PET Imaging May Provide a Novel Biomarker and Understanding of Right Ventricular Dysfunction in Patients With Idiopathic Pulmonary Arterial Hypertension

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Background—The clinical course in pulmonary arterial hypertension (PAH) is variable, and there is limited information on the determinants and progression of right ventricular (RV) dysfunction. The objective is to develop PET metabolic imaging of the RV as a noninvasive tool in patients with PAH.

Methods and Results—We performed PET scanning in 16 patients with idiopathic PAH (age, 41±14 years, 82% women) using 13N-NH3 for perfusion imaging and 18F-fluorodeoxyglucose for metabolic imaging. The myocardium was divided into 6 regions of interest (3 left ventricular [LV], 3 RV), and time-activity curves were generated. A 2-compartment model was used to calculate myocardial blood flow (MBF), and Patlak analysis was used to calculate the rate of myocardial glucose uptake (MGU). All patients underwent cardiac catheterization, cardiac MRI, and cardiopulmonary exercise testing with gas exchange. MBF, MGU, and the ratio of RV/LV MGU were correlated to clinical parameters. Pulmonary artery (PA) pressure was 79±19/30±8 mm Hg (mean, 48±10 mm Hg). MBF was 0.84±0.33 mL/g per minute for the LV and 0.45±0.14 mL/g per minute for the RV. Mean MGU was 136±72 nmol/g per minute for the LV and 96±69 nmol/g per minute for the RV. The ratio of RV/LV MGU correlated significantly with PA systolic (r=0.75, P=0.0085) and mean (r=0.87, P=0.001) pressure and marginally with maximum oxygen consumption (r=−0.59, P=0.05). RV free wall MGU also correlated well with mean PA pressure (r=0.66, P=0.03).

Conclusions—PET scanning with 13N-NH3 and 18F-fluorodeoxyglucose is a feasible modality for quantifying RV blood flow and metabolism in patients with idiopathic PAH. (Circ Cardiovasc Imaging. 2011;4:641-647.)

Key Words: hypertension pulmonary □ positron-emission tomography □ 18F-FDG

Pulmonary arterial hypertension (PAH) is a progressive condition with a poor prognosis if not identified and treated early in the course of the disease. Before the advent of targeted PAH therapy, the National Institutes of Health Primary Pulmonary Hypertension Registry reported a mean survival of 2.8 years from diagnosis in patients with idiopathic PAH (IPAH).1,2 More recently, intravenous epoprostenol has been shown to reduce mortality in patients with IPAH,3–5 whereas endothelin receptor antagonists and phosphodiesterase inhibitors have improved hemodynamics and exercise capacity in patients with PAH.6–9

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Little attention has been devoted to how right ventricular (RV) dysfunction may be best detected and measured, how RV dysfunction evolves structurally and functionally, or what interventions might best preserve RV function. Nevertheless, even the proportionately limited information related to RV dysfunction in PAH and its impact on the outcome of PAH suggests that RV dysfunction is an important contributor and that further understanding of these issues is of pivotal importance. Advancing knowledge through research about the molecular, cellular, and functional characteristics of the RV and its vulnerability to disease will lead to progress in the treatment of PAH.

Morbidity and mortality in PAH have been correlated with mean pulmonary artery (PA) pressure, pulmonary vascular resistance (PVR), right atrial pressure, cardiac index, mixed venous oxygen saturation, exercise capacity, and New York Heart Association (NYHA) functional class.10–14 Therefore, current clinical evaluation of patients with PAH includes invasive evaluation of hemodynamics through right heart catheterization, noninvasive imaging of RV size and function, and measurement of exercise capacity using the 6-minute walk test and cardiopulmonary exercise testing (CPET). However, there is considerable variability in the clinical course of patients with PAH. Therefore, additional serum biomarkers15,16 and noninvasive imaging modalities, which
could identify patients at risk for RV dysfunction and adverse outcomes, might be useful in the clinical evaluation of patients with PAH.

