Myocardial O2 supply and O2 utilization of the right ventricle in pulmonary arterial hypertension

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SUPINE EXERCISE-INDUCED OXYGEN SUPPLY TO THE RIGHT MYOCARDIUM IS ATTENUATED IN PATIENTS WITH SEVERE IDIOPATHIC PULMONARY ARTERIAL HYPERTENSION

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ABSTRACT

Background
Impaired right ventricular (RV) myocardial blood flow (MBF) has been associated with RV dysfunction and fatal RV failure in idiopathic pulmonary hypertension (IPAH) during stress. Both MBF and O₂ extraction from myocardial capillaries (O₂ extraction fraction, OEF) influence myocardial O₂ supply. The objective was to determine how the baseline RV OEF affects the amount of MBF increase induced by supine exercise, we hypothesize that higher baseline OEF (H-OEF) results in limited O₂ extraction during exercise and that MBF must therefore be increased to obtain sufficient O₂.

Methods
In 18 patients with IPAH, baseline OEF, resting MBF and exercise-induced MBF at 40% of maximal cardiopulmonary exercise testing load were measured using PET and [¹⁵O]O₂ and [¹⁵O]H₂O and [¹⁵O]CO.

Results
For the whole population, exercise increased RV MBF from 0.68±0.16 to 1.13±0.38 mL/min/g (p<0.0001). The MBF exercise-to-rest ratio (reserve) was 1.7 ± 0.7. Median baseline OEF was 0.73, at which the patient population was split into H-OEF and lower baseline OEF (L-OEF). Baseline MBF values (0.61 ± 0.11 and 0.74 ± 0.17 mL/min/g, respectively) were similar and exercise induced significant MBF increase in both groups (p=0.0001). However, exercise-induced increase in MBF was significantly less in the H-OEF group than in the L-OEF group (0.97 ± 0.30 and 1.30 ± 0.39 mL/min/g, respectively, p<0.05). Moreover, H-OEF patients had lower baseline stroke volume and cardiac output than the L-OEF group (52 ± 19 mL and 4.0 ± 1.1 L/min versus 78 ± 18 mL and 5.5 ± 0.9 L/min, respectively, both p<0.05).

Conclusions
H-OEF patients were haemodynamically poorer and showed a lower exercise-induced MBF increase compared to the L-OEF patients, suggesting exercise-induced O₂ supply limitation.
INTRODUCTION

Right heart failure in idiopathic pulmonary arterial hypertension (IPAH) has been associated to insufficient O₂ supply to the hypertrophied cardiomyocytes during stress.¹ Myocardial blood flow (MBF) and myocardial oxygen extraction from blood, that is, O₂ extraction fraction (OEF), are determinants of O₂ supply and can compensate for each other in order to meet myocardial O₂ demand.² ³ This is especially important for the normal right myocardium, which has a relatively low O₂ metabolism. Animal studies previously reported significantly lower baseline O₂ extraction (~46%)²,⁴ ⁵ and right coronary artery (RCA) flow (~0.5 mL/min/g)⁴ ⁵ for the right heart compared with the left heart (O₂ extraction of 60 - 80% and left coronary flow of ~1 mL/min/g).⁶ ⁸

In IPAH, however, increased right ventricular (RV) afterload causes hypertrophy and fatal RV failure. Due to this elevated RV stroke work in IPAH, the resting right myocardial O₂ demand already is increased. In animal models for pulmonary hypertension, reduced capillary density was observed, suggesting compromised MBF in the overload hypertrophied right heart.⁹ ¹¹ Clinically, this is supported by the finding of stress-induced ischemia in certain regions of the RV myocardium of severe IPAH patients, as demonstrated in a single photon emission computerized tomography study.¹ Furthermore, in a group of IPAH and pulmonary arterial hypertension (PAH) secondary to scleroderma patients a reduced RV myocardial perfusion reserve (MPR) index was observed.¹²

