RIGHT VENTRICULAR FAILURE IN IDIOPATHIC PULMONARY ARTERIAL HYPERTENSION IS ASSOCIATED WITH INEFFICIENT MYOCARDIAL OXYGEN UTILIZATION


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**ABSTRACT**

**Background**

In idiopathic pulmonary arterial hypertension (IPAH), increased right ventricular (RV) power is required to maintain cardiac output. For this, RV O$_2$ consumption (MVO$_2$) must increase by augmentation of O$_2$ supply and/or improvement of mechanical efficiency – ratio of power output to MVO$_2$. In IPAH with overt RV failure, however, there is evidence that O$_2$ supply (perfusion) reserve is reduced, leaving only increase in either O$_2$ extraction or mechanical efficiency as compensatory mechanisms. We related RV mechanical efficiency to clinical and haemodynamic parameters of RV function in IPAH patients and associated it with glucose metabolism.

**Methods and Results**

The patients included were NYHA class II (n=8) and class III (n=8). They underwent right heart catheterization, MRI and [15O]H$_2$O-, [15O]O$_2$-, [15O]CO- and [18F]FDG-PET. RV power and O$_2$ supply were similar in both groups (NYHA class II vs class III: 0.54 ± 0.14 vs 0.47 ± 0.12 J/s; and 0.109 ± 0.022 vs 0.128 ± 0.026 ml O$_2$/min/g, respectively). RV O$_2$ extraction was near-significantly lower in NYHA class II compared with NYHA class III (63 ± 17% vs 75 ± 16%, respectively, p=0.10). As a result, MVO$_2$ was significantly lower (0.066 ± 0.012 vs 0.092 ± 0.010 ml O$_2$/min/g, respectively, p=0.006). RV efficiency was reduced in NYHA class III (13.9 ± 3.8%) compared to NYHA class II (27.8 ± 7.6%, p=0.001). Septal bowing, measured by MRI, correlated with RV efficiency (r=-0.59, p=0.020). 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).

**Conclusion**

RV failure in IPAH was associated with reduced mechanical efficiency that was partially explained by RV mechanical dysfunction, but not by a metabolic shift.
INTRODUCTION

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 has to be generated by the right ventricle, which requires more O2. Recently, however, Gomez et al. observed stress-induced ischaemia in the RV wall of a subset of pulmonary arterial hypertensive (PAH) patients with overt RV failure and suggested an association between RV ischaemia 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 where mechanical efficiency is reduced, mechanical efficiency in overt RV failure is unknown.

Because of the vascular anatomy of the human right ventricle, 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 non-invasively measured using the spatial resolution of state-of-the-art positron emission tomography (PET) scanners and [15O]O2 and [15O]CO tracers. Here, we also measured RV perfusion, using [15O]H2O-PET next to OEF to calculate RV MVO2.

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; haemoptysis 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 7). 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, anaemia (haemoglobin <0.13 g/mL). Assessment of the World Health Organization (WHO) 1998’s adapted New York Heart Association (NYHA) classification, was performed prior to study participation by the clinicians responsible for the patient (AVN and AB). The protocol was approved by the medical ethics review committee of the VU University Medical Center. Each patient gave written informed consent before the study. YYW and GR analysed the images blinded for the clinical state of the patients.
Study design

