

Inhaled Beta-adrenergic
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Vascular Disease in Heart
Failure with preserved EF (BEAT
HFpEF): A Randomized
Controlled Trial

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Abstract:

Heart failure (HF) is the most common cause of pulmonary hypertension (PH, WHO Group 2) (1). Approximately half of patients with HF have preserved ejection fraction (HFpEF) (2); PH is common in this cohort and is clearly associated with increased mortality (3)(4)(5)(6). While early stages of HFpEF are characterized by purely passive PH, recent studies have shown that the majority of patients referred for invasive assessment display significant pulmonary vascular disease (HFpEF-PH) manifest by elevation in pulmonary vascular resistance and decreases in pulmonary artery compliance (7)(8). Patients with HFpEF-PH frequently display right ventricular (RV) dysfunction, which is associated with even worse outcome, independent of the severity of PH (9). We have recently shown that the RV in HFpEF displays greater afterload-dependence as compared to healthy controls (9), suggesting that there may be greater opportunity to improve hemodynamics and functional capacity with pulmonary vasodilators in this population. We have also shown that even in the earliest stages of HFpEF, there is abnormal pulmonary vasodilation associated with impaired RV reserve.(10) This suggests potential for patients with HFpEF to benefit from pulmonary vasodilators, but no approved therapies are available directly targeting the pulmonary vasculature in HFpEF.

Our group has recently shown that the pulmonary vasculature in patients with HFpEF-PH is very favorably responsive to beta-adrenergic stimulation from intravenous dobutamine (11). Compared to controls, dobutamine produced significantly greater reductions in pulmonary artery (PA) pressure, resistance and more improvement in PA compliance in subjects with HFpEF. This observation serves as the **guiding hypothesis** for the proposed study: that acute treatment with an inhaled beta-agonist (albuterol) can improve pulmonary vascular function at rest and during exercise in patients with HFpEF-PVD. Demonstration of such an acute effect from a novel inhaled therapy would represent a major step forward in the potential treatment of a large population of patients with pulmonary vascular disease for whom there is currently no effective pharmacotherapy.

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A. Rationale: In contrast to heart failure (HF) with reduced EF, there is no effective treatment for HF with preserved EF (HFpEF). Pulmonary hypertension (PH) is highly prevalent in HFpEF and is associated with right ventricular (RV) dysfunction and increased mortality, particularly when both the former and latter are present. Recently, we have also shown that there is depressed pulmonary artery (PA) vasodilation during exercise, even when resting indices of function are normal. This is associated with impaired RV reserve and reduced exercise capacity. Dobutamine, a nonselective β -agonist, improves PA vascular function at rest in HFpEF, but is limited by the fact that it is an intravenous therapy that is not feasible for chronic ambulatory use. Albuterol is an inhaled β -agonist routinely used to treat reactive airway diseases that could provide an alternate way of improving PA vascular function in patients with HFpEF-PH.

B. Hypothesis: Acute inhaled albuterol will improve PA vascular function at rest and during exercise in subjects with HFpEF-PH.

C. Innovation:

- The hypothesis proposed is based on our own data and has not been entertained by other groups and β -agonists (albuterol) have never been suggested to treat HFpEF
- The use of exercise hemodynamics to measure an intervention's effect is highly novel while also being clinically meaningful. Very few centers in the world could carry out this study.
- This application is based upon a highly innovative hypothesis that HFpEF is caused by dynamic abnormalities in cardiac reserve rather than simply resting diastolic dysfunction.
- The concept of a therapy that can be given prophylactically before activity in HFpEF is highly innovative.
- The commonly used bronchodilator albuterol has never been tested as a pulmonary vasodilator. If effective this could lead to further studies in other forms of pulmonary hypertension

D. Significance:

- HFpEF currently afflicts 2-3 million Americans, and with the aging population the prevalence is growing by 1% per year. This makes identification of effective treatments a major unmet public health need that will change our practice.
- Mayo is already a leader in the invasive characterization of HF, and publication of the results of these studies will further enhance our international reputation as a center of excellence.
- By conducting trials of novel interventions like albuterol in HFpEF, this trial will enhance referrals of patients with unexplained dyspnea and exercise intolerance to Mayo.
- Identification of a beneficial effect of albuterol on hemodynamics would provide critical preliminary data to support a larger Mayo-centered, NIH-sponsored clinical trial of chronic albuterol therapy in HFpEF.