One prior study has evaluated quantitative myocardial glucose utilization (MGU) in the RV, as measured by dynamic 18F-fluorodeoxyglucose (18F-FDG) PET scanning, among a population of patients with varied etiology of PAH. This study found no association between RV MGU and PA pressure or PVR. However, it did find a correlation between the ratio of RV/LV MGU and PVR, albeit based on relatively reduced left ventricle (LV) MGU rather than on increased RV MGU. We hypothesized that MGU is increased in the RV and LV in patients with IPAH and that RV MGU and RV/LV MGU correlate with hemodynamic parameters and exercise capacity in these patients.

Methods

Patient Selection

Patients with IPAH aged 18 to 65 years who were referred to New York Presbyterian Hospital at Columbia University Medical Center for treatment were recruited for this study. All patients underwent right heart cardiac catheterization, CPET, 2D Doppler echocardiography, and cardiac MRI within 30 days of PET imaging. All patients were stable, and no active medical interventions were performed between the tests and PET imaging. The severity of PAH was determined on the basis of right heart catheterization and assessment of clinical symptoms. Patients were excluded if they had diabetes, abnormal LV function, primary left-sided valvular disease, or other forms of PAH. In addition, patients were excluded if they were pregnant, claustrophobic, unable to cooperate with the scanning protocol, or unable to lie flat in the supine position for the duration of the PET scan. All patients gave written, informed consent, and the protocol was approved by the Columbia University Institutional Review Board as well as by the Radioactive Drug Research Committee and the Joint Radiation Safety Committee of the university.

PET Scanning

In preparation for PET imaging, patients fasted overnight for at least 6 hours after a regular meal. The baseline fasting blood glucose was measured, and patients were excluded from the study if their level was >125 mg/dL. The scanning protocol began with a 2-minute scan to ensure appropriate positioning within the scanner followed by a 20-minute transmission scan using a 68Ge source. Although the intrinsic in-plane resolution was 6.5 mm (full width at half maximum), images were reconstructed using an iterative algorithm and a Hann filter (cutoff frequency, 0.4), yielding an effective resolution of 10.5 mm. For resting myocardial perfusion imaging, patients received an intravenous bolus of 0.28 mCi/kg of 13N-NH3, with a simultaneous 2D dynamic acquisition protocol (10 s/frame×12, 30 s/frame×2, 180 s/frame×1). The patients then received 50 g of oral glucose load and were injected with 10 mCi of 18F-FDG IV 1 hour later. The PET scanning began simultaneously, using a 2D dynamic acquisition protocol over 60 minutes (10 s/frame×12, 30 s/frame×10, 120 s/frame×10, 300 s/frame×6). Plasma glucose was measured 0, 15, 30, and 60 minutes after 18F-FDG injection. PET images were acquired on a Siemens ECAT Accel high-resolution PET scanner. All images were corrected for scatter and measured photon attenuation. Image reconstruction was performed using iterative reconstruction and a Butterworth filter.

Quantitative Analysis

For quantitative analysis, the myocardium was divided into 6 regions of interest, 3 for the LV (anterior, lateral, and inferior) and 3 for the RV (apex, free wall, and septum). Time-activity curves and input functions were generated for each region of interest and for the blood pool by placing a small region of interest within the basal LV blood pool on the midventricular slice. A 2-compartment kinetic model was used to calculate myocardial blood flow (MBF) in each region of interest using 13N-NH3. Patlak analysis was used to calculate the rate of MGU from 18F-FDG washout curves for each region of interest and globally for the RV and LV. Values obtained from Patlak analysis were corrected for differences in uptake and phosphorylation of 18F-FDG and glucose using a lumped constant of 0.67. The partial volume effect was corrected based on the RV free wall thickness measured by MRI and the recovery coefficient derived from the phantom study. The corrected MGU was calculated by the following equation: corrected MGU = MGU/recovery coefficient. The recovery coefficient was 0.5 to 1.0. The partial volume recovery coefficient was calculated by convolution with Gaussian kernel representing the reconstructed PET image resolution. The transaxial MRI images corresponding to PET images were selected, and end-diastolic wall thickness of the RV free wall, interventricular septum, and LV free wall were measured for partial volume effect correction of the PET emission data.

