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The Effect of Acute Coronary Perfusion Change on Cardiac Function measured by Shear Wave Elasticity Imaging

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Abstract

The possibility of measuring cardiac function noninvasively has generated wide interest in elastography imaging techniques. Shear Wave Elasticity Imaging (SWEI) is an ultrasound-based elastography technique used to measure stiffness of tissues. While this technique has been studied extensively in static homogenous tissues such as liver, breast or prostate, there is still a significant need to study its capabilities to measure cardiac stiffness and function. In this research, we have studied the potential of SWEI to evaluate the coronary perfusion pressure effect on systolic and diastolic stiffness referred to as elastance and compliance of the heart. Five isolated rabbit hearts were used in this study in a Langendorff preparation. SWEI measurements of stiffness were recorded in two steps. In the first step, coronary perfusion was set to normal and then was reduced to half-normal. After 40 minutes of half-normal perfusion, it was returned to normal perfusion for the second step. SWEI velocity decreased from 6.003 m/s to 4.713 m/s in systole and from 1.948 m/s to 1.507 m/s in diastole in the first step. During the second step raising the perfusion to normal, SWEI stiffness showed an increase from 3.760 m/s to 5.468 m/s in systole and from 1.678 m/s to 2.156 m/s during diastole. Our results show that SWEI measurements of stiffness can characterize the cross talk between coronary perfusion and cardiac stiffness and also has the potential to measure compliance and elastance of the heart in systole and diastole.

I. Introduction

Cardiovascular diseases are one of the leading causes of death in the world. Many of these diseases involve changes in the cardiac tissue mechanics and stiffness. One of the major participants in these conditions is the coronary perfusion. Therefore, the cross talk between coronary vasculature and cardiac tissue mechanics has been under investigation for the last several decades.[1] Researchers have been trying to illustrate the mechanical effect of coronary perfusion pressure on cardiac compliance and elastance using techniques primarily based on pressure-volume loop measurements. Recently, a number of elastography techniques based on Magnetic Resonance (MR) or ultrasound imaging have been developed. In these methods, the tissue is excited and the response is measured. More information regarding different techniques and different excitation methods can be found in the papers by Nightingale, Doherty et al. and Greenleaf et al.[2–4]

Shear Wave Elasticity Imaging (SWEI) is an ultrasound-based technique used to measure the stiffness of tissues. As the tissue is excited by an Acoustic Radiation Force Impulse (ARFI), a shear wave is generated that propagates through the tissue. The velocity of the transverse shear wave propagation is related to the Young's modulus and shear modulus of stiffness through the following formula assuming linearly elastic isotropic medium:

$$C_t = \sqrt{\frac{\mu}{\rho}} = \sqrt{\frac{E}{2(1+\nu)\rho}} \quad (1)$$

Where μ (kPa) is shear modulus and E (kPa) is Young's modulus, ν is Poisson's ratio and ρ (Kg/m^3) is the density of the tissue. Shear wave elastography has been used in different tissues such as liver, breast and prostate to measure stiffness of healthy and diseased parts of the organ. It has also been used in the cardiac tissue to measure the stiffness of the heart throughout the cardiac cycle. In the past researchers using the MR or Ultrasound techniques showed that Shear Wave elastography is linearly related to the preload pressure during diastole.[5] Pernot et al. showed that isopreterenolol, which is an inotropic agent, increases systolic stiffness measurements made using SWEI.[6] In addition, Pislaru et al. and Pernot et al. have reported preliminary results on SWEI measurements of stiffness in myocardial infarction.[7], [8]

Cardiac chamber stiffness is a parameter that is a function of different variables. Loading conditions, inotropic state, cardiac tissue structure (intracellular and extracellular) and coronary vasculature are the more significant ones. While there have been a number of studies looking at loading conditions, inotropic state and infarcted cardiac tissue using shear wave elastography, the effect of coronary perfusion pressure on the cardiac stiffness has not been studied using this technique.

The coronary perfusion pressure effect on cardiac tissue is dependent on the cardiac cycle. During systole, this effect has been called Gregg effect.[1] It has been shown using pressure volume loop measurements that as the perfusion pressure is decreased the cardiac stiffness during systole (elastance) decreases. On the other hand, the coronary perfusion effect on cardiac stiffness during diastole is called the garden-hose or Salisbury effect.[9] This effect is similarly defined as a decrease in cardiac stiffness (increase in compliance) with a decrease in coronary perfusion. Gregg and garden-hose effects only apply to acute changes in coronary perfusion pressure. In this study we made SWEI stiffness measurements of these two phenomena.

