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Wave Propagation of Myocardial Stretch: *Correlation with Myocardial Stiffness*

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Abstract

The mechanism of flow propagation during diastole in the left ventricle (LV) has been well described. Little is known about the associated waves propagating along the heart wall s. These waves may have a mechanism similar to pulse wave propagation in arteries. The major goal of the study was to evaluate the effect of myocardial stiffness and preload on this wave transmission.

Methods—Longitudinal late diastolic deformation and wave speed (V_p) of myocardial stretch in the anterior LV wall were measured using sonomicrometry in sixteen pigs. Animals with normal and altered myocardial stiffness (acute myocardial infarction) were studied with and without preload alterations. Elastic modulus estimated from V_p (E_{VP} ; Moens-Korteweg equation) was compared to incremental elastic modulus obtained from exponential end -diastolic stress-strain relation (E_{SS}). Myocardial distensibility and α - and β -coefficients of stress-strain relations were calculated.

Results— V_p was higher at reperfusion compared to baseline (2.6 ± 1.3 m/s vs. 1.3 ± 0.4 m/s; $p=0.005$) and best correlated with E_{SS} ($r^2=0.80$, $p<0.0001$), β -coefficient ($r^2=0.78$, $p<0.0001$), distensibility ($r^2=0.47$, $p=0.005$), and wall thickness/diameter ratio ($r^2=0.42$, $p=0.009$). Elastic moduli (E_{VP} and E_{SS}) were strongly correlated ($r^2=0.83$, $p<0.0001$). Increasing preload increased V_p and E_{VP} and decreased distensibility. At multivariate analysis, E_{SS} , wall thickness, and end-diastolic and systolic LV pressures were independent predictors of V_p ($r^2_{\text{model}}=0.83$, $p<0.0001$).

Conclusions—The main determinants of wave propagation of longitudinal myocardial stretch were myocardial stiffness and LV geometry and pressure. This local wave speed could potentially be measured noninvasively by echocardiography.

Keywords

Diastole; diastolic function; echocardiography; imaging; myocardial infarction; myocardial stiffness

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CONFLICT OF INTEREST

Nothing to disclose

INTRODUCTION

Mitral inflow generates flow waves that propagate with different speeds within the left ventricular (LV) chamber, governed by intraventricular pressure gradients and mechanisms that generate vortex formation and vortex propagation [4, 14, 20, 44, 48]. A fast (pressure) and a slow wave (vortex propagation) have been described, both during early and late diastole. The slower wave carries most of the kinetic energy and has been most frequently studied during early diastole due to its link to LV relaxation [4, 20]. Reduced flow propagation during early diastole is commonly seen in patients with impaired LV relaxation [4, 12, 20].

Propagating waves during diastole have also been described along the myocardial walls. An earlier study described a sequential onset of circumferential lengthening in different parts of the LV, which is suggestive of a wave propagating from LV base to apex [25]. Other groups have measured this wave propagation using ultrasound strain rate imaging [45, 46, 49]. Nevertheless, the significance of this wave speed remains poorly understood.

One hypothesis is that the onset of ventricular filling after the atrial systole stretches the LV base and generates a wave propagating towards the apex with a speed proportional to the elasticity of the myocardial wall. This concept would be similar to pulse wave propagation in elastic arteries and tubes [22, 27]. A similar hypothesis has been advanced for flow propagation in the LV by Pai et al. [32], using measurements in terms of time delays (i.e., the A-Ar interval) between the inflow at the level of the mitral leaflets tips and the LV outflow tract [3, 33].

To test if the same hypothesis holds true for waves travelling along the myocardial walls, in this study we investigated longitudinal wall motion during late diastole. During this phase, myocardium is quasi-relaxed and reacts to pressure/volume changes like an elastic material. Measurements during this phase should depend primarily on tissue properties and forces acting on the wall (loading). The tension in the wall may create favorable conditions for wave transmission of any brief impulses acting on the wall, such as the onset of late diastolic ventricular filling.

