Published in final edited form as:

Ultrasound Med Biol. 2011 August ; 37(8): 1185–1195. doi:10.1016/j.ultrasmedbio.2011.05.002.

The diastolic function to cyclic variation of myocardial ultrasonic backscatter relation: the influence of parametrized diastolic filling (PDF) formalism determined chamber properties

Christopher W. Lloyd¹, Leonid Shmuylovich², Mark R. Holland¹, James G. Miller¹, and Sándor J. Kovács²

¹Department of Physics, Washington University in Saint Louis, Saint Louis, Missouri

²Cardiovascular Biophysics Laboratory, Cardiovascular Division, Department of Internal Medicine, Washington University School of Medicine, Saint Louis, Missouri

Abstract

Myocardial tissue characterization represents an extension of currently available echocardiographic imaging. The systematic variation of backscattered energy during the cardiac cycle (the “cyclic variation” of backscatter) has been employed to characterize cardiac function in a wide range of investigations. However, the mechanisms responsible for observed cyclic variation remain incompletely understood. As a step toward determining the features of cardiac structure and function that are responsible for the observed cyclic variation, the present study makes use of a kinematic approach of diastolic function quantitation to identify diastolic function determinants that influence the magnitude and timing of cyclic variation. Echocardiographic measurements of 32 subjects provided data for determination of the cyclic variation of backscatter to diastolic function relation characterized in terms of E-wave determined, kinematic model-based parameters of chamber stiffness, viscosity/relaxation, and load. The normalized time delay of cyclic variation appears to be related to the relative viscoelasticity of the chamber and predictive of the kinematic filling dynamics as determined using the parametrized diastolic filling formalism (with r-values ranging from .44 to .59). The magnitude of cyclic variation does not appear to be strongly related to the kinematic parameters.

Keywords

Cyclic Variation; Parametrized Diastolic Filling Formalism; Tissue Characterization; Myocardial Ultrasound

Background

Myocardial tissue characterization represents an extension of currently available echocardiographic imaging. Measurements of the systematic variation of backscattered energy during the cardiac cycle (known as the cyclic variation of backscatter) provide an

© 2011 World Federation for Ultrasound in Medicine and Biology. Published by Elsevier Inc. All rights reserved.

Address correspondence to: Sándor J. Kovács, PhD, MD, Cardiovascular Biophysics Laboratory, Washington University Medical Center, 660 South Euclid Ave, Box 8086., St. Louis, MO. 63110, Phone (314) 454-8901, FAX (314) 454-5265, sjk@wuphys.wustl.edu.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

approach for myocardial characterization (Madaras 1983). Changes in the pattern of cyclic variation of backscattered ultrasonic energy from a region of myocardium have been studied in a wide range of cardiac pathologies (Milunski 1989; Perez 1992; Perez 1996; Yuda 2002; Di Bello 2003; Giglio 2003; Ohara 2005). The results of these studies indicate that the cyclic variation of backscatter can be used to monitor changes in the underlying structural and elastic properties of the myocardium. Although a number of studies have described mechanisms thought to contribute to cyclic variation, a complete understanding of the underlying factors responsible for the cyclic variation of backscatter has not been achieved (Wickline 1985; Holland 2004; Micari 2006).

Another characterization approach, known as the parametrized diastolic filling formalism, is an established kinematic approach for modeling the diastolic function of the heart, using information derived from Doppler measurements of blood flow through the mitral valve (Kovács 1987). This method is a causality-based generalization of the standard phenomenologic approach employed in cardiology and physiology for diastolic function assessment via the characterization of blood flow through the mitral valve (the ‘triangle’ approach). This formalism accounts for the mechanical suction-pump role of the left ventricle by applying a damped harmonic oscillator as an analog kinematic model to characterize the Doppler transmitral velocity profiles corresponding to the early rapid filling wave (E-wave) and the subsequent late filling wave (A-wave) driven by atrial contraction. Transmitral blood flow velocity is thus a consequence of a balance between chamber derived elastic, inertial, and damping forces as required by Newton’s Law. During filling, the elastic driving force that generates recoil is due to systolic loading of elastic elements in the chamber (titin, visceral pericardium, elastin, and collagen (Robinson 1986; Granzier and Labeit 2004; Jobsis 2007)). Relaxation unmask these stored elastic forces and thereby generates acceleration forces subject to inertial constraints, which are opposed by resistive (damping) forces. The interaction of these three forces (elastic restoring force, inertia, and damping), in the context of an equation of motion, is reflected in the values of the three mathematically independent model parameters: the spring constant k , the damping constant c , and the initial spring displacement x_0 . The equation of motion (Newton’s Law, per unit mass) can be solved for the E-wave velocity, which yields a closed form expression for the E-wave contour, in terms of the model parameters (c , k , and x_0) (Hall and Kovács 1994).

This formalism draws a causal connection between the E-wave contours and tissue recoil and associated viscoelasticity. These parameters have physiologic analogues that have been experimentally validated in-vivo (Lisaukas 2001; Bauman 2004; Chung 2006; Zhang 2010), and have also been tested and validated in subjects with a wide range of cardiac pathologies, such as heart failure, hypertension and diabetes (Kovács 1997; Rich 1999; Dent 2001; Lisaukas 2001; Riordan 2005). This expression for the E-wave velocity additionally permits the calculation of parameters (AT , DT , VTI , E_{peak} , A_{peak}) that are traditionally calculated using a ‘triangular shape’ approximation for determination of E-wave features.

The quantity and forcefulness of blood delivered to the peripheral circulation during systole is highly dependent upon the diastolic filling that precedes that systolic contraction (the Frank-Starling mechanism). Furthermore, diastolic dysfunction precedes systolic dysfunction in many cardiac pathologies (Grossman 1991; Aeschbacher 2001). These suggest that relating results obtained with the parametrized diastolic filling formalism to measurements of the cyclic variation of backscatter may represent an approach for determining the role of diastolic function in the observed cyclic variation of backscatter. The hypothesis underlying this work is that the dynamic viscoelastic properties of the myocardium that influence diastolic function are likely to be reflected in the cyclic variation of backscatter. The goal of this study of 32 subjects was to elucidate and characterize the

impact of diastolic function on the cyclic variation of backscatter by employing the parametrized diastolic filling formalism for diastolic function quantitation.