The relationship between OEF and MBF in the hypertrophied right myocardium of IPAH patients is poorly defined. Animal experiments have provided conflicting data, using diverse protocols, about increased RV O₂ demand. One canine study reported that the increased O₂ demand upon physical exertion was initially drawn from the O₂ extraction reserve, before additional O₂ was recruited from the RCA flow reserve in the normal right heart.² In a canine chronic pulmonary arterial banding model, an increase in baseline O₂ extraction was observed,⁴ whereas in an acute pulmonary artery banding model, a significant increase in RCA flow was found while the O₂ extraction remained low upon exertion.¹³ In this study, we use state-of-the-art positron emission tomography (PET) to explore the relation between baseline RV OEF and MBF at baseline and after an increase in myocardial O₂ demand induced by physical exercise in patients with IPAH.

METHODS

Study population

Between April 2008 and October 2010, a total of 18 patients with IPAH were included: 9 patients with WHO-adapted NYHA class II and 9 patients with WHO-adapted NYHA class III. Exclusion criteria were as follows: unstable IPAH, known history of coronary vascular disease and/or ischemia, atrial fibrillation, diabetes mellitus or presence of anaemia (haemoglobin <12g/dL). The study protocol was approved by the local medical ethics review committee. All patients gave written informed consent before inclusion in the study. Prior to the PET study, patients underwent cardiopulmonary exercise testing (CPET), a six-minute walk test, cardiac magnetic resonance imaging (cMRI) and right heart catheterisation (RHC). All tests were performed within a 2-week period, except for three patients, for which the study period had to be extended
to a maximum of 55 days due to logistical reasons. This extension was justified, as the disease condition of these patients was stable.

**PET Scanning protocol**

PET scans were obtained using an ECAT EXACT HR+ scanner (Siemens/CTI, Knoxville, TN, USA) at least 2h after a light breakfast. The patients fitted with an i.v. catheter in the lower arm for injection of $[^{15}O]H_2O$ and a cannula in the radial artery to determine the arterial $O_2$ content and recirculated water during the $[^{15}O]O_2$-scan. The scanning sequence is shown in Figure 6.1. After a short transmission scan to locate and position the myocardium in the center of the field of view, a 15 min transmission scan was performed to correct the subsequent emission scans for photon attenuation. A bolus injection of 1100 MBq of $[^{15}O]H_2O$ was administered to measure the resting, baseline MBF. Simultaneously, a 10 min dynamic emission scan consisting of 40 frames with progressively increasing frame lengths was initiated. For 10 min after the scan, the tracer was allowed to decay and subsequently, the myocardial OEF was determined via bolus inhalation of 7 GBq of $[^{15}O]O_2$. Simultaneously, a 10 min dynamic scan was started, which consisted of 41 frames with progressive increase in frame duration. Subsequently, blood pool imaging was performed by inhalation of at least 2 GBq of $[^{15}O]CO$ for 2 min. Starting 1 min after the end of inhalation to allow for equilibration in the blood pool, we acquired a static emission scan of 6 min. At the end of the 10 min decay period, patients started cycling on a recumbent bicycle (Lode, Groningen, The Netherlands), which was mounted on the scanner bed. Exercise load was set to 40% of patient’s maximal load, achieved during CPET. Supine cycling was at a minimum speed of 60 rpm and lasted for 12 min: 2 min to reach exercise-induced steady state prior to injection of $[^{15}O]H_2O$ and a subsequent 10 min period during the exercise perfusion scan. The acquisition protocol for exercise perfusion was similar to that used for the baseline perfusion scan. A final transmission scan was obtained to correct for movement during exercise. During scanning systemic blood pressure, peripheral saturation, heart rate and ECG were monitored at set times.