E. Brief Synopsis of Methods:

- 1) Enroll subjects with normal EF referred to the cath lab for evaluation of dyspnea.
- 2) Measure resting and exercise hemodynamics with expired gas analysis as per clinical practice.
- 3) After exercise, in a randomized, double-blinded fashion, administer inhaled albuterol or placebo (prepared by research pharmacy).
- 4) Repeat rest-exercise hemodynamics/expired gas analysis exactly as above.
- 5) Compare resting and exercise hemodynamic response after albuterol or placebo relative to the initial assessment (analysis of covariance, ANCOVA).
- 6) Perform simultaneous echo with measurement of RV function using tissue Doppler echocardiography and PA flow using pulsed wave Doppler of the RV outflow tract during rest and exercise phases.

F. Preliminary studies to support feasibility: The enormous and rapidly growing burden of HFpEF has led to a need to better understand the pathogenesis and treatment options for this morbid disease. Recent research from our group has shown that RV dysfunction is present in a third of patients with HFpEF and the presence of pulmonary vascular disease and pulmonary hypertension (PH) is very high (related to both pulmonary venous hypertension as well as pulmonary vascular disease) ((12)) ((5)). Both of these have been associated with adverse outcomes and exercise intolerance but no therapy is currently available directly targeted at the pulmonary vasculature in HFpEF ((9)).

We recently demonstrated significant improvements in pulmonary vascular function with dobutamine (a β_2 agonist) administered acutely in HFpEF (11). As an intravenous therapy, this is not suitable for chronic outpatient use. Hospitalized patients with heart failure often demonstrate symptomatic improvement with inhaled β_2 agonist therapy, even in the absence of pulmonary disease, and animal studies have also shown improved resolution of pulmonary edema with albuterol (13), (14,15). In the proposed randomized, placebo-controlled trial, we seek to evaluate whether the commonly used inhaled bronchodilator albuterol, administered through a high-efficiency nebulizer device, improves pulmonary vascular function in patients with HFpEF-PH as compared to placebo. This has the potential to lead to a simple cost effective intervention to improve symptoms in HFpEF-PH, and potentially be tested in other WHO PH groups.

In the absence of frank signs of congestive heart failure, patients with early HFpEF can only be reliably diagnosed by exercise right heart catheterization, which is routinely performed at Mayo Clinic as part of the evaluation of patients with unexplained dyspnea. The presence of elevated pulmonary capillary wedge pressures (PCWP) at rest (>15 mmHg) or with exercise (>25 mmHg); and elevated mean pulmonary artery pressures at rest (>25 mm Hg) and with exercise (>40 mmHg) has been used to invasively diagnose HFpEF with exercise pulmonary hypertension with a high degree of validity and reliability (16). Just as exercise stress unmasks abnormalities in LV diastolic function in early stage HFpEF, we have very recently shown that exercise stress reveals early abnormalities in PA vascular function as compared to controls without HF that are not apparent from resting data alone.(10)

Using objective diagnoses of HFpEF and exercise induced PH, we seek to evaluate the hemodynamic changes with exercise in pulmonary vascular resistance, peak cardiac output and subjective dyspnea before and after inhaled albuterol therapy for pulmonary vasodilation.

G. Study design: This study will be performed in a randomized, double blind placebo-controlled fashion using inhaled albuterol or inhaled saline (prepared by research pharmacy) administered through a novel high-efficiency nebulizer in a 1:1 fashion. Patients will undergo RHC with expired-gas analysis using high Fidelity micromanometer catheters at rest and with exercise, at baseline and following treatment with study drug, using a novel study design that we have previously utilized and reported (17). Rest and exercise measurements will be repeated after receiving inhaled albuterol or control therapy.

