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ASSESSMENT OF DIASTOLIC FUNCTION USING ULTRASOUND ELASTOGRAPHY

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Abstract

Shear wave elasticity imaging (SWEI) is a novel ultrasound elastography technique for assessing tissue stiffness. In this study, we investigate the potential of SWEI for providing diastolic functional assessment. In 11 isolated rabbit hearts, pressure-volume (PV) measurements were recorded simultaneously with SWEI recordings from the left ventricle free wall before and after induction of global ischemia. PV-based end diastolic stiffness increased by 100% after ischemia ($p < 0.05$), and SWEI stiffness showed an increase of 103% ($p < 0.05$). The relaxation time constant (τ) before and after ischemia derived from pressure and SWEI curves showed increases of 79% and 76%, respectively ($p < 0.05$). A linear regression between pressure-derived and SWEI-based (τ) showed a slope of 1.164 with $R^2 = 0.80$, indicating the near equivalence of the two assessments. SWEI can be used to derive (τ) values and myocardial end diastolic stiffness. In global conditions, these measurements are consistent with PV measurements of diastolic function.

Keywords

Shear wave imaging; Elastography; Diastolic function; HFpEF; Lusitropy; Isovolumic relaxation time constant

INTRODUCTION

Heart failure with preserved ejection fraction (HFpEF) is a major cause of death, affecting approximately 3 million diagnosed patients in the United States. It has been shown that approximately 81% of HFpEF patients experience diastolic dysfunction (Writing Group Members et al. 2016). Diastolic dysfunction is defined as the inability of the ventricle to receive a sufficient amount of blood during diastole. Histologic studies have shown that myocardial hypertrophy, increased interstitial disposition of collagen and infiltrative mechanisms yield stiffer cardiac tissue (Jeong and Dudley 2015). These processes affect the active relaxation and passive myocardial properties, deteriorating ventricular relaxation and the compliance of the heart. The isovolumic relaxation time constant (τ) and ventricular stiffness (inverse compliance) values have been proposed as two major indices for

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assessment of diastolic function (Burkhoff et al. 2005; Gross 2009; Jeong and Dudley 2015). These indices are derived experimentally from intra-ventricular pressure-volume (PV) recordings, considered to be the gold standard technique; however, this method requires an invasive procedure and is not used routinely in the clinic.

In clinical practice, the presence of a combination of factors is used to determine the diagnosis of diastolic heart failure, including the presence of the signs and symptoms of heart failure, normal ejection fraction and increased diastolic pressure or impaired filling of the ventricle (Jeong and Dudley 2015). Echocardiography and Doppler imaging usually are used for assessment of diastolic function. However, these measurements can be normal in some conditions during the intermediate stages of diastolic dysfunction, an occurrence referred to as *pseudonormalized measurements* (Oh et al. 2011). Recently, speckle-tracking echocardiography and strain analysis have been used to track myocardial wall motion during the cardiac cycle (Dusch et al. 2014). These measurements are usually load dependent and do not provide a direct measurement of tissue stiffness or of the relaxation time constant. In addition, valvular disorders and irregularities in heart rhythm that could change the atrial mechanics, such as atrial fibrillation, can affect the accuracy of these measurements (Vorovich et al. 2014). Therefore, it is of great importance to develop a non-invasive technique that can provide direct diastolic functional indices of the myocardium analogous to the PV-derived indices.

Ultrasound-based elasticity imaging has been developed recently to measure the static stiffness of tissues (Doherty et al. 2013; Greenleaf et al. 2003). This technique can be thought of as palpating the tissues virtually using ultrasound. To implement this technique, an acoustic radiation force impulse (ARFI) is generated, which pushes the desired location of the tissue and generates shear waves. The propagation of these waves in the perpendicular direction is tracked. This technique is called shear wave elasticity imaging (SWEI). The velocity of the propagating shear waves is proportional to the stiffness of the tissue (Doherty et al. 2013). SWEI is now being used in the clinic to detect changes in tissue stiffness to detect fibrosis or lesions in the liver (Doherty et al. 2013).

Recent studies have shown the feasibility of using SWEI to record the dynamic stiffness in the heart (Pernot et al. 2011, 2016; Pislariu et al. 2014; Vejdani-Jahromi et al. 2016). An example of the dynamic stiffness changes during the cardiac cycle is illustrated in Figure 1. The value of these methods in assessing ablation treatments has been previously shown (Eyerly et al. 2015; Kwiecinski et al. 2014). In addition, multiple researchers have shown the feasibility of transthoracic SWEI measurements in human patients (Correia et al. 2016; Kakkad et al. 2015; Song et al. 2016; Strachinaru et al. 2017), raising the possibility of a completely non-invasive method of cardiac diastolic functional analysis.