The aims of the study were three-fold. The first aim was to investigate whether there is a relationship between the speed of wave propagation of longitudinal myocardial stretch during late diastole (V_p) with myocardial stiffness and to identify the major determinants of this wave speed. The second aim was to study the effect of loading on this wave transmission. The third aim was to demonstrate the feasibility of measuring V_p by echocardiography in a group of normal volunteers. To validate the concept, we used a swine model that has LV/myocardial properties and heart size comparable to humans, which are important conditions for reproducing wave propagation in humans. Wall motion was tracked by an invasive technique (sonomicrometry) that has high precision and high spatial and temporal resolution necessary to track this fast wave propagation. To cover a wide range of myocardial stiffness, animals were studied before and after acute myocardial infarction, which is known to alter tissue properties [10, 34]. The feasibility of measuring this wave propagation in humans was tested using high frame rate tissue Doppler imaging (TDI).

METHODS

Both animal and human studies were performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

Animal Study

The experimental protocol was approved by the Institutional Animal Care and Use Committee. We used an animal model of acute myocardial infarction which induces changes in myocardial stiffness at regional level, while minimizing global changes in LV function.

Farm pigs (3–4 months old, $n=16$) were sedated (telazol 5 mg/kg, atropine 0.05 mg/kg, xylazine 2 mg/kg), intubated and anesthetized (continuous inhalation of isoflurane 1–2%) and mechanically ventilated. A dual-sensor pressure catheter (Millar Instruments, Houston, Texas, United States) was inserted via the right carotid artery to measure LV and aortic pressures. After median sternotomy, the heart was suspended in a pericardial cradle.

Piezoelectric crystals (Sonometrics, Ontario, Canada) were placed in pairs in the subendocardium of the anterior and inferolateral LV walls to measure segment lengths (SL) and LV chamber radii (short-axis and long-axis). Four crystals placed in-line in the anterior LV wall were used to track wall motion in different segments along the anterior LV wall and to measure local wave propagation (V_p) during late diastole (Figure 1A). Crystal placement was guided by ultrasound imaging (5 MHz transducer) and by continuous display of pressure -segment length loop in the computer. The position was also confirmed postmortem in explanted hearts. Long axis was measured by implanting crystals in the LV apex and basal anterolateral LV wall just below the atrioventricular groove. All signals were digitized online at > 500 Hz and continuously recorded.

Anterior LV wall ischemia was induced by ligation of the mid left anterior descending coronary artery for 30 minutes up to 3 hours, followed by reperfusion for 1–2 hours. As described by Reimer and Jennings [39], the “wavefront progression” of myocardial necrosis progresses from subendocardium to subepicardium and induces various extents of ischemic injury (necrosis) in the area at ischemic risk, from stunning (30 minutes of occlusion) to full transmural myocardial infarction (3 hours of occlusion).

Cotton snares were placed around the ascending aorta and inferior vena cava (IVC). Preload manipulation was achieved by transient IVC occlusion (preload decrease), intravenous saline bolus (0.5–1 L over 5 min; preload increase) and partial constriction of the ascending aorta (preload and after load increase). The occlusions/constrictions were applied for about 10–15 seconds, and were repeated if arrhythmia occurred. A 5 minutes equilibration period was allowed between each step. All tests were completed within 30–40 minutes. These tests were performed at baseline and after 1 hour of reperfusion. At the end of the experiment, animals were euthanized using sodium pentobarbital overdose and hearts were explanted for measurement of infarct size.

Data Analysis

For each time point, SL data for 3–5 heart cycles were selected in expiration. Regional strain (ε) or shortening was calculated by normalizing instantaneous SL to end-diastolic SL:

$$\varepsilon(t) = 100 * [SL(t) - SL(t_0)] / SL(t_0) \quad (1)$$

where t varied from 0 (end-diastole) to the end of the ECG RR-interval. Strain rates were obtained by differentiation of strain with respect to time. End-diastole was manually identified at the onset of rise in LV dP/dt (above the level of noise) and end-systole at the time of minimum LV dP/dt .

V_p was measured from strain rate traces as shown in Figure 1A. The time difference (dt) in the onset of late diastolic motion in the target (apical) segment and the adjacent (proximal) segment was measured using the foot-to-foot method, similar to the method used for pulse wave velocity in arteries [16]. The distance between segments was measured from the center of the segments (Figure 1A). Local wave speed was calculated as $V_p = \text{distance}/dt$.

