Impact of Ranolazine on Coronary Microcirculatory Resistance (MICRO Study)

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I. Background:

The coronary microcirculation (CMC) plays an essential and complex role in regulating coronary blood flow and myocardial perfusion. Recent clinical classification of CMC dysfunction by Camici et al includes a heterogeneous group of patients including those with CMC dysfunction without evidence of obstructive epicardial coronary artery disease (CAD) or myocardial disease (Type I); CMC dysfunction in the presence of myocardial diseases such as primary and secondary cardiomyopathies (Type II); CMC dysfunction in the presence of obstructive CAD (Type III) and iatrogenic CMC dysfunction (Type IV) [1]. Unlike epicardial CAD, where the link between ischemia and angiographic coronary anatomy lends a target for therapy, the study and treatment of the disorders of the CMC are still in evolution. However, over the last two decades our understanding of CMC has broadened and our ability to study CMC function has evolved.

Importance of the Coronary Microcirculation: CMC function is adversely effected by various forms of myocardial diseases [2-4] and both endothelial dependant and independent CMC dysfunction can increase long-term risk of adverse cardiovascular events among patients with all types of CMC dysfunction[5, 6].

Assessment of Coronary Microcirculation: In the absence of direct visualization, there are several approaches to indirectly measuring CMC function. Non-invasive tools have included perfusion cardiac MRI, positron emission topography and myocardial contrast echocardiography based measurement of microcirculatory blood flow [7-10]. However, requirements for dedicated software programs, lack of uniform definition of findings and inferior reproducibility strongly limit non-invasive assessment of the CMC. Currently, the gold standard for measuring CMC function involves invasive measurement using Doppler or thermodilution methods to quantify coronary blood flow and vasoreactivity in response to vasoactive stimuli [11, 12]. Historically, the more accurate invasive method of measurement has been limited by complicated protocols which mandate pre-procedural mixing of restricted medications such as acetylcholine; the need to withhold chronic medications and the lack of reproducibility of the measurements obtained.

A simpler and more reproducible method of measuring global coronary microcirculatory resistance has recently been validated[13-16]. The index of microcirculatory resistance (IMR) is based on the premise that at peak hyperemia, variability of resting vascular tone and hemodynamics is reduced to give an accurate assessment of minimum microvascular resistance. It is defined as distal coronary pressure divided by the inverse of the hyperemic mean transit time (a correlate to absolute flow), measured simultaneously using a temperature sensor/ pressure tipped guidewire. Compared to traditional Doppler based coronary flow measurements, IMR is easier to use, allows quantification of blood flow and pressure measurements while reducing the impact of basal flow conditions to provide superior reproducibility and less hemodynamic variability compared to doppler based measurements [15]. An IMR measurement of <20u is associated with normal CMC function.

Treatment of Coronary Microcirculatory Dysfunction: Treatment of patients with CMC dysfunction has focused on reducing atherosclerotic burden and symptom relief. There is a paucity of data evaluating the impact of drug therapy on CMC function. Ranolazine is a late sodium current inhibitor thought to

decrease left ventricular compressive forces resulting in increased myocardial blood flow and improvement in signs and symptoms of angina [17-23]. In a porcine model, Ranolazine was also shown to cause transient increase in epicardial coronary blood flow and decrease in coronary vascular resistance via alpha-1 blockade[24]. Direct impact of Ranolazine on the microcirculation remains unknown. Clinically, among patients with Type I CMC dysfunction (CMC dysfunction in the absence of obstructive CAD or myocardial disease), Ranolazine has been shown to improve symptoms of angina and cardiac MRI based perfusion compared to treatment with placebo [25]. Whether this symptomatic improvement is due to actual improvement in CMC function remains unknown.

II: Specific Aims

1: Does Ranolazine treatment improve CMC function among patients with Type I CMC dysfunction?
2: Is symptomatic improvement in chest pain with Ranolazine related to improved CMC function?

III: Design and Methods

This single center, prospective study is designed as a pilot proposal evaluating the effect of Ranolazine among patients with Type I CMC dysfunction.