Important to the clinical translation of SWEI is an understanding of this new measure in terms of existing measures of the functional properties of the heart during systole and diastole, including the compliance, the relaxation time constant and the contractility of the heart. In our previous studies, we have shown the potential of this technique to measure cardiac contractility and cardiac compliance using the coronary perfusion pressure (garden hose/turgor and Gregg) effects on cardiac function (Vejdani-Jahromi et al. 2015, 2016).

Moreover, in our earlier work, we showed that the relaxation time constant (τ) can be derived from SWEI measurements during the cardiac cycle (Vejdani-Jahromi et al. 2016).

A number of reports have been published on cardiac tissue assessment using SWEI for diastolic properties assessments. Using pressure-segment length measurements, researchers have shown the potential of SWEI to detect changes in passive stiffness in diastole (Pernot et al. 2016; Pislariu et al. 2014). Further details of these studies are included in the Discussion section. Although some conceptual similarities exist between pressure-segment and PV measurements, they use two techniques for volume and strain measurement. In this report, we use PV measurements for characterizing end diastolic properties in addition to characterizing the active relaxation properties of the myocardium in diastole.

Table 1 presents a comparison of the characteristics of PV-derived versus elastography-derived measurements. In this study, for the first time, the relationship between the intra-ventricular pressure-derived measurements of the relaxation time constant (τ) and SWEI-derived relaxation time constant is shown. The aim of this study is to compare SWEI measurements of active relaxation and passive myocardial properties with the gold standard PV-derived indices of diastolic function. To this end, we induced global ischemia in isolated rabbit hearts and recorded PV and SWEI measurements before and after ischemia.

MATERIALS AND METHODS

Experimental setup

Experiments were performed using 11 white New Zealand rabbits with an average weight of 3.1 ± 0.3 kg. The study was performed according to the Institutional Animal Care and Use Committee at Duke University (Durham, NC, USA) and conformed to the Guide for the Care and Use of Laboratory Animals.

The perfusion apparatus was built using a combination of Radnoti Glassware (Radnoti LLC, Monrovia, CA, USA) and custom-built parts suitable for PV measurements and elasticity imaging. A schematic diagram of the setup is presented in Figure 2.

The heart received perfusion from the preload chamber connected to the left atrium through the atrial cannula, and the coronaries were perfused as the blood was ejected by the left ventricle (LV) to the aorta. The aortic cannula was designed to achieve the shortest possible length between aorta and the compliance chamber. The cannula was connected to the compliance and afterload chambers to mimic peripheral resistance and compliance. An air bubble of at least 15 mL was induced inside the compliance chamber by a syringe connected to a valve on the compliance chamber. The atrial cannula consisted of a Y connector with a hemostasis valve for insertion of the PV catheter. Further details on the setup and perfusion solution can be found in earlier publications (Kelly 2010; Vejdani-Jahromi et al. 2015).

The perfused heart was placed in a chamber designed for elasticity imaging with acoustic windows. Submerging the heart in the chamber caused the heart to tilt off axis, affecting coronary perfusion; to resolve this, the right ventricular free wall was supported to prevent tilting. The ultrasound probe was positioned in the acoustic window to image the left

ventricular free wall at an approximate focal distance of 16 mm. Next, a Millar PV catheter for rabbits (SPR-877, Millar Inc., Houston, TX, USA) was inserted into the left atrium and LV through the hemostasis valve of the Y connector. The position of the catheter was adjusted based on the shape of the loops to achieve the largest possible loop area, and the position was confirmed by ultrasound imaging.

The catheter was connected to a Millar MPVS Ultra system and Labchart/Powerlab data acquisition system (ADInstruments, Colorado Springs, CO, USA), and the intra-ventricular pressure, volume and electrocardiogram (ECG) signals were recorded simultaneously. The number of volume segments used on the catheter was adjusted based on the size of the hearts. Pressure calibration and multiple steps of volume calibration, including cuvette calibration, were done using the MPVS Ultra software. Cardiac output was measured by collecting the output of the heart over 1 min and was used to calculate the α factor for volume calibration. Baseline SWEI measurements were recorded with the PV catheter and the ultrasound probe. Global ischemia was induced by stopping the inflow perfusion for 10 min. The hearts were reperfused for at least 10 min, after which PV and SWEI measurements were taken at several steps through time. This duration ranged 10–150 min, depending on the condition of the heart (Table 2). For post-ischemic evaluations, the last acquisition with reliable PV and SWEI measurements was used for assessments.