**PET data analysis**

All emission data were reconstructed as described previously. The anatomical tissue fraction, generated by subtracting the normalised $[^{15}O]CO$ blood pool image from the transmission image, was resliced into short-axis images according to the anatomic axes of the left ventricle. The same reslicing parameters were applied to all dynamic $[^{15}O]H_2O$ and $[^{15}O]O_2$ images. Using the anatomical tissue fraction, anterior, lateral and posterior RV wall regions of interest were defined on basal, distal and apical planes (see also Figure S6.1) and were projected onto dynamic $[^{15}O]H_2O$ and $[^{15}O]O_2$ images to generate time-activity curves. Next, for each scan volume weighted averages of basal, distal and apical time-activity curves were generated. MBF was determined from these average time-activity curves using the standard single tissue compartment model. The OEF of the RV myocardium was determined from the $[^{15}O]O_2$ scan using a novel implementation of a model previously described, in which RV MBF, perfusable tissue fraction, arterial blood volume and RV spill-over were fixed to values determined from the $[^{15}O]H_2O$ scan and in which a correction for spill-over from activity in the pulmonary gas volume was applied as described previously. The $[^{15}O]O_2$ input function was based on the volume of interest drawn in the ascending aorta and was corrected for the amount of recirculated water as measured in the arterial blood samples.
Cardiopulmonary exercise testing
The CPET protocol was previously detailed. Briefly, stepwise incremental loading was used up to a work rate at maximum tolerance on an electromagnetically braked cycle ergometer (Lode, Groningen, The Netherlands). Maximal load was the load at cessation of exercise as determined by the patient due to leg fatigue or dyspnoea. ECG, pulse oximetry and gas exchange were recorded (Vmax 229, Sensormedics, Yorba Linda, CA).

Right heart catheterization
RHC was performed under continuous ECG monitoring. A balloon tipped and flow directed 7.5 F Swan-Ganz VIP+ catheter (834HF75, Edwards Lifesciences Corporation, Irvine, CA, USA) was placed via the internal jugular vein in the main pulmonary artery to determine pressure in the right atrium and right ventricle. Systolic blood pressure, heart rate and cardiac output were obtained at baseline and during exercise. During PET scanning, patients also performed physical exercise at 40% of the maximal load on the recumbent bicycle during 5 min period. In a subset of 5 patients, additional comparison of O2 uptake (ml/kg/min) during supine exercise measured during RHC was made and found to correspond to the anaerobic threshold of the CPET (Table S6.1).

Calculations
RV ejection fraction is calculated as the forward stroke volume divided by the RV end diastolic volume, both derived from cardiac MRI. The calculation of OEF is described elsewhere. RV perfusion is the MBF of the free wall of the right ventricle. MPR was calculated as the ratio of MBF during exercise over MBF at rest. Coronary driving pressure (CDP) was calculated as the difference between mean systemic pressure and mean right atrial pressure. Myocardial O2 consumption (mL/min/g) is the product of OEF, MBF and arterial O2 content. To the best of our knowledge, there is no data on the OEF value in the normal human right ventricle. Experimental animal values may not be representative of the human right ventricle. Thus, a cut-off level based on the literature cannot be used. Therefore, in order to determine whether the increase of exercise-induced MBF was determined by the height of baseline OEF, we divided the study population into two groups – the lower baseline OEF group (L-OEF) and the higher baseline OEF group (H-OEF) – using the median baseline OEF as cut-off point.

Statistical analysis
Data are presented as mean ± SD. The paired Student’s t-test was used between rest and exercise. A nonparametric (Mann-Whitney U) test was used for comparisons between groups. Pearson’s correlation coefficients are given where necessary. Two-way analysis of variance (ANOVA) was performed to compare the two groups with each other before and after exercise, with subsequent Bonferroni post hoc test. P<0.05 was considered significant.

RESULTS
Patient population
Patients were under optimal treatment and received either single or combined treatment with a phosphodiesterase type-5 inhibitor, an endothelin receptor antagonist and/or i.v. prostacyclin.
Medications were continued during the study. One patient was newly diagnosed with IPAH and included prior to the start of PAH therapy. The exercise protocol was well tolerated and it was sufficient to increase the haemodynamic parameters significantly (Table 6.1). CDP increased significantly (p=0.025) from 78 ± 12 mmHg to 84 ± 12 mmHg (Figure 6.2A).