Methods

Subject Population

Subjects for this study were recruited from patients who had been referred for elective, diagnostic cardiac catheterization to the Cardiac Procedure Center at Washington University Medical Center's Barnes-Jewish Hospital in Saint Louis, Missouri. These subjects ($n = 32$) were scheduled for elective diagnostic cardiac catheterization to rule out the presence of coronary artery disease at the request of their referring physician. All subjects provided informed consent prior to the procedure in accordance with a protocol approved by the Barnes-Jewish Hospital/Washington University Human Research Protection Office. The inclusion criteria included normal valvular function, no acute ischemia, and no significant merging between echocardiographic E- and A-waves. All subjects had normal left ventricular ejection fractions, which facilitates legitimate comparisons between global and local parameters in this study. Subjects with issues that would make the acquisition of data untenable, such as poor echocardiographic windows, tachycardia, or significant mitral regurgitation or aortic stenosis, were excluded.

Clinical Data Acquisition

The simultaneous echocardiography-cardiac catheterization procedure utilized for acquisition of the data has been previously described (Lisauskas 2001). Prior to catheterization, a complete echocardiographic examination was performed on the subject in the catheterization laboratory, using a Philips iE33 echocardiographic imaging system (Andover, MA, USA) in accordance with ASE guidelines (Gottdiener 2004). This examination was performed by a certified sonographer and included 2-D and 3-D imaging of the heart in standard views, as well as Doppler tissue and flow characterization. The examination results were used to determine the eligibility of the subject, as noted above. Due to limitations imposed by the setting, the subject was imaged in the supine, rather than the left lateral decubitus position. This position has the potential disadvantage of introducing additional visual artifacts, but these artifacts can be minimized or eliminated through careful manipulation of the transducer. In addition, the configuration of the imaging system was such that the digitized image data was nearly linearly related to the log-compressed received signal, to allow for the accurate measurement of cyclic variation. The configuration for the iE33 system was determined to be nearly linear in the log-compressed domain for the M1 grayscale map (a system-defined mapping between received power and displayed grayscale), with 40 dB compression, and the lateral and time gain compensation held constant. A further offline grayscale remapping was later applied to achieve linearity.

After the initial echocardiographic examination, arterial access was obtained via the femoral artery, and a 6-F micromanometer-tipped pigtail pressure-volume (conductance) catheter (Millar Instruments, Houston, TX, Model SPC 562) was directed into the left ventricle (LV) in a retrograde fashion across the aortic valve under fluoroscopic control. The ventricular pressures were fed to the catheterization laboratory amplifier (GE Healthcare, Fairfield, CT), and output simultaneously into the auxiliary input port of the echocardiographic imaging system and into a digital converter connected to a customized PC. Echocardiographic video clips, consisting of several consecutive heartbeats (typically four), were first obtained for the parasternal long axis view, to be analyzed off-line to determine the cyclic variation from the posterior wall of the LV. The echocardiographic view was then shifted to the apical four-chamber view, and a Doppler sample volume, gated to a 1.5 to 2.5 mm depth, was placed between the tips of the mitral valve leaflets. With the Millar catheter in place, simultaneous

pressure, volume and transmitral flow data were collected during the acquisition of approximately 25 to 50 consecutive cardiac cycles. Continuous Doppler data was recorded to DVD. To synchronize the hemodynamic and Doppler data, a fiducial square wave signal was fed from the catheter transducer control unit to both the echocardiographic imager and the PC. Following the acquisition of research data, the remainder of the diagnostic procedure was performed. After the clinical study, the acquired ultrasonic and pressure-volume data were archived for subsequent, off-line analysis.

Determination of E-Wave Parameters

Triangle Approach—Each subject had an average of 10 to 20 cardiac cycles selected for quantitative analysis. Conventional triangle approximations of the E- and A-wave shapes (Appleton 2000; Armstrong 2010), acquired in a manner illustrated with Figure 1a, provided the following parameters: E-wave acceleration and deceleration times (AT and DT) and duration (E_{dur}), and the E-wave and A-wave peaks (E_{peak} , A_{peak}) and velocity-time integrals (VTI_E , VTI_A). The ratio of E_{peak} to A_{peak} (E_{peak}/A_{peak}) and VTI_E to VTI_A (VTI_E/VTI_A) were also calculated for all heart cycles.

Parametrized Diastolic Filling Approach—The E-waves selected for each subject for the conventional triangle approximation to E-wave shape approach were also subjected to parametrized diastolic filling model-based image processing, which yielded specific mass-normalized kinematic model parameters (the relaxation/viscosity parameter c ($1/s$), the stiffness parameter k ($1/s^2$), and the initial load parameter x_0 (m)) for each E-wave. These parametrized diastolic filling parameters were determined for an E-wave by solving the “inverse” problem, using the clinical E-wave contour as the input and the parameters as the output of a model that is fit to the contour (Hall 1994; Hall and Kovács 1994). Briefly, the process of extracting these parameters from an individual wave involves selecting a single transmitral flow image, cropping the image around the Doppler velocity profile, and loading the cropped image into a custom LabVIEW (National Instruments, Austin, TX) interface. Within the interface the E-wave maximum velocity envelope was digitized, and then a Levenberg-Marquardt algorithm (Press 1986) was applied to this envelope to extract the best-fit parametrized diastolic filling model parameters specific to the contour. This process is shown in Figure 1b, for E-wave shapes well fit by underdamped and overdamped kinematic regimes. After the kinematic model parameters (c , k , and x_0) were determined, four composite indices with physiologic meaning were computed. These composite indices are: kx_0 (the peak driving force (Bauman 2004)), $\frac{1}{2} kx_0^2$ (the initial potential energy available prior to mitral valve opening), $\beta = c^2 - 4k$ (an index of the balance between viscosity/relaxation and stiffness in the system (Kovács 1997; Rich 1999)), and $y = c / (2\sqrt{k})$ (a dimensionless damping to stiffness ratio, in which $y = 1$ separates the underdamped from the overdamped kinematic regime of motion (Zhang 2010)).

