

Title: The Effects of Ranolazine on CPET Parameters in Ischemic
Cardiomyopathy Patients (ERIC)

Principle Investigator: Agostino Ingraldi, MD, FACC

Institution: Cardiovascular Institute of the South

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1. Introduction/Background

Coronary heart disease (CHD) is a leading cause of death and disability in developed countries. In 2010 the American Heart Association reported that 17.6 million persons in the United States have CHD, including 8.5 million with MI and 10.2 million with angina pectoris (1) Heart failure is estimated to affect 23 million persons worldwide (2) and has multiple etiologies; however the most common cause of heart failure is ischemia from CHD.

Myocardial ischemia has a number of pathophysiologic effects, the earliest of which is an increase in the intracellular calcium concentration that results in diastolic dysfunction. Intracellular calcium has an affinity for the contractile proteins within the myocardial cells and this coupling result in myocardial stiffening or diastolic dysfunction. Diastolic dysfunction results in impaired cardiac filling or a decrease in preload. This reduction in preload contributes to reductions in cardiac output.

Ranolazine is an anti-myocardial ischemia with a unique mechanism of action and has been shown to reduce angina, nitroglycerine use and increase exercise tolerance. It is approved for use in patients with coronary artery disease (CAD) (3) The drug decreases the late sodium current at the end of depolarization in the cardiac cycle resulting in decreased sodium-calcium overload in the cytoplasm (4) This effect is thought to improve myocardial relaxation during diastole in the ischemic myocardium resulting in improved energy utilization, thereby reducing oxygen demand and decreasing the oxygen supply-demand mismatch during ischemia (5) Improving the oxygen supply-demand mismatch should result in increased myocardial work efficiency, allowing exercise capacity to increase before the onset of symptoms. Improvement in exercise capacity has been suggested in previous trials utilizing treadmill stress testing in which changes were small and primarily, non-quantitative, without objective data that would allow assessment of mechanism of improvement. This proposal is designed to quantitatively address the cardiovascular benefits of Ranolazine in patients with ischemic heart disease with reduced left ventricular function.

Evaluating exercise capacity utilizing a treadmill with the Bruce protocol has significant limitations and it is difficult to quantitative changes in cardiac function. Patients could vary exercise treadmill time (ETT) by holding on to the treadmill rails to a lesser or greater degree. Therefore this method does not estimate unsupported exercise capacity and does not accurately translate into metabolic cost of the work performed at the time the patient stops exercise from symptoms. The ETT does not accurately reflect work capacity or peak VO₂. Cardiopulmonary exercise testing (CPET) measures gas exchange and provides a direct assessment of energy expenditure equivalents of both the aerobic and anaerobic types. It is recognized in the medical literature as the GOLD standard for functional/exercise capacity assessments because it directly measures O₂ uptake and also concurrent CO₂ output from buffering of lactic acid accumulation secondary to anaerobic metabolism during exercise. Specifically, as noted in the next paragraph, the following determinations can be made from each test: 1) peak VO₂: measures the peak transport of O₂ to the tissues when O₂ extraction from the blood is maximal; 2) The anaerobic threshold (AT): measures the sustainable work capacity in units of VO₂; 3) the O₂-pulse measurements at the AT and peak VO₂: estimate stroke volume at those levels of exercise; and 4) the relationship of O₂ uptake to work rate (VO₂/WR): provides information on the ability of the cardiac output to increase appropriately for the work rate increase.

