

Date: 12 February 2013
Name and degree(s): Michael Wesley Milks, MD
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Pager #: 806-3939
Current Residency Year: HO2

Faculty mentor and co-principal investigator: R. Brandon Stacey, MD
Second co-principal investigator: Bharathi Upadhya, MD
Title of Project: *Right Ventricular Stress Testing Response in Coronary Artery Disease*

Previous research experience (summarize experience below and attach your CV/resume):

An interest in biomedical research began in my undergraduate career at Dartmouth College when I worked with James Gorham, MD, PhD in the field of autoimmune liver disease. My role as an undergraduate research assistant included conducting experiments such as microarray analysis and quantitative RT-PCR to investigate gene expression differences in a mouse model of autoimmune hepatitis based on targeted deletion of the *TGF- β 1* and *IFN- γ* genes. This work resulted in the award of overall winner of the Medical Student Section poster symposium at the American Medical Association Interim Meeting 2007 and a first-author publication in the journal *Liver International* (PMID: 19490417).

A passion for cardiovascular medicine subsequently developed during medical school, and I worked with Richard Gumina, MD, PhD, an interventional cardiologist, to investigate potential cardioprotective techniques based on the purine nucleotide regulatory axis. His laboratory used a transgenic mouse that overexpresses *CD39*, the gene product of which is an enzyme that results in accelerated degradation of ADP and increased production of adenosine. The result is a transgenic animal that is resistant to multiple vascular insults, including oxidant-mediated thrombosis of the carotid artery and myocardial infarction from surgical ligation of the LAD artery. My direct animal work in ischemia-reperfusion injury resulted in several local and regional poster presentations as well as an invited speakership at the Tenth Annual Ohio State University Medical Center Research Day in 2011. A co-primary authorship publication of this work in the *American Journal of Pathology* was released in July, 2012 (PMID: 22613024).

In my time at Wake Forest I have assisted Bryon Rubery, MD in the enrollment of patients for the PRE-DETERMINE: Biologic Markers and Sudden Cardiac Death Study, which is a planned multicenter prospective cohort study of patients with coronary artery disease with left ventricular systolic function *greater* than 35%, individuals who are at risk for sudden cardiac death (SCD) but who do not fulfill criteria for ICD therapy. This investigation is aimed at stratifying patients' SCD risk on parameters *other than* LV systolic function such as genetic polymorphisms or circulating biomarkers.

Statement of career goals including any research plans after residency:

The applicant plans to pursue cardiovascular medicine fellowship training and subsequently a career in academic cardiology following completion of internal medicine residency. Detection of elevated risk for coronary heart disease and cardiac death are of particular interest, as correlated by these current choices in research topics.

Research Plan:

Context

Heart disease has remained the leading cause of death in the United States for over 75 years (9), and detection and treatment of coronary artery disease can be lifesaving. Noninvasive cardiac stress testing focuses almost exclusively on the left ventricle. Whereas the left ventricle (LV) has a robust midwall circumferential muscle layer that is predominantly responsible for contraction and forward systemic blood flow, the thin-walled right ventricle has poorly developed circumferential myocardial fibers and contracts predominantly by longitudinal shortening (6), which, with its location encased about the dynamic LV, renders imaging of the RV difficult. The apex of the right ventricle is supplied by the left anterior descending artery and the majority of the RV is perfused via the right coronary artery. Although detection of perfusion defects of the right ventricle is difficult in the absence of RV hypertrophy, efforts to do so may augment the sensitivity of stress testing to identify some clinically significant LAD or RCA coronary lesions.

Background

The first description of abnormal right ventricular perfusion due to RCA stenosis was by Brachman and colleagues in 1981 (3). They presented two patients in whom stress thallium scintigraphy identified reversible perfusion abnormalities with detection at 40 minutes after injection of radiotracer, rather than the contemporary standard 4 hours used for evaluation of left ventricular perfusion defects (3). In a subsequent case series, Lahiri et al. posited that RV ischemia with exercise is likely only detectable in patients with severely compromised ventricular function (1). Perhaps because of this reasoning, interest in routine detection of RV perfusion defects remained sporadic.

In 1994, Travin and colleagues described a series of 33 patients who underwent low-level exercise technetium 99m sestamibi (SPECT) imaging 6 to 14 days following inferior myocardial infarction (2). They showed that 30% of these patients had an identifiable RV perfusion defect which, in 50% of the subgroup was shown to be reversible (2). Whereas this “proof of principle” was certified, namely that right ventricular ischemia could be effectively detected using standard technologies, the implications for routine clinical cardiovascular care remained nebulous.

