**Title:** **Magnetic Resonance Elastography of Cardiac Transplant Rejection**

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# Contents

## 1. Objectives

To establish the relationship between the "gold standard" invasive histologic assessment of cardiac transplant rejection (CRT) by direct endomyocardial biopsy (EMB) and noninvasive viscoelastic (i.e. stiffness) assessments for CRT by magnetic resonance elastography (MRE). This will be accomplished by collecting as many MRE data sets as possible that correspond temporally to standard-of-care EMB procedures for statistical comparisons.

## 2. Background

Cardiac transplant rejection is a significant cause of mortality (11% of deaths) during the year post-transplantation[1]. Histology of myocardial tissue is the "gold standard" for CTR surveillance, subjecting patients to repetitive EMB[2]. CTR is typically graded for acute cellular rejection[3]. However, due to: 1. sampling error related to patchiness of CTR; 2. variability in histological interpretations; and 3. non-routine screening for antibody-mediated rejection, biopsy-negative CTR is common ($\leq$ 20%)[4]. Consequently, significant myocardial injury can occur before immunosuppression is intensified. Furthermore, EMB is: 1. invasive (0.5–1.5% complications); 2. expensive; and 3. disliked by patients. These factors hinder needed monitoring, thereby limiting titration of immunosuppressants[2,5]. Thus, non-invasive approaches to evaluating CTR are desired.

The pleuipotentiality of cardiac magnetic resonance (CMR) makes it an excellent candidate. T2-relaxation is most often investigated for detecting CTR because it is directly proportional to myocardial water content/edema[6]. Unfortunately, evidence supporting T2-weighted imaging for CTR is to date inconsistent[7-9]. In addition, late-enhancement CMR has demonstrated insufficient sensitivity to detect the microscopic and diffuse myocyte necrosis associated with CTR[9,10].

MRE is a validated MRI technique for quantitating soft-tissue mechanical properties based on propagation of shear waves during MRI; it is FDA-approved for evaluating liver stiffness related to fibrosis. Use of MRE to quantitatively assess viscoelastic properties of the heart in animals has been reported[11].

## 3. Patient Selection

Entry to this study is open to men and women aged 18 years and older, and to all racial and ethnic subgroups. Up to 15 cardiac transplant patients will be enrolled.

### *3.1 Inclusion Criteria*

3.1.1 Patients must have undergone cardiac transplantation at the Ohio State University Ross Heart Hospital.
3.1.2 Patients must be able to lie flat on their back in the scanner for up to 60 minutes
3.1.3 Patient must be able to hold their breath for up to 15 seconds at a time.

3.2 *Exclusion Criteria*

3.3.1 Patients who are claustrophobic
3.3.2 Patients who are pregnant, due to potential risks to the fetus.
3.3.3 Patients with any unapproved, non-MRI safe metal/devices in their bodies.

## 4. MRE Procedure

MRE is an MRI-based technique. The procedure for performing MRE is much the same as that used for CMR. The main difference is the use of a small, silicone device (passive driver) that is placed on the outside of the chest. The passive driver represents a small drum which transmits sound waves non-invasively through the chest wall into the heart. The passive driver is driven by an active driver that is placed outside the scan room. Sound waves are transmitted from the active driver to the vibrating/humming passive driver via a hollow plastic tube. (See illustration)

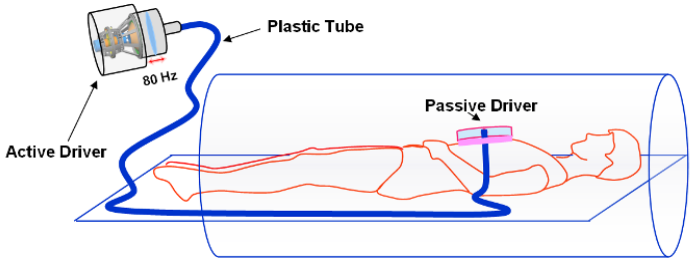


**Figure 1. Non-Invasive MRE Driver Introduces Waves.**

Waves are generated from an active driver placed outside the scan room. The waves propagate through the air within a hollow plastic tube. A passive driver (a drum with thin diaphragm) is placed on the chest wall. Sound waves are non-invasively transmitted through the chest wall into the heart.

The patient will be asked to lie down on the scanner bed. The small passive driver will be placed on the patient's chest and secured with Velcro straps to enhance contact. One end of the plastic tube will be connected to the passive driver; the other end will be connected to the

active driver outside the scan room. Vibrations of frequencies in the range of 20Hz – 2kHz will be produced by the active driver and transferred to the passive driver on the patient's chest, producing mild vibrations/humming. These vibrations produce wave images and are captured by the MRI scanner.

