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Title: Development of a PET/MRI exercise stress test for determining cardiac glucose dependence in pulmonary arterial hypertension

Running Title: PET/MRI exercise test in pulmonary arterial hypertension

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Abstract

Patients with pulmonary arterial hypertension (PAH) exhibit cardiac metabolic remodeling, which precedes right ventricular (RV) dysfunction and subsequent heart failure. In this proof-of-concept study of two PAH patients, we demonstrate RV glucose dependency that is unmasked by exercise using a novel in-bore PET/MRI metabolic stress test.

To the Editor:

Pulmonary arterial hypertension (PAH) is a silent progressive disease of the pulmonary vasculature that often presents late in the disease course. Elevated pulmonary artery pressure (PAP) and pulmonary vascular resistance (PVR) cause right ventricular (RV) pressure overload, metabolic shifts, and myocardial remodeling resulting in impaired RV contractility, dysfunction, and subsequent RV failure^{1,2}. Notably, RV function is known to be a better prognostic factor than PAP or PVR in PAH³. The treatment for PAH focuses on reducing RV afterload with vasodilator therapy, yet despite reduction in PVR, the resting RV dysfunction may progress in patients with PAH³. Thus, the reason for right heart failure cannot be completely attributed to the changes in pulmonary blood flow dynamics but may also involve intrinsic metabolic shifts in the RV.

RV metabolic shifts and myocardial remodeling result in impaired RV contractility and occur early in the progression to RV failure,^{1,2} as cardiac metabolism shifts from predominantly fatty acid metabolism to increasing utilization of glucose⁴. However, tools to evaluate the RV metabolic state are limited, and may not be sufficient to detect early disease. Exercise testing can be added to imaging protocols and may aid in earlier identification of disease states. When combined with imaging modalities such as positron-emission tomography/magnetic resonance imaging (PET/MRI), this has the

potential to offer greater diagnostic capacity, providing robust information on RV structure and function, and permitting the determination of RV metabolic shifts in the setting of PAH.

Whether exercise can unmask RV glucose dependency early in PAH disease progression remains unclear. This has not been tested previously in part because classic PET/MRI protocols involve a single bolus of radiotracer with imaging 1 hour later, and thus do not capture real-time metabolic changes in response to stressors such as exercise. Therefore, the purpose of this proof-of-concept study was to develop a rest-stress single scanning PET/MRI protocol that could identify the effect of exercise on cardiac metabolic substrate flexibility in patients with PAH. Further, we hypothesized that the RV in PAH patients would demonstrate a preferential increase in glucose utilization relative to the LV during exercise.

Methods

Participants

Two newly diagnosed PAH patients with scleroderma (Subject 1: Female; Subject 2: Male) were recruited prior to initiation of vasodilator therapy from the University of Wisconsin-Madison Pulmonary Hypertension Clinic and provided informed consent to participate. This study was approved by the Institutional Review Board (2019-0286).

PET/MRI protocol

Subjects underwent a serial rest-stress test in a 3.0 T PET-MRI scanner (GE Signa PET/MR Discovery 750W, GE Healthcare, Waukesha, WI). Participants completed baseline balanced steady-state free precession (bSSFP) cardiac MRI sequences, acquired consistent with standard clinical cardiac imaging for the determination of end-diastolic volume (EDV), end-systolic volume (ESV), stroke volume (SV), cardiac output

(CO), and ejection fraction (EF), respectively. Flow through the main pulmonary artery (MPA) and aorta (Ao) was assessed with cardiac gated, cine two-dimensional (2D) phase contrast (PC) sequences during rest and exercise. MPA flow was used to assess the change in SV and CO from rest to exercise since this reflects the output of the RV. In-scanner exercise prescription was based on 6MWD performance, and patients performed 10 minutes of supine exercise (Mean power output: 33 ± 4 Watts) using a commercial MR-compatible recumbent stepper (Cardio Stepper Module, Ergospect GmbH, Innsbruck, Austria).

PET imaging consisted of 15 minutes of resting PET data acquisition followed by the onset of in-bore exercise in which subjects performed stepping exercise for 10 minutes, followed by a 10-minute recovery period (**Figure 1A**). To determine cardiac glucose uptake, 18-fluorodeoxyglucose (18F-FDG) was administered in two separate boluses of 5mCi each prior to rest and exercise imaging, with dynamic 18F-FDG PET data acquired continuously. PET images were manually segmented (ITK-SNAP analysis software)⁵. Plasma time activity curves were determined from the PET LV blood pool and Patlak analysis was used to determine RV and left ventricular (LV) glucose uptake rates (K_i)^{6,7}, to determine the ratio of RV/LV K_i as previously described⁸ (**Figure 1B**).

All data are expressed as mean and standard deviation unless otherwise stated. Given this is a proof-of-concept study involving two subjects, there were no statistical analyses performed.