Much of the recent focus on imaging the right ventricle has been on the assessment of RV function or development of RV scarring *following* right ventricular myocardial infarction (5) for further prognostication or risk stratification. Indeed, depressed RV ejection fraction (RVEF<40%) predicts poor prognosis, independent of LV ejection fraction and LV infarct size, late after myocardial infarction (8). To date, there has been limited description of the prospective detection of coronary lesions producing reversible RV ischemia.

Cardiac magnetic resonance imaging (cMRI) is now considered the reference standard for functional studies of the right ventricle (6). With cMRI representing improved technology to detect RV ischemia during rest and exercise, the challenges which thus far have limited the usefulness of RV imaging in identification of ischemic coronary artery lesions may be surmounted. The proposed study seeks to determine whether a significant association exists between right ventricular perfusion defects in cMRI stress testing and coronary artery disease.

Objectives

1. To determine whether there is an association between stress-induced right ventricular change in size and distinct coronary artery lesions by measuring right ventricular size changes from stress and rest perfusion cMR images.
2. To determine whether stress-induced perfusion defects in the right ventricle during contrast infusion are associated with certain coronary artery lesions.
3. To determine whether baseline right ventricular systolic function is associated with certain coronary artery lesions.

Hypothesis

Stress-induced right ventricular dimensions, perfusion defects, and/or systolic function are associated with certain coronary artery stenotic lesions.

Study Design

The proposed case-control study has aim to determine if stress-related changes in right ventricular size or right ventricular perfusion defects are associated with coronary artery disease.

Subject selection and recruitment. The subject selection criteria are (1) those patients who underwent cardiac MRI stress testing prior to cardiac catheterization and, (2) had subsequent percutaneous coronary intervention of a single coronary artery. Using the Apollo reporting system, MRI stress test reports will be used to identify individuals with positive stress tests, regardless of prior diagnosis of coronary artery disease or MI. The resulting list will be cross-referenced with the catheterization laboratory database to identify those individuals who also underwent subsequent left heart catheterization and/or percutaneous coronary intervention. A waiver of informed consent has been requested to the institutional review board given that risk of harm to patients is minimal. This is a proposed retrospective study which does not involve any new or additional interventions to the participants. Patient confidentiality will be protected using unique study identifiers on the data collection forms and, following data collection, subject identifying information will be destroyed within one week.

Sample size. Wake Forest Baptist Health has a robust cardiac MR imaging program with adequate study volume to support the proposed investigation. The authors intend to identify 125 total cases, regardless of prior history of coronary artery disease or myocardial infarction, specifically:

- 25 cases with an LAD lesion
- 25 cases with a proximal RCA lesion
- 25 cases with a distal RCA lesion
- 25 cases with a left circumflex lesion
- 25 cases with non-obstructive findings at cardiac catheterization, to serve as control

Measurements. Cardiac MR images will be reviewed on WebPax Cardiac Imaging System for analysis by the resident author and the faculty mentor in a blinded fashion. The contrasted right ventricular size will be measured at the base, mid, and apical areas using perfusion images during stress and resting conditions. The stress and rest perfusion of the right ventricle will be scored using the same nomenclature utilized in assessing left ventricular perfusion. The right

ventricular function will be assessed by measurement of the right ventricular end-diastolic and end-systolic volumes.

Medical history and prior cardiac imaging. Presence or absence of comorbid conditions in each subject will be determined using medical chart review. Comorbid conditions of interest include hypertension, diabetes mellitus, hyperlipidemia, bronchospastic lung disease (COPD or asthma), and peripheral vascular disease: comorbidities will be used as binary variables in statistical analysis when appropriate. Pre-intervention echocardiography reports will be reviewed for RV size, RV function, and pulmonary artery systolic pressure and this information will be correlated with the cardiac MR data obtained.

Proof of coronary lesions. Chart review will be used to obtain cardiac catheterization reports which describe the target coronary lesion in the disease cases, or absence of obstructive coronary stenoses in the control cases.

Statistical Analysis

Results will be analyzed initially using descriptive statistics. Comparison between groups will be done using chi square tests for proportions, and t-tests or ANOVA procedures for continuous variables. Regression analysis will be performed to identify independent outcome predictors and other inferential statistical analysis will be conducted as appropriate.

The authors may conservatively assume an approximate anticipated effect size (Cohen's *d*) of 0.5, that presence of a coronary lesion would produce a detectable RV perfusion defect in a disease case and not in a control case, and a probability level of 0.4 that any RV perfusion defect will be detected in a given study. A sample size of 25 for each coronary lesion would have 84.8% power to detect a difference from control by student's *t*-test.

