Rate Adaptive Pacing in the Resynchronized Heart Failure Population

IRB Proposal

Luis Garcia, MD

4/12/10

A. Study Purpose and Rationale

The presence of Chronotropic Incompetence (CI), defined as the inability to increase heart rate in the setting of physiologic demand, has been established as a strong correlate of impaired exercise capacity and as an independent predictor of mortality and cardiovascular morbidity in various populations including patients referred for stress test evaluation(including patients on Beta blocker therapy), those with positive nuclear stress defects, and those with known coronary artery disease[1-5].

In the heart failure (HF) population, the prevalence of CI ranges from 30-70% and its presence also has been associated with functional exercise impairment in patients with systolic and diastolic dysfunction [5,6,7,8].

Restoring chronotropic competence using permanent pacemakers(in the non HF population) has been shown to improve cardiac output during exercise and consequently CI is Class 1 indication for pacemaker therapy . However, in the HF population, prevailing paradigms on the beneficial effects of lower heart rates following beta blockade as well as adverse outcomes in the setting of empiric pacing therapy[9] have rendered consideration of CI as a therapeutic target a controversial proposition.

In the HF population, Cardiac Resynchronization Therapy (Biventricular pacemakers which pace both ventricles) is a common therapeutic modality which has been shown to decrease cardiovascular morbidity and mortality and currently over 120,000 patients have received CRT implanted in the last 4 years[9,10].

Currently CRT devices are capable of delivering RAP however studies exploring improvement of exercise capacity have been minimal.

In a study byTse and colleagues, the acute affects of RAP in a CI (defined mean predicted heart rate <85%) CRT population were evaluated using during cardio pulmonary exercise testing(CPET)[7]. In a post hoc analysis patients with mean predicted hear rate(MPHR) <70% who received RAP improved their exercise tolerance (peak oxygen consumption) significantly. However, it is unknown if functional impairment will continue to improve with permanent programming of RAP.

Accordingly, we will prospectively examine the short and long term impact of RAP on exercise tolerance in the CRT population.

B. Study Design and Statistical Analysis

i. Study Aim- The study will evaluate the impact of acute and chronic rate adaptive pacing on exercise performance in a chronotropically incompetent heart failure population receiving CRT.

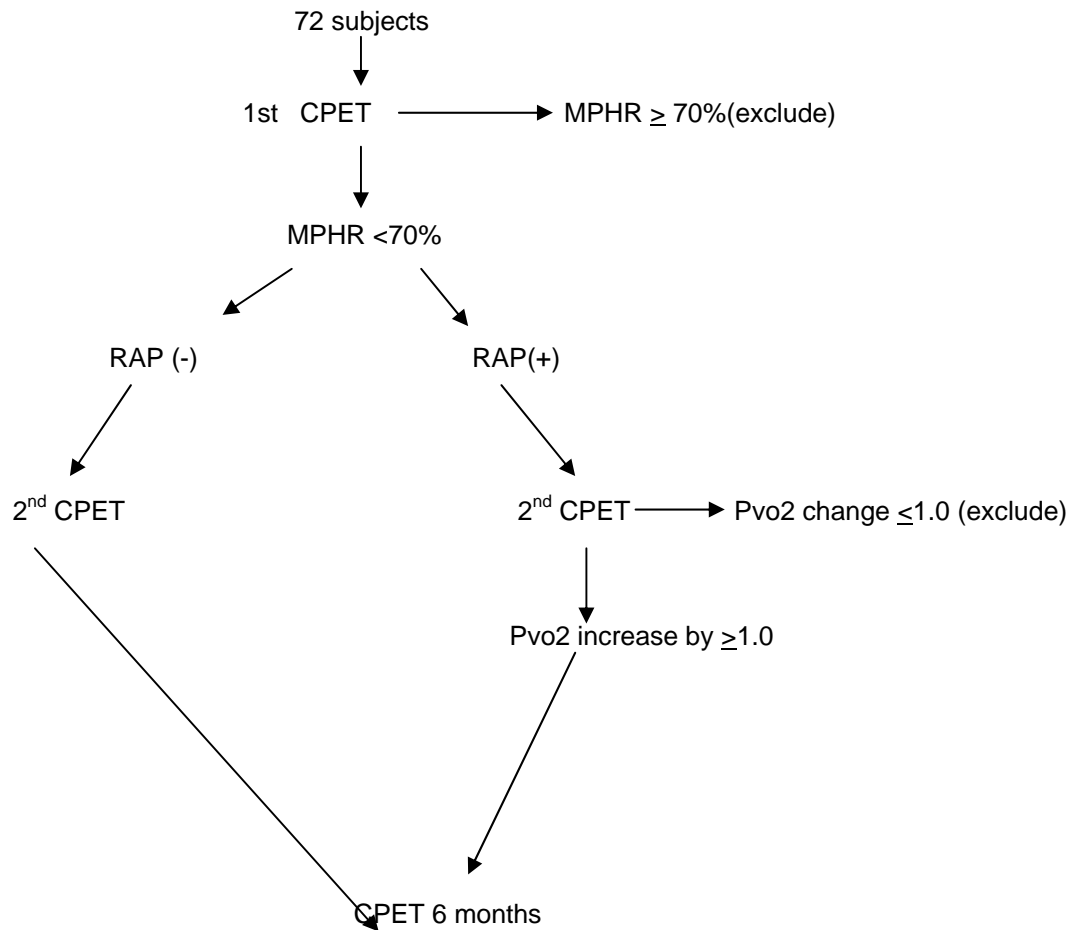 **ii. Study Design**- Randomized double blind single center study

iii. Study Arms-

1. Rate adaptive pacing arm,   **RAP(+)**
2. Non rate adaptive pacing arm, **RAP (-)**

iv. Study entrance and Randomization-

All eligible Subjects will undergo a CPET. CI will be defined as 70% of MPHR (220-age). Subjects determined to have CI <70% will be randomized to RAP(+) or RAP(-).Subjects with a MPHR >70% will be excluded.

