Cardiac Magnetic Resonance Elastography to Estimate Myocardial Stiffness: Initial Feasibility in a Heart Transplant Patient

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Introduction

Heart failure (HF) is one of the leading causes of death in western world. HF affect over 5 million Americans [1], and comprise the leading cause of hospitalization among Medicare beneficiaries [1] and accounts for $39.2 billion in overall medical costs in the US per year [2]. HF has a poor five-year mortality ~50% [3–5] and has been called "a new epidemic" for the 21st century [6].

Heart transplantation (HT) is the most effective therapeutic option with median survival exceeding 10 years for patients with end-stage HF [7, 8]. However, it is known that early HF accounts up to 20% of perioperative deaths in HT recipients owing to ischemic injury during preservation, pulmonary hypertension and acute rejection [8, 9]. Acute cardiac allograft rejection (AR) reflects the greater risk during the first postoperative year of HT [8]. The highest risk of AR is in the first six months, though it can occur months to years later [10]. Because most patients are asymptomatic, it is important to diagnose and treat acute rejection as early as possible to reverse the process and increase the survival rate.

It is known that inflammation and cell death associated with acute cardiac AR initially leads to myocardial edema and hence increased myocardial stiffness leading to diastolic dysfunction and eventually systolic dysfunction [11, 12]. Currently, endomyocardial biopsy (EMB) is used as a gold standard for diagnosis of cardiac AR [10, 12–17]. EMB is an invasive procedure associated with potentially serious complications such as pneumothorax, tricuspid valve regurgitation as well as vascular or cardiac tissue rupture. Furthermore, it is expensive and has up to 20% of false negative patients [10]. Frequent biopsies should be obtained if an episode of cellular rejection is detected to monitor for reversal of rejection or if the patient has suggestive symptoms. Therefore, there is a need for a technique capable of non-invasively assessing myocardial stiffness, which can avoid the need for EMB.

Magnetic resonance elastography (MRE) is a novel non-invasive imaging technique to estimate stiffness of soft tissues [18–24]. In MRE, cyclic motion is applied to a tissue and a phase-contrast MR image is acquired in which motion-encoding gradients (MEG) are synchronized with the external motion. This produces MRI images of the waves propagating in the tissue. The wave displacements obtained from these images are mathematically converted to stiffness maps.

Previous studies [25-32] have demonstrated application of MRE to estimate *in-vivo* myocardial stiffness. However, to date MRE has not been applied to monitor changes in myocardial stiffness

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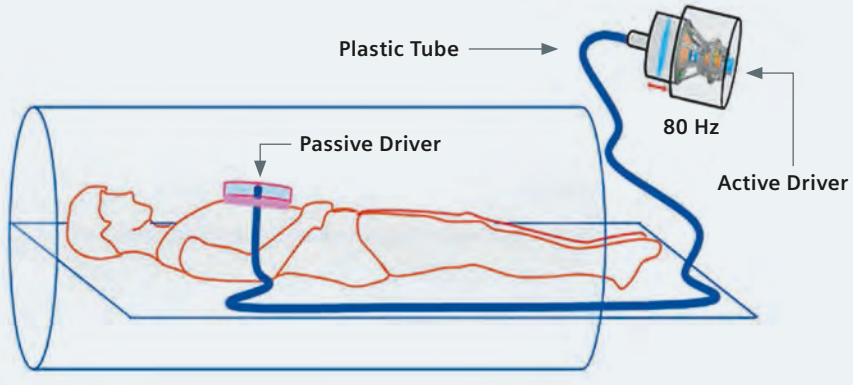


1 Shows the cardiac MRE experimental setup. A passive driver is placed on the chest wall connecting to an acoustic speaker sitting outside scan room using a plastic tube to send 80 Hz mechanical waves into the chest wall to the myocardium.

Table 1: Image acquisition parameters for all sequences performed.

Sequence	b-SSFP Cine	Cine GRE MRE	T2 Prep B-SSFP
Parallel acceleration	GRAPPA rate 2	GRAPPA rate 2	GRAPPA rate 2
Acquisition matrix	256 × 120	256 × 64	192 × 126
FOV (mm)	300 × 400	400 × 400	400
Slice thickness, mm	8	8	8
TR/TE, ms	2.8/1.21	12.5/9.0	3 × R-R/0,24,55
Band width, Hz/pixel	1149	501	930
Flip angle, °	56	25	70
MRE time Offsets	–	4	–
MEG/Excitation frequency, Hz	–	160/80	–
Number of segments	16	16 (+/–)	–
Temporal Resolution(ms)	44.8	200	–

b-SSFP indicates balanced steady state free precession; GRE: gradient echo; MRE: magnetic resonance elastography; MOLLI: Modified Look-Locker inversion recovery; GRAPPA: generalized auto calibrating partially parallel acquisitions; TR: repetition time; TE: echo time, MEG: motion encoding gradients. 16 (+/–) indicates 8 segments for positive MEG and 8 segments for negative MEG for reconstructing a phase contrast image.