All patients underwent right heart catheterization (RHC), cardiac magnetic resonance imaging (cMRI) and PET that consisted of three consecutive scans using [15O]H2O, [15O]O2, and [15O]CO to measure myocardial perfusion or blood flow (MBF), OEF and MVO2 and fractional blood volume, respectively (Figure 7.1). 15O-PET scans were performed 2 hours after a light breakfast. One day after the 15O-PET scans, a 15F-2-fluoro-2-deoxy-D-glucose ([18F]FDG) scan was performed to quantify myocardial glucose uptake rate (MRGlu) (Supplementary Figure S7.1 A,B and Text). When possible, RHC, cMRI and PET studies were performed within one week of each other. In three subjects, for logistical or personal reasons, the interval between RHC and PET was 20 to 55 days, and between cMRI and PET 20 to 36 days. As these patients had stable IPAH under drug treatment, that is, less than 10% change in 6MWD over 6 months prior to inclusion (5 ± 3%), 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 [15O]H2O and [15O]CO scans has been described previously. Briefly, scans were performed in 2D acquisition mode using an ECAT EXACT HR+ scanner (Siemens/CTI, Knoxville, TN, USA). After transmission scan, used to correct all subsequent scans for tissue attenuation, subjects underwent three consecutive scans as shown in Figure 7.1. First, a dynamic emission scan (10 min, 40 frames with progressive increase in duration) was started simultaneously with injection of 1100 MBq of [15O]H2O. A second identical emission scan was started at the same time as a bolus inhalation 7 GBq of [15O]O2. During the [15O]O2 scan, five arterial blood samples were obtained to measure recirculating [15O]H2O concentration. An additional arterial sample was drawn to determine arterial O2 content. Finally, a 6 min static emission scan was acquired, starting 1 min after end of bolus inhalation of 4 GBq [15O]CO gas to allow imaging of ventricular blood volumes. Approximately 20% of the administered radioactivity during [15O]O2 and [15O]CO inhalation is taken up by the blood. 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. The anatomical tissue fraction (ATF) images, generated by subtracting the [15O]CO blood pool image from transmission image, were resliced into short-axis images according to anatomic axes of the LV. The same reslicing parameters were applied to both dynamic [15O]H2O and [15O]O2 images. Using anatomical tissue fraction images, RV wall regions of interest (ROIs)
were defined on basal, distal and apical planes (Figure 7.2). These ROIs were projected onto dynamic $[^{15}\text{O}]\text{H}_2\text{O}$ and $[^{15}\text{O}]\text{O}_2$ 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 $[^{15}\text{O}]\text{O}_2$ scan using dynamic implementation\(^{11}\) of a previously described model,\(^{14}\) re-using MBF, perfusable tissue fraction, arterial blood volume and RV spill-over as determined from the $[^{15}\text{O}]\text{H}_2\text{O}$ scan and applying a correction for spill-over from activity in the pulmonary gas volume as described previously.\(^{16}\) $[^{15}\text{O}]\text{O}_2$ input function was based on volume of interest drawn in ascending aorta and corrected for contribution of recirculating water measured in the arterial blood samples.

![Figure 7.2 Example of a cMRI and $[^{15}\text{O}]\text{CO}$-PET image of a patient with idiopathic pulmonary arterial hypertension (IPAH) with New York Heart Association (NYHA) class III.](image)

(A) Cardiac MRI image of a patient’s heart with severe IPAH at short axis view, cut at mid level of the heart. (B) $[^{15}\text{O}]\text{CO}$-PET image, reconstructed as an attenuation tissue fraction, a so-called ‘negative image’ of the ventricular blood volumes after inhalation of $[^{15}\text{O}]\text{CO}$. Using the image of panel B the right ventricular (RV) wall was defined, depicted as the marked region in (C). The RV wall regions of base, distal and apical levels were combined to a RV wall volume. This was then projected onto the dynamic $[^{15}\text{O}]\text{H}_2\text{O}$ and $[^{15}\text{O}]\text{O}_2$ images for quantification RV blood flow and $\text{O}_2$ extraction, respectively.

**Right heart catheterization**

The protocol has been detailed previously.\(^{26}\) 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 (SvO$_2$). Pulmonary vascular resistance (PVR) was calculated as: $(\text{mPAP}-\text{PCWP})/\text{CO}$, where mPAP is mean pulmonary arterial pressure and PCWP pulmonary capillary wedge pressure.

**Cardiac magnetic resonance imaging**

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 right myocardial tissue on each slice using MR-Analytical Software System (Media, Leiden, Netherlands). RV end-diastolic, end-systolic volumes and RV free wall mass were calculated.\(^{26}\) 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 two-
chamber view described previously and corrected for RR-time.\textsuperscript{17} 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 part 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.

**Haemodynamic and oxidative calculations**

**Right ventricular power** Combining haemodynamic data from both RHC and cMRI, the power
(J/s) of the right heart was calculated as:

\[
\text{Power} = HR \cdot \text{mPAP} \cdot \text{SV} \cdot 2.22 \cdot 10^{-6}
\]  

(7.1)

where HR is heart rate in beats per minute and mPAP in mmHg; SV, in mL, 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.\textsuperscript{18} The factor $2.22 \cdot 10^{-6}$
converts mmHg·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\textsuperscript{19} and, thus, does not affect the results
qualitatively.

