the time to the peak filling pressure difference. The temporal difference between the invasive measurement and noninvasive estimate of the timing of the peak total pressure difference 

\[ \Delta t_T = t_{[\Delta P_T]_{\text{max}}} - t_{[\Delta P_T']_{\text{max}}} \]

was 0.012±0.045 s. The temporal difference between the invasive measurement and noninvasive estimate of the timing of the intraventricular pressure difference 

\[ \Delta t_{TV} = t_{[\Delta P_{TV}]_{\text{max}}} - t_{[\Delta P_{TV}']_{\text{max}}} \]

was -0.018±0.023 s.

Following administration of isoproterenol in four of the six animals, the invasive measurement of the maximum total and intraventricular pressure difference increased significantly (\([\Delta P_T]_{\text{max}}\): 2.82±0.42 mmHg to 5.32±1.52 mmHg; \([\Delta P_{TV}]_{\text{max}}\): 1.89±0.32 mmHg to 4.43±1.29 mmHg; p<0.01). The relative contribution of the intraventricular pressure difference to the total pressure difference also increased significantly from 68.0±12.1% at baseline to 83.3±5.3% during isoproterenol infusion. These changes were also tracked well by the noninvasive Doppler-derived estimates. The errors between the Doppler-derived estimates and catheter measurements were not significantly different (\(e_T\): -0.04±0.23 mmHg at baseline vs. -0.12±0.49 mmHg with isoproterenol; \(e_{TV}\): 0.03±0.29 mmHg at baseline vs. 0.15±0.49 mmHg with isoproterenol).

These results demonstrate that the intraventricular pressure difference can be estimated from the one dimensional Euler equation using the spatiotemporal velocity
distribution available from color Doppler M-mode echocardiography. This estimation technique was also shown to be capable of following the physiologic change in the magnitude of the intraventricular pressure difference that occurred with pharmacologic intervention. Further study and validation of this technique is desired and necessary in humans.
CHAPTER 6

IMPLICATIONS AND FUTURE DIRECTIONS

6.1 Thesis Summary

This study is the first to apply complex image processing (calculation of partial derivative) and fundamental fluid dynamics (Euler equation) to the analysis of diastolic filling using color Doppler M-mode echocardiography. From an apical scanning window the Doppler M-mode cursor can be aligned parallel with left ventricular inflow giving a spatiotemporal velocity distribution between left atrium and left ventricle throughout the diastolic filling period. The calculation of the transmitral pressure difference using the simplified Bernoulli equation results in significant underestimation and time delay compared to the catheter measurements. Assuming that the Doppler scanline closely coincides with a mitral inflow streamline, the inertial component of ventricular filling can be calculated by spatial integration of flow acceleration and combined with convective forces to estimate the intracardiac pressure differences.

Transmitral pressure difference estimation: Inclusion of the inertial forces in the noninvasive pressure difference calculations provides much more accurate estimates of the peak pressure differences during early filling, almost entirely correcting the systematic time-lag and revealing the mid-diastolic pressure difference reversal, previously missed.
In the animal investigations described in detail in Chapter 4, the inclusion of the inertial forces resulted in no significant difference between the direct catheter measurement and the noninvasive Doppler estimate of the peak transmitral pressure difference using the unsteady Bernoulli equation. The magnitude and timing differences of the calculated peak pressure difference during early filling improved significantly from $\varepsilon_C = -0.91 \pm 0.32 \text{ mmHg}$ and $\Delta t_C = 36 \pm 17 \text{ ms}$ using the simplified Bernoulli equation to $\varepsilon_C+I = -0.01 \pm 0.24 \text{ mmHg}$ and $\Delta t_C+I = 2 \pm 10 \text{ ms}$ with the inclusion of the inertial component. Although the differentiation method employed here introduces noise in the acceleration estimate, the spatial integration that follows tends to reduce the noise, and it is very encouraging that this technique yields accurate results with little adjunctive processing.

The transvalvular pressure difference results from a combination of convective, inertial, and viscous forces. Several investigators have previously shown that for flow through restrictive orifices the convective contribution, $\Delta p_C$, is dominant, and for constant flow $\Delta p_C = I/D^4$, where $D$ is the orifice diameter. This principle has been clinically validated to calculate pressure gradients across stenotic valves from Doppler velocity measurements using the simplified Bernoulli equation. However, as the orifice diameter increases, the convective component, $\Delta p_C$, decreases and the inertial contribution, $\Delta p_I$, to the pressure difference becomes more significant. In fact, the inertial component is proportional to the orifice diameter ($\Delta p_I = D$), and thus the ratio of inertial to convective
forces is proportional to the orifice diameter raised to the fifth power \( (\Delta p_t/\Delta p_C = D^5) \).

While the importance of the inertial contribution to the pressure gradient across nonrestrictive orifices has been previously recognized, it has not been explicitly reported for the mitral valve in vivo.