Determination of Cyclic Variation Parameters

The data consisting of video clips in the parasternal long axis view were viewed using a DICOM reader (Osirix, available from <http://www.osirix-viewer.com/>) in a manner similar to that described in previous reports (Holland 2006). The grayscale for each video clip was remapped using a look-up table to achieve a linear relationship between the digitized image data and the displayed grayscale. A region of interest was defined in the mid-myocardium of the posterior wall of the LV. The regions of interest were typically on the order of 800 pixels in size. These were large enough to produce normal sampling statistics of the backscatter while remaining small enough to only sample the mid-myocardium in the image, which avoids artifacts that would skew the mean. The location, but not the size or shape, of the region of interest was manually adjusted in each frame of the video clip using visual cues in the image to ensure the same physical region was analyzed over the heart cycle. Due to the

limitations associated with 2D echocardiographic imaging, adjustments for out-of-plane motion of the heart could not be explicitly implemented. The mean grayscale value for this region of interest was determined for each frame. These grayscale values were then partitioned into individual heart cycles, using valve motion and ECG to determine the end of diastole.

The grayscale values over the duration of a single heartbeat were converted into backscatter values in dB as mentioned above, and interpolated in time to 101 points (roughly a 50% interpolation at the 49 Hz frame rate utilized), so that each point corresponds to a percentage of the heart cycle. The magnitude of cyclic variation was determined using an automated approach that closely replicates the values reported by experienced observers without the slight inherent operator variability (Lloyd 2009), and is illustrated for a sample data set in Figure 2. The backscatter values were smoothed with fifteen passes of a three-point binomial low-pass filter to minimize the effects of noise. The values for the top fifteen percent of the data were averaged, and likewise the values for the bottom fifteen percent of the data were averaged. The magnitude was calculated as the difference between the averaged high and averaged low values. The magnitude of time delay comes from the observation that, in apparently normal hearts, the nadir in the time-varying magnitude occurs at or near the end of systole, and a measurement of the time to this nadir, relative to the systolic interval, could be scientifically relevant. The ratio comprising the normalized time delay of cyclic variation was calculated by first manually determining the percentage of the heart cycle at which the nadir of cyclic variation was found, and then dividing that value by the percentage of the heart cycle corresponding to systole. Once this analysis had been completed on all of the individual heart cycles for a specific subject, the overall magnitude and the normalized time delay of cyclic variation were computed as the average of these values across all heart cycles, with an average standard deviation of 0.9 dB and 0.10, respectively. Additionally, the normalized time delay had an uncertainty of 0.03, due to the discrete sampling of the backscattered energy in time.

It is important to note that measurements of cyclic variation of backscatter do not require an acquisition of separate reference backscatter measurements, as would be required for “absolute” measurements of myocardial tissue properties. This self-referencing enables the cyclic variation approach to be a robust method for characterizing myocardial tissue. As such, the measured magnitude and timing that characterize the cyclic variation of backscatter are thought to be largely independent of the echocardiographic system or transducer employed.

Comparisons Between Parameters

The E-wave and cyclic variation parameters were compared using linear correlation, in order to identify significant trends. Although none of the subjects had active ischemia at the time of data acquisition the presence of significant anatomical coronary artery disease, and its resulting effects on the myocardium, could potentially confound comparisons between parameters. To address this concern, the results of the clinical angiogram were used to divide the subject population into those with ($n = 21$, of which 12 had multiple vessel disease) and those without ($n = 11$) significant ($\sim >70\%$ luminal diameter narrowing, with no prior evidence of infarction) coronary artery disease. Each correlation between a particular cyclic variation parameter and an E-wave parameter was first tested by performing an analysis of covariance (ANCOVA) with Matlab (The MathWorks, Inc., Natick, MA, USA), to determine if there existed a significant difference between the two populations. If a significant difference existed, then the populations could not be pooled; the populations were pooled for the remaining E-wave parameters. The appropriate line of regression was then tested for significance against the null hypothesis that the correlation coefficient was equal to zero.

These comparisons were performed between the cyclic variation and parametrized diastolic filling parameters, but were also performed between the cyclic variation and the conventional parameters of function. These parameters include the triangle parameters as discussed earlier, but also the invasively determined hemodynamic diastolic function parameters LVEDP (left ventricular end-diastolic pressure) and τ (the time-constant of isovolumic relaxation).

Results

The ANCOVA results for each pair of cyclic variation parameter to diastolic filling parameter were determined, using a significance threshold on the corresponding F-value of $p = 0.05$, and the statistically significant results are indicated in Table 1. A significant difference was found for the E-wave parameters AT , c , k , and y , which indicated that these relationships differed between patient populations with and without coronary artery disease. Accordingly for subsequent analyses the populations with and without coronary artery disease were not pooled when considering these three parameters.

Plots showing the comparisons of the normalized time delay of cyclic variation as a function of the parameters corresponding to myocardial function (E_{peak} , VTI_E , kx_0 , and $\frac{1}{2} kx_0^2$), as measured by the parametrized diastolic filling formalism, are shown in Figures 3 and 4. A similar plot of the normalized time delay of cyclic variation versus both the index $\beta = c^2/4k$ (the relative influence of chamber stiffness vs. viscosity/relaxation) and the index $y = c/(2\sqrt{k})$ (a ratio for the damping and stiffness characteristics of the system) is shown in Figure 5.

The correlation values relating the normalized time delay of cyclic variation to the E-wave parameters and indices derived from them that correspond to function and viscoelasticity are summarized in Table 2, for the values that were statistically significant. The corresponding correlation values for the magnitude of cyclic variation against the same E-wave parameters are summarized in Table 3, though these comparisons lacked statistical significance.

Discussion

Continued improvements in echocardiographic imaging system technology are likely to encourage expanded use of methods for myocardial tissue characterization that complement information provided by real-time imaging and blood flow visualization. Such improvements include speckle tracking and automatic region-of-interest analysis, which potentially will minimize the time and effort required to perform myocardial tissue characterization. As a consequence of a significant number of reported studies, the cyclic variation of backscattered energy appears to be a meaningful approach to the characterization of a range of cardiac pathologies despite the fact that the underlying physical mechanisms responsible have not yet been fully determined. As a step toward determining these mechanisms, the goal of this paper was to relate diastolic function quantitated via the parametrized diastolic filling formalism to the cyclic variation of backscatter, to determine the role of diastolic function in the observed cyclic variation of backscatter, while also utilizing standard echocardiographic parameters such as E , A , and DT as metrics for comparison.

