Exercise Physiology in Systolic and Diastolic Heart Failure: A Matched, Cohort Analysis of Cardiopulmonary Exercise Testing Variables in Patients Stratified by Left Ventricular Ejection Fraction

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A. Study Purpose and Rationale

Recent investigations into congestive heart failure have demonstrated that a rational way to subgroup patients with this condition is into those with low left ventricular ejection fractions (systolic heart failure) and those with normal ejection fractions (so-called diastolic heart failure).[1] Whereas the pathophysiology of systolic heart failure (SHF) has been well-defined and targeted therapies have been developed, much less is known about the mechanisms underlying diastolic heart failure (DHF). One method used to understand and demonstrate physiologic derangements in heart failure is cardiopulmonary exercise testing (CPXT). In CPXT, multiple physiologic parameters are measured as a patient performs a graded exercise protocol on a treadmill. Specifically, the parameter of peak oxygen consumption (VO2max) has been shown to correlate with the severity of heart failure symptoms and predicts patient mortality. [2]

The Fick Principle states that VO2max can be related to other variables via the following equation:

VO2max = SVmax * HRmax *13.6*Hgb*(Sa02max-SvO2min),

where SV=stroke volume, HR=heart rate, Hgb=serum hemoglobin concentration, SaO2 =arterial oxygen saturation, and Sv02=mixed venous oxygen saturation.

In SHF, all of the variables on the right side of the above equation are abnormal compared to healthy controls. SVmax and IiRmax are low secondary to impaired response to adrenergic stimuli and impaired contractility[3]. Hgb is low in many SHF patients, perhaps secondary to renal hypoperfusion and decreased erythropoietin production[4]. SaO2max is lower than normals secondary to ventilation/perfusion mismatch in the lungs[5], while SvO2max is higher than expected owing to the inability of the skeletal muscle to efficiently extract oxygen from the bloodstream[6]. Abnormalities in these variables nicely demonstrate multiple different derangements of normal physiology exhibited by SHF patients.

Recently, data has emerged from the first study looking at exercise physiology in more than a handful of DIM patients.[7] This work, comparing 363 SHF patients to 46 patients with heart failure and a normal ejection fraction found that VO2max does have prognostic power in DHF, while VO2 max was significantly higher in the DIM group (18.4+/-6.8m1/kg*min vs. 16.1+/-5.5m1/kg*min, $p<0.01$). This suggests that abnormalities in exercise physiology are less severe in DBE patients compared to those with SHF. However, there are several limitations of this data set: the SHF and DEW groups were not clearly shown to have similar severity of heart failure symptoms at baseline, the DHF group was small, and only 12% of the DHF group were female (compared to >50% in most contemporary registries of DHF patients). Furthermore, no one has yet looked at the variables on the right side of the VO2 equation in DHF patients. Such data could better characterize the differences in exercise physiology between SHF and DHF patients.

The purpose of the present study is to compare variables of exercise physiology in matched cohorts of SHF and DIM patients. VO2max will be measured as the primary outcome, to determine if a significant difference exits between the two groups when disease severity is controlled for and a

representative sample of SHF and DHF patients are studied. Furthermore, all of the variables on the right side of the Fick equation will be measured or calculated and serve as secondary outcomes. If more can be learned about the mechanisms of abnormal exercise physiology in DHF patients, there is the potential to generate hypotheses with regard to potential targeted therapies for this patient population.

B. Study Design and Statistical Analysis

This study is designed as a matched-pair cohort study of exercise physiology in ambulatory SHF and DI* patients. All study participants must meet the standard Framingham definition of congestive heart failure.[8] A transthoracic echocardiogram will be performed on all patients referred for consideration. Those with a calculated left ventricular ejection fraction >50% will be eligible for the DHF group, while those with LVEF <50% eligible for the SHF group. Exclusion criteria for this study are described in section G. Final participants in the study will be selected from the pool of eligible patients as matched pairs. DHF and SHF subjects will be matched 1:1 by gender, age (+/3 years), body mass index (+/- 2 kg/m^2), and NYHA Class. NYHA class will be determined by a 7 question questionnaire -- the results of which were recently validated and shown to correlate with VO2max. [9]

