RIGHT VENTRICULAR OSCILLATORY POWER IS A CONSTANT FRACTION OF TOTAL POWER IRRESPECTIVE OF PULMONARY ARTERY PRESSURE

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ABSTRACT

Rationale and Objectives: Pulmonary hypertension is characterized by increased arterial load requiring more right ventricular (RV) hydraulic power to sustain adequate forward blood flow. Power can be separated into a mean and oscillatory part. The former is associated with mean and the latter with pulsatile blood flow and pressure. Because mean power provides for net blood flow, the ratio of oscillatory to total power (oscillatory power fraction) preferably should be small. It is unknown whether this is the case in pulmonary arterial hypertension (PAH).

Objectives: To derive components of power generated by the right ventricle in PAH.

Methods: Thirty-five patients with idiopathic PAH (IPAH) and 14 non-PH subjects were included. The patients were divided in two groups, ‘moderate’ and ‘high’ based on pulmonary artery (PA) pressure. PA pressures were obtained by right heart catheterization and PA flows by MRI. Total hydraulic power ($Power_{total}$) was calculated as the integral product of pressure and flow. Mean hydraulic power ($Power_{mean}$) as mean pulmonary artery pressure times mean flow. Their difference is oscillatory power ($Power_{oscil}$).

Measurements and Main Results: Total hydraulic power in non-PH subjects, compared with moderate and high IPAH was 0.29±0.10 (n=14), 0.52±0.14 (n=17) and 0.73±0.24 (n=18) Watt, respectively. The oscillatory power fraction is ~23% and not different between groups.

Conclusions: In this study oscillatory power fraction is constant at 23% in non-PH and IPAH, implying that a considerable amount of power is not used for forward flow making the RV less efficient with respect to its arterial load. Our findings emphasize the need to develop new therapy strategies to optimize RV power output in PAH.
INTRODUCTION

Oxygen consumption is used for cell integrity, including ion equilibrium and excitation-contraction coupling (together “internal power” or chemical energy), and for power delivered to the arterial system (external power or hydraulic power). Total oxygen consumption is thus used for “internal power” on the one hand and external power on the other hand. The latter is the external work per unit time performed by the ventricle to propel blood from ventricle to the arterial circulation. Right ventricular hydraulic load is increased in pulmonary arterial hypertension (PAH) and will lead to right ventricular failure if treatment fails to reverse the course of the disease. To understand RV failure, as well as the effect of treatment, information and understanding of power generation is required. However, until now, studies on right ventricular power and the importance of its load are lacking in PAH.

Hydraulic power consists of two components. The energy per time (power) expended to produce steady (or non-pulsatile) net flow is the steady (or mean) external power, and is the product of mean pulmonary artery (PA) pressure and mean flow. The energy used in the production of pulsatile component of flow and pressure is the oscillatory (or pulsatile) power. The sum of mean and oscillatory power, forms the total external hydraulic power generated by the ventricle. Since mean flow determines transport, mean power may be considered as useful, and oscillatory power as ‘wasted’, and their ratio, should, preferably, be small.

The external oscillatory power fraction (ratio of oscillatory to total power) of the left ventricle is about 10% and increases in systemic hypertension. The external oscillatory power fraction of the right ventricle is about 25-30%, but what happens in PAH is not clear.

Therefore, the aim of this study is to explore what happens to oscillatory, mean, and total right ventricular power in patients with Idiopathic PAH (IPAH) and to compare it with non-PH subjects.

METHODS

Study population

Patients suspected of PAH were referred to our institution for a diagnostic work up according to current guidelines. We included 35 IPAH patients and 14 patients who appeared not to have PAH during right heart catheterization, although some of them had other limitations reflected in an abnormal NYHA score in 12 subjects. Other causes of PAH were excluded.

The study protocol was approved by the institutional ethics committee, and informed consent was obtained from all subjects.
Right heart catheterization
Pulmonary hemodynamics was assessed during right heart catheterization. PA pressures were obtained with a 6-Fr fluid-filled, single-lumen, multipurpose catheter (Cordis, Miami Lakes, Florida). The pressure signal and ECG were digitally recorded at a sample frequency of 250 Hz using Chart 5™ (ADInstruments, UK) installed on a laptop. Pressures over one respiratory cycle were selected and then averaged. All patients in this study were catheterized at baseline. Patients were considered normal if mean PA pressure was less than 25 mmHg.

