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● *Original Contribution*

VISCOELASTIC PROPERTIES OF NORMAL AND INFARCTED MYOCARDIUM MEASURED BY A MULTIFREQUENCY SHEAR WAVE METHOD: COMPARISON WITH PRESSURE-SEGMENT LENGTH METHOD

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Abstract—Our aims were (i) to compare *in vivo* measurements of myocardial elasticity by shear wave dispersion ultrasound vibrometry (SDUV) with those by the conventional pressure-segment length method, and (ii) to quantify changes in myocardial viscoelasticity during systole and diastole after reperfused acute myocardial infarction. The shear elastic modulus (μ_1) and viscous coefficient (μ_2) of left ventricular myocardium were measured by SDUV in 10 pigs. Young's elastic modulus was independently measured by the pressure-segment length method. Measurements made with the SDUV and pressure-segment length methods were strongly correlated. At reperfusion, μ_1 and μ_2 in end-diastole were increased. Less consistent changes were found during systole. In all animals, μ_1 increased linearly with left ventricular pressure developed during systole. Preliminary results suggest that μ_1 is preload dependent. This is the first study to validate *in vivo* measurements of myocardial elasticity by a shear wave method. In this animal model, the alterations in myocardial viscoelasticity after a myocardial infarction were most consistently detected during diastole. (E-mail: Pislaru.Cristina@mayo.edu)

Key Words: **Echocardiography, Elasticity, Elastography, Myocardial stiffness, Myocardial infarction, Shear elasticity, Shear wave, Ultrasound, Viscoelasticity.**

INTRODUCTION

Physiologic (*e.g.*, aging) and pathologic processes are associated with modifications in tissue elasticity, including myocardium. Several conditions such as ischemic heart disease, cardiomyopathies and heart failure with normal ejection fraction are associated with alterations in ventricular and myocardial stiffness (Burkhoff et al. 2005; Burlew and Weber 2002; Diamond and Forrester 1972; Kawaguchi et al. 2003; Zile et al. 2004). These alterations may contribute to diastolic dysfunction, elevated filling pressures and exercise intolerance in these patients. Thus, quantification of mechanical properties of the myocardial tissue may help with the assessment of the health of the tissue. Comprehensive echocardiographic evaluation of systolic and diastolic function provides objective evidence for functional abnormalities that corroborate with clinical presentation and patient symptoms. However, a significant number of patients have inconclusive results and are sent for invasive evaluation. Echocardiography (ECG) provides information on ventricular chamber stiffness from blood flow kinetics, but measurements suffer from the influence of confounding factors (Little et al. 1995; Nagueh et al. 2009; Oh et al. 2006).

Several shear wave techniques have recently been developed to evaluate tissue elasticity and viscoelasticity using magnetic resonance (Muthupillai et al. 1995; Rump et al. 2007; Vappou 2012) and ultrasound (Bercoff et al. 2004; Chen et al. 2009; Kanai 2005; Nightingale et al. 2003; Sarvazyan et al. 1998) imaging. These techniques share the same principle: Shear waves are induced by an external force, wave propagation is measured by motion tracking and shear elasticity (or viscoelasticity) is estimated from the speed of wave

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propagation using different models and approaches. Measurements on the heart have been reported using magnetic resonance elastography, acoustic radiation force imaging, supersonic shear wave imaging and shear wave dispersion ultrasound vibrometry (SDUV) (Couade et al. 2011; Hsu et al. 2007; Kanai 2005; Kolipaka et al. 2010; Nenadic et al. 2011; Nightingale et al. 2003, Pislaru et al. 2009; Urban et al. 2013), among other techniques. To our knowledge, shear wave measurements on the myocardium have not been validated *in vivo*. Shear elasticity is related to tensile elasticity (*i.e.*, Young's elastic modulus), which is the most common measure of tissue elasticity. Considering the evidence for changes in tissue stiffness with various developing pathologies and in different organs, it is hoped that measurements of myocardial shear elasticity may be of clinical value.

