SYSTOLIC PULMONARY ARTERY PRESSURE AND HEART RATE ARE MAIN DETERMINANTS OF OXYGEN CONSUMPTION IN THE RIGHT VENTRICULAR MYOCARDIUM OF PATIENTS WITH IDIOPATHIC PULMONARY ARTERIAL HYPERTENSION


ABSTRACT
Aims
Increased afterload in idiopathic pulmonary arterial hypertension (IPAH) causes right ventricular (RV) hypertrophy and failure. Since RV remodeling occurs with alterations in RV oxygen metabolism, increasing our understanding in the factors determining RV O₂ consumption in IPAH is necessary. In the left ventricle, it is known that heart rate and systolic blood pressure are the main determinants of myocardial O₂ consumption (MVO₂). However, the normal right heart has lower oxygen extraction and perfusion than the left myocardium and RV energy metabolism is changed in hypertrophy. Therefore, it is not obvious that the relations of pressure and heart rate to MVO₂ hold for the overloaded human right heart. We hypothesize that systolic pulmonary artery pressure (PAP) and heart rate (HR) are the major determinants of RV MVO₂ in IPAH.

Methods
In eighteen IPAH patients (NYHA class II and III), RV MVO₂ was determined using positron emission tomography and ¹⁵O-tracers. PAP and HR were measured during right heart catheterisation.

Results
RV MVO₂ related to systolic PAP (R²=0.54, p<0.001), inversely to stroke volume (R²=0.32, p=0.015) and HR (R²=0.32, p=0.014). Relations of MVO₂ with the Rate Pressure Product (RPP), i.e., systolic pressure times HR, and wall stress were R²= 0.55, p<0.001, and R²=0.30, p=0.020, respectively. Multiple regression of MVO₂ on HR and systolic PAP gave R²=0.59, p=0.001.

Conclusion
Systolic PAP and heart rate are the major determinants of RV MVO₂ in IPAH. Further increase of heart rate and PAP with IPAH progression suggests a compromised RV myocardial oxygen availability.
INTRODUCTION

In the face of an elevated pulmonary artery pressure (PAP) and pulmonary vascular resistance (PVR) in idiopathic pulmonary arterial hypertension (IPAH), right ventricular (RV) workload increases, which in turn causes RV remodelling with hypertrophy and dilatation. The larger ventricular workload demands a higher cardiac metabolism and thus augmented myocardial O₂ consumption (MVO₂). In theory, if the MVO₂ in the hypertrophied right ventricle is elevated, a further increase in MVO₂ is restricted due to limitations in oxygen supply,¹⁻³ RV pump function will be limited, which may contribute to the development of in fatal RV failure. It is therefore of crucial importance to gain more insight into the determinants of MVO₂ for the diseased RV myocardium.

In the normal and the diseased left ventricle, it is accepted that MVO₂ is related mainly to two haemodynamic variables, heart rate (HR) and systolic blood pressure.⁴⁻⁸ The product of HR and systolic pressure is called the heart rate (blood) pressure product or simply the rate pressure product (RPP) and is an accepted haemodynamic indicator of MVO₂.⁴⁻⁸ It is assumed that similar relationships of HR and pressure to MVO₂ exist in the right ventricle since the parameters of RV MVO₂ are difficult to measure.⁹ From experimental studies in animals it is known that in the normal right heart the oxygen extraction and coronary flow are much lower than in the left myocardium.¹⁰,¹¹ In chronic RV hypertrophy, experimental studies report an elevated oxygen extraction¹¹,¹² whereas other studies observed conflicting baseline right coronary flow or perfusion.³,¹²⁻¹⁴ It is thus not clear if pressure and HR are the main determinants of MVO₂ of the human diseased right myocardium secondary to IPAH.

The present study was conducted to investigate these relationships in a population of IPAH patients. We determined the MVO₂ of the hypertrophied and failing right ventricle in vivo using state-of-the-art positron emission tomography (PET). We related the RV MVO₂ to systolic PAP, HR and their product. The associations with stroke volume and RV wall stress were also investigated.