The IPAH patients were divided in two equally sized groups of ‘moderate’ and ‘high’ based on the median value of the PA pressure (58mmHg) of the complete patient group. Thus three groups were studied: non-PH subjects, patients with moderate and patients with ‘high’ PA pressure.

MRI protocol
Magnetic Resonance Imaging (MRI) was performed within 12 hours before or after right heart catheterization for the purpose of this study. MRI was performed

Table 1. Baseline characteristics of non-PH subjects and IPAH patients

<table>
<thead>
<tr>
<th>Variable</th>
<th>Non-PH (n=14) mean ± SD</th>
<th>IPAH (n=35) mean ± SD</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographic characteristics</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gender (m/f)</td>
<td>1/13</td>
<td>7/28</td>
<td>.018</td>
</tr>
<tr>
<td>Age (yrs)</td>
<td>54 ± 13</td>
<td>44 ± 13</td>
<td>.018</td>
</tr>
<tr>
<td>Clinical characteristics</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NYHA (I,II,III,IV)</td>
<td>2, 12, 0, 0</td>
<td>2, 13, 12, 8</td>
<td>.867</td>
</tr>
<tr>
<td>6MWD (m)</td>
<td>468 ± 120</td>
<td>460 ± 136</td>
<td>.867</td>
</tr>
<tr>
<td>NT-Pro BNP (ng/l)</td>
<td>136 ± 186</td>
<td>957 ± 1125</td>
<td>.000</td>
</tr>
<tr>
<td>Hemodynamic characteristics</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RAP (mmHg)</td>
<td>3 ± 2</td>
<td>6 ± 5</td>
<td>.051</td>
</tr>
<tr>
<td>mPAP (mmHg)</td>
<td>19 ± 6</td>
<td>55 ± 14</td>
<td>.000</td>
</tr>
<tr>
<td>sPAP (mmHg)</td>
<td>33 ± 9</td>
<td>87 ± 23</td>
<td>.000</td>
</tr>
<tr>
<td>dPAP (mmHg)</td>
<td>10 ± 4</td>
<td>35 ± 9</td>
<td>.000</td>
</tr>
<tr>
<td>CI (l/min/m²)</td>
<td>3.9 ± 1.0</td>
<td>2.7 ± 0.8</td>
<td>.001</td>
</tr>
<tr>
<td>SvO₂ (%)</td>
<td>75 ± 5.5</td>
<td>65 ± 11</td>
<td>.002</td>
</tr>
<tr>
<td>PVR (dyne·s·cm⁻⁵)</td>
<td>189 ± 99</td>
<td>1005 ± 416</td>
<td>.000</td>
</tr>
</tbody>
</table>

NYHA, New York Heart Association functional class; 6MWD, six-minute walking distance; NT-Pro BNP, N-terminal Pro Brain Natriuretic Peptide; RAP, right atrial pressure; mPAP, mean pulmonary artery pressure; sPAP, systolic pulmonary artery pressure; dPAP, diastolic pulmonary artery pressure; CI, cardiac index; SvO₂, mixed venous oxygen saturation; PVR, pulmonary vascular resistance.
using a 1.5-T whole-body system (Siemens Avanto; Siemens Medical Solutions; Erlangen, Germany) equipped with a circularly polarized phased-array body coil.

**Flow measurements.** Instantaneous pulmonary flows were measured using phase contrast flow quantification \(^6^9\) in the main PA. This imaging was performed during continuous breathing using a gradient echo MRI sequence, with velocity encoding perpendicular to the imaging plane and a velocity sensitivity of 120 cm/sec. This flow sequence was run with the following parameters: orientation = orthogonal to the PA, slice thickness = 6 mm, field of view = \(240 \times 320 \text{ mm}^2\), matrix size = \(140 \times 256\), echo time = 2.8 ms, repetition time = 6.5 ms, temporal resolution = 13 ms, flip angle = 25°.

After the flow measurement was acquired, a phantom was imaged with identical imaging parameters, to serve as correction for the background phase error of the measured flow in the main PA. \(^1^0\)

**DATA ANALYSIS**

Pressures and flows were averaged signals, and heart rate differed less than 5% between the flows and pressures used. Post-processing of the flow images and pressure curves was performed using in-house developed software in MATLAB 7.0, R14 (The Mathworks, Natick, MA).

