(RTMPE for CAV) Real Time Myocardial Perfusion Echocardiography for Detection of Coronary Allograft Vasculopathy in Cardiac Transplant Patients

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INTRODUCTION & BACKGROUND

Cardiac allograft vasculopathy (CAV) is an important cause of morbidity and mortality among pediatric and adult transplant recipients.(13-15) Due to the often asymptomatic nature of disease progression serial surveillance is recommended for all cardiac transplant recipients, however current techniques are either invasive and/or lack sensitivity to detect early stages of CAV due to its significant effect on coronary microvasculature. Real time myocardial perfusion echocardiography (RTMPE) is a safe and feasible non-invasive technique commonly used to diagnose coronary disease, and offers an attractive alternative for CAV detection.

The incidence of CAV is approximately 10% at 1 year post-transplant, 30% at 5 years and 50% at 10 years, and it has become one of the leading causes of graft loss and death after the first year.(13) CAV is a diffuse and accelerated fibro-proliferative process that affects both the large epicardial and small intramyocardial allograft coronary arteries (Figure 1).(16) Early detection of CAV is critically important because it allows alterations to medical therapy to slow progression before revascularization is required. Early detection is challenged by the often asymptomatic nature of disease progression, making routine CAV screening the current standard of care for transplant recipients. Invasive coronary angiographic (ICA) imaging is the gold standard for the detection of CAV, but is invasive (and may require a general anesthetic in the pediatric population) and exposes the patient to ionizing radiation, while current noninvasive methods best evaluate the large vessels with limitations for the detection of small vessel disease.

The objectives of this study are to determine the feasibility and diagnostic accuracy of RTMPE to detect CAV in pediatric and adult transplant recipients. We hypothesize that RTMPE is an effective non-invasive method for CAV detection in these populations, and that perfusion deficits will correlate with significant coronary artery stenosis identified by standard stress echocardiography and invasive angiography.

Real-time myocardial perfusion echocardiography (RTMPE) may offer an attractive alternative to ICA for the detection of CAV.(17-20) RTMPE utilizes the intravenous administration of biologically-inert microbubbles to assess myocardial perfusion,(6) and has demonstrated utility for identifying small vessel coronary artery disease.(7) Although contrast echocardiography has found common application for evaluation of coronary artery disease in adult non-transplant recipients,(6) this safe and potentially useful imaging modality remains understudied in CAV with only two small single center studies published in the current literature (Figure 2).(21,22) The contrast medium administered in RTMPE is routinely used without significant side effects in adults (8,23,24) and has been studied in pediatric populations with no adverse effects.(12) The purpose of this study is to evaluate the feasibility and diagnostic utility of RTMPE for the detection of CAV in adult and pediatric transplant recipients from a multicenter experience

Cardiac transplant recipients followed at Mayo Clinic (Rochester, MN) will be included. The study population will be divided into adult and pediatric subgroups. Consenting patients will undergo rest and pharmacologic stress perfusion RTMPE. Results of RTMPE will be correlated with wall motion assessment by standard stress echocardiography and clinically indicated invasive coronary angiography (including intravascular ultrasound findings when available). We expect that RTMPE will be well tolerated and findings of myocardial perfusions defects will correlate with current CAV surveillance techniques. RTMPE may represent a preferred method and new clinical standard for CAV surveillance among adult and pediatric cardiac transplant recipients.
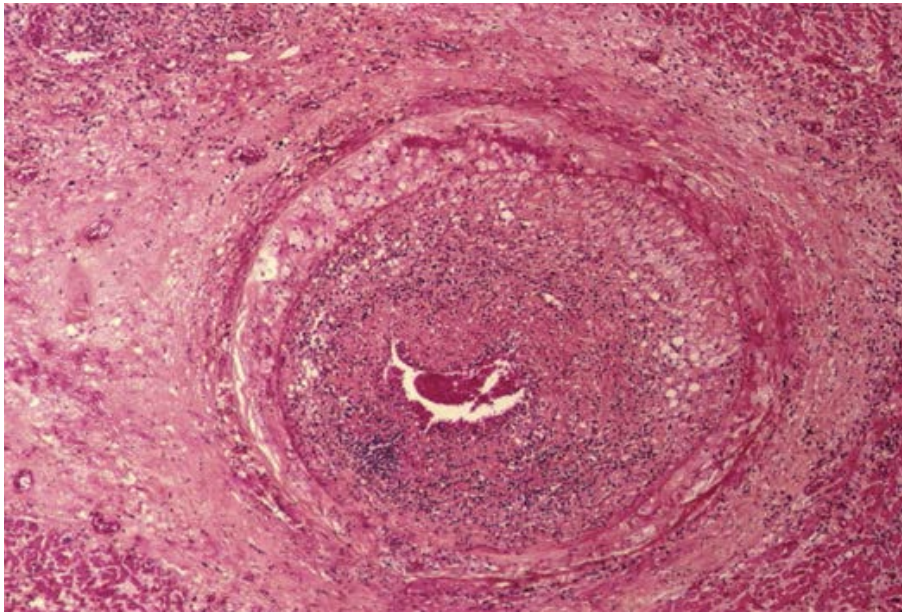