A second CPET will be performed after programming to ensure the new pacemaker settings will be tolerated, the subjects randomized to RAP (-) will have no changes to the settings.   If subjects randomized to the RAP (+) do not increase pVo2 by 1.0 ml/kg/min they will be excluded.

72 subjects

1st CPET ⟶ MPHR ≥ 70%(exclude)

MPHR <70%

RAP (-)   RAP(+)

2nd CPET 2nd CPET ⟶ Pvo2 change ≤1.0 (exclude)

Pvo2 increase by ≥1.0

CPET 6 months

v. Primary outcome-

    1. Improvement of peak oxygen consumption **(pVO2)** of 1ml/kg/min during RAP at 6months

vi. Secondary outcomes

    1. Improvement of oxygen consumption at anaerobic threshold of 1ml/kg/min (sub maximal exercise) at 6 months

vi. Statistical analysis

Sample Size – Using the unpaired t-test and a power of 80% and an alpha of 0.05, a mean difference of pVO2 of 2.5 ml/kg/min and SD of 0.5 between arms, results in approximately 6 subjects needed in each arm.

However, the prevalence of a MPHR <70% is approximately 33% of the heart failure population, attrition is possible, and PVO2 may not improve during RAP(18% of subjects in Tse study did not improve). Accounting for these factors, a target of 12 subjects per arm will be set and 72 subjects will undergo CPET for eligibility for randomization.

The continuous variables of pVO2 and VO2 at anaerobic threshold will be analyzed using the unpaired Student's t-test.

C. Study Procedure.

Upon enrollment all patients will undergo a symptom limited Cardiopulmonary Exercise Test (CPET), Naughton protocol, which is not routinely indicated in clinical management unless patients are undergoing heart transplant evaluation. This test is typically performed on a treadmill or bike, and a graded exercise protocol is performed. The subjects' expiratory Oxygen and Carbon dioxide content is measured with an oral mouth piece. Patients will be monitored by a physician with ecg recording at all times. No pain or discomfort is expected, however patients may feel shortness of breath. The entire exercise time is variable and may be as short as 2 minutes and may be as long as 12-13minutes.

The CPET will be completed if:

1. The subject requests to stop the test for any reason, or

2. The patient completes the protocol

The mean predicted heart rate (MPHR), (220- age) will be calculated for each subject. Subjects who are unable to attain 70% of MPHR will be categorized as having Chronotropic Incompetence (CI). This population will be randomized to Rate Adaptive Pacing, RAP (+) arm, or the control arm which will have no RAP (-).

In the RAP (+) arm the device will be set to a target HR of 85% of MPHR. A predetermined slope of HR acceleration based on the device's ability to sense physical exertion will be programmed.

All subjects will undergo a second CPET (no earlier than 2 hours and within 24 hours) assessing for tolerance of new programming. If subjects are unable to tolerate their programming or peak Vo2 does not increase by 1ml/kg/min, they will be excluded from the study and RAP will be turned off

At 6 months subjects will undergo a third CPET. After the third CPET RAP(+) control arm will be programmed off. Estimated participation time would be approximately 8- 9 months

D. Study Drugs

NA

E. Medical Device.

CRT, specifically Biventricular devices with an atrial lead are commercially available from a number of different device manufacturers. Implantation is indicated in HF patients, who are receiving optimal medical therapy and have QRS >120ms. CRT has been found to reduce mortality, heart failure hospitalizations and induce beneficial cardiac remodeling (REFERENCE). The patients will have a preexisting indication for these devices to enter the trial. RAP is a programming feature of the device and no additional surgery or procedure is needed to deliver this therapy.

F. Study Questionnaires

NA

G. Study Subjects

i. Inclusion Criteria:

1. Age 21-75 years old
2. CRT implantation within in last 3-6 months

3. Receiving beta blocker and Ace-Inhibitor therapy with no change in dosing over last 3 months

ii. Exclusion criteria

1. Heart failure hospitalization or myocardial infarction in the last 2 months,

2. Percutaneous coronary intervention or heart surgery in the last 3 months

3. COPD requiring pharmaceutical and or oxygen therapy

4. Permanent atrial fibrillation or atrial fibrillation at the time of the CPET

5. Unable to complete CPET for any reason

H. Recruitment of Subjects

Subjects will be recruited by referral from CUMC cardiology, electrophysiology and heart failure clinics

and will be recruited after CRT is determined to be warranted.

I. Confidentiality of Study Data

All date will be uniquely coded and all information will be stored in secure location available only to the

investigators.

J. Potential Conflict of Interest

No conflicts of interest to report

K. Location of the Study

The study will take place at the CUMC Cardiopulmonary Exercise Laboratory

L. Potential Risks

Elevation of heart rate in the setting of normal daily activities and/or exercise may potentiate shortness of breath or chest discomfort. It is possible this may result in worsening heart failure, myocardial infarction or death.

The study participant may be randomized to the RAP (+) and this treatment may decrease exercise tolerance.

M. Potential Benefits

The participant may attain an improved exercise tolerance.

N. Alternative Therapies

Currently there are no other pacing therapies available.

0. Compensation to Subjects

All CPET will be provided free of charge to all of the subjects. No other compensation will be provided.

P. Costs to Subjects

There will be no cost to the subjects.

Q. Minors as Research Subjects

No minors will be enrolled in the trial; earliest age of enrollment will be 21 years of age

R. Radiation or Radioactive Substances

Radiation therapy is not part of the trial design.

S. References

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