Right Ventricular Failure in Idiopathic Pulmonary Arterial Hypertension Is Associated With Inefficient Myocardial Oxygen Utilization

Yeun Ying Wong, MD; Gerrina Ruiter, MD; Mark Lubberink, PhD; Pieter G. Rajmakers, MD, PhD; Paul Knaapen, MD, PhD; J. Tim Marcus, PhD; Anco Boonstra, MD, PhD; Adriaan A. Lammertsma, PhD; Nico Westerhof, PhD; Willem J. van der Laarse, PhD; Anton Vonk-Noordegraaf, MD, PhD

Background—In idiopathic pulmonary arterial hypertension (IPAH), increased right ventricular (RV) power is required to maintain cardiac output. For this, RV O₂ consumption (MVO₂) must increase by augmentation of O₂ supply and/or improvement of mechanical efficiency—ratio of power output to MVO₂. In IPAH with overt RV failure, however, there is evidence that O₂ supply (perfusion) reserve is reduced, leaving only increase in either O₂ extraction or mechanical efficiency as compensatory mechanisms. We related RV mechanical efficiency to clinical and hemodynamic parameters of RV function in patients with IPAH and associated it with glucose metabolism.

Methods and Results—The patients included were in New York Heart Association (NYHA) class II (n=8) and class III (n=8). They underwent right heart catheterization, MRI, and H₂¹⁵O₂-,¹⁵O₂-, C¹⁵O₂-, and ¹⁸FDG-PET. RV power and O₂ supply were similar in both groups (NYHA class II versus class III: 0.54±0.14 versus 0.47±0.12 J/s and 0.109±0.022 versus 0.128±0.026 mL O₂/min per gram, respectively). RV O₂ extraction was near-significantly lower in NYHA class II compared with NYHA class III (63±17% versus 75±16%, respectively, P=0.10). As a result, MVO₂ was significantly lower (0.066±0.012 versus 0.092±0.010 mL O₂/min per gram, respectively, P=0.006). RV efficiency was reduced in NYHA class III (13.9±3.8%) compared with NYHA class II (27.8±7.6%, P=0.001). Septal bowing, measured by MRI, correlated with RV efficiency (r=−0.59, P=0.02). No relation was found between RV efficiency and glucose uptake rate. RV mechanical efficiency and ejection fraction were closely related (r=0.81, P<0.001).

Conclusions—RV failure in IPAH was associated with reduced mechanical efficiency that was partially explained by RV mechanical dysfunction but not by a metabolic shift. (Circ Heart Fail. 2011;4:700-706.)

Key Words: idiopathic pulmonary arterial hypertension ■ right ventricular mechanical efficiency ■ oxygen supply and consumption ■ right ventricular failure ■ positron emission tomography

In idiopathic pulmonary arterial hypertension (IPAH), both pulmonary vascular resistance and right ventricular (RV) afterload increase progressively. This causes RV hypertrophy and may lead to RV failure. To maintain cardiac output during the increasing afterload in IPAH, sufficient power output must be generated by the RV, which requires more O₂. Recently, however, Gomez et al observed stress-induced ischemia in the RV wall of a subset of PAH patients with overt RV failure and suggested an association between RV ischemia and dysfunction. The same study also suggests that RV perfusion reserve at rest may be exhausted in severe PAH, which would restrict the RV in a further adaptive response. If perfusion reserve is indeed limited, the only possibility for the RV to meet its energy requirements is to increase its mechanical efficiency, which is proportional to the ratio of ventricular power output and myocardial O₂ consumption (MVO₂). However, unlike left ventricular (LV) disease and heart failure in which mechanical efficiency is reduced, mechanical efficiency in overt RV failure is unknown.

Clinical Perspective on p 706

Because of the vascular anatomy of the human RV, its venous pO₂ has not been determined invasively. Recently, we demonstrated that O₂ extraction fraction (OEF) of the thickened RV wall in IPAH can be noninvasively measured using...
The purposes of this study were to (1) determine the relationship between RV power output and MVO2 in IPAH patients and (2) relate RV mechanical efficiency to RV function, using both clinical and functional assessments in IPAH patients. We also determined whether mechanical RV dysfunction and RV glucose uptake rate related to the RV efficiency that was found.

