Echocardiographic assessment of pulmonary transit time following exercise

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1.0 Background

The prevalence of heart failure with preserved ejection fraction (HFpEF) is comparable to that of heart failure with reduced ejection fraction (HFrEF), carries a similarly grim prognosis **[1]**, and there are no effective disease-modifying medical therapies **[2-5]**. A common and diagnostic characteristic of HFpEF is dyspnea in response to physiologic stress, such as exercise, that can correlate with increased left-sided filling pressure as measured by invasive hemodynamics **[6-7]**. While definitive, this modality is not practical to apply widely in clinical practice and remains challenging to pursue even for research studies that aim to evaluate underlying physiologic mechanisms and responses to treatment. Therefore, a non-invasive approach to estimating left-sided filling pressure post-exercise would be helpful in this regard. Standard tissue Doppler imaging on echocardiography (i.e. E/e'), which can be helpful at rest to estimate pulmonary arterial wedge pressure (PAWP) **[8]**, may be less accurate due to fusion of E and A waves at the higher heart rates expected post-exercise.

Prior work using echocardiographic contrast to derive pulmonary transit time (PTT) has suggested that a related metric, pulmonary blood volume (PBV), correlates with PAWP at rest **[9-12; IRB #110362, #131075, #131355]**. The current study proposes to measure PTT and PBV post-exercise. Demonstration of technical plausibility of this approach would justify future studies to compare directly echocardiographically-derived PBV and invasive exercise hemodynamics post-exercise. If PBV were shown to be a reasonable surrogate for PAWP with exercise, the capability to study the defining feature of HFpEF could be expanded to a non-invasive technique.

2.0 Rationale and Specific Aims

While PTT in patients at rest has been successfully measured via contrast-echocardiography, whether post-exercise data can be reliably obtained and analyzed is unclear. Therefore, we propose to conduct a feasibility study to achieve the following aims:

1. Record the flow of ultrasound contrast across the pulmonary circulation after a standardized exercise protocol
2. Compare PTT and PBV pre- and post-exercise in the same cohort
3. Compare the time from contrast administration to appearance in the right-heart pre- and post-exercise (i.e. vein-to-heart time)
4. Compare PTT obtained by analysis of time-intensity curves to the PTT estimate obtained by visual assessment

3.0 Animal Studies and Previous Human Studies

As above, prior studies have used essentially the same methodology to obtain PTT. The main difference in the proposed study is the addition of post-exercise acquisition of PTT. Ultrasound contrast is commercially available and is widely used in Echocardiography Laboratories worldwide, including at VUMC.

4.0 Inclusion/Exclusion Criteria

To be eligible for enrollment, patients must meet all the following criteria:

Inclusion Criteria:

1. Age ≥ 18 years old
2. Able to give informed consent

To be eligible for enrollment, patients cannot meet any of the following criteria:

Exclusion criteria:

1. Known allergic reaction to Definity or Optison ultrasound contrast
2. Pregnancy/Nursing – as assessed/disclosed by the participant
3. Any faculty/staff whose performance will be directly and formally evaluated by the investigator or sub-investigators

5.0 Enrollment/Randomization

As this study is limited in size and aims to evaluate PTT post-exercise, we will concentrate enrollment efforts towards a focused group of prospective participants with (self-reported) adequate exercise capacity. Namely, the focus will be on individuals that attend conferences/meetings given by the Division of Cardiovascular Medicine who report engaging in relatively regular exercise (i.e. some form of aerobic exercise at least twice per month). This group includes faculty, sonographers, administrators, support staff, and occasional guests from other departments (particularly for inter-disciplinary conferences). Within this pool of potential candidates, there is sufficient demographic diversity to be permit inclusion of individuals across a range of age, gender, and ethnicity. Cardiology fellows and NPs are not eligible to avoid the appearance of undue influence to participate.

Invitations to participate in the study will be made to those in attendance at divisional conferences (i.e. Faculty Meeting, Echocardiography conference) and will not target specific individuals within the above groups. Interested individuals will contact KSP, who will then help facilitate the study visit at the CRC.

6.0 Study Procedures

All study procedures will take place over a single day during a single visit to the CRC. Participants will experience the following:

1. **Baseline demographics and anthropomorphic measurements.** Basic information on age, gender, and self-identified ethnicity will be collected along with height and weight.
2. **Pre-exercise echocardiographic evaluation**. This assessment will be performed by the CRC sonographer and will include heart rate, LVOT diameter, LVOT VTI, mitral valve inflow, mitral valve tissue Doppler imaging, IVC size/respirophasic changes in caliber, and a recording of the apical 4-chamber

view (the view in which contrast flow will be recorded) to ensure adequate visualization.