Inclusion Criteria:

- Patients with subjective symptoms of ischemia without flow limiting angiographic CAD (<50% epicardial coronary stenosis) and abnormal IMR (>20 U).
    - Definition of ischemia (any one):
        - chest pain with dynamic ischemic ECG changes (t wave inversions or > 1 mm ST depressions
        - Exercise treadmill testing induced chest pain with ≥1 mm of downsloping or flat ST segment depression during exercise or recovery; ≥2 mm of ischemic ST depression at a low workload (stage 2 or less or ≤130 beats/min); early onset (stage 1) or prolonged duration (>5 min) of ST depression; multiple leads (>5) with ST depression
        - Nuclear stress perfusion defect > 10%
        - Stress echocardiogram with stress induced wall motion abnormality

Exclusion Criteria:

- Age < 18 yrs
- Flow Limiting epicardial CAD >50%
- Life expectancy < 6 months
- Recent (<1 week) myocardial infarction or positive biomarkers
- Severe aortic stenosis
- Contraindications to IMR testing including inability to utilize antithrombotic therapy and/or intravenous adenosine
- Contraindications to Ranolazine therapy:
    - -Patients with known hepatic insufficiency, prolonged QT or renal failure (GFR < 60)
    - -use of drugs that inhibit CYP3A such as diltiazem, verapamil, ketoconazole, macrolides and HIV protease inhibitors
    - Pregnancy, breastfeeding
    - Patients taking drugs which prolong QT interval

Study Flow:

Patients meeting entry criteria will undergo detailed history regarding demographics, cardiovascular risk profile, clinical presentation, laboratory analysis and current medical therapy. After enrollment in the study, participants will initiate Ranolazine for 4 weeks. The participant's usual anti-anginal medication

regimen will be continued unchanged throughout study duration. Patients will receive Ranolazine 500 mg orally twice daily for 1 week, and the dose will be increased to 1,000 mg twice daily for an additional 3 weeks if tolerated.
-All participants will complete baseline Seattle Angina Questionnaire (SAQ) and Duke Activity Status Index (DASI).
-1 week: Patients will undergo phone f/u and if tolerated, drug dose will be increased to 1000 mg twice daily.
- 4 weeks: Patients will be scheduled to return for a follow-up cardiac catheterization and IMR at no charge. Patients will be asked to complete SAQ and DASI questionnaires.

Procedures:

Coronary Angiogram and left heart catheterization: Patients will undergo an initial clinically indicated coronary angiogram and left heart catheterization with IMR testing and then undergo post Ranolazine follow-up coronary angiogram and left heart catheterization using standard technique by one of three experienced interventional cardiologists (B.A, M.S or M.R). The study sponsor will pay for the follow –up cardiac catheterization and IMR.

Assessment of Coronary Microvascular Function: Coronary physiologic indexes will be measured in a stenosis free area of the left anterior descending coronary artery when possible, or in the left circumflex artery as a secondary choice. Appropriate coronary guide catheter will be used to engage left main coronary artery. After adequate heparinization, a temperature sensor/ pressure tipped guidewire (Radi pressure wire, St Jude Medical Systems) will be advanced through the guide catheter and placed and secured at least 3 cm distal to guide catheter in the coronary artery and secured. After injecting 3 cc of room temperature normal saline, proximal and distal temperature sensors on guidewire will calculate mean transit time using thermodilution. This is repeated three times to obtain an average baseline transit time. Next, intravenous adenosine (140 µg per kilogram of body weight per minute through a central vein) is used to induce hyperemia. We then inject 3 cc of room temp normal saline and calculate hyperemic transit time. This is performed at 120, 150 and 180 seconds after initiation of intravenous adenosine and averaged to obtain a mean hyperemic transit time. In addition, simultaneous hyperemic pressure gradient is measured in the proximal and distal vessel. Once data is obtained, the following calculations are made:

1: Index of Microvascular Resistance (IMR): IMR is defined as hyperemic distal coronary pressure divided by the inverse of hyperemic mean transit time. IMR is based on the assumption that at peak hyperemia the variability of resting vascular tone and hemodynamics will be eliminated, and the *minimum* microvascular resistance will be achieved. Studies have correlated IMR value <20 to normal microvascular resistance [13, 16, 26].