Methods

Patients
Twenty-six patients with IPAH were eligible for study. Five patients refused to participate and 5 other patients gave consent but were subsequently withdrawn because of emergence of severe clinical condition (n=2: hemoptysis and endocarditis) or because of unsuccessful cannula placement in the radial or brachial artery (n=3). In total, 16 patients were included, of which 15 patients were on optimal treatment and diagnosed with IPAH for a median time of 3 years, ranging from 2 months to 7 years. All patients continued receiving treatment (Table 1). One patient was newly diagnosed with severe IPAH and included right before start of drug treatment. Exclusion criteria were known history of coronary artery disease or diabetes mellitus, atrial fibrillation, and anemia (hemoglobin <0.13 g/mL). Assessment of the World Health Organization’s 1998 adapted New York Heart Association classification was performed before study participation by the clinicians responsible for the patient (A.V.N. and A.B.). The protocol was approved by the Medical Ethics Review Committee of VU University Medical Center. Each patient gave written informed consent before study. Y.Y.W. and G.R. analyzed the images blinded for patient’s clinical state.

Table 1. Patient Characteristics and Hemodynamics

<table>
<thead>
<tr>
<th></th>
<th>All</th>
<th>NYHA Class II (n=8)</th>
<th>NYHA Class III (n=8)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>44.8±12.8</td>
<td>42.4±12.4</td>
<td>47.1±13.6</td>
<td>NS</td>
</tr>
<tr>
<td>Female/male</td>
<td>15/1</td>
<td>7/1</td>
<td>8/0</td>
<td>...</td>
</tr>
<tr>
<td>Prostacyclin all/single treatment, n</td>
<td>2/0</td>
<td>4/2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ERA all/single treatment, n</td>
<td>7/3</td>
<td>3/0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PDE5 all/single treatment, n</td>
<td>4/1</td>
<td>4/1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6MWD, m</td>
<td>455±116</td>
<td>496±104</td>
<td>415±119</td>
<td>NS</td>
</tr>
<tr>
<td>mRAP, mm Hg</td>
<td>9±7</td>
<td>5±5</td>
<td>13±8</td>
<td>0.022</td>
</tr>
<tr>
<td>mPAP, mm Hg</td>
<td>52±14</td>
<td>46±12</td>
<td>57±14</td>
<td>NS</td>
</tr>
<tr>
<td>Heart rate, bpm</td>
<td>76±15</td>
<td>67±63</td>
<td>85±15</td>
<td>0.012</td>
</tr>
<tr>
<td>Stroke volume, mL</td>
<td>64±24</td>
<td>81±16</td>
<td>48±19</td>
<td>0.002</td>
</tr>
<tr>
<td>Cardiac output, L/min</td>
<td>4.6±1.2</td>
<td>5.3±0.8</td>
<td>3.9±1.1</td>
<td>0.009</td>
</tr>
<tr>
<td>RV mass, g</td>
<td>102±29</td>
<td>93±35</td>
<td>111±19</td>
<td>NS</td>
</tr>
<tr>
<td>RV EDV, mL</td>
<td>165±50</td>
<td>154±55</td>
<td>177±46</td>
<td>NS</td>
</tr>
<tr>
<td>RV EF, %</td>
<td>35±16</td>
<td>46±15</td>
<td>25±9</td>
<td>0.002</td>
</tr>
<tr>
<td>PVR, dyne·s·cm⁻5</td>
<td>697±345</td>
<td>504±222</td>
<td>890±279</td>
<td>0.008</td>
</tr>
<tr>
<td>NTproBNP, ng/L</td>
<td>1242±1777</td>
<td>540±669</td>
<td>1693±2330</td>
<td>NS</td>
</tr>
<tr>
<td>SvO₂, %</td>
<td>67±6</td>
<td>71±3</td>
<td>63±4</td>
<td>0.002</td>
</tr>
<tr>
<td>Arterial O₂ content</td>
<td>0.18±0.02</td>
<td>0.18±0.02</td>
<td>0.18±0.01</td>
<td>NS</td>
</tr>
</tbody>
</table>

NYHA indicates New York Heart Association; ERA, endothelin receptor antagonist; EDV, end-diastolic volume; EF, ejection fraction; mPAP, mean pulmonary artery pressure; mRAP, mean right atrial pressure; PDE5, phosphodiesterase type 5 inhibitors; PVR, pulmonary vascular resistance; 6MWD, 6-minute walk distance; RV, right ventricle; and SvO₂, mixed venous O₂ saturation.

Values are mean±SD. P values were tested using t test.

the spatial resolution of state-of-the-art PET scanners and 15O and 15O₂ tracers.11 We also measured RV perfusion, using H15O-PET next to OEF to calculate RV MVO2.12

The purposes of this study were to (1) determine the relationship between RV power output and MVO2 in IPAH patients and (2) relate RV mechanical efficiency to RV function, using both clinical and functional assessments in IPAH patients. We also determined whether mechanical RV dysfunction and RV glucose uptake rate related to the RV efficiency that was found.