In this study, we compared the SWEI measurements with PV-derived measurements validated by two major indices of the cardiac function: end diastolic stiffness and isovolumic relaxation time constant. The ventricular stiffness constant is an index of diastolic function based on end diastolic pressure volume relationship (EDPVR). We used an exponential curve fit according to $p = Ce^{bV}$, where p is the intra-ventricular pressure, V is the ventricular volume, b is the chamber stiffness index and C is a constant. (Burkhoff et al. 2005). The (b) value or the ventricular stiffness derived in this model has units of 1/mL. This model is one of the most commonly used versions of EDPVR and is referred to as *ventricular stiffness*. We present further discussions on other methods and advantages and limitations of the technique in the Discussion section. The EDPVR measurement was derived from eight cardiac cycles during inflow occlusion. In each subject, two preload occlusions were performed before and two after ischemia. The mean of the two (b) values corresponding to ventricular stiffness was calculated. In 4 instances out of 40 measurements, only seven and five loops were used for the occlusion test because of poor signal quality.

The isovolumic relaxation time constant (τ) was derived from simultaneous intra-ventricular pressure curves and SWEI data before and after ischemia. An exponential curve fit of the intra-ventricular pressure signal was used to derive the pressure based τ value (Gross 2009). The minimum derivative point of the pressure curve corresponding to the closure of the aortic valve was used as the curve starting point (Schierreck et al. 1987). Researchers have used the time of dP/dt minimum with or without a short interval afterward to define the starting point for relaxation time constant measurements (Kass 2000). Because of the limited sampling rate for SWEI in this study and to maximize the number of samples included in the calculation, the dP/dt min was chosen as the starting point for both the pressure and SWEI-based calculations of the time constant. Because this is done on both pressure and SWEI curves simultaneously, the selection of the common starting point at the minimum dP/dt is

not expected to have an effect on the correlation between the measurements. The endpoint was defined by a constant duration of 70 ms to keep consistency between measurements.

When SWEI is recorded during the cardiac cycle, the stiffness increases during systole and decreases during diastole. For examples of SWEI throughout the cardiac cycle and further discussion please refer to Vejdani-Jahromi et al. (2016). In this study, we recorded SWEI through the cardiac cycle simultaneously with intra-ventricular pressure. To derive τ values based on the SWEI curve, we used the start and end points corresponding to the start and end points of pressure-derived τ to maintain consistency between measurements. In 2 out of 32 recordings, the ending SWEI data points were not measurable because of the poor signal quality, and duration in these 2 cases was decreased to 50 ms for both the pressure and SWEI-based measurements. For each condition, the average of two τ recordings is reported.

Imaging setup

Imaging sequences were implemented on a Siemens Antares scanner (Siemens Healthcare, Ultrasound Business Unit, Mountain View, CA, USA) programmed for SWEI Imaging. A linear probe (VF10-5) was positioned with short-axis view of the left ventricular free wall. Further details of the imaging system can be found in Vejdani-Jahromi et al. (2015). An acoustic radiation force impulse was used to push the tissue, and the resulting shear wave propagating in the perpendicular direction was tracked. The velocity was related to the shear modulus of stiffness of the tissue using the following formula, assuming a linearly elastic and isotropic medium:

$$C_t = \sqrt{\frac{\mu}{\rho}} \quad (1)$$

where C_t (m/s) is the shear wave velocity, μ (kPa) is the shear modulus of stiffness and ρ (kg/m^3) is the density of the tissue.

SWEI measurements of stiffness were acquired at a rate of 35 samples/s for 1.2 s. A signal from the ultrasound machine representing the transmit was recorded on the Labchart system to synchronize the measurements. Details on displacement estimation, shear velocity calculations and quadratic motion filtering can be found in Vejdani-Jahromi et al. (2015). End diastolic SWEI ventricular stiffness was measured based on the timing of simultaneous pressure recordings at the end of diastole. To calculate the relaxation time constant based on SWEI, the SWEI curve was upsampled using linear interpolation to the same frequency as the pressure curve (1 kHz). The start and endpoints derived from the simultaneous pressure curves were used for SWEI curves. The average of two measurements are reported for each condition.

Statistical analysis

Data processing and statistical analysis were performed in Matlab software (The MathWorks, Natick, MA, USA) and R (R Foundation). Pre- and post-ischemic values of the PV-derived stiffness, SWEI stiffness, pressure-derived relaxation time constant and SWEI-derived time constant were compared individually using a paired t -test analysis. In this

study, a paired *t*-test analysis was used for statistical comparisons because the experiments were done as pre- and post-ischemic conditions on the same hearts. It has been shown previously that EDPVR measurements can be affected by multiple parameters if used for comparison among groups with different conditions (Burkhoff et al. 2005). Although the variety of conditions among groups was very small in our study, analysis of variance was performed on EDPVR data, considering the subjects, pre-post conditions and the two measurements at each condition as independent variables. In addition, the crossed effect of EDPVR slopes with subjects and pre-post conditions was assessed.

A linear regression model with zero intercept was used to correlate the two derived relaxation time constants, in which all of the data points pre- and post-ischemia were combined in a single analysis. In one of the subjects, EDPVR data were not included in the final analysis because of the uncharacteristic shape of the PV loops and the volume signal. In the event of measured shear velocities higher than 9 m/s or of a measured tissue displacement profile that did not follow a shear wave propagation pattern, the shear wave speed measurements were considered as artifacts and removed from the τ measurement analysis. These conditions occurred in three of the subjects and were usually caused by speckle decorrelation most likely because of out-of-plane motion of the heart.