Indices of Myocardial Stiffness

- *Coefficients of myocardial stiffness* (α , β) were obtained from exponential end-diastolic pressure-SL and stress-strain relationships reconstructed from loading alterations [26]:

$$\sigma = \alpha (\exp(\beta \varepsilon) - 1) \quad (2)$$

where ε is strain = $(SL - SL_0)/SL_0$, SL_0 is unstressed segment length and α and β are preload-independent indices of myocardial stiffness. Wall stress (σ) was obtained from LV pressure (P), midwall semi-minor diameter (b) and wall thickness (h ; measured by B-mode ultrasound), assuming the LV as an ellipsoid [51]:

$$\sigma = P (b/2h) (1 - h/2b)^2 \quad (3)$$

This measurement was performed at baseline and after 1 hour of reperfusion (Figure 1B).

- *Incremental (tangent) elastic modulus* (E_{SS} , Pa; Figure 1B) was calculated from the stress-strain relationship as the slope to the stress-strain relation at operating wall stress:

$$E_{SS} = \Delta \sigma / \Delta \varepsilon \quad (4)$$

- *Regional myocardial distensibility* (Db , %/mmHg) was calculated from the amplitude of segment deformation (% strain) and changes in LV pressure (P) from the onset of atrial systole (ECG P-wave) to end-diastole. The inverse of distensibility is a measure of effective stiffness and reflects the amount of pressure needed to deform the segment by 1%:

$$1/\text{distensibility} = \Delta P / (\Delta SL / SL) \quad (5)$$

- *Myocardial elastic modulus* (E_{VP} , Pa) was estimated from V_p using Moens-Korteweg equation which describes the wave propagation in elastic tubes and commonly used to assess arterial stiffness:

$$\text{Wave speed} = \sqrt{(Eh / \rho D)} \quad (6)$$

where E is elastic modulus of the material, h and D are tube thickness and diameter, respectively, and ρ is material density (assumed as 1060 kg/m³). Higher wave speed indicates stiffer wall material. This model was chosen according to the working hypothesis, i.e., that wave propagation along the heart wall behaves like wave propagation in arteries. This modulus (E_{VP}) was compared to modulus estimated by the stress-strain method (E_{SS}).

Quantification of Infarct Size

Explanted hearts were sliced in a plane passing through the crystals in the anterior LV wall and approximately parallel to the LV long-axis. Slices were immersed in triphenyltetrazolium chloride solution to delineate viable (positive staining) from nonviable (unstained) myocardium, then photographed. The extent of infarction (% area from total LV area) and infarct transmural (i.e., the average amount of wall thickness involved in the necrotic process) were quantified as previously described [35]. Animals were classified as either nontransmural infarct (<50% of wall thickness infarcted) or transmural infarct (50–100% of wall thickness infarcted).

Human Study

The study was approved by the Institutional Review Board and informed consent was obtained prior to inclusion into the study. Ten healthy volunteers apparently free of significant cardiovascular conditions and with no more than trivial valvular dysfunction were recruited.

Longitudinal tissue velocities of the LV myocardium were measured in standard apical views by TDI (Vivid E9, GE Healthcare). Data were acquired at 350–450 frames/s. The LV wall was carefully aligned with the ultrasound beams to minimize the errors due to Doppler angle. Data were analyzed offline (EchoPac, GE Healthcare). The LV base to apex tissue velocities during late diastole were reconstructed along a curved line passing through the middle of the wall. The velocity scale was shifted to create aliasing and facilitate identification of the onset of motion. V_p was measured as the slope of isovelocity wavefront propagating in time and space (over a 4–5 cm segment) (Figure 2). A global V_p per subject was calculated by averaging values from all six LV walls. Elastic modulus (E_{VP}) was estimated as described above (equation 6). Strain rates were also reconstructed from tissue velocities, however these data were less reliable (more noisy).

Statistics

Analysis was performed using JMP software (version 10.0, SAS Institute Inc., Cary, North Carolina). Values are presented as mean $\pm$ standard deviation. Normal distribution was tested with the Shapiro-Wilk statistic, and logarithmic transformations were used when appropriate. Differences between baseline and reperfusion were evaluated using paired t -tests. The strength of the relationship between parameters was evaluated using Pearson's correlation coefficient. Univariate analysis was used to evaluate the influence of potential factors (α and β -coefficients, distensibility, systolic and diastolic LV pressure, heart rate, LV tau, wall thickness, LV diameter, etc.) on V_p and E_{VP} . Multivariate regression analysis was performed to identify the potential variables (univariate, $p < 0.1$) which had an effect on V_p . To account for possible covariance of α and β -coefficients, we compared stress values at fixed strain (i.e. WS_{10} at 10% strain); a similar approach was suggested for LV stiffness [6]. Statistical significance was considered for $p < 0.05$.