**Right ventricular oxygen consumption and supply** Regional myocardial $O_2$ consumption
(MVO$_2$ in ml/min/g cardiac tissue) was calculated for the right myocardium as follows:\textsuperscript{14}

\[
\text{MVO}_2 = \text{OEF} \cdot \text{MBF} \cdot \text{CaO}_2
\]  

(7.2)

where CaO$_2$ is arterial $O_2$ content (mL O$_2$/mL blood).\textsuperscript{14} Myocardial $O_2$ supply (ml/min/g) was
calculated as MBF × CaO$_2$.

**Mechanical efficiency** was calculated from the ratio of RV power output (equation 7.1) and
MVO$_2$ (equation 7.2). As MVO$_2$ in equation 7.2 is calculated per gram, RV mass is included here
for calculation of MVO$_2$ by whole right myocardium. 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 the right myocardial tissue oxidizes free fatty acid and glucose equally:

\[
\text{Mechanical efficiency} = \frac{\text{Power}}{\text{MVO}_2 \cdot \text{RVmass} \cdot 0.34} \times 100\% 
\]  

(7.3)

**Statistical analysis**

All results are expressed as mean ± SD. The two groups (i.e. NYHA class II and class III) were
compared using t-tests; the non-parametric Mann-Whitney U test was used where indicated.
Pearson’s 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 haemodynamics are summarized in Table 7.1; some parameters are
also shown in Figure 7.3. In accordance with severity of IPAH, NYHA class III patients had lower
INEFFICIENT O₂ USE BY FAILING RIGHT HEART IN PAH

SV and CO (Figure 7.3A), despite higher heart rate as compared to NYHA II. Mean PAP was near significantly higher in NYHA class III as compared to II (Figure 7.3B; 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 SvO₂ were lower in NYHA class III. Six-minute walk distance was not significantly lower in the severely ill.

PET derived parameters for the right myocardium per cardiac mass are shown in Table 2. Neither MBF (corrected for RV mass, Figure 7.3C) nor OEF (Figure 7.3D) were significantly higher in NYHA class III patients (MBF: p=0.088, t-test; OEF: p=0.105, Mann-Whitney U test). There was, however, a significantly higher MVO₂ per gram (Table 7.2). In contrast, RV O₂ supply per gram right myocardium was similar in NYHA class II and class III patients (Table 7.2). For total right myocardium, MVO₂ was also higher in the severely ill (Figure 7.3F), 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 7.3G).

A tight relationship was found between the mechanical efficiency and the RVEF, which is a haemodynamic index of systolic RV function (Figure 7.4, r=0.81, p<0.001). There was also a high correlation between the RV efficiency and the SvO₂ (r=0.76, p<0.001).

### Table 7.1 Patients’ characteristics and haemodynamics.

<table>
<thead>
<tr>
<th>NYHA class</th>
<th>all</th>
<th>II (n = 8)</th>
<th>III (n = 8)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yrs)</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 (mmHg)</td>
<td>9 ± 7</td>
<td>5 ± 5</td>
<td>13 ± 8</td>
<td>0.022</td>
</tr>
<tr>
<td>mPAP (mmHg)</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 (dyn.s.cm⁻⁵)</td>
<td>697 ± 345</td>
<td>504 ± 222</td>
<td>890 ± 279</td>
<td>0.008</td>
</tr>
<tr>
<td>Nt-proBNP (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>

Mean ± SD; 6MWD, six-minute walk distance; ERA, endothelin receptor antagonist; EDV, end diastolic volume; EF, ejection fraction; mPAP, mean pulmonary artery pressure; mRAP, mean right atrial pressure; Nt-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; PDE5, phosphodiesterase type 5 inhibitors; PVR, pulmonary vascular resistance; RV, right ventricle; SvO₂, mixed venous O₂ saturation. P values were tested using t-test.
In search for an underlying mechanical cause for the reduced efficiency, post-systolic isovolumic period was plotted against the RV efficiency, showing a negative correlation ($r=-0.594$, $p=0.020$, Figure 7.5). No correlation was found between the RV MRglu and RV efficiency ($r=-0.38$, $p=0.18$, Figure S7.1C).