RESULTS

Figure 3 presents the PV loops measured in one of the subjects and EDPVR lines fit from the PV data for pre- and post-ischemia. All PV- and SWEI-based stiffness values pre- and post-ischemia in all of the subjects are reported in Figure 4. In eight hearts, PV-derived stiffness showed a statistically significant increase of 100% after ischemia (mean of 2.010 to a mean of 4.027 mL⁻¹, $p < 0.05$). SWEI measurements of stiffness at the end of diastole also showed a significant increase of 103% after ischemia in the same hearts (mean of 5.353 to a mean 10.855 kPa, $p < 0.05$). In two of the hearts (6 and 7), the ventricular diastolic stiffness decreased after reperfusion. SWEI stiffness measurements also showed the same pattern of decrease. According to the literature, reperfusion can impair or improve diastolic compliance, depending on the degree of the ischemic injury (Apstein and Grossman 1987). These two hearts were excluded from the paired *t*-test analysis of the mean change. Analysis of covariance showed significance for pre-post and subject variables and no significance for the two measurements at each step, as expected.

To characterize the relationship between PV-derived and SWEI-derived stiffness values, in one of the hearts, measurements were taken every 20 min after ischemia for 60 min. The PV-derived stiffness values were recorded as 5.820, 5.364, 10.66 and 13.58 mL⁻¹; SWEI stiffness measurement were recorded as 5.998, 3.258, 21.83 and 23.27) kPa. These two measurements were linearly related with each other with a slope of 0.37 mL⁻¹/kPa and an $R^2 = 0.94$.

Figure 5 shows the relaxation time constant measurements based on the pressure and SWEI curves. The *solid red dot* indicates the beginning point of the exponential curve fit, and the *circular red dot* indicates the 70-ms interval and the end of the curve fit. These points have been identified using the method mentioned in the final paragraph of the experimental setup

in the Methods section. Figure 6 presents the τ values pre- and post-ischemia based on intra-ventricular pressure and SWEI recordings in eight rabbits. Tau values showed a statistically significant increase after ischemia in both pressure-derived and SWEI-derived measurements ($p < 0.05$). They showed an average 79% increase (71 ms to 127 ms) for pressure-derived measurements and a 76% increase (87 to 153 ms) for SWEI-derived measurements. To characterize the relationship between the τ values derived from pressure and SWEI, a linear regression model with zero intercept was used. The results are presented in Figure 7. The slope of this relationship was 1.16 with $R^2 = 0.80$, which indicates the similarity of relaxation time constant values between the two methods.

DISCUSSION

In this report, we studied cardiac diastolic functional assessment using the ultrasound elastography technique, SWEI. We compared diastolic stiffness changes derived from PV measurements and measured directly using SWEI before and after ischemia. We showed that both PV-derived and SWEI measurements of end diastolic stiffness displayed significant changes after ischemia. In addition, our results indicate that the relaxation time constant measured using SWEI elastography is similar to the relaxation time constants derived from intra-ventricular pressure. The measured change of τ after ischemia was significant using both of these methods.

Diastolic function assessment using elastography techniques has recently been investigated by other groups. Researchers have found excellent agreement between magnetic resonance (MR) elastography-derived and PV-based measures of shear modulus of stiffness in a spherical phantom model proposed in the literature. (Kolipaka et al. 2009; Mirsky and Parmley 1973). Researchers in this study reported static and cyclic pressure condition comparisons between the spherical phantom PV-derived and MR-based elastography-derived values of shear modulus. Correlation coefficients of 0.98 and 0.97 between the PV- and MR-based elastography estimates of shear stiffness measurements were obtained. In another study, hypertrophy of the myocardium was induced in rats, and a significantly higher diastolic stiffness in the hypertrophic rat heart compared with the control group was reported, demonstrating the capability of SWEI imaging to measure changes in cardiac compliance (Pernot et al. 2011). In an *in vivo* large-animal model, it has been shown that measurements of passive myocardial elasticity quantified by shear wave imaging were correlated with the elastic modulus measured by the invasive pressure-segment length method (Pislaru et al. 2014). They concluded that the measurements correlated well, and the effect of an acute intervention (MI) was clearly detectable over a wide range of elasticity.