METHODS

Study design

Between April 2008 and October 2010, patients with IPAH with World Health Association (WHO)-adapted New York Heart Association (NYHA) class II (n=9) and III (n=9) were included. All were under optimal treatment, except for one with NYHA class III who was newly diagnosed and included prior to the start of treatment. Exclusion criteria were: a history of coronary vascular disease, atrial fibrillation and anaemia (haemoglobin <12g/dL). During the study protocol, single or combi-treatment with a phosphodiesterase type-5 inhibitor, endothelin receptor antagonist or i.v. prostacyclin was continued. All patients underwent a right heart catheterization (RHC) and a cardiac magnetic resonance imaging (cMRI) within the scope of follow-up or diagnosis.

To determine RV MVO₂, patients underwent a PET study using three consecutive ¹⁵O-scans. Except for three patients, all examinations, including PET, were performed within 1 week. For logistical reasons, in these three subjects the interval between RHC and PET was 20, 29 and 55 days, and between cMRI and PET it was 20, 29 and 36 days. Because all three had stable IPAH under drug treatment, this prolonged interval was considered acceptable. The study was approved by the Medical Ethics Review Committee of the VU University Medical Center. All patients gave written informed consent prior to inclusion.
**Right heart catheterization**

The protocol has been described in detail elsewhere. Briefly, under continuous ECG monitoring, a balloon-tipped, flow-directed 7.5F Swan-Ganz VIP+ catheter (B34HF75, Edwards Lifesciences Corporation, Irvine, CA, USA) was inserted in an internal jugular vein and moved to the main pulmonary artery. Cardiac output was measured by means of thermodilution. Pulmonary vascular resistance (PVR) was calculated as the difference between mean PAP and pulmonary capillary wedge pressure divided by cardiac output.

**Cardiac magnetic resonance imaging**

Scans were acquired on a 1.5T Sonata scanner or a 1.5T Avanto whole body scanner (Siemens Medical Solutions, Erlangen, Germany) according to the scanning protocol previously described. RV volumes and mass were measured from the stack of short axis images by manual detection of the endocardial and epicardial borders of the right ventricle on each slice using the MR-Analytical Software System (Media, Leiden, The Netherlands). Right ventricular free wall mass was calculated at end-diastole and end-systole by multiplying the RV free wall volume by 1.06. Luijnenburg et al. determined the inter-observer variability of RV free wall mass, which was 6.2%, using a stack of short-axis cine images acquired with steady-state free precession imaging similar to our present study. It was also addressed by Bradlow et al., who reported a variability coefficient of 14.2%. The RV end-diastolic volume was also determined; the RV ejection fraction was derived as the ratio of stroke volume to RV end-diastolic volume.

**Positron emission tomography protocol**

PET scans were performed 2 hours after a light breakfast. Patients received a cannula in the radial artery for blood sampling and a cannula in the radial vein for tracer injection. The protocol for cardiac [15O]H2O, [15O]O2 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 a transmission scan, used to correct all subsequent emission scans for tissue attenuation, subjects underwent three consecutive scans. First, a dynamic emission scan (40 frames in 10 min with progressive increase in frame duration) was started simultaneously with an injection of 1100 MBq of [15O]H2O to measure myocardial blood flow (MBF). A second identical emission scan was started together with a bolus inhalation of 7 GBq of [15O]O2 administered via a nasal cannula to determine the RV oxygen extraction fraction (OEF) and utilization. During this extraction scan, five arterial blood samples were obtained to measure the recirculating concentration of [15O]H2O. An additional arterial sample sample was drawn to calculate the arterial blood O2 content at the time of the [15O]O2 scan. Finally, a 6 min static emission scan was acquired, starting 1 min after the end of a bolus inhalation of 4 GBq [15O]CO to measure the RV blood pool. Systemic blood pressure, peripheral saturation and HR were monitored during the scan.