3. **Pre-exercise PTT measurement**. Following placement of a standard peripheral IV by a CRC nurse, ultrasound contrast will be administered and the pathway of the contrast from entry into the right-heart through appearance in the left-heart will be recorded in order to obtain the data necessary to measure PTT. The interval between the beginning of the contrast injection and the appearance in the right-heart will be recorded. The IV line will then be flushed with saline to remove any residual contrast. After the acquisition of these data, the 'FLASH' feature of the ultrasound machine will be employed to rapidly remove the remaining contrast from the field of view such that there is minimal, if any, residual contrast when it is time for administration of contrast post-exercise.
4. **Exercise protocol**. Participants will exercise on a treadmill (provided by the Metabolic Core) following a Standard Bruce Protocol until their heart rate reaches ~ 2.5-times their baseline level or until they reach maximum effort. Exercise capacity, blood pressure, and heart rate will be recorded at standard intervals throughout exercise. If it proves to be more logistically favorable, an exercise bicycle (also supplied by the Metabolic Core) can be used rather than a treadmill.
5. **Post-exercise PTT measurement**. This administration of contrast will be similar to the pre-exercise PTT measurement and will occur as soon as an adequate echocardiographic image can be obtained following exercise. Heart rate will also be recorded during this step. Mitral valve inflow, mitral valve tissue Doppler imaging, and IVC size/respirophasic changes in caliber will be re-assessed as well.
6. **Contingencies for additional contrast administration**. Should there be unforeseen technical issues with contrast administration or image acquisition at pre- or post-exercise, additional doses of contrast can be given as permitted by the remaining volume in the vial (typically, 1-2 mL of contrast are used per injection and a single vial yields 8-10 mL of contrast).

7.0 Risks

The key study procedures that could incur risk include placement of a peripheral IV, administration of echocardiographic contrast, and treadmill/stationary bicycle exercise.

The risks associated with peripheral IV placement include damage to the vein, inadvertent arterial puncture, infection, and infiltration into the underlying skin. In general, and in this setting in particular (i.e. non-acutely ill individuals having an IV placed by an experienced nurse), complications of peripheral IV placement are rare.

The safety record of Definity and Optison ultrasound contrast, the two agents approved for clinical use in the United States, is long-established and has been presented in prior protocols cited above. In summary, studies reporting on hundreds of thousands of administered doses have shown extremely low adverse event rates.

Specifically, with Definity, serious cardiopulmonary reactions (including fatalities) have occurred during or following administration; most serious reactions occur within 30

minutes of administration. These include: Cardiovascular: Flushing (1%) Central nervous system: Headache (2%) Gastrointestinal: Nausea (1%) Neuromuscular & skeletal: Back pain (1%) Renal: Renal pain (1%).

Specifically, with Optison, serious cardiopulmonary reactions (some fatal) have occurred uncommonly during or within 30 minutes following administration. Serious anaphylactoid reaction. Cardiovascular: Flushing (4%), chest pain (1%) Central nervous system: Headache (5%), dizziness (3%), chills (≤1%), fatigue (≤1%), malaise (≤1%) Gastrointestinal: Nausea (≤4%), vomiting (≤4%), dysgeusia (2%) Local: Discomfort at injection site (1%) Neuromuscular & skeletal: Weakness (≤1%) Respiratory: Dyspnea (1%), flu-like symptoms (1%) Miscellaneous: Fever (≤1%).

The risks associated with exercise on the treadmill (Standard Bruce Protocol) or exercise bicycle include mechanical injury (from loss of balance or equipment failure), muscle/joint pain, orthopedic injury, and unanticipated cardiac events (i.e. triggering of acute coronary syndrome or arrhythmias). In the population targeted for this study, these risks are anticipated to be small.

8.0 Reporting of Adverse Events or Unanticipated Problems involving Risk to Participants or Others

Adverse events determined to be related to the study will be reported to the VUMC IRB by either the PI or KSP as required by VHRPP policy III.L within 7 calendar days of the PI's knowledge of the problem.

9.0 Study Withdrawal/Discontinuation

Patients who wish to be withdrawn from the study for any reason will notify the PI or other study personnel. Patient data that have not been used or analyzed prior to this notification will be deleted from the REDCap database.

10.0 Statistical Considerations

As there are no current data on (or estimates of) the differences in PTT between rest and exercise, there is no formal power calculation to determine sample size. We will aim for a cohort of 15 participants, realizing that there may be a 'learning curve' that could render data from the initial participants unable to be used in quantitative analyses.

The primary analysis will consist of an intra-individual comparison of pre- and post-exercise PTT and PBV. As these will be paired observations that will likely not be normally distributed, the Wilcoxon matched-pairs signed rank test will be used for this evaluation. Similar methodology will be used to analyze the vein-to-heart times pre- and post-exercise. Bland-Altman analysis will be used to compare PTT obtained by two different techniques (intensity-time curves and visual assessment).

