Study Title: Determinants of Chronotropic Incompetence in Patients with Heart Failure and a Preserved Ejection Fraction (HFpEF)

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PURPOSE:
The purpose of this study is to test the hypothesis that chronotropic competence (the ability to increase heart rate during exercise), as assessed by the HR response to beta-adrenergic stimulation and increasing central command, is preserved in patients with heart failure and a preserved ejection fraction (HFpEF) compared to healthy age-matched controls.

Study Design:
To assess our hypothesis, we will need to complete screening on 15 patients with HFpEF and 30 healthy control subjects. Screening will occur after informed consent and include history and physical, screening EKG, bloodwork for potassium levels and renal function. Following screening, all 45 participants will complete Day 1 testing, including familiarization and a maximal exercise test with cardiopulmonary stress echocardiogram. This testing determines maximal exercise capacity, the HR/work rate relationship, and excludes provocable ischemia. However, not every subject who enrolls in the study will go onto complete all testing. During this Day 1 testing, exclusion criteria may be identified requiring disqualification from the study; examples include manifest ischemic heart disease, valvular disease, or the identification of coronary artery disease in the healthy subjects.

The 2nd day of testing for all qualified subjects will include static handgrip exercises to determine heart rate response to central command and drug infusion studies using glycopyrrolate, dexmedetomidine and isoproterenol to assess adrenergic response.

STUDY PROCEDURES
1) Day 1: This visit consists primarily of a maximal exercise test with the measurement of echo derived wall motion and systolic volumes, blood pressure, ECG, heart rate, oxygen uptake, cardiac output (acetylene re-breathing method), stroke volume, total peripheral resistance, and a-vO2 difference. Goals of this day are to: 1) estimate the peak VO2; 2) carefully assess for the presence of provocable ischemia via both ECG and contractile imaging.

2) Day 2: This visit consists of the hand grip test, drug infusion study and will last approximately 4.5 hours. This visit will assess central command and measure beta-adrenergic responsiveness/sensitivity. a. Instrumentation – Subjects will first empty their bladders to avoid any urinary retention problems from glycopyrrolate/dexmedetomidine administration. They will then be instrumented with an ECG for HR, pulse oximeter for oxygen saturation, a finger and arm cuff for BP and 2 peripheral IVs.

b. After 20 minutes in the supine position, baseline data will be collected including the HR and blood pressure response to fatiguing static handgrip exercise at 40% of a maximum voluntary contraction followed by 2 minutes of post-exercise circulatory arrest (see enclosed manuscript for experimental details). This protocol will allow the quantification of the HR response to central command.

c. Complete autonomic blockade will then be established with a 15 ug/kg bolus of glycopyrrolate followed by 7 ug/kg/hr maintenance infusion. Heart rate may increase slightly after the bolus and subjects will be observed for 15 minutes (establishes steady state) before proceeding to dexmedetomidine infusion. Dexmedetomidine will then be
given as an IV bolus of 0.225 ug/kg over 6 minutes followed by maintenance rate of 0.3 – 0.5 ug/kg/hr. The maintenance dose will start at 0.3 ug/kg/hr and increased to 0.5 ug/kg/hr if necessary (see next subheading). Subjects will be monitored closely with a pulse oximeter and respirometer to monitor the sedating effects of dexmedetomidine. One of the medications (glycopyrrolate) may also cause dry mouth and urinary retention which resolves as the medication wears off within 1 to 2 hours. To minimize or alleviate dry mouth, we offer subjects Biotene Moisturizing Mouth Spray. We offer this spray several times throughout the drug study to minimize the sensation of dry mouth and improve comfort level when the subjects are on the mouthpiece. This is an over-the-counter medication comprised of water, glycerin and castor oil. It is sugar and alcohol free. Subjects will also be queried every 5 minutes during infusion regarding sedation status using a visual analog scale (0 – 100; 0 – completely alert, 100 – very sedated). The combination of glycopyrrolate/dexmedetomidine (gly/dex) achieves central autonomic blockade similar to pentolinium and trimethaphan, two drugs previously used but that have since been discontinued for clinical use. Dr. Levine’s collaborator and colleague Dr. Michael Joyner (Mayo Clinic, Rochester, MN) has used this gly/dex combination in previous studies (see attached publication). In addition, our group has extensive experience with ganglionic blocking agents and Dr. Levine has an IND for trimethaphan (seen enclosed publications). However trimethaphan and pentolinum are no longer available even for experimental studies thus forcing us to seek other alternatives.

d. 20 minutes following administration of gly/dex, a Valsalva maneuver will be performed (30 mmHg x 20 seconds) to document the absence of autonomic reflexes as previously described. If there is still a > 10 bpm rise in HR, dexmedetomidine maintenance infusion will be increased to 0.4 ug/kg/hr and Valsalva will be rechecked in 20 minutes. If HR responsiveness is still present, the maintenance dose will be increased again to 0.5 ug/kg/hr.

e. Resting cardiovascular variables including HR, BP, and non-invasive cardiac output will then be repeated. This will establish the intrinsic heart rate (i.e., the HR in the absence of autonomic influences).

f. Isoproterenol will then be infused at 3.5, 7.0, 14.0, and 35 ng/kg/min with each stage lasting 6 minutes each. During each infusion, HR will be measured from minute 4:30 to 5:00 of each infusion. The infusion will be stopped when the HR rises by 30 bpm. At each infusion level, 10 ml of blood will be drawn for isoproterenol and norepinephrine levels to be sent to the Goldstein lab at NIH at the same time as HR measured. This will allow us to calculate a true dose-response relationship which will provide a robust measure of adrenergic sensitivity.

g. Subjects will remain supine for ~ 2 hours, or until the Valsalva response returns to normal. They will not be allowed to leave until they are clearly making saliva, and have a normal BP during 5 minutes of quiet standing.

BIOSTATISTICS:
The project has been NIH reviewed and will not require a stats section.