Progress Report: 12/15/2016

Ischemic Heart Disease, in the absence of obstructive coronary artery disease, is prevalent in women, and constitutes a major risk factor for life-altering adverse cardiovascular events, including myocardial infarction, stroke, and new onset heart failure. Annual mortality rates for women with ischemic heart disease are ten-fold higher than mortality from breast cancer, and the annual cost to the US health care system to care for women with angina/effort intolerance exceeds $162 billion. Despite these alarming statistics, etiology and treatment remain elusive.

Sex-specific research initiatives, including the National Heart, Lung, and Blood Institute Sponsored Women’s Ischemic Syndrome Evaluation study, have established Coronary Microvascular Dysfunction (CMD) as a cardinal feature of ischemic heart disease in women. Emerging evidence suggests that common cardiovascular risk factors (estrogen deficiency, hypertension, dysglycemia) promote a pro-inflammatory and pro-oxidative state, leading to dysregulation of the coronary microvasculature.

Our major new hypothesis is that dysregulation of coronary microvessels triggers functional myocardial ischemia and impairs ventricular relaxation; culminating into diastolic dysfunction.

In Aim 1 of the proposed research, we will establish the relationship between functional myocardial ischemia and diastolic dysfunction in women with coronary microvascular dysfunction. In Aim 2, we will verify that diastolic function is improved by alleviating functional myocardial ischemia with acute treatment with a phosphodiesterase type 5 inhibitor. In the last year, we have made tremendous progress on the aims of this grant.

Progress on Aims 1 and 2:

I was recruited to the University of Texas at Arlington just prior to the beginning of this award (January, 2016). In the past 12 months, I have been able to fully staff my laboratory with a postdoctoral fellow, a PhD student, and 3 Master’s of Science (thesis-based) students.

Shortly after moving to UT Arlington, I obtained IRB approval and an IND-exemption for the use of Tadalafil (Phosphodiesterase type 5 inhibitor) for the proposed studies.

We have also made great progress on transferring the laboratory protocols and experimental set-up to UT Arlington. We have formed tremendous relationships with several key clinical investigators (Dr. Tom Sarma, Cardiologist, University of Texas at Southwestern Medical Center; Dr. Monica Sanghavi, Cardiologist, UTSouthwestern Medical Center; Dr. Vlad Zaha, Cardiologist, UTSouthwestern Medical Center; Dr. Jarett Berry, Cardiologist, UTSouthwestern Medical Center; and Dr. Paul Bhella, Cardiologist, JPS Health Network) and the imaging staff at the Advanced Imaging Research Center. As evidence of our productivity, we have made significant progress on the development of a “diastolic stress test” to induce functional myocardial ischemia in women with coronary microvascular dysfunction (2 separate abstracts already submitted to the annual Experimental Biology meeting). Our preliminary data are shown in the following tables and figures.

Figure 1 illustrates the progress we have made in the development of a “diastolic stress test”. The data, show the utility of using isometric handgrip exercise and the cold pressor test to stimulate the sympathetic nervous system and cause reflex increases in myocardial oxygen demand and alter diastolic function. These promising results show that we can effectively challenge the hearts of our patients with coronary microvascular dysfunction to test the hypothesis that functional myocardial ischemia can trigger diastolic dysfunction (Aim 1).

![Figure 1: Development of a diastolic stress test.](image-url)

- **A**: Young Women vs. Elderly Women
- **B**: Heart Rate (bpm) vs. Systolic Blood Pressure (mmHg)
- **C**: Tadalafil vs. Placebo
- **D**: Heart Rate (bpm) vs. Systolic Blood Pressure (mmHg)
- **E**: Cold Pressor vs. Rest
- **F**: Tadalafil vs. Placebo

In both cases, the sympathetic nervous system is potently stimulated and produces an adverse diastolic ventricular response in a group of elderly females (n = 6), compared to young healthy female controls (n = 5).
Figure 2 illustrates our recent cardiac MRI data, using a novel MR compatible exercise ergometer designed to test the hypothesis in Aim 1 (i.e. does functional myocardial ischemia trigger diastolic dysfunction in women with coronary microvascular dysfunction). The data suggest that we can easily, and reproducibly, simulate activities of daily living (2-5 METS) inside the MRI environment. This is important because the majority of patients with coronary microvascular dysfunction report symptoms during activities of daily living (walking, stair climbing, lifting, etc). With this device, we are confident we can evoke functional myocardial ischemia in our patients (Aim 1). The data also shows that we can reliably measure cardiac hemodynamics and function at a metabolic cost equivalent to that expected when symptoms occur (2-3 METS).