Figure 1. Marked concentric intimal hyperplasia and proliferation associated with cardiac allograft vasculopathy. Pollack et al, JACC CV Img 2013.
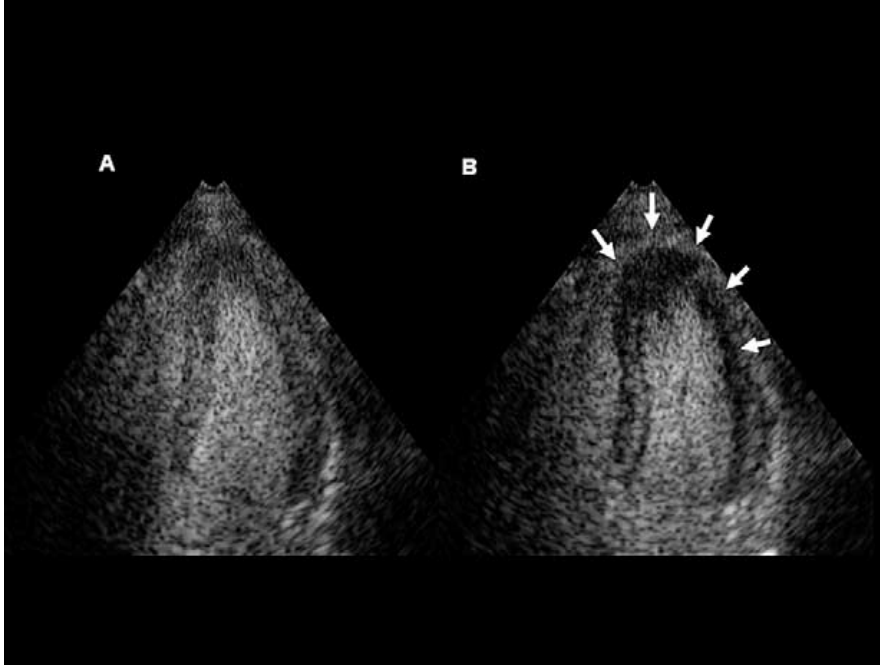
Figure 2. Myocardial contrast echocardiography from the apical 4-chamber view demonstrating an apical and lateral wall perfusion defect (arrows) during peak dobutamine stress (right) compared with normal perfusion at rest (left). Rodriguez et al, JASE 2005.

OBJECTIVES

- To determine the feasibility of real time myocardial perfusion echocardiography (RTMPE) for the detection of coronary allograft vasculopathy (CAV) in pediatric and adult cardiac transplant recipients.
- To determine the diagnostic accuracy of RTMPE for the detection of CAV in pediatric and adult cardiac transplant recipients compared with current standardized methods.

HYPOTHESIS

RTMPE is a feasible and effective non-invasive method to detect significant CAV in pediatric and adult cardiac transplant recipients. Perfusion deficits will correlate with significant coronary artery stenosis identified by standard stress echocardiography and ICA, and may identify diffuse small vessel disease more effectively than current noninvasive techniques.

STUDY DESIGN

This will be a prospective, observational cohort study. The study population will be divided into adult (age ≥18 years-old) and pediatric (age <18 years-old) subgroups, each with a separate

recruitment process and data analysis. Eligible subjects will be screened and recruited through the Transplant Clinic. Consenting patients will undergo rest and dobutamine stress RTMPE at in the echocardiography laboratory using a standardized imaging protocol.(8) Relevant clinical data will be collected from the electronic medical records.

Dobutamine stress echocardiograms will be performed per institutional protocol.

For adults, standard dosing of DEFINITY® (Perflutren Lipid Microsphere) Injectible Suspension ultrasound contrast agent will be used. For each adult, the vial of DEFINITY® contrast will be divided in half (~0.75 mL) and drawn up into two 30 mL syringes pre-filled with 29.25 mL of normal saline. Hand injections of the solution will be performed at baseline, pre-peak, and peak perfusion stages.

For pediatric patients > 60 kg, the standard adult dosing will be used. For pediatric patients under 60 kg, the dose will be 20 microL/kg diluted to the same concentration used in the adult dosing. Hand injections will be performed at baseline, pre-peak, and peak perfusion stages.

INCLUSION CRITERIA
- Cardiac transplant recipients (≥10 months post transplant)
- Clinically followed at Mayo Clinic (Rochester MN)

EXCLUSION CRITERIA
- Standard contraindications to the use of ultrasound contrast and pharmacologic stress (6,25)
- Recent (<3 months) hospitalization for heart failure, acute coronary syndrome or allograft rejection
- Multi-organ transplant
- Known or suspected right-to-left, bi-directional or transient right-to-left cardiac shunts
- Hypersensitivity to perflutren

ENDPOINTS

The primary study endpoint will be presence of a perfusion defect by RTPME. Results of RTMPE will be correlated with wall motion assessment by standard stress echocardiography (available at the time of RTMPE) and with clinically indicated ICA (including intravascular ultrasound findings when available) performed within 3 months of RTMPE. Pediatric cardiac transplant recipients at Mayo Clinic undergo annual or bi-annual surveillance ICA, while adult

cardiac transplant recipients at Mayo Clinic undergo annual surveillance ICA. Grading of ICA (13) and RTMPE (8) will be performed independently by two experienced reviewers in a blinded fashion. Safety and adverse event data for RTMPE will be collected.