A. Langendorff Setup

White Newzealand rabbits ($n=5$, weight= 3.96 ± 0.38 kg) were studied according to the Institutional Animal Care and Use Committee (IACUC) at Duke University and conformed to the Guide for the Care and Use of Laboratory Animals. Rabbits were anaesthetized by an initial IM dose of Ketamine (35 mg/kg) and Xylazine (10 mg/kg) followed by an initial IV dose of Ketamine (35 mg/kg) followed by 10 mg/kg steps until the reflexes disappeared. The heart was exposed by a bilateral thoracotomy and was isolated and placed in a Tyrode

solution at 0-4°C. The aortoa was identified and cannulated and the heart was mounted on the setup. The heart was set in constant flow mode to stabilize for at least 15 minutes.

Tyrode solution was made on the day of each experiment. Before the addition of Ca^{2+} , the solution was oxygenated with carbogen (95% O_2 and 5% CO_2) to prevent precipitation. Then the solution was filtered by 5-microne filters. The concentration of Na^+ , K^+ , Ca^{2+} , PH, and O_2 saturation was confirmed with blood gas and electrolyte measurements. The perfusion solution was heated by a double walled chamber to 37-38°C and the O_2 Partial Pressure was confirmed to be more than 300 mmHg with 100% saturation. A small vent tube was placed in the left ventricle through the left atrium to avoid solution build up in the left ventricle. Three ECG electrodes were placed in the bath, and the signal was input to a bioamp and to the Labchart software to record ECG. Aortic pressure was recorded by a fluid filled catheter and the signal was recorded by a Powerlab/Labchart data acquisition system (ADInstruments, Colorado Springs, CO, USA). The heart was submerged in a normal saline bath kept at 37-38°C.

B. Imaging Setup

To collect our measurements, we used a Sonoline Antares ultrasound scanner (Siemens Healthcare, Ultrasound Business Unit, Mountain View, CA, USA) with a linear probe (VF10-5). The probe was positioned in the bath with short axis view of the left ventricular free wall. The focal point was set at 16 mm and the distance between the probe and the wall was set between 10-15 mm. SWEI measurements were recorded at 35 Hz sampling rate through the cardiac cycle for 1.2 seconds. A synchronous timing signal, output from the scanner, was recorded by the Labchart system simultaneously with ECG signal. Acoustic radiation force impulses were used to generate shear waves created with 300 cycles of 5.7 MHz excitation. Subsequent image frames for tissue tracking were made at 8 MHz. Pulse Repetition Frequency (PRF) was set at 4.3 KHz. A push F-number of 1.5 and tracking F-number of 2 were used.

The normal perfusion flow was set for each rabbit to keep the aortic pressure under 100 mmHg and the heart rate constant and stabilized. Experiments were done in two steps. In the first step, the perfusion flow was set to normal and then reduced to half-normal and SWEI measurements were taken before and after this step. The second step was done after 40 minutes of the heart being perfused at half-normal perfusion by returning the perfusion back to normal. A plot of these two steps and the timing of SEWI measurements are shown in fig. 1. SWEI measurements were recorded in this step before and after the change. In case of a PVC (Premature Ventricular Contraction), another image were taken. This happened in two out of 20 acquisitions.

Systolic stiffness was measured at the start of the T wave. The diastolic measurement was taken at the maximum of the P wave. The displacements were calculated by Loupas displacement algorithm, a phase shift based estimation.[10] The intrinsic motion of the heart was filtered from the displacement measurements by applying a quadratic motion filter. The speed of the shear wave propagation was calculated based on the Radon Sum algorithm described by Rouze et al.[11] When the displacement profile was too noisy to calculate SWEI velocity, data from the following time point in the cardiac cycle was used. This

applied only to one measurement out of 20. Data were analyzed using Matlab (The MathWorks, Natick, MA, USA). A paired *t*-test analysis was used to determine significance.