Power analysis was performed using the data from Guazzi et al which found an absolute difference in VO2 of 2.3 ml/kg*min between the two groups with a standard deviation of 6.8 in the DHF group. This study is designed to have 80% power to detect a difference in VO2max of 2.3m1/kg*min between the groups given an alpha of 0.05. The calculation is as follows:

n= 1 + 16(SD/effect) 2
n= 1 + 16(6.8/2.3) 2
n=141 subjects in each group

The study procedures are described in section C. Baseline demographic characteristics will be recorded. All study participants will undergo transthoracic echocardiography, a 12-lead electrocardiogram, Swan-Ganz catheterization, and cardiopulmonary exercise testing.

All continuous data will be reported as mean +/- standard deviation for each of the two groups. The baseline characteristics of the two groups (including demographic, echocardiographic, and hemodynamic data) will be compared using unpaired t-test analysis for continuous variables and chi-squared analysis for proportional data. Differences between the groups with respect to the primary outcome (VO2max) and each of the secondary outcomes (HRmax, SVmax, Hgb, SaO2max, SVO2max) will be evaluated using unpaired t-test analysis. A p value of less than 0.05 will considered significant for all tests.

C. Study Procedure

Immediately before participating, all study participants will undergo the following tests/procedures:

1. Transthoracic echocardiography. This noninvasive ultrasound technique will allow for measurement of the following parameters of interest: left ventricular ejection fraction, left ventricular end-diastolic dimension, septal thickness, left ventricular free wall thickness, left atrial dimension, degree of mitral regurgitation, degree of mitral stenosis, degree of aortic regurgitation, degree of aortic stenosis, degree of tricuspid regurgitation.
2. 12-lead electrocardiogram (ECG)
3. Swan-Ganz catheterization. This technique involves cannulation of the right internal jugular vein (or alternatively the left subclavian vein) with an introducer device and advancement of a catheter through the introducer into the right heart. When the catheter tip reaches the pulmonary artery, a balloon will be inflated to allow for measurement of the pulmonary capillary wedge pressure. Baseline hemodynamics will be recorded and a sample of

pulmonary artery blood will be obtained for a measurement of its oxygen saturation. An additional sample will be collected to measure serum hemoglobin concentration. This procedure will be performed by an interventional cardiologist certified in the procedure. Local anesthesia with 2% lidocaine will be used to minimize patient discomfort during the procedure.

Study participants will then undergo symptom-limited cardiopulmonary exercise testing using a graded treadmill protocol designed to reach maximum exertion within 8-10 minutes. During exercise, heart rhythm will be monitored continuously, with 12-lead ECGs recorded continuously. Arterial oxygen saturation will be recorded at 30 second intervals. Blood pressure will be monitored at 1-minute intervals using an automated sphygmomanometer. During CPXT, a breath-to-breath analysis of minute ventilation (Ve), oxygen uptake (V02), carbon dioxide output (VCO2) will be obtained. At peak exercise (when VO2max is achieved), instantaneous measures of BR and Sa02 will be recorded. In addition, a sample of pulmonary arterial blood will be obtained and its oxygen saturation will be measured. Maximal stroke volume will be calculated using the Fick equation, as all other variables in the equation will be known.

After CPXT, the Swan-Ganz catheter and introducer will be removed. At this point, each subject's participation in the study protocol is complete. The duration of patient participation in this study should be less than 4 hours.

D. Study Drugs

No pharmaceutical agents will be used in this study.

E. Medical Device

No medical devices will be used in this study.

F. Study Questionnaires

Two questionnaires will be used in this study – one survey to obtain demographic and baseline health information and a second 7-question questionnaire to determine NYHA functional class.

G. Study Subjects

Inclusion criteria:

- Ambulatory outpatients
- >18 years of age with the diagnosis of congestive heart failure (as defined by Framingham criteria[8]) will be eligible to participate.