*WIP, the product is currently under development and is not for sale in the US and other countries. Its future availability cannot be ensured.

in a HT patient. This study demonstrates the feasibility of applying MRE in a HT patient to monitor changes in myocardial stiffness during first 4 months of post-transplant and correlate to EMB.

Methods

This study was approved by institutional review board. Written informed consent was obtained and documented from the patient. Cardiac MRE was performed in a volunteer (31-year-old male) who underwent HT.

Image acquisition

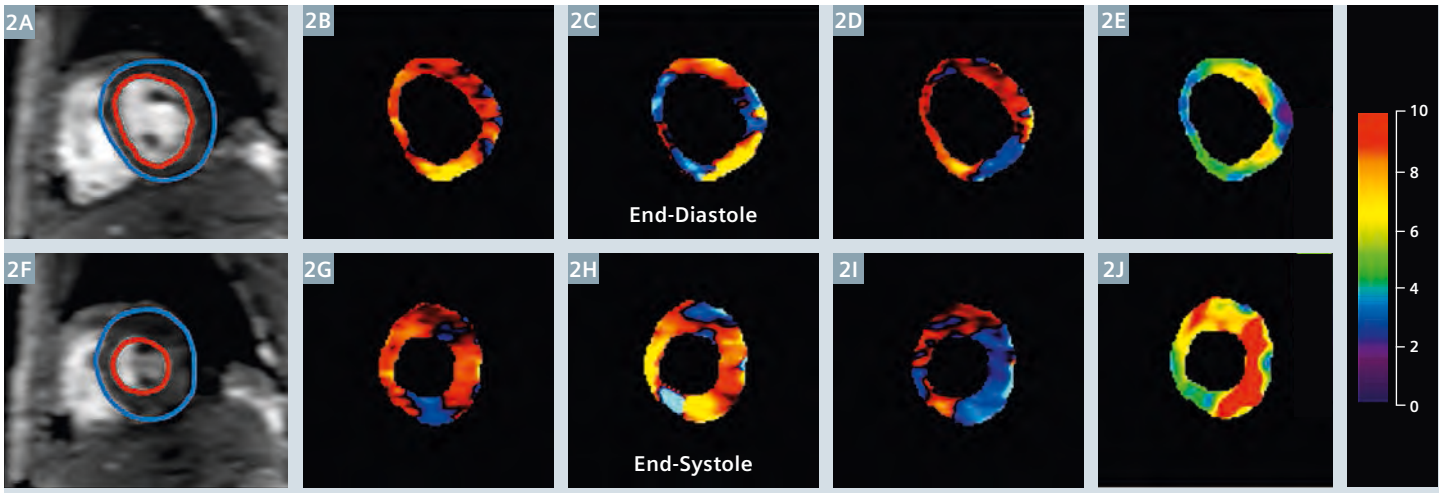
All imaging was performed using a commercially available 1.5T MRI scanner (MAGNETOM Avanto, Siemens Healthcare, Erlangen, Germany) post 8, 9, 10 and 13 weeks of HT. The volunteer was laid in the supine position and placed head first in the scanner. External vibrations were induced into the heart using a pneumatic driver system (Resoundant, Mayo Foundation for Medical Education and Research, Mayo Clinic, Rochester, MN, USA) by placing the passive driver on the chest wall as shown in figure 1. The pneumatic driver system consists of two parts; an acoustic speaker also known as active driver, and a passive driver. The active driver is placed outside the scan room. The passive driver and active driver are connected through a plastic tube to send the 80 Hz vibrations into the heart muscle as shown in figure 1. A cine gradient-echo prospective gated MRE sequence was used to measure the external motion in the myocardium in a single short-axis slice. In the same short axis slice T2-prepared balanced-steady state free precession (b-SSFP) sequence was used to map the T2 values of the myocardium [33]. Similarly, b-SSFP cine imaging was performed covering the entire ventricle to obtain cardiac function parameters. A phased array receive-only coil was used for all acquisitions. All the imaging parameters are shown in Table 1.