III. RESULTS

Fig. 2 panel A shows the SWEI measurements throughout the cardiac cycle in one of the isolated hearts. Panel B is the simultaneous ECG recording. Fig.3 panel A shows an example of SWEI measurements through the cardiac cycle in a normal (blue) and half normal (red) coronary perfusion at the first step. Panel B shows the half normal perfusion (red) to normal perfusion (blue) step in the same subject.

As the perfusion was decreased to half of normal, during systole, the average SWEI velocity significantly decreased from 6.003 m/s to 4.713 m/s ($p < 0.05$). During diastole, SWEI velocity showed a significant reduction of 1.948 m/s to 1.507 m/s ($p < 0.05$). As for the second step, increasing perfusion from half-normal to normal, the SWEI velocity increased from 3.760 m/s to 5.468 m/s in systole and 1.678 m/s to 2.156 m/s during diastole. All the *p*-values were less than 0.05. These results are shown in fig. 4. The left panel shows the first step and the right panel shows the second step.

Maximum perfusion pressure for each step was found for each rabbit. The average of the perfusion pressure at normal steps was calculated to be 78 mmHg, and the half-normal steps to be 41 mmHg. Therefore, assuming a linear relationship between perfusion pressure and SWEI velocity measurements, the slope of the first step in systole was 0.035 m/s/mmHg and in diastole was 0.012 m/s/mmHg. During the second step in systole and diastole this slope was calculated to be 0.046 m/s/mmHg and 0.013 m/s/mmHg respectively.

IV. DISCUSSION

The results of this study show that SWEI measurements of stiffness can be used to characterize the effect of acute coronary perfusion changes on cardiac stiffness. These changes are different in systole and diastole. During systole, the decrease of perfusion to half of normal resulted in a decrease in stiffness consistent with what other researchers have reported in the past as the Gregg effect. During diastole, the same pattern was recorded, previously referred to as garden-hose effect measured by pressure-volume loops.

The effect of a change in coronary perfusion pressure during systole was 3 to 4 times higher than during diastole, because a reduction in coronary flow is expected in systole, this result is counter intuitive. A number of theories have been proposed to explain this phenomenon; these include Starling's law and microvasculature volume changes or a change in Ca^{2+} concentration, but to our knowledge, there is no universally accepted explanation. A detailed description of the phenomenon can be found in the review published by Westerhof et al.[1]

A slight decrease in the normal perfusion systolic stiffness and an increase in diastolic stiffness before the first step compared to normal perfusion after the second step in systole. Similarly, during the 40 minutes of half-normal perfusion, systolic stiffness decreased and diastolic stiffness increased. This could be due to edema changing the compliance and a loss of function. The elastance can change in a heart perfused by crystalloid solution. In a typical

Langendorff preparation, the heart loses its functionality or becomes edematous at a rate of about 5-20% per hour.[12], [13] According to our results, normal systolic stiffness showed a 9% decrease and for diastolic stiffness it showed 11% increase. While during half-normal perfusion, diastolic stiffness increased and systolic stiffness decreased by 11% and 20% respectively.

Furthermore, this increase in diastolic stiffness and decrease in systolic stiffness can be explained by the ischemic effect of hypo-perfusion on the heart. In a review published by Apstein et al. they stated that in the rabbit, an acute decrease in coronary perfusion will increase the compliance of the heart for the first 30 minutes due to the 'garden-hose effect'. After 30 minutes of global ischemia, the compliance will reverse its pattern and the heart will start to stiffen as a result of ischemia.[9]

It is well known that fiber orientation affects the shear wave conduction velocity in the heart. [14] The change in fiber orientations results in SWEI velocity variations through the cardiac tissue depth.[15] In our study we kept the probe position constant, so that imaged the same location for all of the measurements in each subject. In addition, we report SWEI velocity measurements instead of converting them to shear or Young's modulus of stiffness to avoid a reliance on the assumptions of a linearly elastic and isotropic medium.

V. Conclusion

SWEI measurements of stiffness can be used to measure the effect of acute coronary perfusion on cardiac tissue stiffness throughout the cardiac cycle. In a rabbit Langendorff preparation, this effect is characterized by a likely passive mechanical effect during systole and diastole, with an additional active effect during systole, which is likely the result of increased perfusion on contraction coupling.