This study had two aims. The first was to compare myocardial elasticity estimated by SDUV against standard measures of myocardial elasticity and stiffness obtained with the conventional pressure-segment length method in a large animal model. The second aim was to characterize differences in viscoelastic properties of the myocardium during systole and diastole in normal and infarcted myocardium. We hypothesized that alterations in myocardial stiffness caused by acute ischemia and reperfusion (Diamond and Forrester 1972; Pirzada et al. 1978) can be quantified *in vivo* by the shear wave method, SDUV. The effect of preload on viscoelastic estimates was also assessed.

METHODS

All procedures were designed in accordance with the National Institutes of Health guidelines. The protocol was approved by the Mayo Clinic Institutional Animal Care and Use Committee. Farm pigs (3–4 month old) were sedated (telazol 5 mg/kg, atropine 0.05 mg/kg, xylazine 2 mg/kg), anesthetized (continuous inhalation of isoflurane 1%–2%) and mechanically ventilated. A dual-sensor pressure catheter (Millar Instruments, Houston, TX, USA) was used to measure left ventricular (LV) and aortic pressure. After sternotomy, the heart was suspended in a pericardial cradle. Piezoelectric crystals (Sonometrics, London, ON, Canada) were inserted, 1–1.5 cm apart, from the epicardial side into the subendocardium of the anterior and inferolateral LV walls to measure segment lengths and LV chamber minor radius. Preload was increased by rapid intravenous saline infusion (0.5–1 L). ECG and pressure signals were digitized and continuously recorded.

Acute myocardial infarction (MI) was induced by ligature of the mid- to distal left anterior descending coronary artery for 1–3 h, followed by 1–2 h of reperfusion. Presence of severe ischemia was confirmed by segment lengthening (bulging) during systole and development of cyanosis. Reperfusion was achieved by removal of the ligature. At the end of the experiment, the transmural extent of infarction in the target area was quantified by triphenyltetrazolium chloride staining of the excised hearts, as previously described (Pislaru et al. 2001).

Shear wave dispersion ultrasound vibrometry

This technique is based on shear wave velocity dispersion (*i.e.*, the variation of wave speed with frequency) and Lamb's theory of wave propagation in plates (Lamb 1917) for estimating material viscoelastic properties (Kanai 2005; Nenadic et al. 2011). The details of the technique and some preliminary results in normal animals were previously reported (Pislaru et al. 2009; Urban et al. 2013). Shear elasticity (shear elastic modulus, μ_1, in kPa) and viscosity (viscous coefficient, μ_2, in Pa·s) can be estimated from a small region of interest (~1 cm). The viscoelastic properties of the myocardium were modeled as an elastic spring (μ_1) in parallel with a dashpot (μ_2) (*i.e.,* Voigt model). Thus, μ_1 represents the storage modulus (frequency-independent), whereas μ_2 is a constant responsible in part for the frequency-dependent increase in wave speed. The method assumes local homogeneity, isotropy and incompressibility.

Figure 1 illustrates the experimental setup. Small sinusoidal vibrations (10–100 μm in amplitude) were applied on the surface of the heart using a mechanical actuator (V203, Ling Dynamic Systems, Hertfordshire, UK), driven with a signal generator (33120 A, Agilent, Santa Clara, CA, USA) and an amplifier (XLS 202, Crown Audio, Elkhart, IN, USA). The signal generator was used to vary the amplitude and frequency of excitation. The resulting shear wave motion propagating along the heart wall was tracked with a 5-MHz linear array transducer (L9-4/38) and Sonix RP scanner (Ultrasonix Medical, Vancouver, BC, Canada) using eight M-mode lines and frame rates between 2000 and 2500 Hz. The transducer was oriented approximately parallel to the long axis of the left ventricle. The transducer was attached to the surgical table, and measurements were performed on the same myocardial segment throughout the experiment. Care was taken to fine-tune the position of the rod to obtain robust motion data measurable by ultrasound, while minimizing the pressure applied on the heart and avoiding the obstruction of coronary arteries and major branches. Ultrasound data were acquired at fixed frequencies between 50 and 400 Hz, in 50 Hz increments, continuously for 2.5–3 s. For clarity, here we present wave velocity results between 100 and 350 Hz, which was generally the frequency range used for