### Table 6.1 Patients’ characteristics and haemodynamics at baseline and during supine exercise

<table>
<thead>
<tr>
<th></th>
<th>baseline</th>
<th>exercise</th>
<th>p</th>
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</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>46 ± 13</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Sex (Female / Male)</td>
<td>17 / 1</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>6MWD (m)</td>
<td>439 ± 134</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Nt-proBNP (ng/L)</td>
<td>1252 ± 1671</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>PVR (dyn.s.cm-5)</td>
<td>701 ± 348</td>
<td>681 ± 362</td>
<td>0.96</td>
</tr>
<tr>
<td>Heart rate (bpm)</td>
<td>75 ± 13</td>
<td>104 ± 16</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Cardiac output (L/min)</td>
<td>5.1 ± 1.4</td>
<td>8.2 ± 3.7</td>
<td>0.0012</td>
</tr>
<tr>
<td>Mean PAP (mmHg)</td>
<td>53 ± 15</td>
<td>69 ± 17</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Mean RAP (mmHg)</td>
<td>8 ± 7</td>
<td>12 ± 7</td>
<td>0.0006</td>
</tr>
<tr>
<td>Mean blood pressure (mmHg)</td>
<td>86 ± 11</td>
<td>96 ± 11</td>
<td>0.001</td>
</tr>
<tr>
<td>SaO2 (%)</td>
<td>92 ± 6</td>
<td>91 ± 6</td>
<td>0.29</td>
</tr>
<tr>
<td>SvO2 (%)</td>
<td>64 ± 9</td>
<td>42 ± 14</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

6MWD, six-minute walk distance; Nt-proBNP, N-terminal pro-B-type natriuretic peptide; PAP, pulmonary artery pressure; PVR, pulmonary vascular resistance; RAP, right atrial pressure; SaO2, peripheral oxygen saturation; SvO2, mixed venous oxygen saturation.

### Table 6.2 Comparison baseline patients’ characteristics and haemodynamics after division into two groups using the median cut off point of OEF of 0.73.

<table>
<thead>
<tr>
<th></th>
<th>Lower OEF</th>
<th>Higher OEF</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>NYHA class II / class III</td>
<td>7 / 2</td>
<td>2 / 7</td>
<td>0.017</td>
</tr>
<tr>
<td>Mean PAP</td>
<td>50 ± 11</td>
<td>56 ± 18</td>
<td>0.57</td>
</tr>
<tr>
<td>Cardiac output (L/min)</td>
<td>5.5± 0.9</td>
<td>4.0 ± 1.1</td>
<td>0.013</td>
</tr>
<tr>
<td>Stroke volume (mL)</td>
<td>78 ± 18</td>
<td>52 ± 19</td>
<td>0.022</td>
</tr>
<tr>
<td>Heart rate (bpm)</td>
<td>71 ± 11</td>
<td>79 ± 15</td>
<td>0.22</td>
</tr>
<tr>
<td>PVR</td>
<td>724 ± 376</td>
<td>678 ± 339</td>
<td>0.80</td>
</tr>
<tr>
<td>RV MVO2 (mL/min/g)</td>
<td>0.067 ± 0.014</td>
<td>0.089 ± 0.016</td>
<td>0.019</td>
</tr>
<tr>
<td>Exercise work load (Watt)</td>
<td>27 ± 12</td>
<td>25 ± 16</td>
<td>0.97</td>
</tr>
</tbody>
</table>

6MWD, six minute walk distance; H-OEF, higher baseline OEF; L-OEF, lower baseline OEF; MVO2, myocardial oxygen consumption; PAP, pulmonary artery pressure; PVR, pulmonary vascular resistance; RVEF, Right ventricular ejection fraction.
Median baseline (resting) OEF of the patient group was 0.73. RV MBF increased from baseline to supine exercise (0.68 ± 0.16 versus 1.13 ± 0.38 mL/min/g, p<0.0001) (Figure 6.2B). Mean MPR was 1.7 ± 0.7. MPR was unrelated to baseline mean pulmonary artery pressure (p=0.39), RV ejection fraction (p=0.50) or RV end-diastolic volume (p=0.78).