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References

1. Westerhof N, Boer C, Lamberts RR, Sipkema P. Cross-Talk Between Cardiac Muscle and Coronary Vasculature. *physiol Rev.* 2006; 86:1263–1308. [PubMed: 17015490]
2. Nightingale K. Acoustic Radiation Force Impulse (ARFI) Imaging: a Review. *Curr Med Imaging.* 2011; 7(4):328–339.
3. Doherty JR, Trahey GE, Nightingale KR, Palmeri ML. Acoustic radiation force elasticity imaging in diagnostic ultrasound. *IEEE transactions on ultrasonics, ferroelectrics, and frequency control.* Apr. 2013 60(4):685–701.
4. Greenleaf JF, Fatemi M, Insana M. Selected methods for imaging elastic properties of biological tissues. *Annual review of biomedical engineering.* Jan.2003 5:57–78.
5. Kolipaka A, McGee KP, Manduca A, Anavekar N, Ehman RL, a Araoz P. In vivo assessment of MR elastography-derived effective end-diastolic myocardial stiffness under different loading conditions. *Journal of magnetic resonance imaging: JMRI.* May; 2011 33(5):1224–8. [PubMed: 21509882]

6. Pernot M, Couade M, Mateo P, Crozatier B, Fischmeister R, Tanter M. Real-time assessment of myocardial contractility using shear wave imaging. *Journal of the American College of Cardiology*. Jun.2011 58(1):65–72. [PubMed: 21700091]
7. Pernot M, Lee W-N, Couade M, Mateo P, Crozatier B, Bell A, Tanter M, Messas E. In Vivo non invasive quantitative assessment of passive diastolic stiffness of infarcted myocardium using shear wave imaging. *European heart journal*. 2012
8. Pislaru C, Urban M, V Pislaru S, Clinic JFGM. Shear elasticity-pressure relationship in normal and infarcted myocardium. *European heart journal*. 2013; 34:366.
9. Apstein CS, Grossman W. Opposite initial effects of supply and demand ischemia on left ventricular diastolic compliance: the ischemia-diastolic paradox. *Journal of molecular and cellular cardiology*. Jan.1987 19(1):119–28. [PubMed: 3550105]
10. Loupas T, Powers JT, Gill RW. An axial velocity estimator for ultrasound blood flow imaging, based on a full evaluation of the Doppler equation by means of a two-dimensional autocorrelation approach. *IEEE Transactions on Ultrasonics, Ferroelectrics and Frequency Control*. Jul.1995 42(4):672–688.
11. Rouze NC, Wang MH, Palmeri ML, Nightingale KR. Robust estimation of time-of-flight shear wave speed using a radon sum transformation. *IEEE transactions on ultrasonics, ferroelectrics, and frequency control*. Dec.2010 57(12):2662–70.
12. Gross, D. *Animal Models in Cardiovascular Research*. Springer US; New York, NY: 2009. p. 109-130.
13. Dhein S. *The Langendorff Heart. Practical Methods in Cardiovascular Research*. 2005:155–172.
14. Bouchard RR. *Acoustic Radiation Force Impulse-Driven Shear Wave Velocimetry in Cardiac Tissue*. 2010
15. Lee W-N, Pernot M, Couade M, Messas E, Bruneval P, Bel A, Hagège A. a, Fink M, Tanter M. Mapping myocardial fiber orientation using echocardiography-based shear wave imaging. *IEEE transactions on medical imaging*. Mar.2012 31(3):554–62. [PubMed: 22020673]

Figure 1. Normal and half-normal coronary perfusion steps. Number 1 and 2 show the time of SWEI measurements at first step and numbers 3 and 4 correspond to the second step measurements.

Figure 2.
Panel A: SWEI measurements of stiffness through the cardiac cycle in one of the subjects.
Panel B: simultaneous ECG recordings.

Figure 3.

SWEI measurements of stiffness through the cardiac cycle in one of the subjects. Blue and red colors correspond to normal and half-normal coronary perfusion. Panel A shows the first step (normal to half-normal perfusion change) and Panel B shows the second step (going from half-normal to normal perfusion).

Figure 4.

Left panel shows the average SWEI stiffness measurements in all the subjects for the first step (normal to half-normal perfusion) in systole and diastole. Right panel shows the average SWEI measurements in all subjects for the second step (half-normal to normal perfusion). Error bars show one standard deviation of the data.