Results

Clinical and baseline cardiac functional characteristics

Two PAH patients with scleroderma completed clinically standard diagnostic assessment, revealing mPAP: 33.5 ± 7.8 mmHg, PVR: 5.7 ± 1.84 Woods units; CI:

2.14±0.47 L/min/m²; 6-minute walk distance: 401±8 m; Brain natriuretic peptide (BNP): 102±81 pg/ml; NYHA functional class: II.

Resting cardiac structure and function measures were as follows: LV (EDV: 134±48 ml, ESV: 61±36 ml, SV: 73±12 ml, CO: 4.36±1.60 L/min, EF: 56±11 %, mass: 68±41 g), and RV (EDV: 154±34 ml, ESV: 90±33 ml, SV: 65±2 ml, EF: 43±9 %, mass: 19±7 g).

PET/MRI exercise stress measures

The exercise challenge resulted in expected increases as derived from 2D-PC MPA flow in heart rate (HR) (59±12 bpm vs. 81±7 bpm), SV (72±16 ml vs. 104±3 ml), and CO (4.28±1.81 L/min vs. 8.43±0.96 L/min), respectively. Notably, there was a substantial increase in the rate of glucose uptake (53%) in the RV for each patient rest to exercise (Subject 1: 0.0181 min⁻¹ vs. 0.0246 min⁻¹; Subject 2: 0.00179 min⁻¹ vs. 0.00305 min⁻¹), respectively. In the LV, there was a much more modest increase glucose uptake (6%) from rest to exercise (Subject 1: 0.0426 min⁻¹ vs. 0.0433 min⁻¹; Subject 2: 0.0082 min⁻¹ vs. 0.0091 min⁻¹), respectively. Overall, this resulted in a preferential increase in RV/LV K_i (Subject 1: 0.425 min⁻¹ vs. 0.568 min⁻¹; Subject 2: 0.219 min⁻¹ vs. 0.337 min⁻¹) (Figure 1C).

Discussion

The purpose of this study was to determine the feasibility of a PET/MRI exercise stress test to determine the cardiac glucose metabolic flexibility in PAH patients. We hypothesized that the RV in PAH patients would demonstrate a preferential increase in glucose utilization during exercise relative to the LV. The main findings of this study were that the RV exhibited a 53% increase in K_i while the LV exhibited a 6% increase in K_i, and the RV/LV K_i showed an overall increase of 43% from rest to exercise. These changes in RV glucose uptake were observed in parallel with a 43%, 50%, 122%

increase in HR, SV, and CO, respectively. Presumably, the non-failing LV primarily increased fatty acid utilization during exercise (not measured here), while the dysfunctional RV had significantly greater glucose dependence.

The myocardium is a metabolic omnivore⁹ and in healthy myocardium, substrate metabolism is superbly coupled to contractile function and enables the myocardium to adapt to stress on a beat-to-beat basis. Loss of metabolic flexibility is a hallmark of various cardiac diseases⁴. During the process of heart failure, cardiac metabolism shifts from predominantly fatty acid metabolism to increasing utilization of glucose metabolism¹⁰. Attenuated metabolic flexibility, with potential changes to adenosine triphosphate (ATP) production in the myocardium, highlight perturbations in substrate metabolism which are now considered as causes rather than consequences of cardiac disease¹¹. Previous work in PAH patients demonstrated altered metabolism with increased RV dependency for glucose which was inversely associated with contractile function and directly related to PVR¹². Furthermore, the RV metabolic milieu has been shown to be sensitive to therapeutic treatments in PAH patients demonstrated by a reduction in RV glucose utilization which was dose-dependent after six months of carvedilol therapy³, which suggests the ability to augment metabolic flexibility. Although these previous works demonstrate both RV glucose dependency in PAH and that the metabolic environment is sensitive to alteration following chronic therapeutic administration, to date there has not been the development of a test to assess metabolic substrate flexibility in the acute setting in a manner relevant to everyday activities. Similar to these previous studies exhibiting increased glucose utilization in the RV, the data in this pilot study show that the use of a physiological stressor permitted the unmasking of a preferential use of glucose in the RV.

In this pilot study, we tested the feasibility of performing a PET/MRI stress test in two PAH patients as a way to determine acute metabolic adaptations in the RV using a relevant workload that is akin to the 6MWD. We found that the RV exhibits a greater glucose dependency relative to the LV in PAH. Previous studies probing RV glucose uptake have utilized the standard clinical protocol which is a single bolus of ^{18}F -FDG followed by a static scan 1-hour after bolus injection to measure standard uptake values. The novelty of this work is the utilization of dynamic PET acquisition and the use of two mini boluses of ^{18}F -FDG, which serves two purposes. In concert with dynamic PET acquisition, the use of two bolus injections (i.e. at rest and just prior to exercise) permits the quantification of real-time RV and LV glucose uptake using kinetic modeling^{6,7} during a serial rest-stress protocol. Future work utilizing this PET/MRI technique in PAH patients should assess whether greater RV glucose dependency at baseline or during therapy is an independent predictor of adverse outcomes. Further, the technique may be useful to assess for metabolic effects of current vasodilators or novel therapies, as there are currently no specific RV targeted therapies for PAH.