**Image processing and data analysis**

All emission data were reconstructed as previously described. The anatomical tissue fraction, generated by subtracting the [15O]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 both dynamic [15O]H2O and [15O]O2 images. Using the
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Anatomical tissue fraction, RV wall regions of interest were defined on basal, distal and apical planes and were projected onto dynamic [15O]H2O and [15O]O2 images to generate time-activity curves. Next, volume-weighted averages of basal, distal and apical time-activity curves were averaged. RV Myocardial blood flow (MBF) was determined from these average time-activity curves using the standard single tissue compartment model. OEF of the RV myocardium was determined from the [15O]O2 scan using a novel implementation of a model previously described, in which RV MBF, perfusable tissue fraction, arterial blood volume and RV spill-over are fixed to values determined from the [15O]H2O scan and in which a correction for spill-over from activity in the pulmonary gas volume was applied as described previously. The [15O]O2 input function was based on the volume of interest drawn in the ascending aorta and was corrected for the contribution of recirculating water as measured in the arterial blood samples. Any small inter-individual differences in the size of the ventricular regions of interest were corrected by the perfusable tissue fraction and spill-over fraction in the tracer kinetic models.

Myocardial oxygen consumption of the RV free wall (mL/min/g) was calculated as follows:

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

(5.1)

where \( \text{CaO}_2 \) is the arterial \( \text{O}_2 \) content (mL \( \text{O}_2 \)/mL blood), calculated from the product of 1.39 (conversion factor), haemoglobin (g/mL) and \( \text{O}_2 \) saturation (fraction), leaving out the term 0.003PaO2 since it is negligible. To obtain oxygen consumption and blood flow for the whole RV free wall, the data per gram were multiplied by the (end-diastolic) RV mass (in grams). The RPP of the right ventricle is the product of systolic PAP and HR determined by RHC.

The RV wall stress was estimated according to an adaptation of the Laplace’s formula by Arts, in which end-systolic ventricular volume and wall mass obtained from cardiac MRI, instead of the ventricular radius and wall thickness, were used:

\[ \text{Systolic wall stress} = \frac{3 \times \text{Psystole}}{\ln(1 + \frac{\text{RVwall}_{ES}}{\text{RVlumen}_{ES}})} \]  

(5.2)

where \( \text{Psystole} \) is the systolic PAP, \( \text{RVwall}_{ES} \) is the end-systolic RV free wall mass and \( \text{RVlumen}_{ES} \) is the end-systolic RV volume.

Statistical analysis

All results are expressed as mean ± SD. Pearson’s correlation and multiple regression analyses were performed where necessary. P<0.05 was considered significant.

RESULTS

A total of 18 patients were included in the present study with a wide range of disease severity from mild IPAH to severe IPAH with RV failure. The patients’ characteristics and haemodynamics are shown in Table 5.1.

For the total population, the arterial \( \text{O}_2 \) content was 0.18 ± 0.02 mL \( \text{O}_2 \)/mL blood. Using PET, the mean \( \text{O}_2 \) extraction fraction (OEF) was found to be 69 ± 17% and the mean perfusion (MBF) was 0.92 ± 0.30 mL/min/g; mean RV MVO2 was 0.079 ± 0.018 mL/min/g.

The MVO2 of the whole RV wall correlated significantly with the systolic PAP (Figure 5.1A) and the HR (Figure 5.1B). RV MVO2 and stroke volume were inversely related (Figure 5.1C).
Linear multiple regression analysis with only systolic PAP and HR gave: $RV \text{ MVO}_2 = 6.52 \times 10^{-2} \text{sPAP} + 4.47 \times 10^{-2} \text{HR} - 2.74; R^2 = 0.59, p=0.001$. Inclusion of the stroke volume in the multiple regression analysis did not increase the explained variance. The product of systolic PAP and HR, RPP, resulted in a relationship to $RV \text{ MVO}_2$ that was, in fact, similar to the above-mentioned multiple regression formula (Figure 5.1D). Furthermore, a similar relationship was also found between PVR and the whole $RV \text{ MVO}_2 (R^2 = 0.53, p=0.0002)$. No relationship between RV mass and $MVO_2$ per gram right ventricle was found ($p=0.13$), and also no significant relationships existed for the above-mentioned parameters with $MVO_2$ per gram right ventricle.