**Figure 7.3** Overview of the determinants of right ventricular (RV) mechanical efficiency. Primary measurements are cardiac output (panel A) measured by cardiac MRI, mean pulmonary artery pressure (mean PAP, panel B) acquired by right heart catheterization, myocardial blood flow (panel C) that was measured by $[^{15}O]H_2O$-PET and RV $O_2$ extraction fraction (panel D) obtained by $[^{15}O]O_2$-PET. RV power (panel E) is the product of cardiac output and mean PAP (Equation 7.1, Methods Section) and myocardial $O_2$ consumption (panel F) is the product of $O_2$ extraction fraction, myocardial blood flow and arterial $O_2$ content (equation 7.2). Mechanical efficiency (panel G) is the ratio of power and myocardial $O_2$ consumption (equation 7.3). There was a trend toward significant difference for mean pulmonary artery pressure ($p=0.083$, Mann-Whitney U), $O_2$ extraction fraction ($p=0.105$, Mann-Whitney U test) and myocardial blood flow ($p=0.088$). Each panel shows results for New York Heart Association (NYHA) class II (left bar) and class III (right bar) patients. **$p<0.01$; ***$p<0.001$.

In the present study, we demonstrate that the 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 7.4) stresses the fact that a 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 as this was similar between the two groups (Figure 3E), but NYHA class III patients had higher MVO$_2$ of both total right heart (Figure 7.3F) and per unit RV mass (Table 7.2) as compared to NYHA class II.

**DISCUSSION**

In the present study, we demonstrate that the 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 7.4) stresses the fact that a 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 as this was similar between the two groups (Figure 3E), but NYHA class III patients had higher MVO$_2$ of both total right heart (Figure 7.3F) and per unit RV mass (Table 7.2) as compared to NYHA class II.
To the best of our knowledge, there are no previous data on human OEF and perfusion of the normal right heart to compare with our patient data. Based on canine studies, normal RV OEF has been estimated as 45 to 50%,\(^{20,21}\) indicating that the right myocardium has a substantially higher \(O_2\) extraction reserve than the left heart (OEF values are 60 to 80% in healthy men).\(^4,5\) Additionally, Hart et al.\(^{21}\) demonstrated that during heavy exercise, RV \(O_2\) utilization increases initially by maximizing OEF before coronary reserve is mobilized. Interestingly, we found a mean RV OEF of 69 ± 17% in our IPAH patients (Figure 7.3D) approximating that of normal LV. Our data suggests that, in analogy with the normal (canine) right ventricle during strenuous exercise, the pressure overloaded right heart in IPAH has already a reduced \(O_2\) extraction reserve as a consequence the resting \(O_2\) demand becomes predominantly dependent on perfusion. We found similar MBF in the hypertrophied right ventricle in the mild and severe IPAH. We therefore hypothesize that the dysfunctional right myocardium is unable to increase its perfusion in mild PAH; and thus \(O_2\) supply cannot increase to meet a higher \(O_2\) demand (e.g. during physical exercise). RV ischaemia is then the result, which is in accordance with the observation by Gomez et al. who demonstrated stress-induced RV wall ischaemia in IPAH patients with severe heart failure.\(^1\) The high RV OEF in our study 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 7.3E), despite lower SV and CO (Table 7.1, Figure 7.3A). However, we have to take into account that RV power is significantly higher compared with the normal right ventricle (Figure S7.2). Previous studies also demonstrated that patients with advanced IPAH had significantly reduced CO, but similar mPAP as compared to mild IPAH.\(^{22-24}\) The RV power that can be calculated from the data provided in these studies\(^{22-24}\) is also not significantly lower in the progressively IPAH patients, which is in agreement to our data. It follows from the lower CO and unchanged mPAP that PVR is higher in the NYHA class III patients (Table 7.2). 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 7.4), which has also been shown in patients with ischemic LV heart disease.\(^6\) Reduced \(SvO_2\) is a strong prognostic determinant in IPAH, as it is associated with a decreased CO in the severely ill. It is noticeable that RV efficiency independently correlates well with \(SvO_2\), emphasizing once more that mechanical efficiency is a strong indicator for RV function.

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**Table 7.2** Perfusion and \(O_2\) consumption of RV per unit mass measured by PET.