Patients referred to the cardiac catheterization laboratory for invasive exercise stress testing will be prospectively recruited. Standard right heart catheterization using high fidelity micromanometers (Millar Instruments) will be performed at rest and during supine exercise with simultaneous expired gas analysis (MedGraphics) as is our current practice. The protocol is rest-20 Watts exercise x 5 minutes, and then graded workload increases in 10-20W increments (3 minute stages) to exhaustion. Hemodynamic, arterial and mixed venous blood gas and expired gas data are acquired at rest, during each exercise stage and at peak exercise. Venous blood samples will be obtained at rest and at peak exercise. Perceived symptoms of dyspnea and fatigue will be quantified using the Borg dyspnea and effort scores at each stage of exercise. Limited echocardiography will be performed by a cardiologist skilled in imaging (MO) focussed on measures of RV morphology and function.

After the initial exercise study and hemodynamics have returned to baseline, study drug (normal saline placebo or albuterol 2.5 mg) will be inhaled through a high efficiency nebulizer over 5 minutes. After a 10 minute observation period, resting hemodynamic and expired gas data will be acquired exactly as in the initial run. Subjects will then repeat the 20 Watt x 5 minutes exercise phase. Subjects will repeat

exercise only at the 20 Watt stage, rather repeating the entire study. This is done to increase the feasibility and shorten the time of the case. We have previously observed that the vast majority (>85%) of the elevation in cardiac filling pressures and reduction in venous oxygen content in people with HFpEF occurs at the low 20 Watt workload (16), so repeating exercise hemodynamic assessment at this load should be sufficient to detect any clinically meaningful treatment effect from albuterol.

Blood tests: No additional blood tests will be collected beyond those needed for clinical use in the right heart catheterization.

Data collected: This will be a randomized double-blind trial. A web data base will be created (Redcap) using dual data entry from the paper case report forms. All hemodynamic data will be assessed at end expiration using standard methods by the PI to minimize interobserver variability. Data will be supplied for analysis as an SAS data base. The specific hemodynamic and expired gas data along with blood tests obtained are itemized in Appendix I.

Primary Endpoint: The primary endpoint will be the PVR at 20 Watts exercise after study drug relative to the PVR at 20 Watts exercise in the initial assessment prior to study drug.

Secondary Endpoints: Secondary endpoints will be changes in resting PVR after study drug as well as rest and exercise changes in PA compliance, right atrial pressure, pulmonary artery pressure, PCWP, cardiac output, RV systolic and diastolic function, PA input impedance VO_2 , Ve/VCO_2 slope and Borg effort/dyspnea scores.

We will also perform a prespecified tertiary analysis of Beta blocker+ vs Beta blocker- subjects enrolled to see if there is any difference in treatment effect.

Inclusion Criteria: HFpEF is defined by clinical symptoms of dyspnea and fatigue, normal left ventricular ejection fraction ($\geq 50\%$), and elevated LV filling pressures at cardiac catheterization (defined as resting PCWP > 15 mmHg and/or PCWP ≥ 25 mmHg during exercise).

Exclusion Criteria: Prior albuterol therapy (within previous 48 hours), current long acting inhaled beta agonist use, significant hypokalemia (< 3 meq/L), other "non-HFpEF" specific causes of heart failure such as significant valvular disease ($>$ moderate left-sided regurgitation, $>$ mild stenosis), high output heart failure, severe pulmonary disease, unstable coronary disease, constrictive pericarditis, or infiltrative, restrictive, or hypertrophic cardiomyopathies. Patients who are pregnant or lactating will also be excluded.

We will include patients on chronic beta blocker (BB) therapy in the study for the following reasons (1) they are commonly prescribed in HFpEF, so to restrict to BB naive patients will limit our ability to generalize the findings, (2) the requirement would limit the pool of patients who might be eligible for the study, (3) chronically, BBs restore beta-adrenergic responsiveness in heart failure, so they are unlikely to significantly attenuate albuterol's effect in the heart and pulmonary vasculature

Study drug preparation and considerations: Medical grade albuterol nebulization solution will be obtained by research pharmacy from the Mayo Clinic pharmacy at a dose of 2.5 mg for nebulization (current FDA approved dose for bronchodilation). Placebo (normal saline) will also be prepared by research pharmacy for nebulization at identical weight-based rate. The randomization scheme will be generated by the cath lab statistician, Ryan Lennon and entered into a computer program.