RESULTS

Animal Study

A total of 16 animals were used. In one animal only baseline data was available (fatal arrhythmia during coronary artery occlusion). Of the remaining 15 animals, 9 developed nontransmural infarct (0–49% of wall thickness infarcted) and 6 animals developed a transmural infarct ($>50\%$ of wall thickness) in the area at ischemic risk.

Hemodynamic parameters did not significantly differ between baseline and reperfusion, except for a decrease in dP/dt_{min} at reperfusion (Table 1). LVEDP and pre-A pressure (at the beginning of atrial systole) were only marginally increased at reperfusion.

Changes in Wave Speed with Infarction

V_p and derived E_{VP} were significantly higher (almost double) in the infarcted wall at reperfusion compared to normal myocardium at baseline (Figure 3). Increases in V_p and E_{VP} post -infarction were associated with a decrease in wall distensibility (i.e., increased effective stiffness). Analysis of stress-strain relationships revealed significant alterations in intrinsic myocardial properties in the infarcted segment, for all levels of preload (higher β -coefficient; Figure 3). LVEDP was only marginally higher at reperfusion (+1.3 mmHg in average, $p = 0.06$). Calculated WS_{10} was 0.4 ± 0.2 vs. 2.3 ± 2.6 kPa, baseline vs. reperfusion, respectively ($p = 0.012$). These results suggest that the increase in V_p at reperfusion was most likely due to changes in intrinsic tissue properties with infarction.

Effect of Loading on Wave Speed

As preload has a direct effect on myocardial stiffness, we investigated changes in wave speed during loading alterations. Figure 4 shows changes in V_p and E_{VP} during loading compared to resting condition. Overall, V_p increased with increasing preload. Absolute changes in V_p were however small relative to individual variations and within the pressure range tested; statistical significance was reached for relative changes in V_p (% from rest) for all tests except one (preload reduction at baseline). E_{VP} which takes into account local

geometry showed a steady significant increase with preload, both in normal and infarcted myocardium (Figure 4).

Similar trends were found for other stiffness measures, i.e. the inverse of distensibility, which is calculated based on the amplitude of changes in pressure and segment deformation (Figure 4). This index indicated that, at similar LVEDP levels, more pressure was needed to distend the infarcted segment by 1% compared to normal myocardium at baseline (Figure 4).

Effect of Infarct Transmurality

One potential cause for the observed large standard deviation in V_p at reperfusion could be infarct transmural extent. The animals were grouped according to the transmural extent of infarction (<50% or ≥50% of wall thickness). Baseline V_p did not differ between the two groups (1.4 ± 0.4 m/s vs 1.3 ± 0.3 m/s, nontransmural vs. transmural infarct; $p=0.770$). At reperfusion, V_p and E_{SS} were significantly higher in animals with larger infarcts (Figure 5).

Comparison of Elastic Modulus by Wave Method versus Stress-Strain Method

There was a strong correlation between V_p measured at reperfusion with the elastic modulus obtained by the stress-strain method (E_{SS}) (Figure 6; $r^2=0.80$, $p<0.0001$). This correlation was slightly improved for E_{VP} after accounting for geometry ($r^2=0.83$, $p<0.0001$). A fair agreement between the two moduli was also found during loading alterations (Table 2). Of note, at reperfusion, the absolute values were smaller by the wave method.

Independent Predictors of Wave Propagation

At univariate analysis, V_p at reperfusion best correlated with E_{SS} ($r^2=0.80$, $p<0.0001$), β -coefficient ($r^2=0.78$, $p<0.0001$), distensibility ($r^2=0.470$, $p=0.005$), wall thickness ($r^2=0.570$, $p=0.001$), and thickness/diameter ratio ($r^2=0.42$, $p=0.009$). No significant correlations were found for V_p with α -coefficient ($p=0.222$), heart rate ($p=0.905$), LV tau ($p=0.338$), peak systolic LVP ($p=0.205$), and LVEDP ($p=0.361$).