Hemodynamic Evaluation, Exercise Testing, and Additional Imaging

Pulmonary and hemodynamic parameters were obtained by right heart catheterization. Cardiac output was measured by thermodilution (mean of 3 values). A symptom-limited CPET was performed on a cycle ergometer using a 10-W ramp protocol. Heart rate was measured using a Marquette 12-lead electrocardiography system, and maximum oxygen consumption (V˙O2max) on room air was measured using a SensorMedics Vmax metabolic cart. All patients underwent 2D color flow Doppler echocardiography with pulsed and continuous-wave Doppler interrogation. In addition, patients underwent cardiac MRI scanning on a 1.5-T GE Signa MRI scanner with EXCITE software, using a dedicated 8-channel cardiac coil with ASSET. MRI images were obtained using a gated steady-state free precession sequence (Fast Imaging Employing Steady-state Acquisition; GE Healthcare) in sagittal, oblique, and short-axis planes with 9-mm slice thickness, 1-mm interslice gap, and 20 phases per cardiac cycle.

Statistical Analysis

Correlations between PET data and hemodynamic and CPET parameters were evaluated using Spearman correlation coefficients. Statistical significance was defined as P<0.05. Data are presented as mean±SD.

Results

Sixteen patients with IPAH were included in this study. Demographic, clinical, and hemodynamic data are shown in Table 1. Patients were predominantly women (82%) aged 41±12 years (range, 25–71 years). IPAH was diagnosed on an average of 20±4 months before the patients’ enrollment in the study. PA pressure was 79±19/30±8 mm Hg (mean 48±10 mm Hg). Medical therapy for the study population is shown in Table 2. The majority of patients were treated with a standard targeted regimen for PAH, including endothelin receptor antagonists, prostacyclin analogs, phosphodiesterase inhibitors, diuretics, digoxin, and spironolactone. On cardiac MRI, the RV was enlarged (mean RV end-diastolic volume, 202±31 mL), although RV function was largely preserved (mean RV ejection fraction, 46±6%) (Table 3). End-diastolic wall thickness and end-systolic wall thickness were measured, and their mean values for RV (9.2±3.6 versus 9.9±4.1) and LV (11.6±4.2 versus 12.4±4.4 mm) were not significantly different.

All patients underwent 13N-NH3 perfusion imaging. Resting myocardial perfusion was qualitatively and quantitatively...
Table 1. Baseline Patient Characteristics (n=16)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>41±12</td>
</tr>
<tr>
<td>Female sex, n (%)</td>
<td>13 (82)</td>
</tr>
<tr>
<td>Fasting blood glucose, mg/dL</td>
<td>92±8</td>
</tr>
<tr>
<td>PA pressure, mm Hg</td>
<td></td>
</tr>
<tr>
<td>Systolic</td>
<td>79±19</td>
</tr>
<tr>
<td>Diastolic</td>
<td>30±8</td>
</tr>
<tr>
<td>Mean</td>
<td>48±10</td>
</tr>
<tr>
<td>PCWP, mm Hg</td>
<td>10±6</td>
</tr>
<tr>
<td>CI, L/min per m²</td>
<td>3.5±0.4</td>
</tr>
<tr>
<td>Blood pressure, mm Hg</td>
<td></td>
</tr>
<tr>
<td>Systolic</td>
<td>111±11</td>
</tr>
<tr>
<td>Diastolic</td>
<td>68±7</td>
</tr>
<tr>
<td>Heart rate, beats/min</td>
<td>74±7</td>
</tr>
<tr>
<td>NYHA, functional class</td>
<td>1.5±0.7</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>26±6</td>
</tr>
<tr>
<td>V̇O₂max, mL/kg per min</td>
<td>16±2</td>
</tr>
</tbody>
</table>

BMI indicates body mass index; CI, cardiac index; NYHA, New York Heart Association; PA, pulmonary artery; PCWP, pulmonary capillary wedge pressure; V̇O₂max, maximum oxygen consumption.