SAMPLE SIZE & DATA ANALYSIS

A conservative estimated disease prevalence of 25% among adult transplant recipient and 10% among pediatric transplant recipients is anticipated.(13) For both pediatric and adult patients there are no prior large population studies for estimated diagnostic accuracy of RTMPE for detection of CAV, and so sample size estimates are challenging. A target of 25 adult and 25 pediatric patients for appropriate pilot data will be used. Data will be expressed as the mean $\pm$ standard deviation for continuous variables, and as absolute frequencies or relative percentages for categorical variables. Comparison between groups (with and without CAV by ICA) for continuous variables will be done using analysis of variance, and for categorical variables using χ_2 analysis. Comparison of RTMPE with wall motion stress echocardiography and with ICA will be performed using 2x2 contingency tables on a per patient and per coronary artery territory perfusion defect distribution basis. All comparisons of diagnostic accuracy will be made on the basis of binary outcome data analysis of paired within patient data. All p-values will be 2-sided, and a value of ≤ 0.05 will be considered statistically significant. Data analysis will be performed using statistical software.

Safety Statement: RTMPE utilizes the intravenous administration of chemically- and biologically-inert microbubbles to assess myocardial perfusion, and may demonstrate improved detection of small vessel disease. The ultrasound microbubble contrast medium used in RTMPE is routinely used without significant side effects in adults for other indications. It has been used in children on a case-by-case basis with no recognized safety issues unique to children. However, for the purposes of this study (perfusion), it would be considered off-label for both adults and children.

IMPACT AND FUTURE RESEARCH PLANS AND KNOWLEDGE TRANSLATION

This project in pediatric and adult transplant recipients will provide pilot data to support the development of a larger multicenter study designed to compare the utility of a serial RTMPE strategy for CAV surveillance compared with current standard of care of either ICA or alternate stress imaging modality. Such a study would be longitudinal in nature and have the ability to track changes in RTMPE over time, in addition to comparing sensitivities with alternate CAV surveillance strategies. Such research could lead to important potential knowledge translation

regarding the progression of perfusion deficits mediated by small vessel CAV that are asymptomatic and difficult to detect by alternate imaging modalities, improving understanding of both risk factors for CAV progression and appropriate tailoring of noninvasive surveillance strategies.

PROJECT ASSETS

The study team is highly qualified for this project (see RECENT RELEVANT RESEARCH & EXPERIENCE section). The team includes international experts in the use of contrast echocardiography, RTMPE, as well as the medical directors of the pediatric and adult heart transplant programs and echo labs. The contrast agent will be supplied by industry.

RECENT RELEVANT RESEARCH & EXPERIENCE

Our research group has extensive research experience in fields of cardiac transplant medicine and CAV, as well as RTPME.

Dr. Sharon Mulvagh is an echocardiologist at the Mayo Clinic and widely recognized as an international leader in the field of contrast echocardiography, and has extensively published research in the field of RTMPE.(6-8)

Dr. Sudhir Kushwaha is the Medical Director of the adult Cardiac Transplant Program at Mayo Clinic with extensive research in the field of CAV.(9-11)

Dr. Benjamin Eidem is a pediatric cardiologist at Mayo Clinic and widely recognized as an international leader in the fields of pediatric cardiology and echocardiology, including the use of ultrasound contrast in pediatric patients.(12)

Dr. Jonathan Johnson is a pediatric transplant cardiologist at Mayo Clinic with extensive research in this field.(11)

Dr. Runqing Huang is a PhD research assistant with extensive experience in the use of contrast agents in ultrasound imaging.

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LAY ABSTRACT

Heart transplantation is a life prolonging treatment for patients with severe heart failure. Heart transplant recipients are susceptible to developing a unique disease that causes blockages in the arteries of the transplanted heart (coronary arteries) called coronary allograft vasculopathy (CAV). Because CAV often progresses without symptoms, transplant recipients undergo regular surveillance testing so that CAV can be detected and treatment offered before significant damage to the transplanted heart occurs. Current tests used to detect CAV are either invasive (with risk of complications) or may not be able to detect CAV in its early stages. Myocardial contrast perfusion echocardiography is a safe noninvasive diagnostic test that may be well suited for detecting CAV, however has not been well studied in heart transplant recipients. This study will examine the ability of myocardial contrast perfusion echocardiography to detect CAV in adult and pediatric heart transplant recipients, and compare those results to current standard testing strategies such as invasive coronary angiography and standard stress echocardiography. This will help to determine whether myocardial contrast perfusion echocardiography is a better test for regular surveillance of CAV for adult and pediatric transplant recipients.