CPET can accurately assess cardiac function and elucidate underlying mechanisms of cardiac dysfunction. It can also be detect improvements in cardiac function more precisely than exercise studies without gas exchange measurements. In ischemia evaluations, the work rate is gradually increased so that the patient's maximum work capacity is reached in approximately 10 minutes. If a patient has underlying CAD, so that the myocardium does not receive the O₂ needed to maintain myocardial contraction at a specific heart rate or double product, that portion of the myocardium that is ischemic will stop contracting normally. The physiological explanation for why the ischemic portion of the myocardium cannot contract is the failure to regenerate the O₂ supported high-energy phosphate needed to maintain myocardial contraction. Thus, myocardial hypokinesia will develop at and above the ischemic threshold during the course of the stress test. This causes stroke volume to decrease while heart rate increases faster relative to VO₂ in partial compensation, presumably stimulated by tissue hypoxia. Reflecting the failure to maintain the cardiac output increase appropriate for the work rate increase is a decrease in VO₂/WR below 10 ml/min/watt, the normal slope below the ischemic threshold, as described by Belardinelli et al. (6), Contini et al (7), Klainman et al (8), and Itoh et al (9) From the Fick principle [VO₂ = HR X SV X C(a-v)O₂], where HR = heart rate, SV = stroke volume, and C(a-v)O₂ = O₂ content difference between arterial and mixed venous blood, and the O₂-pulse = VO₂/HR = SV X C(a-v)O₂. Failure for cardiac output to increase appropriately can be seen by the decreasing rate of rise in VO₂ relative to work rate increase.

Reflecting the tissue hypoxia brought on by the myocardial ischemia is the maintained steep rise in VCO_2 arising out of HCO_3^- buffering of the newly formed lactic acid. Since the onset of myocardial ischemia and hypokinesia results in a decrease in stroke volume at the ischemic threshold, a low and flattened O_2 -pulse, or a decreasing rather than the normally increasing O_2 -pulse, can be identified. Furthermore, immediately following peak exercise in the patient with myocardial ischemia, the O_2 -pulse often increases in the immediate recovery period, reflecting an increase in stroke volume due to the abrupt decrease in after-load of the heart when systolic pressure, heart rate and double product decrease at the start of recovery. This post-exercise increase in O_2 -pulse is not seen in normal subjects. Two clinical trials have shown that the sensitivity of CPET to detect exercise induced ischemia by the above criteria is in the mid to upper 80% range (6,9). The technique can also be used to demonstrate physiological improvement after therapy (7,8). In patients with a definable ischemic threshold demonstrated by a flattening of the VO_2/WR relationship, treatment with Ranolazine, if it improves myocardial blood flow and/or decreases the myocardial O_2 requirement, might: 1) increase the work rate and VO_2 at which VO_2/WR becomes abnormally shallow 2) reduce the flattening of VO_2/WR , increasing it toward the normal 10 ml/min/watt; 3) increase the peak O_2 -pulse and 4) increase the heart rate and work rate at which the O_2 -pulse reaches its maximum. If Ranolazine improves diastolic relaxation and thereby improves cardiac output during exercise, CPET should reveal an increase in peak O_2 -pulse in proportion to the increase in peak stroke volume. This will likely translate into improved cardiac outcomes in this patient population.

2. Hypothesis

This is a proof of concept trial using Ranolazine in patients with known CAD and reduced left ventricular function, $EF \leq 40\%$. We propose that Ranolazine therapy will result in demonstrative improvements in cardiac function that can be objectively assessed using the parameters measured with CPET. We propose that demonstrative improvement in CPET parameters on Ranolazine will translate into improved patient outcomes for this patient population.

3. Study Design

Selected patients will undergo a CPET evaluation. Beta Blockers will be held day prior to and day of CPET. The initial CPET will identify patients with underlying ischemia and serve as a baseline study. Patients whose CPET results meet the criteria for ischemia will be started on Ranexa 500mg BID and advanced within one week +/- 4 days to 1000mg BID. A second CPET will be performed after 4 weeks +/- 4 days of maximum therapy. CPET results before and after therapy will undergo a statistical comparison. The initial off treatment CPET measurement will serve as the control to assess changes found during therapy. No medication changes or revascularization procedures will occur during the study.

If patients require and undergo a medication change or a revascularization procedure, they will be excluded from the study.

Patients will be contacted at the completion of week one prior to up titration, then at the end of week two to ensure tolerance and compliance with the 1000mg BID dose. Patients will perform the second CPET study at week four +/- 1 week. The trial medication will be assessed and counted to ensure that patients have taken their allotted pill count for the duration of the study. Patients who are found to be noncompliant will be excluded from the study.

4. Endpoints

Endpoints will include changes in CPET parameters, cardiac output and stroke volume. Additional endpoints will include changes in quality of life scores (QOL) as measured Seattle Angina Cardiomyopathy Questionnaire. ST-segment will be assessed for changes and the timing of onset.