Patients will be able to speak with the imaging technologist while they are in the scanner. They will also be given a small ball they can squeeze should they need urgent assistance at any time during the examination.

MRE is a noninvasive and safe non-radiation-based imaging procedure that does not require the use of oral or IV contrast. Some people may experience claustrophobia (a feeling of being closed in) while in the MRI scanner. The passive component of the driver, which is secured with a Velcro straps, may be uncomfortable to some patients. This study population will have undergone multiple, comprehensive medical examinations prior to transplantation; thus, the risk of scanning a patient with a known contraindication to MRI would be exceedingly unlikely.

## 5. MRE Examination Schedule

Myocardial biopsy is a procedure used to detect CTR and is an important part of routine care after cardiac transplantation. Presently, this is the only method available to detect CTR. The frequency of biopsies is the greatest in the first three months post-transplant. The typical biopsy schedule for cardiac transplant patients is as follows:

Every week over month 1
Every other week over months 2-3
Monthly over months 4-12
Every 3 months over year 2
Every 6 months over years 3-5
Yearly starting in year 6

We will begin imaging (MRE and basic CMR) patients in month 2 (so as to avoid post-surgical affects on the myocardium or pericardium), as soon as they are able to lie on the scanner bed for up to 60 minutes and hold their breath for up to 15 seconds. Imaging will ideally occur within one day before or after the patient's scheduled biopsy, but imaging within 3 days of the EMB is acceptable as long as alteration of CRT treatment (i.e. immunosuppression) has not occurred in the interval. If CRT treatment is modified between the MRE examination and the planned subsequent EMB, the data will not be used in the comparison; if post-EMB treatment changes occur before planned corresponding MRE, the MRE examination will not be performed.

De-identified digital image data on study patients will be stored on a secure password-protected research portion on the OSUWMC Vender Neutral Archival system with administrative rights given only to the Principal Investigator; images will be stored for up to 10 years, consisted with current Department of Radiology practices.

**Incentives**

OSUWMC Ross Heart Hospital has the only adult heart transplant program in Central Ohio. Many patients travel over 100 miles one way to receive medical care at the Ross. Subjects will receive $20.00 in pre-paid gas cards at each MRE appointment to help defray the cost of participating in this trial.

**Adverse Events**

All solid organ transplant recipients suffer from transplant related co-morbidities. For the purpose of this study, we will report only those serious adverse events (SAEs) that are possibly, probably, or definitely related to the MRE procedure.

*6.1 Definition*:

An AE is any unfavorable and unintended (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medical treatment or procedure regardless of whether it is considered related to the medical treatment or procedure (attribution of unrelated, unlikely possible, probable or definite). AEs include toxicities which are related to the disease, to study-related procedures, or to other unknown causes. (International Conference on Harmonisation [ICH] E2A, E6).

AEs (expected or unexpected) include worsening of a pre-existing conditions (increased severity, frequency or duration of the condition and/or associated with significantly worse outcomes) which occur during the specified collection period, whether observed by the investigators or by the patient, and whether or not thought to be related to study procedures.

A SAE is any adverse experience that occurs while participating in a clinical trial that results in any of the following outcomes:

Death
A life-threatening adverse drug experience
Inpatient hospitalization or prolongation of existing hospitalization
A persistent or significant disability/incapacity
Congenital anomaly/birth defect

An unexpected AE is one that is not listed as a known toxicity of the investigational procedure in the protocol, the consent form, the package insert, or the investigator's brochure.

Important medical events that may not result in death, be life-threatening or require hospitalization may be considered an SAE when, based upon medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in the definition. [*CTEP, NCI Guidelines: Expedited Adverse Event Reporting Requirements.* December 2004]

*6.2 Reporting*

SAEs or unexpected AEs related to the MRE procedure will be reported to the IRB within 10 working days. Potential risks and adverse events that may reasonably expected while participating in this trial will be described in the informed consent and do not require prompt reporting. These will be reported in summary form at the time of continuing review.

## 6. Duration of Study

Patients will remain in the study for six months after cardiac transplantation or until they decide to withdraw, or until illness or general or specific changes in their health render them unacceptable for MRI.

## 7. Statistical Considerations

The expected small size of the data will set limits on possibilities for statistical analyses. Comparisons of 2 continuous variables (e.g. myocardial stiffness values vs. CRT grades) will likely rely on regression analyses. Comparisons of a continuous variable (e.g. means of myocardial stiffness values) with a categorical variable (e.g. CRT results warranting immunosuppression vs. CRT results not warranting immunosuppression) will likely rely on t-testing.

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