Exclusion Criteria:

- Patients who are unable to perform the treadmill exercise test or in whom CPXT poses and unacceptable health risk will be excluded. These include patients with:
- Unstable ischemia
- Severe valvular disease
- Moderate aortic or mitral stenosis
- Decompensated CHF (NYHA Class IV symptoms)
- Uncontrolled arrhythmias
- 6, Unstable concurrent medical conditions
- Documented angina, ischemic EKG changes, hypotension, or NSVT during exercise
- Uncontrolled hypertension (SBP>160)
- Hypertrophic obstructive cardiomyopathy
- Congenital heart disease

- Second or third degree AV block
- In addition, patients with concurrent medical problems that can lower VO2max will be excluded. These include
- Chronic obstructive pulmonary disease (defined as FEV1<70%)
- Restrictive lung disease (defined as DLCO<50% predicted)
- Muscular dystrophy

Additionally, patients with left bundle branch block on their baseline ECG will be excluded given the increased risk of complete heart block during Swan-Ganz catheterization.

Eligible participants will be split into two groups on the basis of the left ventricular ejection fraction noted on baseline transthoracic echocardiography. Subjects with LVEF> 50% will be paired with those <50% for enrollment into the study as described above in section B.

H. Recruitment of Subjects

Subjects will be identified by their primary physicians and referred for enrollment. We intend to recruit from the outpatient cardiology practices of Columbia University Medical Center staff cardiologists and from cardiologists in the surrounding community. Fliers advertising the study will be placed in and around doctor's offices and clinics on the CUMC campus. Direct mail advertisements will also be sent to local physicians.

I. Confidentiality of Study Data

Each study subject will be given a 7-digit identification number. All paperwork related to their participation in the study will note this number and exclude any identifying data, including the subject's name.

J. Potential Conflict of Interest

There is no potential conflict of interest on the part of the study investigators.

K. Location of Study

All diagnostic tests required for the execution of this study will be performed at Columbia University Medical Center.

L. Potential Risks

Two diagnostic procedures included in this protocol carry known risks to participants.

Swan-Ganz catheterization involves placement of central venous access, placement of a catheter into the right heart, and inflation of a balloon on the catheter tip in a branch pulmonary artery. Known risks of placing central venous access include pneumothorax (<1%), and arterial puncture (1-2%). Catheter advancement carries the risk of ventricular tachyarrhythmias (<1%, usually transient) or ventricular wall rupture (<0.01%). Balloon inflation carries a small risk of pulmonary artery rupture (<0.1%).[10] All of these risks are minimal in the hands of an experienced operator and Swan-Ganz catheterization has long been safely used in clinical investigations of heart failure.

Cardiopulmonary exercise testing carries certain risks of exercise induced complications. By excluding potentially unstable patients, these risks will be minimized. Known complications of CPXT in heart failure patients include hypotension, ventricular tachyarrhythmias (often transient). The event rate of non-sustained ventricular arrhythmias can be as high as 20%. Exercise induced hypotension may occur in approximately 5% of subjects, while life-threatening events are reported in far less than 1% of such

subjects.[11] By excluding those subjects known to be at highest risk for these complications, we expect a far lower incidence of complications in this study. All exercise tests will be monitored by a board-certified cardiologist trained in the administration of these tests.

M. Potential Benefits

While no therapeutic interventions will be made in this study, subjects will be undergoing several diagnostic tests (echocardiography, electrocardiogram, Swan-Ganz catheterization, CPXT). The results of these tests will be made available to the patients' primary physician and may be of use in guiding the clinical management of these patients.

N. Alternative Therapies

There will be no therapeutic interventions performed during the course of this study.

O. Compensation to Subjects

All study subjects will be compensated with a small payment at the completion of their participation in the study.

P. Costs to Subjects

There will be no specific costs incurred on the part of subjects to participate in this study. Travel expenses to and from the CUMC campus will be covered by the investigators.

Q. Minors as Research Subjects

No minors will be enrolled as participants in this study.

R. Radiation or Radioactive

Substances No radiation or radioactive substances will be used in this study.

S. References

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