Mean systolic RV wall stress was $48 \pm 11$ kPa. The wall stress correlated with $MVO_2$ of per gram right ventricle ($R^2 = 0.29, p=0.020$).

**DISCUSSION**

We show that the systolic PAP and the HR are indeed the major determinants of $MVO_2$ of the hypertrophied right ventricle in IPAH patients. The combined measurements of RPP – not surprisingly – and RV systolic wall stress also have a linear relationship with $RV \text{ MVO}_2$, but do not improve the relationship with systolic PAP and HR.

In severe IPAH with RV failure, both systolic PAP and HR are known to be elevated. In general, the systolic PAP equals the systolic RV pressure. Therefore, either one of the systolic pressures may be used in practice. The finding that HR and pressure are related to $RV \text{ MVO}_2$ is consistent...
with previous studies showing that systolic blood pressure and HR are indices of MVO₂ in the left ventricular (LV) myocardium. In 1958, Sarnoff et al. already showed that these relationships exist in the (whole) LV myocardium of healthy dogs. In addition, Katz and Feinberg also observed a relationship between the RPP and LV MVO₂. Since then, these observations have been validated in healthy subjects as well as in patients with left heart disease during both resting and exercise conditions. The present correlations between RV MVO₂ and both HR and systolic pressure appear to be weaker than for LV studies. The weaker correlation could have a methodological cause, e.g. because the PET technique requires the determination of RV mass. Intrinsic myocardial differences between right and left ventricles may contribute to the observed differences, for instance the basal MVO₂. It may be possible that intrinsic myocardial differences, e.g. in the basal oxidative metabolism, are different between right and left ventricles, which could explain the observed differences. Furthermore, recent studies reported RV perfusion limitations in severe pulmonary arterial hypertension (PAH). However, as care was taken to exclude patients with coronary artery disease and RV OEF was 69 ± 17%, it suggests that resting RV ischaemia was not present in our study population and therefore did not affect MVO₂.

From a physiological point of view, cardiomyocytes do not sense ventricular (systolic) pressure, but generate stress, which is an argument to relate (systolic) stress to oxygen consumption.
consumption. For this reason, we evaluated whether wall stress was better associated with MVO₂ than with systolic pressure. Instead of the usual Laplace’s method, we choose the adapted Arts formula to reduce the local variability in ventricular radius and wall thickness throughout the right ventricle in IPAH. This formula circumvents the problems in the measurement of (local) curvature and local wall thickness. By not incorporating the septal mass a systematic error may be introduced, but the correlations are not affected. Both methods yielded comparable wall stress estimations (data not shown). In general, the Laplace’s law holds that, at a certain pressure, increased wall thickness reduces wall stress, while ventricular dilatation increases it. Previous studies indeed demonstrated a close relationship between LV MVO₂ and increased systolic wall stress in cardiac hypertrophy secondary to aortic stenosis. In addition, it has been reported that the RV systolic wall stress in IPAH patients was higher than in controls. The present study completes this aspect, as we demonstrate a significant correlation between systolic wall stress and MVO₂ of the hypertrophied right ventricle in IPAH. This was, however, weaker than with the systolic PAP. The fact that wall stress has no better association with MVO₂ than systolic blood pressure has also been observed for the left ventricle.

There was also a significant association between PVR and RV MVO₂. This, however, is not surprising as PVR is largely derived from PAP, which is correlated to RV MVO₂ (Figure 5.1A). Furthermore, the RV afterload consists not only of resistance but also of compliance. This compliance load (or the oscillatory power) contributes to a significant proportion to the RV load and recently we showed that it is also proportional to, and thus dependent on, the PVR in IPAH patients.