In another recent study, a comparison between SWEI and the end diastolic stress-strain relationship recorded by pressure-segment length measurements was performed *in vivo* in 10 sheep. Researchers induced myocardial stunning and infarction by ligating the left anterior descending coronary artery for 15 and 120 min, respectively, followed by a 40 min of reperfusion. SWEI diastolic stiffness significantly increased after 2 h of ischemia, from 1.7 ± 0.4 to 6.2 ± 2.2 kPa and to 12.1 ± 4.2 kPa after reperfusion. Diastolic myocardial stiffening was confirmed by the exponential constant coefficient, which increased from 8.8 ± 2.3 to 25.7 ± 9.5 . For stunned myocardium, the SWEI measurement was unchanged (2.3

± 0.4 kPa versus 1.8 ± 0.3 kPa). This was confirmed by the stress-strain measurement (9.7 ± 3.1 versus 10.2 ± 2.3). They concluded that SWEI end diastolic measurements could differentiate infarcted myocardium from stunned conditions (Pernot et al. 2016).

Relaxation time constant measurements of diastolic function have been studied in both normal and diseased conditions. Researchers showed, using intra-ventricular pressure measurements, that the relaxation time constant in 10 normal subjects (35 ± 10 ms) was significantly lower than the τ in 47 diastolic heart failure patients (59 ± 14 ms) (Zile et al. 2004). Using MR elastography, the relaxation time constant in healthy human patients was measured in the range 60–80 ms. The MR-elastography-derived relaxation time constant in 11 patients with diastolic dysfunction was found to be 134 ms, significantly longer than in healthy patients (Elgeti et al. 2010; Tzschätzsch et al. 2013). The normal and post-ischemic τ values measured using SWEI in our experiments are in the same range as those in the aforementioned above-mentioned studies.

Recording PV loops, with the associated change in pre-load needed to measure compliance, requires an invasive pressure catheter, and the recorded value is a global measure of cardiac stiffness. These limitations have prevented the technique from becoming a routine clinical procedure. In 1974, the concept of instantaneous PV relationship and time-varying elastance of the ventricular wall was introduced during systole and diastole (Suga and Sagawa 1974). It provided a comprehensive explanation of ventricular elastance (dP/dV or physiologic stiffness) and its variation during the cardiac cycle. Table 1 provides a comparison between the PV measurement of cardiac function and elastography-derived indices. As discussed earlier, PV measurements provide global measurements of cardiac function, while elastography provides a local measurement of myocardial properties. We have shown that in global conditions these two techniques measure similar quantitative changes. In the case of localized myocardial damage, local elastography measurements would need to be combined with measurements from other locations to get an overall assessment of myocardial function. This could be considered both an advantage and a disadvantage of the method. It is important to note that, unlike other ultrasound-based diastolic functional assessments, SWEI diastolic stiffness measurements were shown to be independent of loading conditions in the previously published study by Pernot et al. (2011).

It has been shown previously that in HFpEF patients, the active relaxation time constant and/or passive stiffness of the myocardium is impaired (Jeong and Dudley 2015). These patients have a significant increase in diastolic dysfunction. In this current study, we used a global ischemia model showing that both of these indices changed after ischemia. Although these results do not test the hypothesis that HFpEF patients with abnormal active or passive diastolic dysfunction can be diagnosed with SWEI techniques, they certainly suggest that this might be the case. Furthermore, valvular disorders and arrhythmias could affect the measurements that rely on the motion of the heart and ventricular-volume changes. Most of these techniques require sinus rhythm or atrial contraction for accurate measurements. However, SWEI measurements can be taken directly from the myocardium in any rhythm without the need for atrial contraction. While the isovolumic relaxation time constant might be challenging to obtain during an arrhythmia, end diastolic stiffness is taken during a very short interval compared with the cardiac cycle and should be less affected by irregular

rhythms. As mentioned above, SWEI measurements are based on myocardial properties that do not depend on flow or volume changes; therefore, they are less likely to be affected by valvular disorders.

As outlined in the Methods section, the exponential EDPVR model results in a chamber stiffness, b , with units of mL^{-1} . A number of investigators have multiplied this index by the ventricular wall volume to normalize the value. In this study, we report the chamber stiffness in units of mL^{-1} because of the similarity in the heart size of the subjects and because of the challenge of measuring an accurate ventricular wall volume. A spherical model of the heart has been used to convert the chamber stiffness value into Young's and Shear moduli of stiffness (Mirsky and Parmley 1973). This model was not used in this study because the assumption of spherical geometry seemed inaccurate and because of the challenge of measuring ventricular wall volume. It is important to note that in this study, the relative changes as opposed to the absolute values of ventricular stiffness pre- and post-ischemia were studied for each PV- and SWEI-derived measurement. It would be an important advancement if future studies could characterize the relationship between the absolute values of SWEI-derived shear modulus of stiffness and PV-derived shear modulus of stiffness utilizing a geometric model. This has been done previously *in vitro* using the MR elastography technique and a spherical model (Kolipaka et al. 2009).