The application of the unsteady Bernoulli equation to color Doppler M-mode echocardiographic analysis of diastolic filling pressures assumes that left ventricular inflow is laminar and the ultrasound scanline closely coincides with an inflow streamline. Several investigators have previously described the dynamics of blood entering the left ventricle using both numerical modelling and more recently, noninvasive magnetic phase encoding techniques. These studies indicate that the assumption of laminar flow is most valid for early filling through a normal mitral valve, supporting the application of this technique during the E-wave to investigate peak early filling pressure differences. In the presence of mitral valve stenosis or a prosthetic mitral valve, left ventricular inflow is turbulent and the assumption of laminar inflow is also no longer valid. However, since the orifice is more restrictive in this setting, estimates of transmitral pressure differences have been calculated simply using continuous wave Doppler and the simplified Bernoulli equation.

Mitral inflow streamlines through a normal mitral valve do not exactly coincide with a Doppler scanline but are directed slightly more laterally and follow the curvature of the left ventricular lateral wall. Care was taken in our experiments to position the
Doppler cursor through the middle of the inflow path visualized by two-dimensional color Doppler imaging to obtain a spatiotemporal velocity distribution representing an inflow streamline as close as possible.

Application of the unsteady Bernoulli equation, also assumes that viscous forces are negligible in the estimation of transmitral pressure differences. While it has been suggested that the viscous contribution may be important in the case of prosthetic valves, the time during which blood is in contact with the normal valvular apparatus is very brief and viscous forces may only be important in the immediate proximity of the valve leaflets or left ventricular wall. Falsetti has neglected viscous contributions in analysis of regional left ventricular pressure differences using an argument based on the calculation of a Reynolds number \( \text{Re} = \frac{vL}{\mu} \) and the definition that this nondimensional value represents the ratio of inertial to viscous forces. Using a blood velocity \( v \) of 40 cm/s, a characteristic left ventricular length \( L \) of 2 cm, and blood viscosity \( \mu \) of 0.02 cm\(^2\)/s, they estimate a Reynolds number of 4000 and, therefore, a negligible viscous force that is \( 1/4000 \) of the inertial force.

**Intraventricular Pressure Differences:** The basic concept utilized to calculate transmitral pressure differences has been extended to obtain regional intraventricular pressure differences anywhere along the scanline. Solving the Euler equation allows calculations of incremental spatial pressure gradients \( \frac{\delta p}{\delta s} \) along the ultrasound scanline. Integration of this gradient allows the calculation of an intraventricular pressure
difference between left ventricular base and apex, which has been directly compared a catheter measurement of the intraventricular pressure difference. In the animal investigations described in detail in Chapter 5, the estimation of the intraventricular pressure difference using the noninvasive color M-mode data and the one dimensional Euler equation demonstrated no significant difference in comparison with the direct catheter measurement using the repeated measures analysis. The average difference between invasive measurement and noninvasive estimate of the intraventricular pressure difference was 0.03±0.29 mmHg. The approach was also utilized to track changes in the magnitude of the intraventricular pressure difference due to pharmacologic intervention. Doppler-derived estimates and catheter measurements were not significantly different (0.03±0.29 mmHg at baseline vs. 0.15±0.49 mmHg with isoproterenol).

As important as these data may be to the understanding of ventricular filling and mitral valve physiology, it is perhaps most remarkable that these measurements can be obtained completely noninvasively by quantitative processing of the transmitral color M-mode Doppler echocardiographic image. This implies that the methods described herein may be applicable in the clinical setting to better understand diastolic filling in patients, a significant quantitative achievement of color Doppler flow mapping. This approach could characterize the complex interaction between spatial and temporal relationships of intracardiac pressure gradients in an entirely noninvasive way, with potential important clinical application in ischemic and myopathic heart disease.
6.2 Future Directions

Although there was an excellent agreement between noninvasive color Doppler derived intraventricular pressure differences and invasive pressure measurements in an animal model, this method requires further clinical validation. Furthermore, it is important to determine the absolute values and range for inertial forces contributing to left ventricular filling in the human heart. It is of particular importance to explore whether inertial forces are constant or not. By analogy with mitral stenosis, it may be that the inertial forces are less when mitral valve opening is limited in dilated cardiomyopathy. The current methodology should be applicable to this issue.

High frame rate color Doppler imaging available with the introduction of parallel processing may allow application of this methodology and reconstruction of pressure differences along an arbitrary path defined on two-dimensional images, (allowing even closer approximation of left ventricular inflow), without sacrificing temporal resolution. Continued development of finite element modelling is another area for future extensions of the testing and validation of this methodology.

6.3 Final Remarks

The current implementation of this method involves complex and time-consuming off-line processing of digitally stored color Doppler M-mode images. However with the ever increasing storage capacity and processing speed of current computer technology these algorithms can easily be incorporated within the analysis package of contemporary
echocardiographs. This would fully noninvasive intracardiac pressure difference calculations on-line during the actual echocardiographic examination, similar to the recently reported algorithms to automate calculation of cardiac output.
LIST OF REFERENCES


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