Based on the preliminary evidence presented in Figures 1 and 2, we have been able to apply our protocol advancements to 3 patients with coronary microvascular dysfunction and 4 healthy age-, sex-, and BMI-matched reference controls. The data are very encouraging. With our new “diastolic stress test” procedure, we are showing clear group differences in the left ventricular relaxation pattern in patients compared to controls (Figure 3); which we interpret as evidence of functional myocardial ischemia induced diastolic dysfunction (Aim 1).

Manuscripts Published:
M Bakir, MD Nelson, E Jones, SD Cruz, Q Li, J Wei, PK Mehta, C Shufelt, G Sopko, A Rogatko, CJ Pepine, CN Bairey Merz. Heart failure hospitalizations in women with signs and symptoms of ischemia: A report from the women’s ischemia syndrome evaluation trial. Int J Cardiol. 223: 936-939, 2016.

This publication helps to establish/re-inforce the fundamental hypothesis of this grant, that women with coronary microvascular dysfunction are prone to developing heart failure with preserved ejection fraction – a clinical entity characterized by marked diastolic dysfunction and poor clinical outcomes.

MD Nelson, B Sharif, J Shaw, G Cook-Wiens, J Wei, C Shufelt, PK Mehta, LEJ Thomson, D Berman, RB Thompson, EM Handberg, CJ Pepine, D Li, CN Bairey Merz. Myocardial tissue deformation is reduced in subjects with coronary microvascular dysfunction but not rescued by treatment with Ranolazine. Clinical Cardiology. Accepted 11/23/2016

This publication not only helps to establish our hypothesis that women with coronary microvascular dysfunction often have diastolic dysfunction, but the novel MRI analysis performed in this investigation provides a foundation for the current project to build upon in Aims 1 and 2, using this novel approach during provocative cardiac stress testing in the MRI.

Figure 2. Diastolic stress testing during cardiac magnetic resonance imaging. (A) In 7 men and 7 women (24 ± 4 years of age), we have successfully demonstrated that our new MR compatible exercise device is capable of eliciting enough resistance to simulate activities of daily living (2 – 5 METS or 7 – 17.5 ml O2/kg/min). (B – E) We have successfully piloted this approach inside the MRI environment, showing that we can acquire pristine quality MRI images during dynamic exercise stress.

Figure 3. Functional myocardial ischemia induced diastolic dysfunction in women with coronary microvascular dysfunction. Our preliminary data (n = 3 cases and 4 controls) support our original hypothesis that functional myocardial ischemia, brought about by provocative stress testing, would exacerbate diastolic dysfunction in women with coronary microvascular dysfunction. Here we show the change in early-to-late diastolic strain rate from rest to ischemic handgrip exercise and rest to leg exercise at a metabolic cost equivalent to activities of daily living (2-3 METS).
Abstracts Published/Submitted:


MD Nelson, J Shaw, B Sharif, Galen Cook-Wiens, J Wei, C Shufelt, PJ Mehta, LEJ Thomson, DS Berman, E Handberg, CJ Pepine, RB Thompson, D Li, CN Bairey Merz. Subclinical left ventricular dysfunction in microvascular coronary disease is not altered by late Na channel inhibition: Novel insight from myocardial feature tracking. European Society of Cardiology. 2016 **BEST POSTER PRESENTATION AWARD**

A Al-Badri, CN Bairey Merz, S Landes, EM Handberg, CL Shufelt, PK Mehta, J Wei, MB Minissian, MD Nelson, LEJ Thomson, DS Berman, LJ Shaw, G Cook-Wiens, A Rogatko, CJ Pepine. Typical Angina is associated with greater coronary endothelial and smooth muscle dysfunction but not abnormal vasodilatory reserve: Results from Ranolazine in Coronary Microvascular Dysfunction (RWISE). European Society for Cardiology. 2016