Limitations

As presented in Table 2, the duration of reperfusion before the post-ischemia PV and SWEI measurement varies across subjects. This occurred for two reasons. First, to maximize the effect of ischemia on the measurements, we continued recording PV and SWEI data over time after reperfusion every 20 min. During this reperfusion period, the hearts occasionally developed arrhythmias, and PV measurements could not be recorded. As a result, additional time was given until sinus rhythm returned. Moreover, on a few occasions, the motion of the heart caused artifacts in the SWEI measurements. As it was intended to maintain the location of the probe and the location of PV catheter, a longer period was allowed for the hearts to stabilize, and concurrent PV and SWEI measurements were feasible.

The variation among subjects in the baseline measurements of PV-derived stiffness and in the magnitude of the relative changes could be because of differences in the reperfusion periods, the result of poor inter-subject consistency of volume measurements with the conductance catheter or a reflection of the individual characteristics of each heart. One potential source of the between-subject variation could be the volume calibration in the PV measurement. This calibration scales all the volume measurements and is dependent on a number of factors. Another source of variation could be the anisotropic nature of the myocardium. It has been shown that myocardial fiber orientation affects shear wave velocity of propagation (Bouchard et al. 2009). To minimize the effect of anisotropy, we averaged the SWEI measurements over 1 mm of myocardial wall thickness. As indicated earlier, in this study the relative changes as opposed to the absolute values of ventricular stiffness pre- and post-ischemia were studied for the derived measurement. To provide τ measurements based on SWEI non-invasively, the interval could be determined based on differentiation of the SWEI curve through the cardiac cycle as the technology advances to provide better quality

measurements with an increased sampling rate. In case of limited sampling rate or signal-to-noise ratio, other non-invasive measures could be simultaneously used to detect a gated starting point, including electrocardiogram signal, cardiac Doppler imaging or cardiac phonogram. Future studies are needed to further characterize the effect of the aforementioned factors.

CONCLUSION

We have shown that SWEI elastography can be used to characterize the diastolic function of the heart. SWEI measurements provided indices of active relaxation and passive myocardial stiffness properties, the relaxation time constant and diastolic stiffness, which are consistent with the gold standard PV measurements when characterizing a relatively homogeneous substrate. Using the suggested methods for determining fiducials, this technique could potentially be used in HFpEF patients for diagnosis, measuring treatment effects and evaluating the lusitropic state of the myocardium. In contrast to invasive PV measurements, ultrasound elastography can be implemented on ultrasound scanners that have the advantages of being portable, inexpensive and non-invasive.

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References

- Apstein CS, Grossman W. Opposite initial effects of supply and demand ischemia on left ventricular diastolic compliance: The ischemia-diastolic paradox. *J Mol Cell Cardiol.* 1987; 19:119–128. [PubMed: 3550105]
- Bouchard, RR., Wolf, PD., Hsu, SJ., Dumont, DM., Trahey, GE. Acoustic radiation force-induced shear wave propagation in cardiac tissue. In: McAleavey, SA., D'hooge, J., editors. *Ultrasonic imaging and signal processing.* Vol. 7265. 2009. p. 12-18.
- Burkhoff D, Mirsky I, Suga H. Assessment of systolic and diastolic ventricular properties via pressure-volume analysis: A guide for clinical, translational, and basic researchers. *Am J Physiol Heart Circ Physiol.* 2005; 289:H501–H512. [PubMed: 16014610]
- Correia M, Provost J, Chatelin S, Villemain O, Tanter M, Pernot M. Ultrafast harmonic coherent compound (UHCC) imaging for high frame rate echocardiography and shear-wave elastography. *IEEE Trans Ultrason Ferroelectr Freq Control.* 2016; 63:420–431. [PubMed: 26890730]
- Doherty JR, Trahey GE, Nightingale KR, Palmeri ML. Acoustic radiation force elasticity imaging in diagnostic ultrasound. *IEEE Trans Ultrason Ferroelectr Freq Control.* 2013; 60:685–701. [PubMed: 23549529]
- Dusch MN, Thadani S, Dhillon GS, Hope MD. Diastolic function assessed by cardiac MRI using longitudinal left ventricular fractional shortening. *Clin Imaging.* 2014; 38:666–668. [PubMed: 25034401]
- Elgeti T, Beling M, Hamm B, Braun J, Sack I. Elasticity-based determination of isovolumetric phases in the human heart. *J Cardiovasc Magn Reson.* 2010; 12:60. [PubMed: 20979648]
- Eyerly SA, Vejdani-Jahromi M, Dumont DM, Trahey GE, Wolf PD. The evolution of tissue stiffness at radiofrequency ablation sites during lesion formation and in the peri-ablation period. *J Cardiovasc Electrophysiol.* 2015; 26:1009–1018.
- Greenleaf JF, Fatemi M, Insana M. Selected methods for imaging elastic properties of biological tissues. *Ann Rev Biomed Eng.* 2003; 5:57–78. [PubMed: 12704084]