**PET derived measurements**

Analysis of baseline OEF and resting and exercise-induced MBF showed that there was no relation between the baseline OEF and the exercise-induced MBF increase (p=0.83). After division into two groups (H-OEF and L-OEF), the H-OEF patients had poorer RV function at baseline than the L-OEF patients, with significantly lower baseline stroke volume and cardiac output (Table 6.2). The RV MPR was 1.9 ± 0.8 for the L-OEF group and 1.6 ± 0.5 for the H-OEF group (p=0.44). Two-way ANOVA showed no interaction between the two OEF groups between baseline and exercise MBF (Figure 6.3), as both OEF groups had comparable baseline RV MBF. Exercise induced a significant increase in RV MBF in both groups (p=0.0001). However, exercise-induced RV MBF increased significantly less in the H-OEF group compared to the L-OEF group (post-hoc p<0.05). Two-way ANOVA on the CDP in relation to the OEF groups showed only effect imposed by exercise (p=0.030).
DISCUSSION

In the whole IPAH population of the present study, we found that the baseline OEF of the hypertrophied right ventricle varied largely from low to high OEF, and that the RV MBF increased significantly upon supine exercise, while the increase in RV MBF (or the MPR) was not related to the baseline OEF. Interestingly, when the study population was divided into two groups using the cut-off value of median OEF, we observed that, despite a significant exercise-induced increase of MBF in both groups, the MBF increased significantly less in the H-OEF group compared to the L-OEF group whereas both OEF groups started at similar MBF levels. Moreover, the patients with H-OEF were also in a clinically and haemodynamically poorer condition compared to the patients with L-OEF.

Myocardial oxygen supply of the hypertrophied right ventricle

Myocardial \( \text{O}_2 \) supply depends on OEF and on MBF as well as their capacities to increase during exercise (when \( \text{O}_2 \) demand increases). In IPAH, the elevated afterload considerably increases the metabolic demand of the right heart. The high median baseline (resting) OEF of 0.73 in the present population of IPAH patients reflects this increased \( \text{O}_2 \) demand and is consistent with previous open-chest animal studies using chronic RV overload induced by pulmonary artery banding with significantly higher baseline \( \text{O}_2 \) extraction compared to control (58 vs 51%).

As we lack controls, it is unknown whether the baseline RV MBF found in our IPAH population is different from normal. Other studies showed that the resting RV MBF or RCA flow in chronic hypertrophy right myocardium was either unaltered or elevated compared with control values.

Recently, Vogel-Claussen et al. reported an impaired right MPR index in PAH patients during adenosine-induced hyperaemia as measured by cardiac MRI. Despite different methodologies used for imaging and inducing myocardial hyperaemia, it is interesting that the reported median RV MPR index in the PAH patients (1.7), was comparable to the mean RV MPR found in the present study. In contrast to the study by Vogel-Claussen et al., however, no significant associations between RV MPR and both mean pulmonary artery pressure and RV ejection fraction were observed. The different study populations including patients without PAH and, predominantly, scleroderma PAH patients in the study by Vogel-Claussen et al., may underlie these different findings between the two studies, as well as the aforementioned differences in methodology. It is also possible that the lack of correlation of baseline RV dysfunction or mean
pulmonary artery pressure to the RV MPR in the present study indicates that, once IPAH has developed, other RV (dys)functions become more important determinants of the progression of the disease.

**Baseline OEF is not a determinant of RV MBF increase in IPAH**

The height of baseline OEF did not determine the additional increase in RV MBF during exercise for the whole study population. Interestingly, however, the division of the IPAH population into a higher and lower baseline RV OEF demonstrated that RV dysfunction is associated with a higher baseline OEF (Table 6.2) and a significantly lower exercise-induced hyperaemia despite similar baseline (Figure 6.3). This is inspite of comparable MPR and suggests that the overloaded and more diseased right ventricle exhibits an increase in baseline $O_2$ demand, resulting in a higher RV myocardial $O_2$ consumption in the patients with H-OEF (Table 6.2).