The relationships between the parametrized diastolic filling model parameters and the underlying myocardial properties permit meaningful inferences to be drawn from comparisons between the parametrized diastolic filling parameters and indices derived from them and the cyclic variation parameters. One set of this study's planned comparisons involved the normalized time delay of cyclic variation and the parametrized diastolic filling parameters and PDF derived indices such as kx_0 and $\frac{1}{2} kx_0^2$. The results of these

comparisons, which indicate statistically significant but modest correlations, are found in Table 2. The parameters E_{peak} (the peak E-wave velocity), VTI_E (the velocity-time integral of the E-wave), kx_0 (the maximum force of recoil), and $\frac{1}{2} kx_0^2$ (the maximum stored energy prior to recoil) all correlated with the normalized time delay of cyclic variation. The plots for these comparisons are shown in Figures 3 and 4. For each case, a change in the value of a parametrized diastolic filling parameter, in a manner reflecting poorer diastolic function, results in an increase in the normalized time delay. These results suggest that the normalized time delay of the cyclic variation backscatter data provide information beyond that contained in the more frequently reported magnitude of cyclic variation. Additionally, these results suggest that changes in cardiac function, as assessed by the PDF formalism, might be detected using cyclic variation. Further, the relationships seen here are consistent with the interpretation that the normalized time delay is a measure of global function in the heart, with hearts exhibiting poorer overall function tending to have a higher normalized time delay.

In addition to the trends observed between the normalized time delay of cyclic variation and the parametrized diastolic filling parameters associated with function, a significant correlation was found between the normalized time delay of cyclic variation of backscatter and the indices β and γ . Both of these indices characterize the relationship between chamber stiffness and damping/relaxation. It is also of interest that the viscosity (c) and stiffness (k) of the chamber did not independently correlate with the normalized time delay of cyclic variation, even though the parameters β and γ were positively correlated, as seen in Figure 5. For these subjects, an increase in the normalized time delay corresponded with an increase in the viscosity as well as a decrease in the stiffness, so that subjects with high values of the normalized time delay tended to have less stiff and more viscous hearts. These hearts had a delayed response as a result, which agrees with the increased value of the normalized time delay (as seen by backscatter analysis). As viscosity associated effects increase relative to stiffness, E-wave contours change in a predictable fashion. Relatively symmetric velocity contours characteristic of normal diastolic function are altered towards a delayed relaxation pattern with blunted peak velocity and prolonged deceleration. From a kinematic perspective, this shift represents the transition from the underdamped ($\gamma < 1$) to overdamped ($\gamma > 1$) kinematic regime. Thus the results in Figure 5 are significant, in so far as they suggest that normalized time delay from cyclic variation and the kinematic regime of filling are consonant, and, by extension, may differentiate between normal vs. delayed-relaxation E-wave patterns. Because these results were obtained using an entirely independent method of diastolic function assessment (kinematic modeling) their agreement with previous reports on the increase in the normalized time delay in subjects who have a decreased elasticity due to remodeling, in the presence of diabetes (Perez 1992; Wagner 1995) or post-myocardial infarction (Ohara 2005), is particularly noteworthy.

The effect of hemodynamics on the normalized time delay of cyclic variation was also assessed. Neither the time-constant of isovolumic relaxation τ , nor its inverse $1/\tau$ correlated with normalized time delay to any significant level. LVEDP did not correlate with normalized time delay either. However, the measured LVEDP and τ values, and specifically the heterogeneity of values [8–22 mmHg for LVEDP, (11 ± 2 mmHg is normal), 46–112 msec for τ , (47 ± 10 msec is normal)], suggest that the results of the current study may apply to subjects having a broad range of diastolic function.

The remaining assessments involved the comparison of the magnitude of cyclic variation with parametrized diastolic filling parameters. The results in Table 3 are for the parameters in Table 2, but indicate that the magnitude of cyclic variation did not correlate with any of these parameters. The results, coupled with previous studies that indicate that the magnitude of cyclic variation is altered in the presence of function- and structure-altering pathologies,

suggest that the magnitude of the cyclic variation of backscatter is primarily influenced by systolic function as opposed to diastolic function (Naito 1996; Yuda 2002; Hu 2003).

One result of this study was an identification of some of the mechanisms involved in generating the systematic variation in backscatter from the myocardium. It has been found in prior studies that the alterations in the magnitude and the normalized time delay of cyclic variation associated with reversible myocardial ischemia recover before the resumption of regional myocardial thickening in stunned but viable myocardium (Wickline 1986; Milunski 1989; Takiuchi 1998; Hancock 2002; Iwakura 2003). Additionally, the role of perfusion of the tissue has been considered both in studies by Wickline *et al.* (1985) in which perfusion did not appear to be the dominant effect, and by Micari (2006) in which perfusion was identified as a major source of the cyclic variation in backscatter. The composition of the tissue, and specifically the amount of collagen present, can alter the overall backscatter level (O'Donnell 1981; Hoyt 1984; Picano 1990) but has a less-understood effect on cyclic variation. A model based on changes in impedance has been proposed; this model predicts a decrease in the magnitude of cyclic variation as the collagen content in the heart increases (Wickline 1985; Holland 2004).

The significant correlations shown for this study are modest, but suggest that the active and passive elements of the myocardium have a combined effect on the cyclic variation of backscatter. The lack of significance between any single measure of the diastolic function or viscoelasticity with the magnitude of cyclic variation, combined with past findings concerning the dependence of the magnitude on active contractile properties, suggests that an active, cycle-dependent physical change in the myocardium is responsible for the changes in the level of backscatter corresponding to cyclic variation. From this perspective, an underlying physical change causes a change in the impedance mismatch between neighboring elements in the myocardium (such as myofibers embedded in the extracellular matrix). Additionally, pathologies that affect this impedance mismatch, either by alteration of the efficiency of the active myofibers or by deposition of stiffer materials such as collagen, would affect measurements of the magnitude of cyclic variation. However, the timing of the systematic change in backscatter during the cardiac cycle appears to be governed not only by contraction but also by the tissue properties giving rise to the relaxation properties of the myocardium and the subsequent loading of this tissue by the filling of the ventricles. As the myocardial tissue becomes more viscoelastic, the underlying physical mechanism underlying cyclic variation is delayed in its relaxation to a resting state. As such, the normalized time delay of cyclic variation, a measure of this timing, would be expected to be affected by alterations in the viscoelastic properties of the ventricles and the myocardium composing them. In turn, these myocardial tissue parameters can be measured using the parameterized diastolic filling formalism.