Multivariate analysis showed that V_p at rest was independently related to E_{SS} and thickness/diameter ratio ($r^2=0.88$ for the model, $p<0.0001$). Because LVEDP could be a potential factor influencing V_p , we consolidated the data from both resting and loading to obtain a wide variation in LVEDP. In this consolidated data, E_{SS} , wall thickness, LVEDP, and systolic LV pressure were independent predictors of V_p ($r^2=0.83$ for the model, $p<0.0001$).

Human Study

The age of volunteers was 52 ± 16 years. In these normal subjects, mean V_p was 1.4 ± 0.2 m/s and ranged between 1.1 m/s and 1.6 m/s. Mean wall thickness was 9.7 ± 1.3 mm, and LV diastolic diameter was 47 ± 3 mm. The estimated E_{VP} was 11 ± 3 kPa (range 6 to 15 kPa).

DISCUSSION

This study investigated the determinants of wave propagation of longitudinal myocardial stretch during late diastole. In an animal model approximating cardiac dimensions and

myocardial properties of humans, the speed of this wave propagation was strongly influenced by passive tissue properties, as confirmed by the independent method (stress - strain). Increases in preload had a quantifiable effect on this wave speed consistent with the pressure-dependent increase in myocardial stiffness. These findings were consistent with the behavior of the ventricle acting like a distensible tube and the theory of wave propagation in arteries. The results support the potential of this parameter as a surrogate measure of myocardial stiffness. The results in normal volunteers using high frame rate TDI demonstrate the feasibility of making this measurement using clinical scanners.

Flow vs. Myocardial Wave Propagation

The onset of transmitral inflow generates flow waves that propagate within the LV chamber. Little is known whether and how these waves propagate along the myocardial walls. Flow waves are governed by intraventricular pressure gradients and vortex formation and propagation [44, 48]. Two types of waves have been described. The first type is a faster (pressure) wave, while the second type (most commonly studied) relates to vortex propagation. This second wave travels at almost half the speed of peak inflow velocities and carries most of the kinetic energy. Both types can be seen during early and late diastole. Previous investigations have focused the attention on early diastole due to its link to LV relaxation [4, 20]. Reduced flow propagation was found in patients with abnormal relaxation [4, 12, 20]. This parameter was also used for estimating filling pressures [14] and prognosis [28].

Late diastolic events have received less attention. Earlier studies showed that flow propagation during late diastole was related to age and LV mass [47] and unrelated to LV relaxation and heart rate [4]. Using invasive measurements of LV pressure, Pai et al. [32, 33] demonstrated that a shorter time interval between the mitral inflow at the mitral leaflets tips and the LV outflow tract (A-Ar interval) occurs in subjects with increased chamber stiffness (dP/dV). This shorter time delay suggests faster flow transmission in the chamber. However wave speeds could not be calculated by that method and myocardial properties were not evaluated.

Barely anything is known about the waves propagating along the myocardial wall. Lew and LeWinter [25] were among the first to report that, in normal hearts (dogs), circumferential ventricular lengthening occurs in a progressive sequence from LV base to apex. This suggests wave propagation. The speed of this wave has been measured using ultrasound strain rate imaging in normal subjects [49] and patients with acute myocardial infarction and hypertension [45, 46]; however, the comparison with measures of LV/myocardial stiffness was not done, thus the significance of these measurements remains speculative.

One hypothesis is that the onset of late diastolic ventricular filling stretches first the LV base and acts like an impulse resulting in a wave propagating towards the apex with a speed proportional to the elasticity of the wall. This mechanism is analogous to pulse wave propagation in arteries. A similar hypothesis was proposed for flow propagation in the LV chamber [3, 32, 33]. We speculate that the elasticity of the myocardial wall under tension (with or without intraventricular pressure gradients; [31]) creates favorable conditions for wave transmission along (and guided by) the walls. The higher the wall tension and the

stiffer the material, the faster the wave speed would be. A previous computer model simulating flow wave propagation during early diastole comes in support of this mechanism [31], though atrial contraction was not simulated in that study.

Intraventricular pressure gradients (IVPG) during early diastole can contribute to ventricular filling through an effect on LV relaxation [8, 21]. IVPG and velocity of flow propagation were increased by catecholamines and reduced by acute ischemia and after load [9, 15, 17]. One study reported a weak relation (trend) between flow propagation and IVPG in patients with cardiomyopathies [5]. Also, a computer model reproduced flow propagation in the absence of pressure gradients [31]. Late diastolic IVPG were generally much smaller in amplitude [16]; their effect on wave propagation of myocardial stretch can be only speculative at this time.