11.0 Privacy/Confidentiality Issues

Participant privacy and confidentiality will be protected by the usual practices of the VUMC CRC. The confidentiality of participant data will be protected by maintaining a single master list linking Study ID (from the REDCap database) with Medical Record Number, which will be stored in the REDCap file repository. Any documents or electronic datasheets with identifying information will also be stored in the REDCap file repository. Only the PI and key study personnel will have access to the REDCap database. Given that the participants are likely to be colleagues of study personnel, study personnel will not access participants' charts in the electronic medical record for the purposes of this study except to document participation and consent, as required (i.e. an 'on-study' note).

12.0 Follow-up and Record Retention

Data derived from this study will be kept in a REDCap database. The data will be kept for a minimum of six years and, potentially, indefinitely, particularly if follow-up studies are pursued.

REFERENCES

1. Redfield MM. Heart failure with preserved ejection fraction. New Engl J Med 2016; 375: 1868-77

2. Yusuf S, Pfeffer MA, Swedberg K, Granger CB, Held P, McMurray JJV, Michelson EL, Olofsson B, Östergren J for the CHARM investigators and committees. Effects of candesartan in patients with chronic heart failure and preserved left-ventricular ejection fraction: the CHARM-Preserved trial. Lancet 2003; 362: 777-81

3. Redfield MM, Chen HH, Borlaug BA, Semigran MJ, Lee KL, Lewis G, LeWinter MM, Rouleau JL, Bull DA, Mann DL, Deswal A, Stevenson LW, Givertz MM, Ofili EO, O'Connor CM, Felker GM, Goldsmith SR, Bart BA, McNulty SE, Ibarra JC, Lin G, Oh JK, Patel MR, Kim RJ, Tracy RP, Velazquez EJ, Anstrom KJ, Hernandez AF, Mascette AM, Braunwald E for the RELAX Trial. Effect of phosphodiesterase-5 inhibition on exercise capacity and clinical status in heart failure with preserved ejection fraction: a randomized clinical trial. *JAMA* 2013; 309: 1268-77

4. Pitt B, Pfeffer MA, Assmann SF, Boineau R, Anand IS, Claggett B, Clausell N, Desai AS, Diaz R, Fleg JL, Gordeev I, Harty B, Heitner JF, Kenwood CT, Lewis EF, O'Meara E, Probstfield JL, Shaburishvili T, Shah SJ, Solomon SD, Switzer NK, Yang S, McKinlay SM for the TOPCAT investigators. Spironolactone for heart failure with preserved ejection fraction. *N Eng J Med* 2014; 370: 1383-92

5. Solomon SD, McMurray JJV, Anand IS, Ge J, Lam CSP, Maggioni AP, Martinez F, Packer M, Pfeffer MA, Pieske B, Redfield MM, Rouleau JL, van Veldhuisen DJ, Zannad F, Zile MR, Desai AS, Claggett B, Jhund PS, Boytsov SA, Comin-Colet J, Cleland J, Dungen H-D, Goncalvesova E, Katova T, Saraiva JFK, Lelonek M, Merkely B, Senni M, Shah SJ, Zhou J, Rizkala AR, Gong J, Shi VC, Lefkowitz MP for the PARAGON-HF investigators and committees. Angiotensin-Neprilysin inhibition in heart failure with preserved ejection fraction. *N Engl J Med* 2019; 381:1609-1620

6. Borlaug BA, Nishimura RA, Sorajja P, Lam CS, Redfield MM. Exercise hemodynamics enhance diagnosis of early heart failure with preserved ejection fraction. Circ Heart Fail 2010; 3:588-595

7. Borlaug BA. Mechanisms of exercise intolerance in heart failure with preserved ejection fraction. Circ J 2014; 78: 20-32

8. Nagueh SF, Middleton KJ, Kopelen HA, Zoghbi WA, Quinones MA. Doppler tissue imaging: a non-invasive technique for evaluation of left ventricular relaxation and estimation of filling pressure. J Am Coll Cardiol 1997; 30: 1527-33

9. Brittain EL, Doss LN, Saliba L, Irani WN, Byrd B III, Monahan K. Feasibility and diagnostic potential of pulmonary transit time measurement by contrast echocardiography: a pilot study. Echocardiography 2015; 32:1564-71

10. Boronyak SM, Monahan K, Brittain EL, Merryman WD. An inflection point method for the determination of pulmonary transit time from contrast echocardiography. IEEE Trans Biomed Eng 2015; 62:1853-61

11. Monahan K, Lenihan D, Brittain EL, Saliba L, Piana RN, Robison LL, Hudson MM, Armstrong GT. The relationship between pulmonary artery wedge pressure and pulmonary blood volume derived from contrast echocardiography: a proof of concept study. Echocardiography 2018; 35:1266-70

12. Monahan K, Coffin S, Lawson M, Saliba L, Rutherford R, Brittain E. Pulmonary transit time from contrast echocardiography and cardiac magnetic resonance imaging: comparison between modalities and the impact of region of interest characteristics. Echocardiography 2019; 36:119-24