There were some technical limitations in this study. The study of individuals about to undergo catheterization was beneficial, because this provided a wide spectrum of subjects with a corresponding wide range of cardiac function and myocardial structure. On the other hand, this population represented a significant challenge because of the presence of potentially confounding pathologies. These subjects were difficult to image as a result of a number of factors, including in some cases obesity, age, and a history of smoking, as well as the examination setting (a narrow catheterization table, which required subjects to lie flat on their back). The possibility that the comparisons between the two methods of tissue characterization were confounded by the presence of coronary artery disease was examined, but ultimately was found to be significant only for the comparison concerning γ . For the comparison of γ versus the time delay of cyclic variation, the comparison was only valid for the population with coronary artery disease, perhaps because the range of expressed time delay values was larger for that population. The presence of other pathologies might have

also had confounding effects on the comparisons in this study, although the inclusion criteria required that specific pathologies were to be excluded for the study population.

Previous work has explored the dependence of these model parameters on a variety of potentially confounding factors, including noise, waveform shape, beat variation, and ultrasound machine specifications (Hall 1997; Hall 1998). The results have consistently supported the robustness of the model-based fitting approach. Furthermore, in other published work where similar levels of noise are present in the echocardiographic data, strong physiological correlations have been predicted and observed (Kovács 1997; Rich 1999; Dent 2001; Lissauskas 2001; Riordan 2005). Thus there is strong evidence for the physiological relevance of the model-based parameters with the presence of noise, and as such it is unlikely that noise is the primary cause of the low correlation observed between cyclic variation and model-based parameters.

One limitation inherent to the use of cyclic variation is that the particular values for the magnitude and normalized time delay of cyclic variation are dependent on the echocardiographic view and region of interest used in the acquisition of data (Vandenberg 1989; Finch-Johnston 2000). This study measured the parameters of cyclic variation using the echocardiographic data from the posterior wall of the left ventricle, as viewed in the parasternal long axis view of the heart. The use of one segment only for the characterization of the myocardium circumvents issues arising from the averaging of data from dissimilar segments. However, the use of other segments (especially the lateral or anterior wall) would be expected to generate different values of the normalized time delay than measured in this study. The observed relationships between the normalized time delay of cyclic variation and the parametrized diastolic filling parameters would be altered by the change in the normalized time delay values, but it is anticipated that the trends would still be consistent with the present findings, in that changes in the viscoelastic properties of the myocardium would still be reflected in the changes in the normalized time delay values.

An assumption underlying the use of cyclic variation in this study was that the magnitude and the normalized time delay of cyclic variation were independent parameters, and thus can be independently compared to the E-wave parameters. There are pathologies, such as myocardial infarction and diabetes, which affect both parameters of cyclic variation (Milunski 1989; Perez 1992; Vitale 1995). Additionally, researchers have sometimes chosen to combine these two parameters into a single parameter, such as the magnitude of cyclic variation weighted by a factor derived from the normalized time delay (Wickline 1986; Vitale 1995; Iwakura 2003). There is some precedence for assuming that the underlying mechanisms for the magnitude and the normalized time delay of cyclic variation are different (Ohara 2005). To test this assumption directly, the magnitude and the normalized time delay of cyclic variation were compared and any direct relationship between them determined using linear correlation (data not shown). These parameters were found to be uncorrelated in the current subject population ($n = 115$ heart cycles, $r = 0.086$, $p = \text{NS}$), so the assumption of independence between the cyclic variation parameters seems justified.

In summary, echocardiographic tissue characterization of thirty-two subjects has provided mechanistic insight into the diastolic function to normalized time delay of cyclic variation relation. The determinants include relative viscoelasticity and the viscoelastic ratio determined via the parametrized diastolic filling formalism. By extension, time delay was found to be related to the kinematic regime of filling, which is determined by the balance between stiffness and relaxation chamber properties. This finding appears consistent with a tissue-scattering model of backscatter, as the viscoelastic properties of tissue manifest in a change in the timing of the backscatter. Further, the mechanism underlying the magnitude of

cyclic variation was not strongly coupled with the mechanism underlying the normalized time delay of cyclic variation.

Acknowledgments

The authors would also like to thank the staff of the Cardiac Procedure Center at Washington University Medical Center's Barnes-Jewish Hospital for their assistance and sonographer Peggy Brown for her expert acquisition of the ultrasonic data. This work was supported, in part, by NIH HL040302 and NSF CBET 0717830, the Alan A. and Edith L. Wolff Charitable Trust and the Barnes-Jewish Hospital Foundation. Leonid Shmuylovich is a recipient of an American Heart Association Pre-doctoral fellowship.