Role of Tissue Properties

The strong correlations for Vp with modulus by stress-strain method and regional distensibility (preload-dependent parameters) as well as with β -coefficient (preload-independent) strongly support the initial hypothesis. For a given change in pressure, infarcted (stiffer) myocardial walls showed faster wave speeds and lower segment deformation under pressure (lower distensibility) compared to normal myocardium. This is a typical behavior for stiff materials. Changes in material properties were able to explain a major part (78%) of the variability in wave speed. Local geometry had a weak but significant influence and its inclusion into the model improved the correlations with the independent method. Estimated moduli (by both methods) increased with preload, consistent with pressure-dependence of myocardial stiffness.

The results using TDI confirm previous findings measuring wave propagation using strain rate imaging. In healthy volunteers, Voigt et al. [49] reported an increase in wave speed of strain rate propagation during late diastole with raised legs maneuver (which tentatively increases preload). Conversely, Stoylen et al. [45, 46] reported a lower wave speed in patients with hypertension and acute myocardial infarction compared to younger normal subjects. However, the comparison of our results remains limited since tissue properties, preload and LV geometry were not quantified in those studies and also due to the different methodology used. In our experience, TDI based measurement of wave speed was more robust than strain rate imaging based (more noisy, a well-known limitation of the latter). The comparison between these techniques was beyond the scope of this study. Importantly, the absolute wave speed values obtained by TDI in healthy volunteers were very close to those obtained in normal animals (at baseline) using sonomicrometry.

In this study, we provide a mechanistic explanation for the experimental findings on wave propagation and validate the results against an independent method. Guided wall propagation was largely explained by passive tissue properties, supporting the initial hypothesis. Faster wave speeds were found with more extensive infarcts (at transmural level), while stunning is expected to contribute less to changes in myocardial stiffness [36, 37]. These alterations in myocardial structure change the elasticity of the tissue and the deformation during diastole including the isovolumic periods [40, 41]. The estimated elastic modulus (here using Moens-Korteweg theory) is a quantifiable tissue property, thus

measurements have physiological meaning. However other models could be employed or developed. The measured wave speed could be used as a stand-alone parameter (at similar geometry) avoiding the assumptions made with modeling.

The interaction between flow and wall guided waves needs further evaluation. We speculate that continuous wall-fluid interaction should exist as the heart wall is a hyperelastic structure and tissue properties influence chamber properties. In this study, wall motion was tracked in three dimensions without contamination from flow events, while controlling the influence of some confounders (pericardial constraint, variations in hemodynamics, etc.), thus the results serve as a proof of concept. Findings need to be confirmed in intact chest condition.

Influence of Loading

An acute increase in preload (LVEDP) caused an increase in V_p and elastic modulus and a decrease in myocardial distensibility, both in normal and infarcted myocardium. These results confirm previous findings in healthy volunteers using strain rate imaging [49]. This increase indicates nonlinear material properties of the myocardial tissue and is expected from the exponential stress-strain relation characteristic for the myocardium. The absolute wave speed values in normal (compliant) myocardium and infarcted-reperfused (stiff) myocardium were significantly different when compared at the same pressure level. In normal myocardium, loading had a modest effect on wave speed and distensibility, which is expected for a compliant tissue. However, wave speed values were dominated by material properties and influenced to a small extent by other factors (systolic and diastolic LV pressure, local geometry, and potentially other factors). It must be pointed out that besides preload, after load-induced slowing of relaxation could also contribute to increases in end-diastolic stiffness when systolic function is reduced and diastole is shortened [23, 24]; in such cases, end-diastolic measurements will not purely reflect passive LV/myocardial properties.

Although trends were similar and a fair correlation between the two moduli was also found during loading alterations, a significant difference was observed at higher loading. The exact cause is not clear at this time, but could include errors due to the assumptions made and/or measurements at faster wave speed s , among other causes.