Study Design
All patients underwent right heart catheterization (RHC), cardiac MRI (cMRI), and PET that consisted of 3 consecutive scans using H15O, 15O₂, and C15O to measure myocardial perfusion or blood flow (MBF), OEF and MVO2 and fractional blood volume, respectively (Figure 1). 15O-PET scans were performed 2 hours after a light breakfast. One day after the 15O-PET scans, an 18FDG scan was performed to quantify myocardial glucose uptake rate (online-only Data Supplement Figure I, A and B). When possible, RHC, cMRI, and PET studies were performed within 1 week of each other. In 3 subjects, for logistical or personal reasons, the interval between RHC and PET was 20–55 days and between cMRI and PET, 20–36 days. Because these patients had stable IPAH under drug treatment, that is, less than 10% change in 6-minute walk distance over 6 months before inclusion (5±3%) and no change in medical therapy or NYHA class, the interval was considered acceptable.

PET Imaging Protocol
Patients received a cannula in the radial or brachial artery for blood sampling.

Data Acquisition
The protocol for cardiac H215O and C15O scans has been described previously.11 Briefly, scans were performed in 2D acquisition mode, using an ECAT EXACT HR+ scanner (Siemens/CTI, Knoxville, TN). After a transmission scan used to correct all subsequent scans for tissue attenuation, subjects underwent 3 consecutive scans, as shown in Figure 1. First, a dynamic emission scan (10 minutes, 40 frames with progressive increase in duration) was started simultaneously with injection of 1100 MBq H15O. A second identical emission scan was started at the same time as a bolus injection of 7 GBq 15O2. During the 15O2 scan, 5 arterial blood samples were obtained to measure recirculating H15O concentration. An additional arterial sample was drawn to determine RHC arterial O2 content. Finally, a 6-minute static emission scan was acquired, starting 1 minute after the end of bolus injection of 4 GBq C15O gas to allow imaging of ventricular blood volumes. Approximately 20% of the administered radioactivity during 15O2 and C15O inhalation is taken up by the blood.13 During all scans, systemic blood pressure and peripheral saturation were registered at set intervals. Heart rate and ECG were monitored continuously.

Image Processing and Data Analysis
All emission data were reconstructed as previously described.11 The anatomic tissue fraction images, generated by subtracting the C15O blood pool image from transmission image,14 were resliced into short-axis images according to anatomic axes of the LV. The same reslicing parameters were applied to both dynamic H15O and 15O2 images. Using anatomic tissue fraction images, RV wall regions of

Figure 1. PET protocol time scheme. C15O scan was initiated 1 minute after end of 15O2 inhalation. See text for explanation.
interest were defined on basal, distal, and apical planes (Figure 2). These regions of interest were projected onto dynamic H$_2^{15}$O and $^{15}$O$_2$ images to generate time-activity curves. Next, volume weighted averages of basal, distal, and apical time-activity curves were averaged. MBF was determined from these average time-activity curves, using the standard single tissue compartment model.$^{15}$ OEF was determined from $^{15}$O$_2$ scan using dynamic implementation$^{11}$ of a previously described model.$^{14}$ reusing MBF, perfusable tissue uptake was calculated for the RV as follows$^{14}$:

$$\text{Mechanical efficiency was calculated from the ratio of RV power output (Eq 1) and } \text{MVO}_2 \text{ (Eq 2). As } \text{MVO}_2 \text{ in Equation 2 is calculated per gram, RV mass is included here for calculation of } \text{MVO}_2 \text{ by whole RV. To convert } \text{RV MVO}_2 \text{ to units of metabolic power (J/s), it was multiplied by the caloric equivalent of O}_2: 1 \text{ mL of O}_2/\text{min corresponds to about } 0.34 \text{ J/s, assuming that RV oxidizes free fatty acid and glucose equally:}$

$$\text{Mechanical efficiency} = \frac{\text{Power}}{[\text{MVO}_2 \times \text{RV mass} \times 0.34] \times 100\%}$$

### Hemodynamic and Oxidative Calculations

A brief description is provided for both RHC and cMRI in the online-only Data Supplement.