References

- Aeschbacher BC, Hutter D, Fuhrer J, Weidmann P, Delacretaz E, Allemann Y. Diastolic dysfunction precedes myocardial hypertrophy in the development of hypertension[ast]. *Am J Hypertens.* 2001; 14:106–113. [PubMed: 11243300]
- Appleton CP, Firstenberg MS, Garcia MJ, Thomas JD. The Echo-Doppler evaluation of Left Ventricular Diastolic Function - A Current Perspective. *Cardiology Clinics.* 2000; 18:513–546. [PubMed: 10986587]
- Armstrong, WF.; Ryan, T.; Feigenbaum, H. Feigenbaum's echocardiography. Philadelphia: Wolters Kluwer Health/Lippincott Williams & Wilkins; 2010.
- Bauman L, Chung CS, Karamanoglu M, Kovács SJ. The peak atrioventricular pressure gradient to transmitral flow relation: Kinematic model prediction with in vivo validation. *J Am Soc Echocardiogr.* 2004; 17:839–844. [PubMed: 15282487]
- Chung CS, Ajo DM, Kovács SJ. Isovolumic pressure-to-early rapid filling decay rate relation: model-based derivation and validation via simultaneous catheterization echocardiography. *J Appl Physiol.* 2006; 100:528–534. [PubMed: 16223980]
- Dent CL, Bowman AW, Scott MJ, Allen JS, Lissauskas JB, Janif M, Wickline SA, Kovács SJ. Echocardiographic characterization of fundamental mechanisms of abnormal diastolic filling in diabetic rats with a parameterized diastolic filling formalism. *Journal of the American Society of Echocardiography.* 2001; 14:1166–1172. [PubMed: 11734783]
- Di Bello V, Giorgi D, Talini E, Dell' Omo G, Palagi C, Romano MF, Pedrinelli R, Mariani M. Incremental value of ultrasonic tissue characterization (backscatter) in the evaluation of left ventricular myocardial structure and mechanics in essential arterial hypertension. *Circulation.* 2003; 107:74–80. [PubMed: 12515746]
- Finch-Johnston AE, Gussak HM, Mobley J, Holland MR, Petrovic O, Perez JE, Miller JG. Cyclic variation of integrated backscatter: dependence of time delay on the echocardiographic view used and the myocardial segment analyzed. *J Am Soc Echocardiogr.* 2000; 13:9–17. [PubMed: 10625826]
- Giglio V, Pasceri V, Messano L, Mangiola F, Pasquini L, Dello Russo A, Damiani A, Mirabella M, Galluzzi G, Tonali P, Ricci E. Ultrasound tissue characterization detects preclinical myocardial structural changes in children affected by Duchenne muscular dystrophy. *J Am Coll Cardiol.* 2003; 42:309–316. [PubMed: 12875769]
- Gottdiener JS, Bednarz J, Devereux R, Gardin J, Klein A, Manning WJ, Morehead A, Kitzman D, Oh J, Quinones M, Schiller NB, Stein JH, Weissman NJ. American Society of Echocardiography recommendations for use of echocardiography in clinical trials: A report from the american society of echocardiography's guidelines and standards committee and the task force on echocardiography in clinical trials. *Journal of the American Society of Echocardiography.* 2004; 17:1086–1119. [PubMed: 15452478]
- Granzier HL, Labeit S. The Giant Protein Titin: A Major Player in Myocardial Mechanics, Signaling, and Disease. *Circ Res.* 2004; 94:284–295. [PubMed: 14976139]
- Grossman W. Diastolic dysfunction in congestive heart failure. *N Engl J Med.* 1991; 325:1557–1564. [PubMed: 1834939]

- Hall AF, Aronovitz JA, Nudelman SP, Kovács SJ. Automated method for characterization of diastolic transmitral Doppler velocity contours: Late atrial filling. *Ultrasound in Medicine & Biology*. 1994; 20:859–869. [PubMed: 7886846]
- Hall AF, Bettlach J, Nudelman SP, Kovács SnJ. Echo machine-imposed limit on transmitral spectral Doppler velocity-profile analysis. *Ultrasound in Medicine & Biology*. 1997; 23:1225–1235. [PubMed: 9372571]
- Hall AF, Kovács SJ. Automated method for characterization of diastolic transmitral doppler velocity contours: Early rapid filling. *Ultrasound in Medicine & Biology*. 1994; 20:107–116. [PubMed: 8023423]
- Hall AF, Nudelman SP, Kovacs SJ. Evaluation of model-based processing algorithms for averaged transmitral spectral Doppler images. *Ultrasound Med Biol*. 1998; 24:55–66. [PubMed: 9483772]
- Hancock JE, Cooke JC, Chin DT, Monaghan MJ. Determination of successful reperfusion after thrombolysis for acute myocardial infarction: a noninvasive method using ultrasonic tissue characterization that can be applied clinically. *Circulation*. 2002; 105:157–161. [PubMed: 11790694]
- Holland MR, Gibson AA, Peterson LR, Areces M, Schaffer JE, Perez JE, Miller JG. Measurements of the cyclic variation of myocardial backscatter from two-dimensional echocardiographic images as an approach for characterizing diabetic cardiomyopathy. *J Cardiometa Syndr*. 2006; 1:149–152. [PubMed: 17694597]
- Holland MR, Wallace KD, Miller JG. Potential relationships among myocardial stiffness, the measured level of myocardial backscatter ("image brightness"), and the magnitude of the systematic variation of backscatter (cyclic variation) over the heart cycle. *J Am Soc Echocardiogr*. 2004; 17:1131–1137. [PubMed: 15502786]
- Hoyt R, Skorton D, Collins S, Melton H Jr. Ultrasonic backscatter and collagen in normal ventricular myocardium. *Circulation*. 1984; 69:775–782. [PubMed: 6697461]
- Hu X, Wang J, Sun Y, Jiang X, Sun B, Fu H, Guo R. Relation of ultrasonic tissue characterization with integrated backscatter to contractile reserve in patients with chronic coronary artery disease. *Clin Cardiol*. 2003; 26:485–488. [PubMed: 14579920]
- Iwakura K, Ito H, Kawano S, Okamura A, Asano K, Kuroda T, Tanaka K, Masuyama T, Hori M, Fujii K. Detection of TIMI-3 flow before mechanical reperfusion with ultrasonic tissue characterization in patients with anterior wall acute myocardial infarction. *Circulation*. 2003; 107:3159–3164. [PubMed: 12796131]
- Jobsis PD, Ashikaga H, Wen H, Rothstein EC, Horvath KA, McVeigh ER, Balaban RS. The visceral pericardium: macromolecular structure and contribution to passive mechanical properties of the left ventricle. *Am J Physiol Heart Circ Physiol*. 2007; 293:H3379–H3387. [PubMed: 17933976]
- Kovács SJ Jr, Barzilai B, Perez JE. Evaluation of diastolic function with Doppler echocardiography: the PDF formalism. *Am J Physiol*. 1987; 252:H178–H187. [PubMed: 3812709]
- Kovács SJ, Rosado J, Manson McGuire AL, Hall AF. Can transmitral Doppler E-waves differentiate hypertensive hearts from normal? *Hypertension*. 1997; 30:788–795. [PubMed: 9336374]
- Lisauskas JB, Singh J, Bowman AW, Kovács SJ. Chamber properties from transmitral flow: prediction of average and passive left ventricular diastolic stiffness. *J Appl Physiol*. 2001; 91:154–162. [PubMed: 11408426]
- Lloyd, CW.; Holland, MR.; Miller, JG. Measurements of the Cyclic Variation of Myocardial Backscatter - Does the Analysis Method Matter?. *Ultrasonic Imaging; 34th International Symposium on Ultrasonic Imaging and Tissue Characterization; June 10–12, 2009; Arlington, VA*. 2009. p. 55
- Madaras EI, Barzilai B, Perez JE, Sobel BE, Miller JG. Changes in myocardial backscatter throughout the cardiac cycle. *Ultrasonic Imaging*. 1983; 5:229–239. [PubMed: 6685368]
- Micari A, Pascotto M, Jayaweera AR, Sklenar J, Goodman NC, Kaul S. Cyclic variation in ultrasonic myocardial integrated backscatter is due to phasic changes in the number of patent myocardial microvessels. *J Ultrasound Med*. 2006; 25:1009–1019. [PubMed: 16870894]
- Milunski MR, Mohr GA, Perez JE, Vered Z, Wear KA, Gessler CJ, Sobel BE, Miller JG, Wickline SA. Ultrasonic tissue characterization with integrated backscatter. *Acute myocardial ischemia*,