Role of LV Geometry

Higher wall thickness and thickness/diameter ratio were associated with faster wave speed. At multivariate analysis, geometry had a minor incremental effect. Of note, these animals did not develop marked LV dilation typically seen in patients with dilated cardiomyopathies. Noteworthy, faster flow propagation were reported in patients with elliptical ventricles [1], with aging [47], and normal LV ejection fraction [30] compared to dilated LVs [4, 12, 20].

Implications and Future Directions

Wave propagation studied here could become a new method for noninvasive estimation of myocardial stiffness. This measurement may help with the assessment of the diastolic function. Wave propagation can be measured noninvasively by any technique that has

sufficiently high spatial and temporal resolution. The results in normal volunteers highlight the feasibility of making this measurement in humans by transthoracic echocardiography.

A major advantage is the use of waves generated by physiological events and intrinsic to the heart, without the need to induce artificial waves by external means. Other techniques are now under development to estimate myocardial shear elasticity/viscoelasticity [2, 5, 13, 19, 29, 38, 42, 43]; however, transthoracic measurements are still technically challenging and require special equipment or are based on magnetic resonance imaging, which has limited availability. Conversely, TDI is now available on all commercial systems for cardiac imaging. Speckle tracking could also be used, although temporal resolution is currently a limitation. A comparison between these techniques warrants further investigation.

The incremental clinical value of measurement of myocardial stiffness remains to be proven. Physiological (aging) and pathological conditions are commonly associated with alterations in myocardial stiffness. Increased LV stiffness reduces the preload reserve and may contribute to elevated filling pressures and limitation of exercise capacity [50, 52]. Restrictive filling which occurs in the advanced stage of diastolic dysfunction predicts a poor prognosis [11]. It is hoped that noninvasive measurements of myocardial stiffness may facilitate earlier detection of changes with pathology and may allow monitoring the effect of medical therapies.

Limitations

This was an invasive study in controlled conditions to validate a proof of concept; however, here we demonstrate that noninvasive measurements could be made using echocardiography. Longitudinal motion was measured using implanted piezocrystals that track motion in 3 dimensions with sufficient spatial (0.12 microns) and temporal (<2 ms) resolution to measure high speed events. Small misalignment with the direction of wave propagation and presence of very stiff walls (high wave speed) may introduce some errors.

Only one LV wall (anterior) was evaluated; however we were concerned that a more complicated design would have compromised LV function and add noise and signal interference. The effect of nonuniform tissue characteristics on wave propagation is unknown; however, non-uniform properties should be a common clinical scenario. A global model of myocardial damage would have been associated with more severe alterations, which needed to be accounted for. Current results suggest a minimal effect: local stiffness was the main determinant of local wave speed, despite the presence of non-uniform tissue properties. The influence of anisotropy on myocardial wave propagation remains to be studied.

The absence of atrial systole precludes measurements in late diastole. Future studies could evaluate whether early diastole could be used instead; preliminary analysis (data not shown) showed that heterogeneous relaxation interferes with passive wave transmission. In cases with severely impaired relaxation (e.g., high after load) and/or short diastole (e.g., high heart rates), stiffness measurements at end-diastole may include an active component, as elegantly demonstrated by other investigators [23, 24]. In some animals, Vp during inferior vena cava constriction could not be reliably measured (baseline 4, reperfusion 4) and the results from

this test should be interpreted with caution; we reason that the reduced wall tension at very low preload creates unfavorable conditions for wave transmission (no propagation can occur in a string at slack length).

The assumptions underlying Moens-Korteweg theory are that the structure is a cylindrical tube, wall is homogenous and thin compared to radius, thickness is constant, and there are no reflections. However, the same limitations apply to the arterial system (irregular wall thickness, significant tapering between central and peripheral arteries, inhomogeneous wall material, etc.); yet, pulse wave velocity is the most established clinical method for evaluating arterial stiffness. Highly distorted LVs may not be suitable for this approach. By measuring the onset of late diastolic motion (not peak), the influence of wave reflections should be minimized. The errors associated with choosing a specific model could be avoided by using V_p as a surrogate measure. The assumption of only one elastic constant for material characterization is an oversimplification [18].

Stress-strain technique also has limitations: errors associated with wall stress estimation, curve fitting procedure, and the assumptions made (local homogeneity, negligible viscosity and shear, etc.). Estimation of wall stress remains difficult, and several formulas have been proposed based on several assumptions [51]; we reason that correlations presented should be more relevant than comparison of absolute values of stress and moduli. Small differences in material properties between the onset of atrial contraction (E_{VP}) and end of diastole (E_{SS}) may occur, however values should be closely related.