IV: Data and Analysis

Sample Size: The sample size of 20 patients is not powered for a specific end point as this is a pilot exploratory analysis meant to determine the effect of Ranolazine on IMR. It is our intention to use this data to determine feasibility and power of an appropriately sized multicenter randomized clinical trial.

Feasibility: The historic incidence of CMC dysfunction can vary depending on the patient population being studied. The estimated historical incidence of Type I CMC dysfunction is approximated to be 20-30% [27]. At the University of New Mexico, we anticipate performing approximately 400 cardiac catheterizations for the indication of objective ischemia (as outlined in entry criteria). Of these, we estimate that 50% have non-obstructive CAD. Current data from the IMR patient registry at UNM shows

that approximately 50% of patients with ischemia and non-obstructive CAD have IMR >20 U (mean 26.7 ± 13.1). We conservatively approximate 40 patients per year who meet entry criteria for the study at University of New Mexico.

Data Safety: Data will be monitored by Dr. Abinash Achrekar.

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Primary Endpoint:

1: Relative change in IMR before and after Ranolazine therapy. Mean change between the groups will be analyzed using a paired t test.

Secondary endpoints:

1: Absolute change in SAQ and DASI scores before and after Ranolazine therapy. Mean change between the groups will be analyzed using a paired t test.

2: Compare relative change in IMR among patients with and without symptomatic improvement in angina burden based on SAQ and DASI scores.

V: Scientific Focus

CMC dysfunction continues to be a disease entity with limited therapeutic targets. More recently, therapeutic trials, including those using Ranolazine, have shown improvement in angina burden and myocardial perfusion among patients with CMC dysfunction [25, 28] but no study has evaluated mechanism for this therapeutic effect.

The primary purpose of our study is to obtain pilot data showing mechanistic effect of Ranolazine on microcirculatory resistance. Our project meets the scientific focus put forth and explores a novel diagnostic and therapeutic strategy among patients with coronary microvascular ischemic heart disease. We hope to help elucidate the mechanism of effect of Ranolazine among patients with CMC dysfunction and to correlate invasively measured microvascular resistance with subjective burden of angina. If shown to improve CMC function, Ranolazine would represent a therapeutic strategy among patients with CMC dysfunction and support a larger scale multi-center trial.

VI: Potential Challenges

1: Study Feasibility: There may be two potential limitations to recruitment. One may be due to insufficient patients meeting entry criteria. The true prevalence of Type I CMC dysfunction is speculative. Review of the literature shows a varied rate between 10-30% of patient with chest pain and no epicardial CAD. Buchthal et al. studied 35 women with ischemic chest pain and no flow limiting CAD and found that 20% had abnormal metabolic response to exercise most likely due to CMC dysfunction [27]. We used a similar estimate to calculate annual number of patients who would meet entry criteria for our study. It is conceivable that the true prevalence of Type I CMC dysfunction is lower making feasibility more difficult. I

2: Evidence of true hyperemia: Use of intravenous Adenosine is well validated for the induction of coronary hyperemia. Literature review suggests that mean time to maximal hyperemia using intravenous adenosine is 84±46 seconds (range, 23-125 seconds) and time from discontinuation of infusion to return of coronary flow to basal levels is 145±67 seconds [29]. To ensure standardized IMR measurement under maximal hyperemia, all cases will undergo three measurements at 120 seconds,

150 seconds and 180 seconds after initiation of intravenous adenosine (140 µg per kilogram of body weight per minute through a central vein).

VII: Relevant Contributions

At the University of New Mexico, we have implemented IMR into clinical practice among patients meeting criteria for evaluation of CMC function. Our protocol adheres to meticulous technique and a standardized protocol. In addition to the proposed study, we are currently evaluating the role of CMC dysfunction among patients with ACS and no angiographic culprit. As a clinical fellow, I worked with Dr. Noel Bairey Merz and the WISE study group to develop a protocol for doppler based coronary microvascular testing among women with chest pain and normal coronary arteries at Cedars Sinai Medical Center. In addition, at the University of Vermont, I was an investigator in a pilot project comparing quantitative measures of myocardial blood flow on first-pass CT imaging with microsphere-derived absolute values in an animal model of regional coronary ischemia and hyperemia.

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