RV ejection fraction (EF) was derived as the ratio of stroke volume (SV, assessed from aortic flow) to RV end-diastolic volume. RV post-systolic isovolumic period, which is the time between pulmonary valve closure and tricuspid valve opening, was determined in the 2-chamber view described previously and corrected for RR time.$^{11}$ The interventricular septum plays an important role in RV power generation in PAH. Therefore, total septal mass, determined by LV mass minus LV free wall mass, was divided into a right and left septal mass, assuming that the right and left parts of the septal masses are proportional to their free wall counterparts. The right septal part was included to the RV wall mass in the following calculations.

### RV Power

Combining hemodynamic data from both RHC and cMRI, the power (J/s) of the RV was calculated as

$$\text{Power} = \text{HR} \times m\text{PAP} \times \text{SV} \times 2.22 \times 10^{-6}$$

where HR is heart rate in beats per minute and mPAP is in mm Hg; SV, in milliliters, was assessed from the difference between LV end-diastolic volume and end-systolic volume, which was found to be equally accurate as the forward aortic flow for SV assessment in IPAH.$^{18}$ The factor $2.22 \times 10^{-6}$ converts mm Hg · L/min to J/s. Only mean power output is used in the present study. Saouti et al showed total power equals 1.23 times mean power$^{19}$ and thus does not affect the results qualitatively.

### RV Oxygen Consumption and Supply

Regional MVO$_2$ (in mL/min per gram of cardiac tissue) was calculated for the RV as follows$^{14}$:

$$\text{MVO}_2 = \text{OEF} \times \text{MBF} \times \text{CaO}_2$$

where CaO$_2$ is arterial O$_2$ content (mL O$_2$/mL blood).$^{14}$ Myocardial O$_2$ supply (mL/min per gram) was calculated as MBF × CaO$_2$.

Mechanical efficiency was calculated from the ratio of RV power output (Eq 1) and MVO$_2$ (Eq 2). As MVO$_2$ in Equation 2 is calculated per gram, RV mass is included here for calculation of MVO$_2$ by whole RV. To convert RV MVO$_2$ to units of metabolic power (J/s), it was multiplied by the caloric equivalent of O$_2$: 1 mL of O$_2$/min corresponds to about 0.34 J/s, assuming that RV oxidizes free fatty acid and glucose equally:

$$\text{Mechanical efficiency} = \frac{\text{Power}}{[\text{MVO}_2 \times \text{RV mass} \times 0.34] \times 100\%}$$

### Statistical Analysis

All results are expressed as mean±SD. The 2 groups (ie, NYHA classes II and III) were compared using $t$ tests; the nonparametric Mann–Whitney $U$ test was used where indicated. Pearson correlation was performed where necessary. All statistics were performed using Prism 5 for Windows (GraphPad Software, San Diego, CA). $P<0.05$ was considered significant.

### Results

Patient characteristics and hemodynamics are summarized in Table 1: some parameters are also shown in Figure 3. In accordance with severity of IPAH, NYHA class III patients had lower SV and cardiac output (CO) (Figure 3A), despite higher heart rate as compared with NYHA class II. Mean PAP was near-significantly higher in NYHA class III as compared with class II (Figure 3B; $P=0.083$, Mann–Whitney $U$ test). PVR was increased in NYHA class III, whereas RV mass was similar in the 2 groups. RVEF and SvO$_2$ were lower in NYHA class III. Six-minute walk distance was not significantly lower in the severely ill.

PET-derived parameters for the RV per cardiac mass are shown in Table 2. Both MBF (corrected for RV mass, Figure 3C) and OEF (Figure 3D) were not significantly higher in the NYHA class III (MBF: $P=0.088$, $t$ test; OEF: $P=0.105$, Mann–Whitney $U$ test). There was, however, a significantly higher MVO$_2$ per gram (Table 2). In contrast, RV O$_2$ supply per gram RV was similar in NYHA class II and class III patients (Table 2). For total RV, MVO$_2$ was also higher in the severely ill (Figure 3F), whereas RV power was not significantly lower (Figure 3E). This led to a significant reduction of RV efficiency by ≈50% in the NYHA class III patients compared with the NYHA class II patient group (Figure 3G).

A tight relationship was found between the mechanical efficiency and RVEF, a hemodynamic index of systolic RV function parameter (Figure 4, $r=-0.81$, $P<0.001$). There

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**Figure 2.** Example of a cardiac MRI and C$^{15}$O-PET image of a patient with idiopathic pulmonary arterial hypertension (IPAH) with New York Heart Association class III. Cardiac MRI image of a patient’s heart with severe IPAH at short-axis view, cut at mid level of the heart (A). C$^{15}$O-PET image, reconstructed as an attenuation tissue fraction, a so-called “negative image” of the ventricular blood volumes after inhalation of C$^{15}$O (B). Using this image, the right ventricular (RV) wall was defined, depicted as the marked region in C. The RV wall regions of base, mid, and apical levels were combined to an RV wall volume. This was then projected onto the dynamic H$_2^{15}$O and $^{15}$O$_2$ images for quantification RV blood flow and O$_2$ extraction, respectively.
was also a high correlation between RV efficiency and SvO₂ ($r=0.76$, $P=0.001$).