- reperfusion, and stunned myocardium in patients. *Circulation*. 1989; 80:491–503. [PubMed: 2766504]
- Naito J, Masuyama T, Mano T, Yamamoto K, Doi Y, Kondo H, Nagano R, Inoue M, Hori M. Influence of preload, afterload, and contractility on myocardial ultrasonic tissue characterization with integrated backscatter. *Ultrasound Med Biol*. 1996; 22:305–312. [PubMed: 8783462]
- O'Donnell M, Mimbs JW, Miller JG. Relationship between collagen and ultrasonic backscatter in myocardial tissue. *The Journal of the Acoustical Society of America*. 1981; 69:580–588. [PubMed: 7462481]
- Ohara Y, Hiasa Y, Hosokawa S, Suzuki N, Takahashi T, Kishi K, Ohtani R. Ultrasonic tissue characterization predicts left ventricular remodeling in patients with acute anterior myocardial infarction after primary coronary angioplasty. *J Am Soc Echocardiogr*. 2005; 18:638–643. [PubMed: 15947765]
- Perez, JE.; Holland, MR.; Barzilai, B.; Handley, SM.; Vandenberg, BF.; Miller, JG.; Skorton, DJ. Ultrasonic Characterization of Cardiovascular Tissue. In: Skorton, DJ.; Schelbert, HR.; Wolf, GL.; Brundage, BH., editors. *Cardiac Imaging - A Companion To Braunwald's Heart Disease*. Philadelphia: W. B. Saunders Co; 1996. p. 606-624.
- Perez JE, McGill JB, Santiago JV, Schechtman KB, Waggoner AD, Miller JG, Sobel BE. Abnormal myocardial acoustic properties in diabetic patients and their correlation with the severity of disease. *J Am Coll Cardiol*. 1992; 19:1154–1162. [PubMed: 1564214]
- Picano E, Pelosi G, Marzilli M, Lattanzi F, Benassi A, Landini L, L'Abbate A. In vivo quantitative ultrasonic evaluation of myocardial fibrosis in humans. *Circulation*. 1990; 81:58–64. [PubMed: 2404628]
- Press, WH.; Teukolsky, SA.; Vetterling, WT.; Flannery, BP. *Numerical recipes: The art of scientific computing*. Cambridge: Cambridge University Press; 1986.
- Rich MW, Stitzel NO, Kovács SJ. Prognostic value of diastolic filling parameters derived using a novel image processing technique in patients ≥ 70 years of age with congestive heart failure. *Am J Cardiol*. 1999; 84:82–86. [PubMed: 10404856]
- Riordan MM, Chung CS, Kovács SJ. Diabetes and diastolic function: stiffness and relaxation from transmitral flow. *Ultrasound Med Biol*. 2005; 31:1589–1596. [PubMed: 16344121]
- Robinson TF, Factor SM, Sonnenblick EH. The heart as a suction pump. *Sci Am*. 1986; 254:84–91. [PubMed: 3704622]
- Takiuchi S, Ito H, Iwakura K, Taniyama Y, Nishikawa N, Masuyama T, Hori M, Higashino Y, Fujii K, Minamino T. Ultrasonic tissue characterization predicts myocardial viability in early stage of reperfused acute myocardial infarction. *Circulation*. 1998; 97:356–362. [PubMed: 9468209]
- Vandenberg BF, Rath L, Shoup TA, Kerber RE, Collins SM, Skorton DJ. Cyclic variation of ultrasound backscatter in normal myocardium is view dependent: clinical studies with a real-time backscatter imaging system. *J Am Soc Echocardiogr*. 1989; 2:308–314. [PubMed: 2629869]
- Vitale DF, Bonow RO, Gerundo G, Pelaggi N, Lauria G, Leosco D, Coltorti F, Bordini C, Rengo C, Rengo F. Alterations in ultrasonic backscatter during exercise-induced myocardial ischemia in humans. *Circulation*. 1995; 92:1452–1457. [PubMed: 7664426]
- Wagner RF, Wear KA, Perez JE, McGill JB, Schechtman KB, Miller JG. Quantitative assessment of myocardial ultrasound tissue characterization through receiver operating characteristic analysis of Bayesian classifiers. *J Am Coll Cardiol*. 1995; 25:1706–1711. [PubMed: 7759727]
- Wickline SA, Thomas LJ 3rd, Miller JG, Sobel BE, Perez JE. A relationship between ultrasonic integrated backscatter and myocardial contractile function. *J Clin Invest*. 1985; 76:2151–2160. [PubMed: 3908482]
- Wickline SA, Thomas LJ 3rd, Miller JG, Sobel BE, Perez JE. Sensitive detection of the effects of reperfusion on myocardium by ultrasonic tissue characterization with integrated backscatter. *Circulation*. 1986; 74:389–400. [PubMed: 3524896]
- Yuda S, Dart J, Najos O, Marwick TH. Use of cyclic variation of integrated backscatter to assess contractile reserve and myocardial viability in chronic ischemic left ventricular dysfunction. *Echocardiography*. 2002; 19:279–287. [PubMed: 12047778]