H. Statistical analysis and power considerations:

We will enroll 30 patients (15 in each arm) over a 1 year period. In our previous study, PVR was improved by 0.8 with dobutamine in subjects with HFpEF. Assuming a standard deviation of 0.5 WU in exercise PVR based upon our prior data, this sample size will provide 98% power ($\alpha=0.05$) to detect a drop in exercise pulmonary vascular resistance of this magnitude or greater with albuterol as compared to inhaled placebo.

The effect of albuterol relative to placebo on primary and secondary endpoints will be evaluated by analysis of covariance (ANCOVA) taking into account rest/exercise values prior to study drug and following albuterol or placebo.

Consenting subjects who do not meet the diagnostic criteria for HFpEF at catheterization (resting PCWP>15 mmHg and/or PCWP≥25 mmHg during exercise) will be considered screen failures and will not receive study drug. Given that we currently perform > 250 exercise right heart catheterizations per year at the Mayo clinic and have successfully completed similar acute hemodynamic studies over this time frame, we plan to reach the target of 30 enrolled HFpEF patients within 12 months.

I. Human studies issues:

Informed consent will be obtained from each participant prior to coming to the catheterization laboratory. Albuterol is currently FDA approved at the proposed study drug dose of 2.5 mg through nebulization for treatment of obstructive lung disease. The medication is well tolerated overall and has been used in both young and old patients alike with lung disease with minimal side effects and excellent tolerability. Previous studies using albuterol in much sicker HF patients with decompensation and reduced ejection fraction as well as in critically ill patients have failed to demonstrate harm from the standpoint of tachyarrhythmias or other untoward effects (18-20). Patients with a normal EF and HFpEF are in general less acutely ill than these previously studied patients and are commonly treated with these agents in the presence of coexisting lung disease (which is very common in HFpEF).

Side effects of albuterol are minimal and related to benign palpitations, tremors and anxiety. At higher doses of 10-20 mg, transient hypokalemia can occur through transcellular shift but this is not seen at the doses used in this trial. Patients with significant baseline hypokalemia will also be excluded by study design. Dobutamine and isoproterenol are similar β -agonists that are currently given intravenously in the cath lab as part of routine clinical practice without untoward significant untoward effects.(21,22) With direct pulmonary delivery, systemic side effects from albuterol are expected to be much less likely than would be observed with parenteral use of these IV active β -agonists.

Patients will be monitored in the recovery area typically for up to two hours after their procedure to remove vascular sheaths. Patients will be monitored using continuous telemetry, heart rate and oximetry monitoring. Blood pressure will be monitored as per standard of care. This will allow post procedure observation in a monitored setting to ensure no side effects occur during peak drug concentration.

J. Budget

This study will be done in patients already undergoing cardiac catheterization and exercise hemodynamic study. There will be no additional cost to the patient. The only research charges will be for albuterol/placebo and for preparation and storage in research pharmacy, and for two additional arterial blood gases obtained during the subsequent rest and exercise phases after study drug.

K. References:

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Appendix I: Data Obtained at baseline rest, baseline exercise, post study drug rest, and post study drug exercise stages

Heart rate
Systemic blood pressure (systolic, diastolic mean)
Right atrial pressure
Pulmonary arterial pressure (systolic, diastolic, mean)
Pulmonary capillary wedge pressure (mean, V wave)
Cardiac output (direct Fick method)
Stroke volume
LV and RV stroke work index
Transpulmonary gradient
Pulmonary and Systemic Vascular resistances
Oxygen consumption
Carbon dioxide production
Respiratory exchange ratio
Minute ventilation, tidal volume, respiratory rate
Ventilatory efficiency (V_e/V_{CO_2} slope)
Borg perceived effort (6-20 scale) and dyspnea (0-10) scores
Arterial blood gas and saturation to determine O_2 content
Mixed venous blood gas and saturation to determine O_2 content
Echo derived RV lateral annular tissue Doppler velocity during systole (s')
Echo derived RV lateral annular tissue Doppler velocity during diastole (e')
Echo derived RV outflow tract pulse wave Doppler profile