In search for an underlying mechanical cause for the reduced efficiency, postsystolic isovolumic period was plotted against the RV efficiency, showing a negative correlation ($r=-0.594$, $P=0.020$, Figure 5). No correlation was found between the RV myocardial glucose uptake rate and RV efficiency ($r=0.38$; $P=0.18$, online-only Data Supplement Figure I, C).

**Discussion**

In the present study, we demonstrate that RV mechanical efficiency is lower in NYHA class III than in NYHA class II patients (Figure 3G), indicating a decrease with progression of IPAH. In addition, the strong relation between RVEF and mechanical efficiency (Figure 4) stresses the fact that decreasing mechanical efficiency is a characteristic for deterioration of RV function in IPAH. The reduced efficiency in NYHA class III patients is not related to RV power output, because this was

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### Table 2. Perfusion and O₂ Consumption of Right Ventricle Per Unit Mass Measured by PET

<table>
<thead>
<tr>
<th></th>
<th>NYHA Class II</th>
<th>NYHA Class III</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$(n=8)$</td>
<td>$(n=8)$</td>
<td></td>
</tr>
<tr>
<td>MBF, mL/min per gram</td>
<td>0.61±0.15</td>
<td>0.71±0.16</td>
<td>NS</td>
</tr>
<tr>
<td>O₂ supply, mL/min per gram</td>
<td>0.109±0.022</td>
<td>0.128±0.026</td>
<td>NS</td>
</tr>
<tr>
<td>MVO₂, mL/min per gram</td>
<td>0.066±0.012</td>
<td>0.092±0.010</td>
<td>$&lt;0.001$</td>
</tr>
</tbody>
</table>

NYHA indicates New York Heart Association; MBF, myocardial blood flow; and MVO₂, myocardial oxygen consumption.

Values are mean±SD; $P$ values were tested using $t$ test.
similar between the 2 groups (Figure 3E), but NYHA class III patients had higher MVO2 of both total RV (Figure 3F) and per unit RV mass (Table 2) as compared with NYHA class II.

To the best of our knowledge, there are no previous data on human OEF and perfusion of the normal RV to compare with our patient data. Based on canine studies, normal RV OEF has been estimated as 45–50%, indicating that the RV has a substantially higher O2 extraction reserve than the left heart (OEF values are 60–80% in healthy men). Additionally, Hart et al demonstrated that during heavy exercise, RV O2 utilization increases initially by maximizing OEF before coronary reserve is mobilized. Interestingly, we found a mean RV OEF of 69% in our IPAH patients (Figure 3D), approximating that of normal LV. Our data suggests that in analogy with the normal (canine) RV during strenuous exercise, the pressure-overloaded RV in IPAH already has a reduced O2 extraction reserve at rest, and resting O2 demand becomes predominantly dependent on perfusion. We found similar MBF in the hypertrophied RV between mild and severe IPAH. We therefore hypothesize that the dysfunctional RV is unable to increase its perfusion in severe PAH, and thus O2 supply cannot increase to meet a higher O2 demand (eg, during physical exercise). RV ischemia is then the result, which is in accordance with the observation by Gomez et al, who demonstrated stress-induced RV wall ischemia in IPAH patients with severe heart failure. The high RV OEF that we found may also increase the risk to develop hypoxia in the hypertrophied RV cardiomyocytes.

RV power in the NYHA class III group was similar to NYHA class II (Figure 3E), despite lower SV and CO (Table 1 and Figure 3A), but we must take into account that RV power is significantly higher compared with the normal RV (online-only Data Supplement Figure II). Previous studies also demonstrated that patients with advanced IPAH had significantly reduced CO but similar mPAP as compared with mild IPAH. The RV power that can be calculated from the data provided in these studies is also not significantly lower in the patients with progressive IPAH, which is in agreement with our data. It follows from the lower CO and unchanged mPAP that PVR is higher in the NYHA class III patients (Table 2). Apparently, RV power output cannot be increased in advanced IPAH to maintain CO and SV, which is a sign of RV failure. This is further supported by the tight relationship between RVEF and mechanical efficiency (Figure 4), which has also been shown in patients with ischemic LV heart disease. Reduced SvO2 is a strong prognostic determinant in IPAH, as it is associated with a decreased cardiac output in the severely ill. It is noticeable that RV efficiency independently correlates well with SvO2, emphasizing once more that mechanical efficiency is a strong indicator for RV function.