Instantaneous external hydraulic power generated by the ventricle varies over the heartbeat and is zero in diastole because, when semilunar valves are competent, flow is zero. Thus, external power is only generated during ejection. Hydraulic power was calculated ignoring the quantitatively small kinetic terms.\(^1\) Total external hydraulic power, \(\text{Powertot}\), of the ventricle is calculated as follows:

\[
\text{Powertot} = \frac{1}{T} \int P(t) \cdot Q(t) \cdot dt \tag{1}
\]

where \(P\) is PA pressure in mmHg, \(Q\) is PA flow in ml/s, \(T\) is heart period in seconds and \(t\) is time in seconds. Total external power consists of 2 components; mean and oscillatory power. Mean power, \(\text{Power}_{\text{mean}}\), is calculated as:

\[
\text{Power}_{\text{mean}} = P_m \cdot CO \tag{2}
\]

where \(P_m\) is mean PA pressure and \(CO\) is cardiac output (= average \(Q\) ). Oscillatory power, \(\text{Power}_{\text{oscill}}\), is the difference between total and mean hydraulic power:

\[
\text{Power}_{\text{oscill}} = \text{Powertot} - \text{Power}_{\text{mean}} \tag{3}
\]

Power is expressed in Watt, with 1 W = 7.5 \(10^{-3}\) mmHg·ml/s.
Statistics
Values presented are means ± SD. Baseline parameters between non-PH subjects and IPAH patients were compared using independent Students t-test. The mean and oscillatory power values were compared within a patient using paired Students t-test and between groups using one-way ANOVA. Categorical data were compared using $\chi^2$ test. Parameters which were skewed to the right were log-transformed for comparison. An association between pulse pressure and oscillatory hydraulic power and between the pressure components were explored using simple linear regression.
A p value < 0.05 was considered statistically significant.

RESULTS
The clinical and hemodynamic characteristics of the IPAH patients and non-PH subjects are summarized in Table 1. The majority of the patients in the normal and hypertensive group were female. The clinical and hemodynamic characteristics clearly demonstrate that the patients with IPAH had severe disease.

RV Power
Averaged power data are given in Table 2. These data demonstrate that from non-PH to ‘moderate’ and ‘high’ PA pressures increase and mean power, oscillatory power, and total power also increase.

Table 2. RV hydraulic power in non-PH subjects and IPAH patients

<table>
<thead>
<tr>
<th>Variable</th>
<th>Non-PH (n=14) mean ± SD</th>
<th>‘moderate’ (n=17) mean ± SD</th>
<th>‘high’ (n=18) mean ± SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>$Power_{total}$ (Watt)</td>
<td>0.29 ± 0.10</td>
<td>0.52 ± 0.14*</td>
<td>0.73 ± 0.24†</td>
</tr>
<tr>
<td>$Power_{mean}$ (Watt)</td>
<td>0.22 ± 0.07</td>
<td>0.41 ± 0.12*</td>
<td>0.56 ± 0.19†</td>
</tr>
<tr>
<td>$Power_{oscill}$ (Watt)</td>
<td>0.07 ± 0.04</td>
<td>0.11 ± 0.04*</td>
<td>0.17 ± 0.07†</td>
</tr>
</tbody>
</table>

* ‘moderate’ pulmonary pressure vs. Non-PH, P < .000,
† ‘high’ vs. ‘moderate’ pulmonary pressure, P < .000.

Proportional relation between hydraulic power components
Figure 1 shows the mean, oscillatory and total power in the three groups. Total power is mainly made up of mean power. The RV oscillatory power fraction, ratio of oscillatory to total power is equal and not different in all three groups (about 23%). If all patients are analyzed as a single group (n=35) oscillatory power is 22.1 ± 4.8 % and mean power 77.9 ± 4.8 %. When non-PH and IPAH patients are all combined in a single group (n=49) we find oscillatory and mean power to be 23 ± 5.6 %, and 77 ± 5.6 % respectively.
Proportional relation PA pressures

Figures 2A shows the relations between systolic and diastolic PA pressure with mean pressure in the IPAH patients and non-PH subjects. From this data it follows that the pulse pressure is also proportionally related with mean pressure. Figure 2B conceptually shows this in terms of pressure wave. The linear relationship between the sPAP, dPAP and PP with mPAP is: sPAP = 2.7 + 1.54·mPAP ($r^2=0.98$, $P<.0001$) and dPAP = -1.8 + 0.66·mPAP ($r^2=0.95$, $P<.0001$) and PP = 4.5 + 0.88·mPAP.