Literature cited:

- (1) Lahiri A; Carboni GP; Crawley JW; Raftery EB. Reversible ischaemia of right ventricle detected by exercise thallium-201 scintigraphy. *Br Heart J* 1982 September;48(3):260-4.
- (2) Travin MI; Malkin RD; Garber CE; Messinger DE; Cloutier DJ; Heller GV. Prevalence of right ventricular perfusion defects after inferior myocardial infarction assessed by low-level exercise with technetium 99m sestamibi tomographic myocardial imaging. *Am Heart J* 1994 April;127(4 Pt 1):797-804.
- (3) Brachman MB; Rozanski A; Charuzi Y; Maddahi J; Waxman AD; Berman DS. Thallium-201 stress redistribution abnormalities of the right ventricle: a manifestation of proximal right coronary artery stenosis. *Am Heart J* 1981 March;101(3):288-91.
- (4) Lubiszewska B; Gosiewska E; Hoffman P et al. Myocardial perfusion and function of the systemic right ventricle in patients after atrial switch procedure for complete transposition: long-term follow-up. *J Am Coll Cardiol* 2000 October;36(4):1365-70.
- (5) Buechel ERV; Mertens LL. Imaging the right heart: the use of integrated multimodality imaging. *Eur Heart J* 2012; 33:949-960.
- (6) Contini M; Andreini D; Agostoni P. Cardiopulmonary exercise test evidence of isolated right coronary artery disease. *Int J Cardiol* 2006; 113:281-282.
- (7) Makaryus AN; Boxt LM. "Chapter 3: Cardiac MRI." Miller SW, et al., eds. *Cardiac Imaging*, 3rd ed. Philadelphia: Elsevier, 2009.

- (8) Larose E, et al. Right ventricular dysfunction assessed by cardiovascular magnetic resonance imaging predicts poor prognosis late after myocardial infarction. *J Am Coll Cardiol* 2006;48:1969-1976.
- (9) Hoyert DL. 75 years of mortality in the United States, 1935-2010 NCHS data brief, no. 88. Hyattsville, MD: National Center for Health Statistics. 2012.

Budget (if your project requires any supplies or payment for services please describe the costs and the source of funds that will be used to support the project. It is expected that the mentor will provide this support. In the unusual case that additional funds are needed, please explain.)

Only departmental funds will be used for this investigation. No additional funds are needed.

Timeline: The standard time available for Harrison scholars is two research blocks in the HO2 year with additional elective time (1 to 2 months) that can be used for research in the HO3 year. Please describe a brief timeline for your project, indicating when you will accomplish key steps (such as background literature review, finalizing study design, obtaining needed IRB approvals, conducting the research, analyzing the data, and writing your results):

As the applicant is in the HO2 year of residency, the timeline for the proposed Harrison scholarship will be condensed. Generally, fewer whole months will be used as research electives and more work will be conducted outside of structured work time.

Duties by year of study	HO2 Feb-Jun	HO3 Jul-Dec	HO3 Jan-Jun	ACM
To work closely with cardiology faculty mentors to hone measurement technique in reviewing cardiac MR images and expanding literature review	X			
To achieve IRB approval; then, to identify the group of patients meeting inclusion criteria	X			
To collect and record stress cMRI, background characteristic, echocardiographic, and angiographic data of the study population	X	X		
To interpret the resulting data and evaluate their integrity and reliability, considering any relevant biases or conflicts of interest		X	X	
To organize and share data at Internal Medicine Research Day and in the Seminar Series			X	X
To display, summarize, and discuss findings in the form of abstracts and/or publication			X	X
To identify any other potential topics of interest that relate to the current investigation and pursue them appropriately as time allows			X	X

Specific date goals include the following:

IRB approval anticipated (approximate)	March 15, 2013
Completion of data collection	June 1, 2013
Data analysis and summarization (posters, abstracts)	September 1, 2013

Signatures:

Applicant (by signing this application I agree, if selected, to abide by the requirements of the Harrison Scholars program including presentation of research in the IM Resident Research Seminar series and at IM Research Day)

Electronic Signature: MWM

Mentor (by signing this application I agree to mentor the resident on this project and provide the resources needed for successful completion).

Electronic Signature: RBS

Please return completed application **and a current CV** to Kate O'Hara, MD, ACM for Research: cohara@wakehealth.edu. Applications for the 2013-2014 Academic Year are due by **February 21, 2013**.