Zhang W, Shmuylovich L, Kovács SJ. The E-Wave Delayed Relaxation Pattern to LV Pressure Contour Relation: Model-Based Prediction With in vivo Validation. *Ultrasound in Medicine & Biology*. 2010; 36:497–511. [PubMed: 20172449]

Figure 1.

a) A schematic representation of the Doppler echocardiographic method of transmitral blood flow velocity recording. The E-wave contour shape can be characterized using a ‘triangle approach’. b) The Parametrized Diastolic Filling (PDF) model accurately predicts clinically recorded early rapid filling transmitral flow velocity (E-wave) contours. The model-predicted solution, based on the maximum velocity envelope, is shown, along with indices derived from the model parameters. See text for details.

Figure 2.

A smoothed sample data set of the backscatter from a region of interest over three heart cycles. The quantities required for the determination of the magnitude and the normalized time delay of cyclic variation are illustrated. See text for details.

Figure 3.

Comparisons of the normalized time delay of cyclic variation to E-wave parameters: a) the maximum of the E-wave (in $m\ s^{-1}$), and b) the area under the E-wave (in m), as determined with the parametrized diastolic filling formalism. The lines of best fit are a) $y = -1.04(s\ m^{-1})x + 1.72$, and b) $y = -6.70(m^{-1})x + 1.73$. The 95% confidence interval for the regression lines are displayed as dashed lines. See text for details.

Figure 4.

Comparisons of the normalized time delay of cyclic variation to parametrized diastolic filling parameter derived indices: a) the initial restoring force kx_o (in m s^{-2}), b) the initial potential energy $1/2kx_o^2$ (in $\text{m}^2 \text{s}^{-2}$). The lines of best fit are a) $y = 0.022(\text{s}^2 \text{m}^{-1})x + 1.46$, and b) $y = -0.21(\text{s}^2 \text{m}^{-2})x + 1.25$. The 95% confidence interval for the regression lines are displayed as dashed lines. See text for details.

Figure 5.

Comparisons of the normalized time delay of cyclic variation to parametrized diastolic filling parameter derived indices: a) dimensionless ratio of damping to stiffness $\gamma = c / (2\sqrt{k})$ b) the relative effects of damping versus stiffness $\beta = c^2 - 4k$ (in s^{-2}). The lines of best fit are a) $y = 0.97x + 0.26$, and b) $y = (7.07 \times 10^{-4} \text{ s}^2)x + 1.26$. The 95% confidence interval for the regression lines are displayed as dashed lines. See text for details.

Table 1

Results of the ANCOVA test for significance between populations with and without coronary artery disease. Listed are the F-values for significance between the regression lines for each population, for the variables listed. Diastolic function parameter and index comparisons not present in this table were not significantly different in the presence of coronary artery disease.

Diastolic Function Parameter/Index	E-wave Shape Fit as a Triangle		E-wave Shape Fit Via Parametrized Diastolic Filling Formalism	
	Magnitude	Time Delay	Magnitude	Time Delay
AT	5.58 [*]	6.28 [*]	10.65 ^{**}	9.37 [*]
<i>c</i>	---	---	10.31 ^{**}	11.75 ^{**}
<i>k</i>	---	---	4.65 [*]	4.66 [*]
$c / (2\sqrt{k})$	---	---	6.87 [*]	9.04 ^{**}

* $p < 0.05$,

** $p < 0.01$.

Table 2

Correlation values and their corresponding p-values for the comparisons between the normalized time delay of cyclic variation and the E- and A-wave parameters corresponding to function and viscoelasticity. n = 32 for all subjects, n = 11 for subjects without CAD, and n = 21 for subjects with CAD. Diastolic function parameters and indices are absent if the comparison was insignificant.

Diastolic Function Parameter/Index	Subject Group	E-wave Shape Fit as a Triangle		E-wave Shape Fit Via Parametrized Diastolic Filling Formalism	
		r	p	r	p
E_{peak}	All Subjects	0.58	0.00046	0.59	0.00040
$E_{\text{peak}}/A_{\text{peak}}$	All Subjects	0.41	0.021	0.41	0.018
VTI_E	All Subjects	0.49	0.0045	0.57	0.00072
kx_0	All Subjects	---	---	0.49	0.0044
$\frac{1}{2} kx_0^2$	All Subjects	---	---	0.44	0.012
$c^2 - 4k$	All Subjects	---	---	0.48	0.0053
$c / (2\sqrt{k})$	Without CAD	---	---	0.17	0.62
$c / (2\sqrt{k})$	With CAD	---	---	0.51	0.018

Table 3

Correlation values and their corresponding p-values for the comparisons between the magnitude of cyclic variation and the E- and A-wave parameters corresponding to function and viscoelasticity. The listed parameters correspond to Table 2, and the remaining diastolic function parameters and indices lacked significant correlation. $n = 32$ for all subjects, $n = 11$ for subjects without coronary artery disease (CAD), and $n = 21$ for subjects with CAD. No result was significant at the $p = 0.05$ level.

Diastolic Function Parameter/Index	Subject Group	E-wave Shape Fit as a Triangle		E-wave Shape Fit Via Parametrized Diastolic Filling Formalism	
		r	p	r	p
E_{peak}	All Subjects	0.11	0.55	0.079	0.67
$E_{\text{peak}}/A_{\text{peak}}$	All Subjects	0.13	0.47	0.12	0.50
VTI_E	All Subjects	0.077	0.68	0.071	0.70
kx_0	All Subjects	---	---	0.014	0.94
$\frac{1}{2} kx_0^2$	All Subjects	---	---	0.014	0.94
$c^2 - 4k$	All Subjects	---	---	0.084	0.65
$c / (2\sqrt{k})$	Without CAD	---	---	0.24	0.48
$c / (2\sqrt{k})$	With CAD	---	---	0.06	0.80