- Gross, D. Animal models in cardiovascular research. New York, NY: Springer US; 2009. Measuring cardiac function; p. 65-91.
- Jeong EM, Dudley SJ Jr. Diastolic dysfunction. *Circ J*. 2015; 79:470–477. [PubMed: 25746522]
- Kakkad, V., Kuo, L., Bradway, D., Trahey, GE., Sivak, J., Kisslo, J. IEEE international ultrasonics symposium. Piscataway, NJ: IEEE; 2015. Vivo transthoracic measurements of acoustic radiation force induced displacements in the heart over the cardiac cycle.
- Kass D. Assessment of diastolic dysfunction. *Cardiol Clin*. 2000; 18:571–586. [PubMed: 10986590]
- Kelly A. The effect of pharmacological modulation of the sarcoplasmic reticulum on left ventricular function in the isolated working rabbit heart. 2010
- Kolipaka A, McGee KP, Araoz PA, Glaser KJ, Manduca A, Romano AJ, Ehman RL. MR elastography as a method for the assessment of myocardial stiffness: Comparison with an established pressure-volume model in a left ventricular model of the heart. *Magn Reson Med*. 2009; 62:135–140. [PubMed: 19353657]
- Kwiecinski W, Provost J, Dubois R, Sacher F, Haissaguerre M, Legros M, Nguyen-Dinh A, Dufait R, Tanter M, Pernot M. Quantitative evaluation of atrial radio frequency ablation using intracardiac shear-wave elastography. *Med Phys*. 2014; 41:112901. [PubMed: 25370668]
- Mirsky I, Parmley W. Assessment of passive elastic stiffness for isolated heart muscle and the intact heart. *Circ Res*. 1973; 33:233–243. [PubMed: 4269516]
- Oh JK, Park SJ, Nagueh SF. Established and novel clinical applications of diastolic function assessment by echocardiography. *Circ Cardiovasc Imaging*. 2011; 4:444–455. [PubMed: 21772012]
- Pernot M, Couade M, Mateo P, Crozatier B, Fischmeister R, Tanter M. Real-time assessment of myocardial contractility using shear wave imaging. *J Am Coll Cardiol*. 2011; 58:65–72. [PubMed: 21700091]
- Pernot M, Lee WM, Bel A, Mateo P, Couade M, Tanter M, Crozatier B, Messas E. Shear wave imaging of passive diastolic myocardial stiffness: Stunned versus infarcted myocardium. *JACC Cardiovasc Imaging*. 2016; 9:1023–1030. [PubMed: 27236522]
- Pislaru C, Urban MW, Pislaru SV, Kinnick RR, Greenleaf JF. Viscoelastic properties of normal and infarcted myocardium measured by a multifrequency shear wave method: Comparison with pressure-segment length method. *Ultrasound Med Biol*. 2014; 40:1785–1795. [PubMed: 24814645]
- Schiereck P, Nieuwenhuijs JH, Beer EL, Hessen MWJ, Kaam FAM, Crowe A. Relaxation time constant of isolated rabbit left ventricle. *Am J Physiol Soc*. 1987; 253:H512–H518.
- Song P, Bi X, Mellema DC, Manduca A, Urban MW, Greenleaf JF, Chen S. Quantitative assessment of left ventricular diastolic stiffness using cardiac shear wave elastography: A pilot study. *J Ultrasound Med*. 2016; 35:1419–1427. [PubMed: 27208201]
- Strachinaru M, Bosch JG, van Dalen BM, van Gils L, van der Steen AFW, Jong ND, Geleijnse ML, Vos HJ. Cardiac shear wave elastography using a clinical ultrasound system. *Ultrasound Med Biol*. 2017; 43:1596–1606. [PubMed: 28545859]
- Suga H, Sagawa K. Instantaneous pressure-volume relationships and their ratio in the excised, supported canine left ventricle. *Circ Res*. 1974; 35:117–126. [PubMed: 4841253]
- Tzschätzsch H, Hättasch R, Knebel F, Klaua R, Schultz M, Jenderka KV, Braun J, Sack I. Isovolumetric elasticity alteration in the human heart detected by *in vivo* time-harmonic elastography. *Ultrasound Med Biol*. 2013; 39:2272–2278. [PubMed: 24035628]
- Vejdani-Jahromi M, Nagle M, Trahey GE, Wolf PD. Ultrasound shear wave elasticity imaging quantifies coronary perfusion pressure effect on cardiac compliance. *IEEE Trans Med Imaging*. 2015; 34:465–473. [PubMed: 25291788]
- Vejdani-Jahromi M, Nagle M, Jiang Y, Trahey GE, Wolf PD. A comparison of acoustic radiation force derived indices of cardiac function in the langendorff perfused rabbit heart. *IEEE Trans Ultrason Ferroelectr Freq Control*. 2016; 63:1288–1295. [PubMed: 27008665]
- Vejdani-Jahromi M, Freedman J, Nagle M, Trahey GE, Wolf PD. Quantifying myocardial contractility changes using ultrasound-based shear wave elastography. *J Am Soc Echocardiogr*. 2017; 30:90–96. [PubMed: 27843103]