Table 2. Medical Therapy for IPAH Among the Study Patients (n=16)

<table>
<thead>
<tr>
<th>Medication</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Warfarin</td>
<td>13 (82)</td>
</tr>
<tr>
<td>Digoxin</td>
<td>11 (73)</td>
</tr>
<tr>
<td>Endothelin receptor antagonist</td>
<td>10 (64)</td>
</tr>
<tr>
<td>Phosphodiesterase inhibitor</td>
<td>10 (64)</td>
</tr>
<tr>
<td>Prostacyclin analog</td>
<td>9 (56)</td>
</tr>
<tr>
<td>Diuretic</td>
<td>7 (46)</td>
</tr>
<tr>
<td>Spironolactone</td>
<td>7 (46)</td>
</tr>
<tr>
<td>Calcium channel blocker</td>
<td>6 (38)</td>
</tr>
</tbody>
</table>

IPAH indicates idiopathic pulmonary artery hypertension.

Although most patients were in NYHA functional class I or II, V̇O₂max for these patients was reduced at 16 mL/kg per minute (48% of age- and sex-predicted values). No adverse events occurred during or after CPET. The performance-limiting symptom was shortness of breath in all patients. No patient reported retrosternal chest discomfort, and no ischemic electrocardiography changes were observed during exercise and the recovery period. The mean exercise duration was 406±22 s, heart rate at peak was 128±8 beats/minute, systolic blood pressure at peak was 139±4 mm Hg, and diastolic blood pressure at peak was 80±2 mm Hg (rest data are shown in Table 1). There was a trend toward a negative correlation between the ratio of RV/LV MGU and V̇O₂max (r=-0.59, P=0.05). In addition, there was no significant negative correlation between the ratio of RV/LV MGU and exercise duration.

Discussion

Although the LV is the initial target organ for atherosclerosis and systemic hypertension, the RV is the target organ for PAH. PET scanning using cyclotron-produced radiopharmaceuticals has been used to quantify LV blood flow and metabolism in the myocardium in the normal state and in patients with LV hypertrophy, atherosclerosis, and dilated cardiomyopathy.18–24 The healthy heart relies primarily on fatty acid rather than glucose as a source of energy. In both LV hypertrophy and dilated cardiomyopathy, there is a metabolic shift with an increase in MGU and a corresponding decrease in fatty acid metabolism.18,19 and this shift appears to herald a decompensated state. There is experimental evidence to support the maladaptive aspects of this metabolic remodeling only in animal studies. A shift in substrate metabolism toward glucose utilization is associated with disturbed cardiomyocyte Ca²⁺ homeostasis and an increase in cellular oxidative stress.25 In addition, a shift away from fatty acid utilization is associated with a less-efficient alternative pathway for glucose oxidation that produces less nicotinamide adenine dinucleotide. Magnetic resonance spectros-
copy studies have shown reduced creatine phosphate/ATP ratios in hypertrophied hearts with reduced fatty acid oxidation. In the long term, this metabolic remodeling probably contributes to the development of myocardial failure, but this is not a proven hypothesis in humans. Furthermore, longer-term follow-up of RV function and studies of fatty acid metabolism would be required to confirm a maladaptive process.

Blood flow and substrate metabolism in the RV in the normal state have been poorly characterized largely because in the normal heart, the RV does little work compared with the LV and is thin walled. As a result, the normal RV takes up insufficient radiopharmaceuticals to be accurately measured, given the limited resolution of current PET scanners. However, in patients with IPAH, the hypertrophied and enlarged RV can be seen easily with PET imaging. Although

<table>
<thead>
<tr>
<th>Table 4. MBF and MGU in the LV and RV (n=16)</th>
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</thead>
<tbody>
<tr>
<td>LV</td>
</tr>
<tr>
<td>Lateral</td>
</tr>
<tr>
<td>MBF, mL/kg per min</td>
</tr>
<tr>
<td>MGU, nmol/g per min</td>
</tr>
</tbody>
</table>

MBF indicates myocardial blood flow; MGU, myocardial glucose utilization. Other abbreviations as in Table 3.