<table>
<thead>
<tr>
<th>NYHA class</th>
<th>II (n = 8)</th>
<th>III (n = 8)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>MBF (mL/min/g)</td>
<td>0.61 ± 0.15</td>
<td>0.71 ± 0.16</td>
<td>ns</td>
</tr>
<tr>
<td>(O_2) supply (mL/min/g)</td>
<td>0.109 ± 0.022</td>
<td>0.128 ± 0.026</td>
<td>ns</td>
</tr>
<tr>
<td>(MVO_2) (mL/min/g)</td>
<td>0.066 ± 0.012</td>
<td>0.092 ± 0.010</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

Mean ± SD; MBF, myocardial blood flow; \(MVO_2\), myocardial oxygen consumption; NYHA, New York Heart Association; PET positron emission tomography; RV, right ventricular. P values were tested using t-test.
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 (Supplement Table-S7.1). In contrast, we did find a weak, but significant, inverse relation between the prolonged post-systolic isovolumic period and the reduced RV efficiency (Figure 7.5). 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 cardiac MRI as leftward septal bowing after pulmonary valve closure. It is in fact muscle contraction that consumes O₂ without the 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 7.1). 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 from our study population for histological analysis of morphological changes and capillary density. Preclinical 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. This shift was demonstrated also in the hypertrophied right ventricle 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 seems 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, Figure S7.1C).

The increased MVO$_2$ to power output in severe IPAH suggests inefficient O$_2$ utilization by the failing right ventricle due to cellular processes in which O$_2$ is used for processes other than ATP production for contraction, e.g. ion pumps, protein turnover, mitochondrial uncoupling or oxygen radical formation. Indeed, local administration of XO inhibitor, NO-synthase inhibitor or vitamine C (a reactive oxygen species scavenger) have been shown to ameliorate the low LV efficiency in cardiomyopathy patients, as well it was reported to attenuate RV failure in a PH rat model. Future studies on the isolated RV papillary muscle of PH rats are warranted to test whether these substances also improve the reduced RV efficiency found in PH.

Our data indicate that clinical judgement, i.e. NYHA class – a well known prognostic determinant for survival in PAH – is a reflection of the RV mechanical inefficiency. We hypothesize that there is not only a mere association between NYHA class and mechanical efficiency, but that RV inefficiency is an underlying factor causing clinical deterioration and that it plays a central role in RV failure in IPAH.

Limitations

We acknowledge that the present study lacks a control group. Unfortunately, the normal RV wall is too thin for accurate measurements of MBF and OEF, given the spatial resolution of current PET scanners. Nevertheless, we were able to include patients with sufficiently different disease severity to discover a significant correlation between the RV efficiency and the RVEF. Ideally, all measurements required for the calculation of mechanical efficiency should be acquired simultaneously. This was not possible because of the variety of measurement modalities used. However, only clinically patients with stable IPAH participated in this study and most measurements were performed within 1 week. We have chosen to include a part of the septum...
in the RV myocardial mass. To date, it is not clear how much it contributes to the RV pumping and the MVO₂ in IPAH. Therefore, we also performed calculations of RV efficiency by taking either the full septum into account or only the RV free wall and found qualitatively similar results (Figure S7.3). Finally, it would be interesting to compare the RV mechanical efficiency between different PAH subgroups. Differences in the RV mechanical efficiency may be an underlying factor to explain the differences found in the haemodynamics and the prognosis between patients with IPAH and patients with PAH secondary to scleroderma or Eisenmenger syndrome.

**Conclusion**

RV mechanical efficiency is reduced in severe IPAH compared with milder stages of the disease and is only partially explained by a RV mechanical dysfunction, but not by a metabolic shift to glucose oxidation. The reduction in mechanical efficiency is strongly correlated with the RVEF, implying that the increased O₂ use relative to power output is a feature of RV failure.
REFERENCE LIST


SUPPLEMENTARY DATA

Effect of tricuspid regurgitation on loss of right ventricular power output

Six idiopathic pulmonary arterial hypertension (IPAH) patients (NYHA class II, n=1; NYHA class 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*10^-6 (see Equation 7.1 in manuscript for explanation).

Loss of right ventricular power to tricuspid regurgitation is shown in Table S7.1. Note the large range, which is due to one patient (NYHA class 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.