**Potential Underlying Mechanisms of Mechanical Inefficiency at the Mechanical and/or Cardiomyocyte Level**

Mechanical dysfunction can be due to tricuspid regurgitation, septal bowing, asynchronous activation, and/or diastolic dysfunction. Power output loss caused by tricuspid regurgitation, however, was small and did not influence the mechanical efficiency in our present study (online-only Data Supplement Table I). In contrast, we did find a weak but significant inverse relation between prolonged post-systolic isovolumic period and reduced RV efficiency (Figure 5). Based on recent insight, this prolonged period is related to the post-systolic RV isovolumetric contraction period rather than a prolonged diastolic relaxation time, indicating the presence of abnormal increased RV wall tension in these patients. This prolonged period is visible on echocardiography or cMRI as leftward septal bowing after pulmonary valve closure, increasing RV MVO2 without ejection of blood. The low correlation coefficient found between this period and RV efficiency, however, suggests that the reduced efficiency cannot be explained by this prolonged isovolumic contraction period alone. Prostacyclin was shown to improve the right arterioventricular coupling through reduction of arterial elastance. This treatment was more common in the NYHA class III group (Table 1). Nevertheless, it did not prevent the reduced RV efficiency in our patient population. Furthermore, it is possible that myocardial fibrosis contributes to a reduced mechanical efficiency. Blyth et al found that patients with a lower RVEF had more myocardial fibrosis than patients with a preserved RVEF.

Additional causes for reduced efficiency must be sought at the cardiomyocyte level in advanced RV failure. Unfortunately, it is not possible to obtain RV cardiac tissue in our study population for histological analysis of morphological changes or capillary density. Preclinical pulmonary hypertension (PH) studies, however, show that RV cardiomyocytes are enlarged with reduced capillary density. The oxygen diffusion distance is increased as the result of these changes, which may be an underlying cause for reduction in efficiency. Indeed, we recently showed a similar reduction in mechanical efficiency in the isolated, hypertrophied RV papillary muscle obtained from an experimental PH model.

Chronic heart failure takes place with a metabolic shift from free fatty acids to glucose oxidation, which is demonstrated also in the hypertrophied RV in experimental and clinical PAH studies. In theory, the efficiency should increase because glucose oxidation yields more energy than...
fat oxidation per mole of oxygen. However, in heart failure, the shift to glucose oxidation appears to concur with the presence of reduced mechanical efficiency, suggesting that the glucose shift is a secondary phenomenon to the diminished efficiency. We also measured the glucose metabolism in our patients and found that the RV glucose uptake rate was similar in NYHA class II and NYHA class III patients (P = 0.18; online-only Data Supplement Figure I, C). The increased MVO₂ to power output in severe IPAH suggests inefficient O₂ utilization by the failing RV as the result of cellular processes in which O₂ is used for processes other than ATP production for contraction, for example, ion pumps, protein turnover, mitochondrial uncoupling, or oxygen radical formation. Indeed, local administration of XO inhibitor, NO-synthase inhibitor or vitamin C (a reactive oxygen species scavenger) have been shown to ameliorate the inefficient O₂ utilization by the failing RV as the result of mechanical dysfunction, but not by a metabolic shift to glucose oxidation. The reduction in mechanical efficiency is strongly correlated with RVEF, implying that the increased O₂ use relative to power output is a feature of RV failure.

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Disclosures
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Supplement Methods and Results

Right heart catheterization

The protocol has been detailed previously. Briefly, under continuous ECG monitoring, a balloon-tipped, flow-directed 7.5F Swan-Ganz VIP+ catheter (834HF75, Edwards Lifesciences Corporation, Irvine, CA, USA) was inserted in patient’s internal jugular vein. Cardiac output (CO) was measured by means of thermodilution. Blood was sampled from the main pulmonary artery to measure mixed venous oxygen saturation (SvO₂). Pulmonary vascular resistance (PVR) was calculated as: (mPAP-PCWP)/CO, where mPAP is mean pulmonary arterial pressure and PCWP pulmonary capillary wedge pressure.