Figure 1. Nitrogen 13-NH3 resting myocardial perfusion images of the left and right ventricles, illustrating short-axis images (top) and horizontal long-axis images (bottom). Arrows point to the enlarged right ventricle.

Figure 2. Fluorine 18-fluorodeoxyglucose resting myocardial metabolism images of the left and right ventricles, illustrating short-axis images (top) and horizontal long-axis images (bottom). Arrows point to the enlarged right ventricle.
this compensatory hypertrophy has the beneficial effect to normalize wall stress, in experimental animals, it has been shown to shift nutrient substrate uptake from fatty acids to glucose.27,28 Although fatty acid metabolism was not measured in the present study, the high MGU found and its relationship to afterload combined with the findings from experimental studies in chronic pressure overload support the premise that this increase in glucose utilization represents a metabolic shift away from fatty acid utilization.

The present study evaluated MBF and substrate metabolism for the RV and LV in IPAH to compare the 2 ventricles and to investigate whether RV and LV indices outlined by PET scanning correlate with IPAH severity assessing by hemodynamic and CPET. The results of this study provide insight into the effects of increases in the RV afterload on RV blood flow and RV substrate metabolism and demonstrate the feasibility of using dynamic PET scanning to quantify RV blood flow and metabolism in patients with IPAH. We demonstrated a significant correlation between the ratio of RV/LV MGU and PA pressures. Kluge et al17 evaluated quantitative MGU in the RV, as measured by dynamic 18F-FDG PET scanning in varied etiologies of PAH. These authors found no association between RV MGU and PA pressures but they did find a negative correlation between PA pressures and LV MGU and attributed RV/LV MGU and PA pressure correlation to decreased LV MGU. In the current study, we did not find a negative correlation between LV MGU and PA pressure. In contrast to Kluge et al, we performed CPET and found a trend toward a negative correlation between the ratio of RV/LV MGU and V\textsubscript{O}\textsubscript{2,max}. The differences in these studies also may be due to the differences in partial volume effect correction and the recovery coefficient. In Kluge et al, MGU and perfusion were evaluated using different imaging modalities with different spatial resolution. Therefore, there is a possibility that differences in recovery coefficients affected the right-to-left count ratios. The ventricular wall thickness in the Kluge et al study was not systematically evaluated.

A more recent study by Oikawa et al29 looked at patients with PAH and found that increased RV FDG accumulation correlates with the severity of RV pressure overload. Additionally, the authors found a reduction in RV uptake of 18F-FDG in patients with PAH who responded to treatment with epoprostenol, suggesting that some drugs that target the pulmonary vasculature may favorably change RV substrate metabolism. In Oikawa et al, the authors did not quantify MBF or MGU (Patlak quantification). In addition, they used electron beam CT or MRI for the measurement of RV structure. In contrast, all the patients in the current study underwent cardiac MRI, which is considered the best technique to quantify RV volumes and size. Oikawa et al also had more patients with advanced PAH (NYHA functional class II predominantly) rather than NYHA functional class I/II, which is the population one might target with such testing (ie, the early clinical disease without overt RV failure).

Also recently, Mielniczuk et al30 studied patients with heart failure, which included those with diabetes, ischemic heart disease, and prior infarctions. Fluorine 18-FDG uptake is variable in patients with ischemic cardiomyopathy, and this will have an effect on LV and RV standardized uptake values. In their study, RV ejection fraction was measured by equilibrium radionuclide ventriculography and RV hypertrophy by echocardiography. All the patients in the current study underwent cardiac MRI, which is considered the best technique to quantify RV volumes and size. Mielniczuk et al did not quantify MGU (Patlak analysis), and right heart catheterization was not done for measuring RV systolic pressure.

Compared with these studies, the current study is more comprehensive and in patients with IPAH (NYHA functional class I/II). All the patients underwent MRI, right heart catheterization, quantification of MBF, quantification of MGU, and CPET. In contrast to the aforementioned studies, we compared V\textsubscript{O}\textsubscript{2,max} with RV MGU. V\textsubscript{O}\textsubscript{2,max} is considered a strong predictor of survival in patients with PAH.