Image analysis

Left Ventricular Function: Left ventricular function parameters such as end-diastolic (ED) volume, end-systolic (ES) volume, and ejection fraction (EF) were determined by Simpson's rule using cine b-SSFP images. It was calculated by computer assisted endocardial and epicardial border definition on an advanced Leonardo workstation (Siemens Healthcare, Erlangen, Germany).

Myocardial Stiffness: MRE wave images were masked with left ventricular (LV) epicardial and endocardial contours and analyzed with MRE Lab (Mayo Clinic, Rochester, MN, USA) using local frequency estimation (LFE) algorithm [34]. In LFE, the wave images were filtered using Butterworth band pass filter to remove the longitudinal component of motion and directionally filtered in 8 directions to remove the reflected waves [35]. Then the first harmonic component of the displacement field (x, y, z) was processed to obtain the weighted stiffness map. The mean effective stiffness of the LV myocardium during ES and ED were reported by drawing regions-of-interest (ROI) in the LV short-axis.

T2 Values: T2 values were recorded from quantitative T2 maps by manually drawing ROI in the LV short axis. Care was taken to avoid inclusion of blood pool.



2 An example of cardiac MRE images post 8th week of HT. **(2A, F)** Shows magnitude image during end-diastole and end-systole with red and blue contours delineating LV myocardium. **(2B-D; 2G–H)** Snapshot of wave propagation in all the three directions (x, y, z) during end-diastole and end-systole, respectively. **(2E, J)** MRE-derived weighted effective stiffness map during end-diastole and end-systole. Color bar represents the stiffness values ranging from 0–10 kPa.

Endomyocardial biopsy (EMB): EMB was performed as part of the routine clinical care to determine the AR.

Results and discussion

Volunteer expressed no discomfort during MRI/MRE scans. Table 2 shows ED volume, ES volume, ejection fraction (EF), mean T2 values and mean effective stiffness values at ED and ES in the volunteer during 8, 9, 10, 13 weeks of post HT. All the reported function parameters and T2 values were in the normal range. And also cine b-SSFP images read by an experienced cardiac Radiologist (RDW) indicated normal function.