5. Study Population

Up to Fifty patients will be enrolled in the trial. Patient will be selected by chart review and physician recommendation.

Inclusion Criteria

1. Patients \geq 18 years of age will be enrolled in the trial.
2. Stable patients without hospitalizations, medication changes or cardiac intervention within two weeks of the study will be enrolled.
3. Patients must be able to complete the CPET protocol and must have demonstrable ischemia on the initial CPET evaluation.
4. Patients must have a documented ejection fraction \leq 40%
 - a. L V function can be assessed via:
 - i. Echocardiogram
 - ii. MUGA or Nuclear Perfusion Scan
 - iii. Left ventriculogram
5. Patients must be Ranexa naive and without contraindication for Ranexa Therapy.

Exclusion Criteria

1. QTc > 500 msec on resting EKG
2. Chirosis of the Liver
3. Have received prior treatment with ranolazine

4. Treatment with potent CYP3A inhibitors and, HIV protease inhibitors or consumption of more than eight ounces of grapefruit juice or grapefruit juice containing products
5. Have participated in another trial of an investigational device or drug within 30 days of screening
6. Have end stage renal disease requiring dialysis
7. Have any chronic illness likely to affect compliance with the protocol
8. Have second or third degree atrioventricular block in the absence of a functioning ventricular pacemaker
9. Have uncontrolled clinically significant cardiac arrhythmias, or a history of ventricular fibrillation, torsade de pointes, or other life-threatening ventricular arrhythmias
10. Uncontrolled HTN defined as BP \geq 160/100 mm Hg at three consecutive visits.

6. Informed Consent

All study subjects must provide written informed consent using the applicable IRB approved informed consent form. Each patient must receive a copy of his/her signed consent form. The original signed consent document must be kept on file at the investigative site. The study must be explained in a language that is understandable to the patient and he/she must be allowed sufficient time to decide whether to participate in this study. All subjects will be assured that they have the right to withdraw from the study at any time during the course of the protocol and this decision will not influence his/her relationship with the lead investigator, the treating physician and/or the study staff.

7. Monitoring and Reporting of Adverse Reaction

It will be the responsibility of the research site to monitor all adverse events (AE). Information regarding all reportable AE's will be reported in accordance to IRB reporting guidelines.

8. Institutions Review Board

A copy of the protocol and HIPAA waiver must be submitted to the institution's IRB for written approval. No recruitment/activities will occur until such IRB approval had been granted in writing. The Cardiovascular Institute of the South must receive a copy of the written IRB approval of the protocol before the study is initiated.

The site investigator must submit and, where necessary, obtain IRB approval for all protocol amendments. The investigator must notify the IRB of protocol violations.

9. Record Retention

The site will retain all source documentation that support the data collected on the study patients in compliance with ICH/GCP guidelines. Documents must be retained for at least 2 years after the study completion. The investigator must accept responsibility for ensuring that study documents are not damaged or destroyed. Each patient's study data will be collected and will be securely stored in the site's offices. Patients will be identified using a study identification number. Patient information will be de-identified for data analysis.

10. Study Finances

This study is financed through an unrestricted grant by Gilead, Inc. 333 Lakeside Drive Foster City, CA 94404 USA.

11. Payment

The patients do not receive any payment to be part of the study. Otherwise, they will receive standard medical care, except for what is stipulated in the protocol.

12. Study Medication

Ranolazine is FDA approved for the treatment of chronic Angina. It may be taken with or without meals. Swallow tablets whole, do not crush, break, or chew. Ranolazine tablets should be stored at room temperature between 59°-86°F (15°-30°C). Possible serious side effects are QT prolongation. Most common side effects are dizziness, headache, constipation, and nausea.

13. Study Duration

Total anticipated length of individual's participation: Approximately 8 weeks.

14. Endpoints

Endpoints will include changes in CPET parameters, cardiac output and stroke volume. Additional endpoints will include changes in quality of life scores (QOL) as measured Seattle Angina Cardiomyopathy Questionnaires. ST segment changes and the timing of onset will be assessed.

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