Cardiac magnetic resonance imaging

Scanning protocol is described previously. Cardiac MRI scans were acquired on a Siemens 1.5 T Sonata scanner or Siemens 1.5 T Avanto whole body scanner (Siemens Medical Solutions, Erlangen, Germany). RV volumes and mass were measured from the stack of short axis images by manual detection of the endocardial and epicardial borders of RV on each slice using MR-Analytical Software System (Media, Leiden, Netherlands). RV end-diastolic, end-systolic volumes and RV free wall mass were calculated.
Effect tricuspid regurgitation on loss of right ventricular power output

Six idiopathic pulmonary arterial hypertension (IPAH) patients (NYHA II, n=1; NYHA III, n=5) had moderate to severe tricuspid regurgitation found on echocardiography. ‘Backward’ volume is the amount of regurgitated volume from the right ventricle into the right atrium, calculated by the difference between the right ventricular (RV) end diastolic volume and RV end systolic volume, minus the forward stroke volume obtained from the aortic flow. ‘Backward power’ is the power loss due to backward flow and is the product of the backward volume, heart rate, mean right atrial pressure and the conversion factor $2.22 \times 10^{-6}$ (see Eq 1 in manuscript for explanation).

Loss of right ventricular power due to tricuspid regurgitation is shown in Table-Suppl 1. Note the large range, which is due to one patient (NYHA III) who had severe tricuspid regurgitation after destructive endocarditis on the tricuspid valve two years earlier. The loss of forward stroke volume was almost 50% in this patient! The power loss was 17%, resulting in a 20% loss of mechanical efficiency in this patient. However, the power loss in the other patients with tricuspid regurgitation was negligible and did not affect the RV mechanical efficiency significantly ($P=0.22$). Therefore, we can conclude that, except for the case with destructed tricuspid valves, moderate to severe tricuspid regurgitation had little to no consequences for the RV mechanical efficiency.
RV $^{18}$FDG-PET and myocardial glucose uptake rate

The $^{18}$FDG study occurred 1 day after the $^{15}$O-PET scans (Figure 1, main manuscript). Figure Suppl-1A displays the $^{18}$FDG scan preparation and PET protocol. The patients were prepared with overnight fasting, a single oral dose acipimox 250mg (Nycomed, Netherlands BV) and special carbohydrate and protein-enriched meal.  

Data acquisition and image analysis have been described previously. Briefly, The scan was performed in 3D acquisition mode using an ECAT EXACT HR+ scanner (Siemens/CTI, Knoxville, TN, USA). Two hours after administration of acipimox, a 10-min transmission scan was started to correct subsequent scan for tissue attenuation. Then, $^{18}$FDG (185 MBq) was injected intravenously and a dynamic emission scan started simultaneously (60 min, 39 frames). Venous blood was sampled to measure plasma glucose and free fatty acids during the scan. A similar re-slicing procedure of $^{15}$O-PET image processing as described in the main manuscript was undertaken for $^{18}$FDG images. RV wall ROIs were defined with the summed $^{18}$FDG short-axis image and used to generate time-activity curves by regions of interest projection onto the dynamic images.

Myocardial glucose uptake rate (MRglu, μmol glucose /gram cardiac tissue /min) was calculated using the Patlak method:

$$= \frac{K_i \times \text{plasma glucose concentration}}{\text{lumped constant}}$$  

(Suppl.-Eq. 1)

where $K_i$ is the influx rate constant derived from the $^{18}$FDG time-activity-curve and was determined in the RV wall within the region of the blue line shown in Figure Suppl-1B. The lumped constant for cardiac $^{18}$FDG is considered 1 in our PET-center.
Despite the exclusion of patients with known diabetes mellitus, two patients (one NYHA II and one NYHA III) turned out to have hyperglycaemia (fasting glucose 16.8 ± 0.1 mmol/L), which persisted during the $^{18}$FDG scan. To avoid influence of hyperglycaemia on the calculation of MRglu, these two patients were excluded from further $^{18}$FDG-analysis. Mean plasma glucose at start $^{18}$FDG scan was 5.6 ± 0.8 (3.9-6.9, n=14) mmol/L, mean plasma free fatty acids was 0.65 ± 0.22 (range 0.33-1.04) mmol/L and was lowered after acipimox intake to 0.08 ± 0.03 (range 0.03-0.15, n=14) mmol/L as expected (normal value 0.3-0.9 mmol/L).