The increase of RV MBF upon exercise in the total population is probably the result of several factors: the relatively small but significant elevation in CDP during exercise (Figure 6.2A), the significant increase in heart rate due to elevated stimulation of sympathetic nervous system (Table 6.1) and an elevated RV metabolic demand.\textsuperscript{11, 13} In contrast, the observed lower elevation in exercise-induced MBF in the IPAH patients with H-OEF, that is associated with a poorer RV function, compared with the L-OEF patients may be explained by histological alterations in the right ventricle. Capillary density may be more reduced in the severe IPAH (H-OEF) group to cause a less high exercise-induced MBF compared with the L-OEF patients. In addition, myocardial fibrosis has been observed in the chronic overloaded (failing) right ventricle and associated with increased stiffness in the microvasculature that may restrict additional MBF increase upon exercise.\textsuperscript{9, 11, 26} It may also underlie capillary rarefaction observed in the right ventricle in pulmonary hypertensive rats.\textsuperscript{9, 10} Previous studies using cardiac MRI imaging showed correlations between the extent of RV septal fibrosis (as reflected by delayed contrast enhancement) and severity in RV dysfunction in patients with PAH.\textsuperscript{27-30} Delayed contrast enhancement was not obtained in the present study. Nevertheless, based on the preclinical and cardiac MRI studies, it is a possibility that cardiac fibrosis plays a role in the different increases in blood flow between the L-OEF and H-OEF patients. Moreover, as it has been suggested that endothelial dysfunction may underlie the different response to adenosine hyperaemia in the patients with PAH and healthy control,\textsuperscript{12} it is possible that there is a gradation in this response that further worsens with progression of IPAH. These factors remain, however, a matter of debate, as RV biopsies cannot be obtained from living patients to discern the different IPAH stages. Alternatively, the role of extravascular compressive forces, such as increased wall stress, may be a restrictive factor in limiting MBF increase. We, however, found no correlation in this study (data not shown). Regional MBF of the anterior, lateral and posterior RV free wall were found similar to the global RV MBF in Figure 6.3 except that exercise did not lead to a significant increase of MBF in the posterior region in both OEF groups (Figure S6.1). This could be due to technical difficulties in defining the posterior ROIs, due to spill-over effects of the liver. However, in line with the above and previous perfusion studies,\textsuperscript{1} it cannot be excluded that local microcirculation defects underlie this finding.

It can be argued that the choice of the median OEF as a cut-off parameter is arbitrary. However, using the dichotomous approach allows the additional conclusion of OEF not being a determinant for the RV blood flow increase, which is an important new insight of this study.
Additional analysis based on the division of the study population by NYHA classes II and III gave similar results (Figure S6.2).

**Exercise induced increase in myocardial \( \text{O}_2 \) demand**

Although adenosine infusion is considered to be the gold standard for hyperaemic perfusion it was not preferred in our study as the vasodilatory effects on the pulmonary vascular bed may affect RV afterload, haemodynamics and thus the right MBF. Therefore, exercise-induced hyperaemia was used, as it better reflects the physiological perfusion response. As both OEF groups generated similar power during cycling (Table 6.2), differences in exertion were not the reason for the observed haemodynamic differences between the two groups. The imposed supine exercise of 40% of maximal load was shown to be feasible to obtain hyperaemic myocardial blood flow during \([^{15}\text{O}]\text{H}_2\text{O-PET,}\) which is considered the gold-standard for measuring MBF. Exercise was equal to the anaerobic threshold of CPET, indicating that the level of exercise used (40% of maximal load) led to significant exertion.