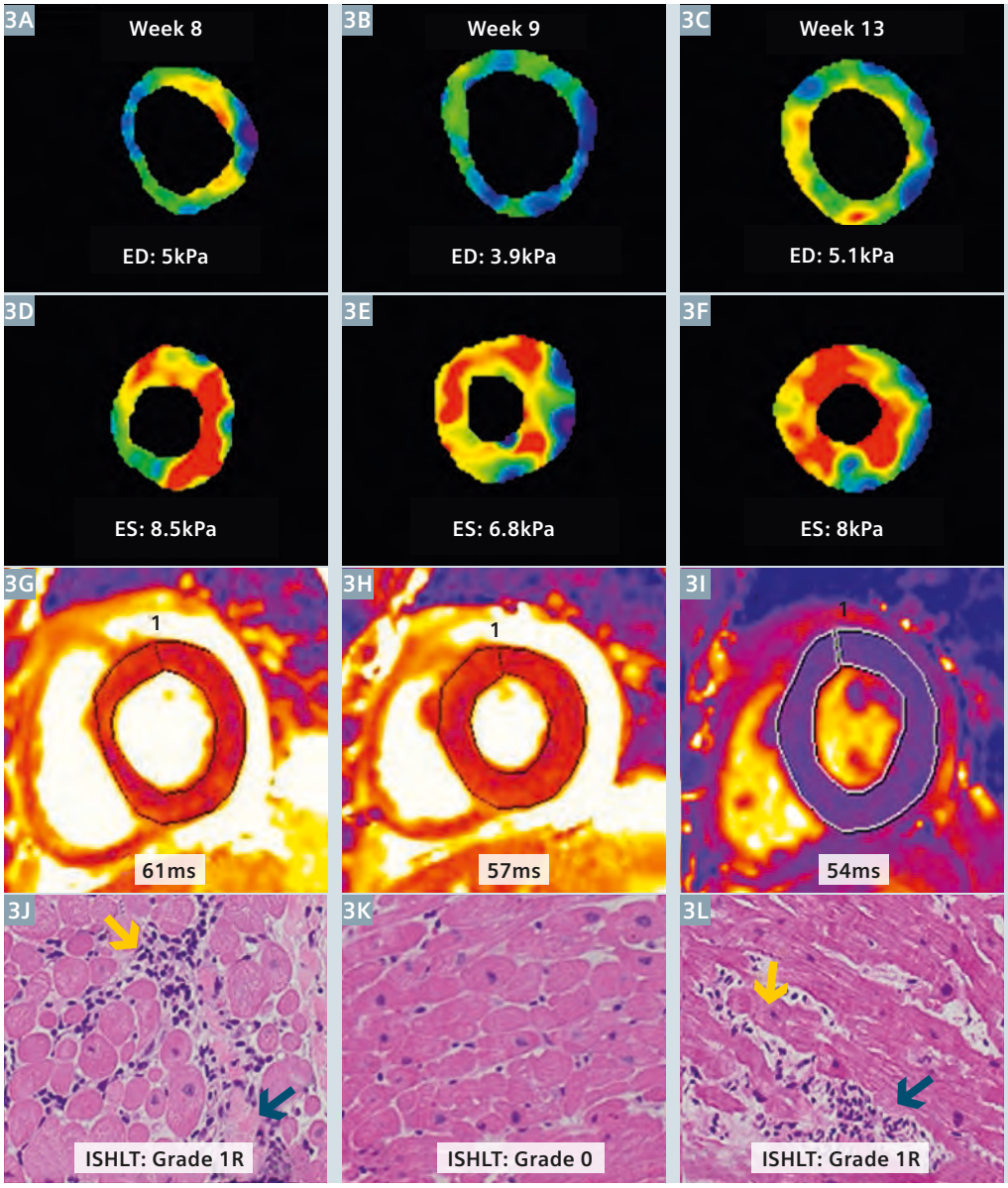
We have observed variation in mean effective stiffness values in ES and ED during 8, 9, 10 and 13 weeks of post HT. Figure 2 shows an example of snap shot of wave propagation (in all directions) and corresponding stiffness maps during ED and ES during 8th week of post HT. Figure 3 shows the stiffness maps (ED, ES), T2 maps and the corresponding EMB images in the volunteer demonstrating the International Society for Heart and Lung Transplant (ISHLT) scores during 8, 9, 13 weeks of post HT. During 8th week of post HT the EMB results indicated ISHLT score of Grade 1R (i.e. moderate focal acute rejection) and the ES and ED stiffness were 8.5 and 5 kPa, respectively. Similarly, during 9th the EMB results indicated ISHLT score of Grade 0 (i.e. no acute rejection) with relatively lower stiffness values at ES (6.8 kPa) and ED (3.9 kPa) when compared to week 8th. In the 10th week, the volunteer experienced serious episodes of tachycardia and was hospitalized and treated, however no EMB was performed. But his MRE-derived effective stiffness at ES was 10.8 kPa and ED was 7.2 kPa, which were relatively higher than the previous weeks. During 13th week, the EMB results indicated ISHLT score of Grade 1R (i.e. moderate focal acute rejection) and his ES and ED stiffness values were 8 kPa and 5.1 kPa, which were similar to week 8th with Grade 1R rejection. Therefore, MRE-derived effective stiffness closely matched/followed the pattern indicated by EMB results.

Table 2: Cardiac function parameters, T2 values and MRE-derived effective stiffness values.

MRI/MRE Imaging Post HT	Week 8	Week 9	Week 10	Week 13
ED Volume (ml)	168	159	161	146
ES Volume (ml)	70	48	67	64
EF (%)	58	70	58	56
T2 values (ms)	58	57	58	54
ES Stiffness (kPa)	8.5	6.8	10.8	8
ED Stiffness (kPa)	5	3.9	7.2	5.1

ED: end-diastole; ES: end-systole; EF: ejection fraction

Previous studies have indicated that inflammation and cell death associated with acute cardiac AR initially leads to myocardial edema and hence increased myocardial stiffness [11, 12]. We have observed changes in the stiffness values but the T2 values (an indicator of myocardial edema) were in normal range (53–61 ms). This indicates that stiffness might provide superior information compared to T2



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Shows the MRE-derived stiffness maps during end-diastole and end-systole in top two rows, T2 maps in the third row and EMB images indicating the cellular rejection (yellow and blue arrows) with ISHLT rejection scores in the last row for weeks 8, 9 and 13.

values in HT patients. However, these results are obtained in only one patient; more patient studies are needed to establish this hypothesis.

In conclusion, this study demonstrated feasibility of performing cardiac MRE in an HT patient. MRE-derived effective stiffness dynamically changed during each week of post HT. These MRE-derived stiffness values also matched to the gold standard EMB based ISHLT scores. However, this is a preliminary case report and more studies are warranted to establish correlation of cardiac MRE-derived stiffness to EMB based ISHLT scores.

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