Magnetic Resonance Elastography Derived Stiffness as a Method to Estimate Myocardial Contractility.

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Introduction: Contractility is the intrinsic ability of the heart to contract independent of preload and afterload. Currently contractility is measured experimentally with pressure-volume (P-V) relationships (i.e. end-systolic P-V relationship) [1] and isolated papillary muscle stretching [2]. However, P-V based methods and *ex vivo* mechanical stretch methods are invasive and are difficult to perform [3,4]. The invasive nature of these measurements has severely limited the understanding of a variety of cardiac disease states. It has been recently demonstrated that magnetic resonance elastography (MRE) [5] can be adapted to measure the shear stiffness of myocardium [6-8]. The purpose of this study is to determine whether increasing left ventricular (LV) myocardial contractility by epinephrine infusion in an *in vivo* pig model is associated with increase in end-systolic (E-S) MRE-derived effective myocardial stiffness.

Figure 1. Schematic of the pig showing the MRE driver placed on the chest wall to induce external motion into the heart and an IV placed in the ear to infuse epinephrine.

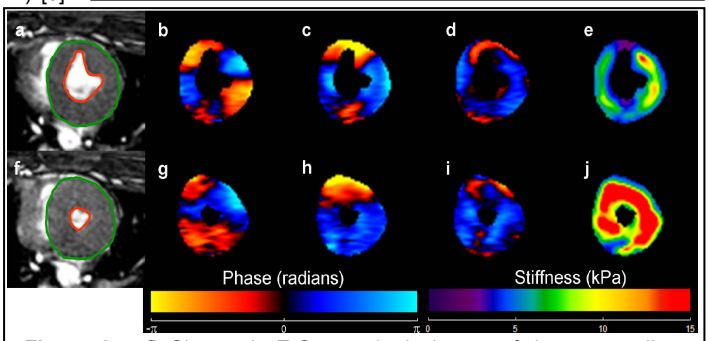

Figure 2. a,f) Short-axis E-S magnitude image of the myocardium with epicardial (green) and endocardial (red) contours in a pig at baseline and after 5th infusion of epinephrine respectively. **b, c, d, g, h, i)** Wave images in x, y, and z motion sensitization directions during end-systole. **e, j)** Corresponding stiffness maps at end-systole with a mean stiffness of 5.95 ± 2 kPa and 14.03 ± 7.6 kPa respectively.

Methods: *In vivo* cardiac MRE was performed on 5 pigs (mean weight 35.8 kg) under inhalation anesthesia and mechanical ventilation. All imaging was performed in a 1.5 Tesla MRI scanner (Signa Excite, GE Health Care, Milwaukee, WI). The pigs were positioned in the supine position and placed feet first into the scanner. MRE was performed at baseline and after intravenous (IV) infusion of epinephrine through ear **(Figure 1),** which was used to increase myocardial contractility and heart rate by 20% from baseline. The infusion was then titrated to increase the heart rate by an additional 20%, and MRE was repeated. This process was repeated four or five times depending on the ability of the pig to tolerate increases in heart rate. A gradient echo cine MRE sequence [7,8] was used to obtain single short-axis slice at mid-ventricular level acquiring 5-10 cardiac phases of induced motion depending on the heart rate. The images with the smallest blood pool were assumed to be the E-S image after each infusion of epinephrine. Mechanical waves were introduced into the heart by a pneumatic driver system as shown in **Figure 1.** Imaging parameters included TE/TR= 9.3/12.5 ms; FOV= 35 cm; α= 30°; slice thickness= 8 mm; acquisition matrix= 220x64; phase; receiver bandwidth= ±62.5 kHz; SENSE acceleration factor of 2; mechanical motion frequency= 80 Hz; heart rate= 85-188 bpm; views per segment for R-R interval (VPS)= 4-8; 4 MRE time offsets; and bipolar 6.25-ms duration (160-Hz) 2.3 G/cm motion-encoding gradients (MEG) applied separately in the x, y, and z directions to measure the in-plane and through-plane tissue motion. During the acquisition the mechanical ventilation was stopped to avoid breathing artifacts in the images. The short-axis E-S image for each pig at each infusion was masked with epicardial and endocardial contours to obtain only the LV myocardium as shown in **Figure 2.** The x, y and z components of motion were analyzed to determine the effective myocardial stiffness using a phase gradient (PG) inversion algorithm. Finite element modeling (FEM) was performed on a spherical shell (assuming heart to be sphere) to determine robustness and range of myocardial wall thicknesses that could be used for PG analysis. Stiffness measurements at baseline and at the initial epinephrine infusion were compared using a paired Student's t-test. A least squares linear regression fit was performed between normalized end-systolic myocardial stiffness and the percent increase in heart rate with epinephrine infusion.

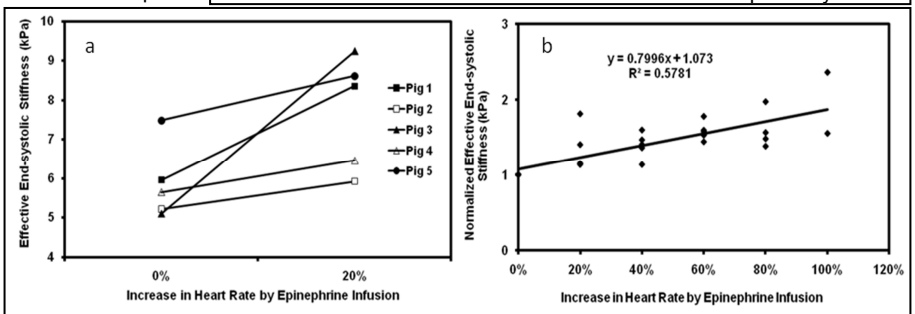

Figure 3. a) Plot of effective end-systolic stiffness versus baseline and 20% increased heart rate during initial infusion of epinephrine. **b)** Plot of normalized effective end-systolic stiffness versus percent increase in heart rate pooled from all the pigs.

Results: FEM results demonstrated that PG inversion provided robust stiffness estimates when thickness of the shell is ~1.5 cm with ±15% error. The myocardial thickness during E-S in our study was ≥ 1.25 cm except for two pigs the thickness was 1.18 and 1.19 cm at baseline. Representative MRE images from pig 1 at baseline and after a 5th infusion of epinephrine are shown in **Figure 2**. Myocardial stiffness significantly increased from baseline to the first infusion in all pigs ($p = 0.047$) (**Figure 3a**), even though systolic and diastolic blood pressure was unchanged or dropped at the initial infusion. This increase corresponds to the expected increase in contractility from activation of β1 receptors at the initial doses of epinephrine. **Figure 3b** shows plot of normalized effective E-S stiffness versus increase in heart rate by epinephrine infusion with a linear correlation of $R^2 = 0.57$.

Discussion: This study demonstrated that E-S MRE-derived effective myocardial stiffness increased with increasing epinephrine infusion, suggesting that MRE-derived effective stiffness may be used as a surrogate for myocardial contractility. However, effective myocardial stiffness increased linearly with epinephrine infusion in 4 of the 5 pigs. While pig 3 showed the expected increase in stiffness with initial doses of epinephrine, the rapid initial increase in stiffness was followed by a plateau, making the linear correlation poor with an R^2 value of 0.1. Pig 3 also required much higher doses of epinephrine than the other pigs to achieve the same increases in heart rate demonstrating physiologic variation when compared to other pigs. In addition, the remaining pigs showed good linear fits with R^2 value ranging from 0.86-0.99, when considered individually. Excluding pig 3 the overall R^2 value was reported to be 0.78 demonstrating good correlation.

References:

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