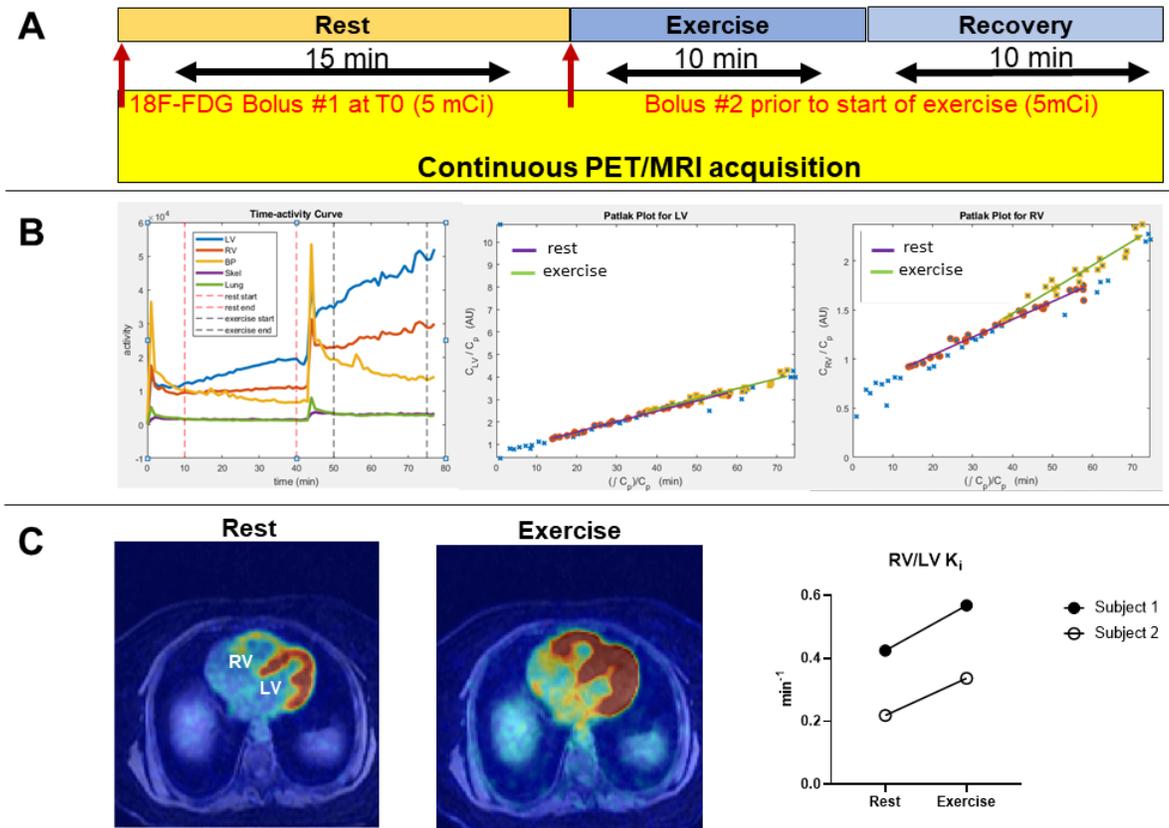


Figure 1. (A) Continuous ^{18}F -FDG PET acquisition using a two-bolus approach permits quantification of the dynamic glucose uptake response in the right (RV) and left ventricle (LV) during a serial rest-stress protocol. (B) Time-activity curves during the dual bolus injection of FDG for the bloodpool, RV, LV, lung, and paraspinal muscles, respectively (left). The LV K_i (middle) and RV K_i (right) at rest and exercise were calculated using Patlak analysis. (C) Representative images from a PAH patient (Subject 1) demonstrating ^{18}F -FDG uptake in the right (RV) and left ventricle (LV) during rest and exercise, respectively. From these representative images, LV K_i was similar during rest and exercise (0.0426 min^{-1} vs. 0.0433 min^{-1}), respectively. However, there was a substantial increase in RV K_i during exercise (0.0181 min^{-1} vs. 0.0246 min^{-1}). Both subjects exhibited a preferential increase in RV/LV K_i during exercise which was coupled with two-fold increases in cardiac output.

Author Contributions

Conceptualization, K.N.G.; methodology, K.N.G., G.P.B., C.J.F., J.R.R., N.C.C., A.B.M., O.W.; validation, K.N.G., A.B.M., G.P.B.; analysis, G.P.B., P.A.C., K.N.G.; writing—original draft preparation, G.P.B.; writing—review and editing, P.A.C., C.J.F., N.C.C., A.B.M., J.R.R., O.W., K.N.G.; funding acquisition, K.N.G; guarantor, K.N.G. All authors have read and agreed to the published version of the manuscript.

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Conflicts of Interest

The authors declare that there is no conflict of interest.

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