One animal experimental study group reported a relationship of RV MVO₂ to RPP and RV systolic pressure in a pulmonary artery constriction canine model, but no correlation was noted with HR. Since they used an anaesthetized open-chest model this may have affected their observations. In spite of the fact that RPP has proven to be an excellent index for MVO₂ elsewhere (r=0.90), it is by definition not an energy parameter. Nevertheless, the multiple regression analysis that includes stroke volume together with systolic PAP and HR did not improve the correlation with MVO₂ compared to the RPP or the combination of systolic PAP and HR (see the Results). Surprisingly, a lower stroke volume was associated with a higher RV MVO₂ and vice versa. Haemodynamically, this can be understood as the low stroke volume is related to a high HR, thereby reflecting the severity of IPAH. Sarnoff et al. demonstrated experimentally that when all other parameters were kept constant, changes in stroke volume had little influence on the LV MVO₂. Thus, it can be concluded that the systolic PAP and HR are the major determinants of MVO₂ of hypertrophied right myocardium in PAH. Fortunately, these are in practice the most easily obtainable measures during the follow-up of IPAH patients.

Because RV venous oxygen content cannot be obtained due to lack of a common venous drainage independent of that of the left ventricle, determination of RV MVO₂ in situ using the Fick method is extremely difficult. So far, it has only been achieved in experimental studies in which the animals underwent an open-chest operation to catheterize the small RV venous vessels prior to the experiment. However, PET, together with on-site-produced short-lived ¹⁵O-tracers, enables quantification of MVO₂ of the hypertrophied right ventricle in IPAH.
Implications

Results of this study indicate that the right ventricle consumes more oxygen when the HR and/or systolic PAP increase. An increase in HR and/or PAP, as can be observed in progressive IPAH, therefore is predicted to elevate RV oxygen demand. Conversely, reduction in the pulmonary arterial stiffness could lower RV MVO₂ since this lowers the RV afterload and thus the pressure, as has been shown recently for the left ventricle. In IPAH, however, the primary therapy to reduce pulmonary arterial stiffness and thus RV MVO₂ would be lowering the PVR. Moreover, emerging evidence shows that increased HR and an over-activated sympathetic nervous system have a negative prognostic influence on the survival of patients with IPAH. We therefore postulate that reduction in the HR and/or PAP, by reducing PVR, is likely to improve the balance between myocardial supply and demand for oxygen. Since the present study only investigated the RV MVO₂ at baseline, future studies are warranted to include interventions in reducing HR or systolic PAP to study their effect on the RV MVO₂. Groepenhoff et al. showed that during exercise in patients with PAH, HR increases rather than stroke volume, while in left heart failure (LHF) the inverse was found. On the basis of our present findings we predict that, at comparable exercise levels, right heart MVO₂ will increase more in patients with PAH than in LHF patients. Boilson et al. showed that in LHF with preserved ejection fraction, pulmonary vasodilation with nitric oxide (NO) did not reduce (systolic) PAP, since capillary wedge pressure increased. Our present results suggest that, since NO does not lower RV pressure, the high MVO₂ also will not be reduced by NO.

Limitations

With only one male patient, our study population represents the known female predominance in IPAH. This male patient, however, had haemodynamic parameters and MVO₂ values similar to the mean values of the whole study population. Unfortunately, due to the limited thickness of the normal RV myocardium, no information on relationships in normal human subjects could be obtained. Nevertheless, by extrapolating open-chest studies in normal dogs and dogs with RV hypertrophy secondary to pulmonary arterial banding, a considerably larger oxygen extraction and consumption in IPAH patients can be expected. [¹⁵O]H₂O-PET is considered to be the gold standard for determining myocardial perfusion \textit{in vivo}. Recently, we showed that the OEF, needed in the calculation of MVO₂ (equation 5.1), is reproducible using the present methodology. Obviously, the various PET-derived parameters contain measurement errors that may explain a large part of the scatter in Figures 1A-D.

Conclusions

The present study provides basal insights on the oxygen metabolism of the hypertrophied right ventricle, demonstrating that systolic PAP and HR are the major determinants of the RV MVO₂ in IPAH patients.
REFERENCE LIST