In Figure Suppl-1C the RV MRglu is plotted against the RV efficiency, showing no association between the two parameters. It must be taken into account that determination of RV MVO$_2$ (and power) occurred under near-fasting conditions, whereas patients underwent the $^{18}$FDG-scan under metabolic preparation to obtain maximal cardiac glucose uptake. Nevertheless, because the PET studies were standardized for all PAH patients, it can be concluded that the lack of correlation between RV efficiency and (maximal) glucose uptake is a true reflection for the whole group. In addition, should the metabolic shift have occurred to maximal glucose oxidation, mechanical efficiency would only increase with 8% maximally, as the caloric equivalent of glucose oxidation is 473 kJ/mol O$_2$ versus 439 kJ/mol O$_2$, by fatty acids oxidation. There was, however, no difference in glucose uptake rate between NYHA II and III patients, whereas RV efficiency reduced by 50% up to 4-fold in the severe PAH patient group compared to NYHA II.
RV power output of the normal right ventricle

The normal RV has a power output of about 0.16 J/s, assuming a mPAP of 12 mmHg and a cardiac output of 6 L/min. When compared to the normal heart, the hypertrophied RV power of both NYHA II and III patients is 4-fold higher (p=0.0001), as a result of an increased RV afterload in PAH (Figure Suppl-2). Assuming that RV efficiency remains stable at the beginning of the disease, MVO2 should increase 4-fold, too, along with RV power. However, the RV power remains similar between the NYHA II and III patients, despite a lower cardiac output and stroke volume in NYHA III. The lower RV efficiency in NYHA III is due an increase of MVO2, which almost doubled.
Interventricular septum in relation to the right ventricle in IPAH

The interventricular septum plays an important role in RV power generation next to the RV free wall in PAH. To date, it is however not clear which part of the septum contributes to RV pumping and O₂ consumption in IPAH.

For this reason we show two alternative calculations of the RV mechanical efficiency, next to the results shown in the main manuscript. First, mechanical efficiency is calculated for the RV free wall alone, in which the MVO₂ of the total interventricular septum is not taken into account (Figure Suppl-3A). Secondly, Figure Suppl-3B shows the mechanical efficiency is calculated for the RV free wall including the MVO₂ of the total interventricular septum. In the latter, the overall mechanical efficiency is reduced by almost 50% compared to Fig. Suppl-3A. Despite different ways in calculating the RV efficiency, it had not effect on the proportional values between the two IPAH groups: the patients with severe IPAH (NYHA III) remained to have significantly reduced RV efficiency in comparison to the NYHA II patients.
### Table Suppl-1

<table>
<thead>
<tr>
<th>PAH pts (n = 6)</th>
<th>Median</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Forward stroke volume (ml)</td>
<td>43.4</td>
<td>39.1 – 63.4</td>
</tr>
<tr>
<td>‘Backward’ volume (ml)</td>
<td>9.2</td>
<td>1.9 – 36.4</td>
</tr>
<tr>
<td>Percentage of total RV volume (%)</td>
<td>15.8</td>
<td>4.7 – 46.9</td>
</tr>
<tr>
<td>Forward RV power (J/s)</td>
<td>0.55</td>
<td>0.42 – 0.65</td>
</tr>
<tr>
<td>‘Backward’ RV power (J/s)</td>
<td>0.004</td>
<td>0.001 – 0.119</td>
</tr>
<tr>
<td>Percentage of total power (%)</td>
<td>0.72</td>
<td>0.38 – 17.6</td>
</tr>
</tbody>
</table>
Supplemental Figure Legends

**Figure Suppl-1**

Panel A Preparation protocol and time schedule of $^{18}$FDG-PET

Panel B Example of a summed $^{18}$FDG-image at basal plane in short-axis view of the same patient in Figure 2 (main manuscript). The MRglu in the RV wall of the shown patient (NYHA IV) in the figure was 0.31 μmol/g ventricular tissue /min. RV right ventricle, LV left ventricle.

Panel C Plot of RV myocardial glucose uptake rate (MRglu) against RV mechanical efficiency. There was no correlation between the two parameters (r ~0.38, P=0.18). Dotted line represents the best fit to the data.

**Figure Suppl-2** Power output of NYHA II and III, as in Fig 3E. The line across the bar graph represents the power output of the normal right ventricle. *** P=0.0001 for both NYHA II and III.

**Figure Suppl-3** Mechanical efficiency of IPAH patients with NYHA II and III calculated for only the RV free wall (Panel A) and RV wall plus total interventricular septum (Panel B).
Supplement Figures

Figure Suppl-1A

Figure Suppl-1B

Figure Suppl-1C
Figure Suppl-2

Power (J/s)

II

III

ns

normal RV

***
Figure Suppl-3

A

Efficiency (%)

II III

p < 0.001

B

Efficiency (%)

II III

p = 0.004
Supplemental References