<table>
<thead>
<tr>
<th>IPAH patients (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>

RV \([^{18}\text{F}]FDG\)-PET and myocardial glucose uptake rate

The \([^{18}\text{F}]FDG\) study occurred 1 day after the \([^{15}\text{O}]PET\) scans (Figure 7.1, main manuscript). Figure S7.1A displays the \([^{18}\text{F}]FDG\) 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.¹

Data acquisition and image analysis have been described previously.² 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, \([^{18}\text{F}]FDG\) (185 MBq) was injected intravenously and a dynamic emission scan started simultaneously (60 min, 39 frames). Venous
Chapter 7

these two patients were excluded from further \textsuperscript{[18F]}FDG-analysis. Mean plasma glucose at start \textsuperscript{[18F]}FDG scan was 5.6 \( \pm 0.8 \) (3.9 - 6.9, \( n = 14 \)) mmol/L, mean plasma free fatty acids was 0.65 \( \pm 0.22 \) (range 0.33-1.04) mmol/L and was lowered after acipimox intake to 0.08 \( \pm 0.03 \) (range 0.03 - 0.15, \( n = 14 \)) mmol/L as expected (normal value 0.3 - 0.9 mmol/L).

In Figure S7.1C 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 \textsuperscript{2} (and power) occurred under near-fasting conditions, whereas patients underwent the \textsuperscript{[18F]}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\textsubscript{2} versus 439 kJ/mol O\textsubscript{2}, by fatty acids oxidation. There was, however, no difference in glucose uptake rate between NYHA class II and class III patients, whereas RV efficiency reduced by 50\% up to 4-fold in the severe PAH patient group compared to NYHA class II.

\textbf{Figure S7.1A} Preparation protocol and time schedule of \textsuperscript{[18F]}FDG-PET.

\textbf{Figure S7.1B} Example of a summed \textsuperscript{[18F]}FDG-image at basal plane in short-axis view of the same patient in Figure 7.2 (main manuscript). The MRglu in the RV wall of the shown patient (NYHA class IV) in the figure was 0.31 \( \mu \text{mol/g ventricular tissue}/\text{min} \). RV, right ventricle; LV, left ventricle.

\textbf{Figure S7.1C} 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.

\textbf{Figure S7.2} Power output of NYHA class II and class III, as in Figure 7.3E. The line across the bar graph represents the power output of the normal right ventricle. *** \( p = 0.0001 \) for both NYHA class II and class III.
blood was sampled to measure plasma glucose and free fatty acids during the scan. A similar reslicing procedure of PET image processing as described in the main manuscript was undertaken for $[^{18}F]$FDG images. RV wall ROIs were defined with the summed $[^{18}F]$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:

$$MRglu = \frac{K_i \times \text{plasma glucose concentration}}{\text{lumped constant}} \quad (S7.1)$$

where $K_i$ is the influx rate constant derived from the $[^{18}F]$FDG time-activity-curve and was determined in the RV wall within the region of the blue line shown in Figure S7.1B. The lumped constant for cardiac $[^{18}F]$FDG is considered 1 in our PET-center.

Despite the exclusion of patients with known diabetes mellitus, two patients (one NYHA class II and one NYHA class III) turned out to have hyperglycaemia (fasting glucose 16.8 ± 0.1 mmol/L), which persisted during the $[^{18}F]$FDG scan. To avoid influence of hyperglycaemia on the calculation of MRglu, these two patients were excluded from further $[^{18}F]$FDG-analysis. Mean plasma glucose at start $[^{18}F]$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 S7.1C 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 $[^{18}F]$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 class II and class III patients, whereas RV efficiency reduced by 50% up to 4-fold in the severe PAH patient group compared to NYHA class 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 class II and class III patients is 4-fold higher (p=0.0001), as a result of an increased RV afterload in PAH (Figure S7.2). 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 class II and class III patients, despite a lower cardiac output and stroke volume in NYHA class III. The lower RV efficiency in NYHA class 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 S7.3A). Secondly, Figure S7.3B 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 Figure S7.3A. 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 class III) remained to have significantly reduced RV efficiency in comparison to the NYHA class II patients.

SUPPLEMENTARY REFERENCE LIST