CONCLUSIONS

This study investigated the relationship between the myocardial stiffness and the speed of wave propagation of longitudinal myocardial stretch during late diastole in open-chest swine. This wave speed varied in large part due to the elasticity of the myocardial wall and to a small but significant extent to LV geometry. The results in normal volunteers highlight the feasibility of this measurement using transthoracic echocardiography.

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FIGURE 1.

A) Measurement of wave propagation during late diastole (V_p) using implanted piezocrystals. The onset of segment lengthening during late diastole (A-SR) occurred later in the apical segment (*solid line*) compared to the proximal segment (*dashed line*). The distance between segments (d) and the corresponding time delay (Δt) were used to calculate local wave speed: $V_p = d / \Delta t$ (1.3 m/s in this example). Elastic modulus was derived using Moens-Korteweg equation. **B)** Example of end-diastolic stress-strain relationship during loading alterations and calculation of tangent elastic modulus (EM_{SS}). These curves were steeper at reperfusion compared to baseline indicating stiffer myocardial tissue.

FIGURE 2.

Reconstructed maps of longitudinal tissue velocities from the left ventricle during late diastole measured by tissue Doppler imaging (TDI, **left images**) in 2 normal subjects. Arrows indicate the direction of wave propagation. The slope of this wave represents wave speed (V_p). Comparable results were obtained by strain rate imaging (SRI, **right images**).

FIGURE 3.

Wave speed (V_p), elastic modulus (E_{Vp}), and inverse of distensibility (stiffness) were higher at reperfusion compared to normal myocardium at baseline. β -coefficient of myocardial stiffness (but not α) derived from stress-strain relationship was higher at reperfusion, indicating the presence of genuine alterations in tissue properties. The end-diastolic LV pressure (LVEDP) did not significantly change.

FIGURE 4.

Effect of preload. Wave speed (V_p) and elastic modulus (E_{VP}) increased progressively with increasing preload, both at baseline and after reperfusion. Bottom row shows corresponding changes in the inverse of distensibility ($1/Db$) and end-diastolic LV pressure (LVEDP). (Abbreviations: IVCC: inferior vena cava constriction; AOC: aortic constriction)

FIGURE 5.

Data grouped according to the transmural extent of infarction. Wave speed (V_p) and elastic modulus (E_{ss}) at reperfusion were >2 times higher in animals with transmural infarct (≥50%; in black) compared to nontransmural infarct (<50%; in white).

FIGURE 6.

Correlations for the wave speed (V_p) and derived elastic modulus (E_{VP}) with the modulus obtained by the stress-strain method (E_{SS}). Baseline values are indicated by *white circles* and reperfusion by *black circles*. Each point represents one animal. For correlations, only reperfusion data were used.

Table 1

Hemodynamic parameters at baseline and after reperfusion.

	Baseline	Reperfusion	p-value
Heart rate, 1/s	79 ± 21	86 ± 21	0.246
Systolic LV pressure, mmHg	89 ± 11	84 ± 12	0.166
Pre-A diastolic LV pressure, mmHg	6.7 ± 2.7	7.5 ± 2.9	0.180
End-diastolic LV pressure (LVEDP), mmHg	8.6 ± 2.7	9.6 ± 3.1	0.060
End-diastolic wall stress, kPa	1.0 ± 0.4	1.2 ± 0.4	0.134
Time constant of LV relaxation (tau), ms	42 ± 9	45 ± 11	0.156
dP/dt _{max} , mmHg/sec	1,125 ± 568	1,208 ± 484	0.335
dP/dt _{min} , mmHg/sec	-1,339 ± 358	-1,046 ± 266	0.025

Table 2

Elastic moduli during loading alterations.

	E_{VP}, kPa	E_{SS}, kPa	p-value
Baseline			
At rest	7.3 ± 3.3	7.8±3.4	0.660
Low preload	5.1±2.7	4.7±2.5	0.674
High preload	21.0±7.8	17.6±11.6	0.399
Reperfusion			
At rest	26.7±24.3	32.3±24.4	0.050
Low preload	4.5±3.1	8.1±4.9	0.099
High preload	48.1±40.7	63.3±55.8	0.020