Assessing Diastolic Function in Mouse Hearts: High-temporal resolution CINE MRI vs. Ultrasound

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TARGET AUDIENCE This abstract is of interest to researchers studying heart failure, diastolic dysfunction, *in vivo* models of myocardial infarction, pre-clinical multi-modality imaging and high-temporal resolution cardiac pulse sequences.

PURPOSE To investigate the performance of high-temporal resolution cardiac MRI for the assessment of diastolic function in mouse models of disease and compare with currently-accepted ultrasound measurements.

INTRODUCTION Cardiac function is widely assessed using quantitative measures of systolic parameters, such as ejection fraction and stroke volume. However, 50% of heart failure patients have preserved systolic cardiac function[1], but present with diastolic dysfunction, meaning that assessment of left ventricular (LV) filling may offer a more sensitive early indicator of a failing heart. Pulsed-wave Doppler ultrasound (US) is routinely used to measure diastolic function in humans and rodents by recording blood flow across the mitral valve[2,3], but is limited by probe positioning, small acoustic window, 1D acquisition, fusion of filling phases and assumptions made between the relationship of blood flow and LV filling. Hence, a more robust method is required. In mice, high-temporal resolution (HTR-) MRI[4,5] offers an alternative volumetric-based method for measuring diastolic function. We present a retrospectively gated HTR-CINE MRI method to measure diastolic function in naïve mice and a mouse model of myocardial infarction, and compare the results to Doppler ultrasound.

METHODS Two studies were conducted: 1) a repeatability study in naïve mice (n = 8). 2) A disease model study in permanently occluded myocardial infarcted mice (n = 14). In both studies, the early- to atrial-filling phase ratio (E/A) was calculated and compared using US and MRI.

Ultrasound: All mice were imaged (24 hours post-surgery) using Doppler ultrasound (Vevo 2100, VisualSonics, CA, USA) to measure mitral inflow in the apical 4 chamber view, from which the ratio of early (E) transmitral velocity and atrial (A) transmitral velocity was calculated.

MR imaging: Immediately after US, mice were scanned on a 9.4T Agilent MRI scanner (Santa Clara, USA). ECG (three-lead subcutaneous electrodes), respiration and RF events were recorded using a datalogger (Power1401, CED, UK). A single-slice retrospectively-gated CINE sequence was developed – simulations showed that a 10 minute acquisition was sufficient for 90 frames per cardiac cycle (TR = 3.1ms, TE = 1.1ms, data matrix = 128^2). For the repeatability study, the naïve mice were imaged again (following animal repositioning) with MRI and then once more using US. For the infarct study, mice were recovered following single MRI and US sessions.

Data Analysis: Retrospective HTR-CINEs were reconstructed offline using custom MATLAB software. Diastolic function was assessed by determination of E/A ratios: 1 < E/A < 1.7 implied normal function, E/A < 1.0 indicated impaired function. MRI-derived E/A ratios were calculated from differentiation of LV volume curves (filling rate). US E/A ratios were determined using manufacturer software.

RESULTS Simulations determined a 10 minute single-slice retrospective HTR-CINE scan sufficiently sampled k-space (>99% lines) for image reconstruction with 90 frames per cardiac cycle, enabling a temporal resolution of 1.1-1.3ms. Figure 1 shows (a) HTR-CINE MRI and (c) US images and corresponding filling rate curves (b,d) showing clear E and A peaks. Bland-Altman analysis (not shown) of the naïve cohort showed that variability in repeat E/A measurements was comparable between MRI and US: SD_{US} = *16.1%* and SD_{MRI} = *16.9%*. Mean E/A values (e) in the naïve cohort showed strong agreement between modalities (MRI_{naive} = *1.42 ± 0.07,* US_{naive} = *1.39 ± 0.10,* $p > 0.05$). In the infarcted cohort, mean E/A values were significantly different between modalities ($MRI_{infarct}$ = *0.94 ± 0.11,* US_{naive} = *1.21 ± 0.11,* $p = 0.04$). Furthermore, MRI showed a significant difference between naïve and infarcted mice ($p = 0.006$), whereas there was no significant difference between US measures ($p > 0.05$).

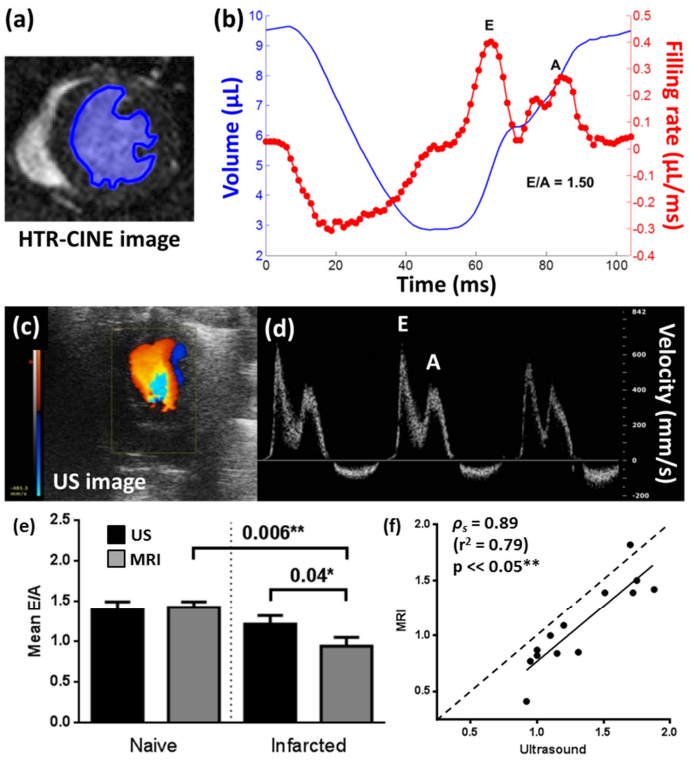

Figure 1: HTR-CINE MRI image showing LV segmentation (blue). (b) MRI-derived LV volume curve (blue) and LV filling rate curve (red). (c) US image showing pulsed wave Doppler ultrasound overlay. (d) US-derived filling rate curves showing transmitral flow velocity. E/A ratio can be used to assess diastolic function in the heart. (e) Mean E/A (+SEM) values across all mice in both the naïve and infarcted cohorts. Significance calculated using Mann-Whitney-U tests. (f) MRI and US showed a strong, significant correlation in the infarct cohort.

DISCUSSION We have developed a robust, reproducible, retrospectively-gated HTR-CINE MRI sequence that can resolve diastolic filling patterns with 1ms resolution. To our knowledge, this is the first study to directly compare HTR MRI with Doppler US for the assessment of diastolic function in mice. HTR-CINE MRI showed a significant correlation with US measurements, however, there was a disparity between US and MRI measures of infarcted mice: US indicated normal heart function (*mean E/A = 1.21*) whereas MRI indicated heart failure (*mean E/A = 0.94*). This may be due to a higher proportion of the diastolic filling peaks merging in the infarcted mice when assessed with US, which were resolvable using MRI. Our results suggest that MRI is more sensitive than US in detecting heart failure in a mouse model of myocardial infarction based on assessment of diastolic function.

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