The shift in MGU may be an early marker of RV dysfunction, possibly a preclinical marker before overt RV failure, given that RV function on MRI in the current study was largely preserved and that most patients were in NYHA functional class I/II. The relations observed support the need for further investigation of MGU as a novel early biomarker that could be a therapeutic target in the treatment and monitoring of PAH. Monitoring MGU level may help to...
optimize treatment to improve function and outcome. Oikawa et al.20 showed a reduction in RV standardized uptake values of 18F-FDG with treatment with intravenous epoprostenol. Whether the current treatments of PAH affect MGU would require further studies. In addition, the current study demonstrates a trend toward negative correlation with VO2max, suggesting that this finding may have some prognostic impact.

The goal of the current study was to develop PET parameters that could aid in the management of patients with PAH and to use a metabolic parameter that can be measured with a widely available radiopharmaceutical (ie, 18F-FDG). Although we used 13N-NH3 (cyclotron produced) for measuring MBF, it is possible that generator-produced 82Rb also can be used to quantify blood flow, which would allow these tests to be more widely performed. The results of this study provide insight into the effects of increases in the RV afterload on RV blood flow and substrate metabolism. Whether RV myocardial metabolic changes contribute to the functional changes and whether myocardial metabolic modulation improves the mortality and morbidity of patients with IPAH will require further studies.

Study Limitations
We did not perform fatty acid imaging; therefore, the metabolic shift with an increase in MGU and a corresponding decrease in fatty acid metabolism was not evaluated. Although all patients in the present study had normal coronary angiography and normal MBF, we cannot exclude the possibility that myocardial ischemia due to severe RV hypertrophy might have increased the RV 18F-FDG metabolism. However, previous animal studies have shown that glucose utilization in rats is increased and free fatty acid utilization decreased in the hypertrophied myocardium with chronic LV or RV pressure overload. There was no control group in this study because in normal subjects, the RV wall is quite thin and MBF and MGU cannot be measured.

Conclusions
PET scanning with 13N-NH3 and 18F-FDG appears to be a feasible modality for quantifying RV blood flow and RV metabolism in patients with IPAH. Further studies are warranted to investigate using metabolic substrate imaging of MGU with PET as a tool to plan and follow therapy aimed at metabolic modulation in IPAH and, hopefully, PAH associated with other conditions.

Acknowledgments
We thank the nuclear technologists in the PET center for their help in studying these patients.

Disclosures
Dr Barst has received speakers bureau fees from Actelion (<$10,000) and Gilead (<$10,000) and consultant/advisory board fees from Pfizer (≥$10,000), Actelion (≥$10,000), Novartis (≥$10,000), and Ikaria (≥$10,000).

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**CLINICAL PERSPECTIVE**

This is a comprehensive study in patients with idiopathic pulmonary arterial hypertension (New York Heart Association functional class I/II). All the patients underwent MRI, right heart catheterization, quantification of myocardial blood flow, quantification of myocardial glucose uptake, and cardiopulmonary exercise testing. The study revealed that PET scanning with $^{13}$N-$\text{NH}_3$ and $^{18}$F-fluorodeoxyglucose appears to be a feasible modality for quantifying myocardial blood flow and RV metabolism in patients with idiopathic pulmonary hypertension. An increased metabolic rate of glucose uptake in the RV presumably indicates early RV functional impairment. The shift in myocardial glucose uptake may be an early marker of RV dysfunction and possibly a preclinical marker before overt RV failure given that RV function on MRI in the current study was largely preserved and that most patients were in New York Heart Association functional class I/II. The relations observed support the need for further investigation of myocardial glucose uptake as a novel early biomarker that could be a therapeutic target in the treatment and monitoring of pulmonary arterial hypertension. In addition, the study demonstrates a trend toward negative correlation with maximum oxygen consumption, suggesting that this finding may have some prognostic impact. Maximum oxygen consumption is considered a strong predictor of survival in patients with pulmonary arterial hypertension. Monitoring myocardial glucose uptake level may help to optimize treatment to improve function and outcome.
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