- Vorovich E, French B, Ky B, Goldberg L, Fang JC, Sweitzer NK, Cappola TP. Biomarker predictors of cardiac hospitalization in chronic heart failure: A recurrent event analysis. *J Card Fail.* 2014; 20:569–576. [PubMed: 24929121]
- Mozaffarian D, Benjamin EJ, Go AS, Arnett DK, Blaha MJ, Cushman M, Das SR, Ferranti DS, Després JP, Fullerton HJ, Howard VJ, Huffman MD, Isasi CR, Jiménez MC, Judd SE, Kissela BM, Lichtman JH, Lisabeth LD, Liu S, Mackey RH, Magid DJ, McGuire DK, Mohler ER, Moy CS, Muntner P, Mussolino ME, Nasir K, Neumar RW, Nichol G, Palaniappan L, Pandey DK, Reeves MJ, Rodriguez CJ, Rosamond W, Sorlie PD, Stein J, Towfighi A, Turan TN, Virani SS, Woo D, Yeh RW, Turner MB. Writing Group Members; American Heart Association Statistics Committee, Stroke Statistics Subcommittee. Heart disease and stroke statistics—2016 update, A report from the American Heart Association. *Circulation.* 2016; 133:e38–e360. [PubMed: 26673558]
- Zile MR, Baicu CF, Gaasch WH. Diastolic heart failure—Abnormalities in active relaxation and passive stiffness of the left ventricle. *N Engl J Med.* 2004; 350:1953–1959. [PubMed: 15128895]

Fig. 1.

The dynamic stiffness (shear modulus) changes during the cardiac cycle recorded by SWEI (*top panel*). The simultaneous intra-ventricular pressure recordings recorded by PV catheter (*middle panel*). The echocardiogram signal (*bottom panel*). SWEI = shear wave elasticity imaging; PV = pressure volume.

Fig. 2. Schematic of the isolated heart setup inside the imaging chamber with acoustic windows. The ultrasound probe is shown recording SWEI measurements from LV free wall through the acoustic window. *Yellow lines* show the acoustic beam and the *gray arrow* in the middle shows the location of the ARFI push. PV catheter positioning and LA and aortic cannulas are also shown. SWEI = shear wave elasticity imaging; LV = left ventricle; ARFI = acoustic-radiation force impulse; PV = pressure volume; LA = left atrial.

Fig. 3. Recorded PV loops during occlusion in one of the patients (*left panel*). The EDPVR fitted to the end diastolic points (*red line*). The *right panel* shows the EDPVR curve for before ischemia (*red line*) and after reperfusion (*blue line*). PV = pressure volume; EDPVR = end diastolic pressure volume relationship.

Fig. 4. PV-derived ventricular stiffness (b) (1/mL) and SWEI stiffness (kPa) at end of diastole in all of the patients before and after ischemia. PV = pressure volume

Fig. 5. Time-constant measurements using pressure and SWEI curves. The intra-ventricular pressure recordings through the cardiac cycle (*top panel*). The SWEI stiffness curve simultaneously recorded (*bottom panel*). Red dots show the beginning and ending points for isovolumic relaxation time constant measurements. SWEI = shear wave elasticity imaging.

Fig. 6. Relaxation time constant (τ) values (ms) derived from pressure and SWEI curves before and after ischemia. Subject numbers are different from end diastolic stiffness figure. SWEI = shear wave elasticity imaging.

Fig. 7.

The relationship between relaxation time constant (τ) derived from intra-ventricular pressure recordings and τ derived from SWEI recordings of stiffness through the cardiac cycle. All the measurements from before and after ischemia are included to increase the range of measurements for the linear regression model. The slope of the linear regression and R2 values are reported.

Table 1

	Field	Stiffness	Compliance	Formula	Measurement	Functional assessment
PV loops Elastography	Physiologic	Elastance	1/Elastance	dP/dV	Global	Ventricular properties
	Mechanical	Elasticity	1/Elasticity	$d\sigma/de$	Local	Myocardial properties

PV = pressure volume.

Table 2

Subject numbers associated with EDPVR and τ measurements in Figures 4 and 6*

EDPVR measurement subject number	1	2	3	4	5	6	7	8	9	10	N/A
τ measurement subject number	1	2	3	4	N/A	N/A	5	6	7	N/A	8
Pre-ischemia duration (min)	60	68	50	54	68	72	79	72	52	86	84
Reperfusion duration (min)	22	22	37	27	31	96	39	60	150	41	10

EDPVR = end diastolic pressure volume relationship.

* Pre-ischemia duration indicates the elapsed time between mounting the heart and taking the pre-ischemia measurement. Reperfusion duration indicates the elapsed time between the start of reperfusion and the post-ischemia measurement in each heart.