**Clinical implications**

This is the first study in patients with IPAH that takes the \( \text{O}_2 \) extraction into account in addition to exercise-induced changes in the myocardial perfusion of the hypertrophied right ventricle. It provides a possible explanation for the development of RV failure in severe IPAH patients. The data suggest that the diseased right ventricle in patients with more severe IPAH is more likely to develop an imbalance between \( \text{O}_2 \) supply and demand during exercise, due to a limited (patho-) physiological response, which is due to both a limited \( \text{O}_2 \) extraction reserve and an attenuated perfusion reserve. Any additional increase in \( \text{O}_2 \) demand may induce cardiac ischaemia, which can certainly cause fatal RV failure in patients with IPAH. Further studies on IPAH treatment must be conducted to either increase the RV perfusion reserve or lower the baseline OEF.

**Limitations**

The current PET-technical low resolutions limited the investigation of thin-walled normal RV myocardium. However, the large variation in disease severity in our relatively small cohort, made the analyses possible. Due to the strict study protocol, it was neither ethical nor feasible to perform all studies on the same day. In nearly all patients, however, the various tests were performed within 2 weeks to reduce variability between study sessions. The question remains on whether the H-OEF and attenuated hyperaemia are indeed determinants of increased mortality in IPAH. This was beyond the scope of the present explorative study. Interestingly, though, two patients in the H-OEF group died of RV failure and one underwent heart-lung transplantation at the time of writing, whereas all L-OEF patients survived.

**Conclusions**

Mean baseline OEF varied largely in the IPAH population. The height of baseline RV OEF did not predetermine the exercise-induced increase in RV MBF, which increased significantly for all IPAH patients. In contrast, higher baseline OEF (OEF>0.73) was associated with poorer NYHA class and more severe RV failure. Moreover, although exercise-induced MBF increased significantly from baseline level, it was significantly attenuated compared to the patients with L-OEF, suggesting that H-OEF patients are more prone to RV ischaemia during exercise.
REFERENCE LIST


SUPPLEMENTARY DATA

Table S6.1 CPET at anaerobic threshold and VO\textsubscript{2} during supine exercise.

<table>
<thead>
<tr>
<th></th>
<th>CPET</th>
<th>RHC (40% max load)</th>
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<tbody>
<tr>
<td>VO\textsubscript{2} at rest</td>
<td>0.30 ± 0.07</td>
<td>0.27 ± 0.06</td>
<td>0.55</td>
</tr>
<tr>
<td>VO\textsubscript{2} at AT</td>
<td>0.63 ± 0.19</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Maximally achieved VO\textsubscript{2}</td>
<td>0.87 ± 0.37</td>
<td>0.63 ± 0.19</td>
<td>0.90</td>
</tr>
<tr>
<td>Work load (Watt)</td>
<td>55 ± 26</td>
<td>23 ± 13</td>
<td>0.005</td>
</tr>
</tbody>
</table>

Patients with idiopathic pulmonary arterial hypertension: n=5, AT, anaerobic threshold; CPET, cardiopulmonary exercise testing; RHC, right heart catheterization; VO\textsubscript{2}, oxygen consumption.

Figure S6.1 Regional RV myocardial blood flow values of the two subgroups during rest and exercise. The panels A to C display the MBF in the anterior (Panel A), lateral (Panel B) and posterior RV wall regions (Panel C), from which the global MBF is derived (Figure 6.3 in the manuscript). Panel D depicts schematically in short axis-view the different regions (no. 1 - 3), from which the regional MBF are determined, in the dilated right ventricle typical for IPAH (mid plane). * p<0.05; ** p<0.01; *** p<0.001. MBF, myocardial blood flow; IPAH, idiopathic pulmonary arterial hypertension; LV, left ventricle; RV, right ventricle.
Figure S6.2 Myocardial blood flow of the RV wall during baseline and exercise, for the study population divided by NYHA classification. The overall RV MBF increased significantly upon exercise. Interestingly, patients with NYHA class II had significantly higher increase in RV MBF upon exercise compared to NYHA class III patients, indicating that the myocardial perfusion reserve is smaller in the clinically worse IPAH patients. * P<0.05; ** P<0.01; *** P<0.001.