Figure 3 shows the correlation between PA pulse pressure and the oscillatory power ($r^2 = 0.64$, $p < 0.0001$).

Figure 1. Hydraulic power (Watt) in non-PH, ‘moderate’ and ‘high’ pulmonary pressure in IPAH. The RV oscillatory power fraction, ratio of oscillatory and total power, equals 25%, 21%, and 23% in the 3 groups, respectively.

Fig 2. A) Relation systolic/diastolic pulmonary pressure with mean pulmonary pressure. B) Example of the change in pulmonary artery pressure wave from a non-PH individual to pulmonary hypertension. Notice that systolic, diastolic (their difference is the pulse pressure) and mean pressure rise proportionally.
DISCUSSION

The present study demonstrates that the fraction of oscillatory power to total power is about 23% in health and IPAH. This oscillatory power fraction is considerable and, more remarkable, this fraction remains the same in non-PH people and IPAH patients over a wide range of PA pressures. We also show a proportional relation between systolic and diastolic PA pressure with mean pressure, a result in agreement with earlier reports.\textsuperscript{11,12}

To move a given blood volume the RV has to generate power to overcome the hydraulic load in the pulmonary arteries. So, both properties of the pulmonary vasculature and the pumping ability of the right ventricle determine hydraulic power. A consequence of the pulsatile nature of blood flow is that the external hydraulic power consists of a steady and an oscillatory part.

At first glance the constant fraction of oscillatory power in health and IPAH seems remarkable, however, as we explain mathematically in the appendix, we assume that the constant fraction of oscillatory power in non-PH individuals and in varying degrees of pulmonary hypertension in IPAH patients is a consequence of the proportionality between pulse pressure and mean pressure (Fig 2). Right ventricular external hydraulic power increases as a result of increased pressures and possibly decreased flow in the PA. In the appendix it is shown that flow affects total and oscillatory power similarly and it is therefore pressure that remains as the major determinant of power (Fig 3). Our linear relation of systolic and diastolic PA pressure with mean PA pressure is similar to what was found by Chemla et al. and Syyed et al.\textsuperscript{11,12}

Our results show that the pulmonary external hydraulic power has a fundamentally different relationship between oscillatory and mean power as compared with the systemic external hydraulic power. In health, the left ventricle generates a total external hydraulic power which is about 5 times as large as the RV power. However, because oscillatory phenomena in the PA (pulse pressure is about equal
to mean pressure) are larger than in the aorta (pulse pressure is about 40% of mean pressure), oscillations play a more important role in the pulmonary vascular bed, and therefore the RV oscillatory power fraction is much larger (23%) than in its systemic counterpart (10-13%). In the systemic circulation, the ratio of oscillatory to total power does not remain the same during the development of systemic hypertension. This is probably attributable to the non-proportional relation between pulse pressure and mean pressure in the systemic circulation. Nichols et al. and O’Rourke et al. reported an increase in the fraction of oscillatory power of the LV in systemic hypertensive patients compared to normotensive patients, indicating that the coupling of LV and arterial system has become less efficient. Our data (Fig 2) show that mean PA pressure by vasodilatory treatment reduces mean and systolic pressure proportionally, our analysis (appendix) therefore shows that mean and oscillatory power are reduced in proportion. This is in contrast to what would happen systemically where with decreased mean pressure the oscillatory power fraction would decrease and mean power fraction increase.

In clinical practice right ventricular afterload is usually expressed as PVR, which is based on steady hemodynamics only, thus ignoring the considerable pulsatile nature of pressure and blood flow produced by the intermittent contraction of the RV. With the constant oscillatory power fraction of 23%, the standard steady hemodynamics data obtained from routine catheterization (e.g. mean PA pressure and CO) can be used to estimate total RV hydraulic power. Mean power derived from mean PA pressure and CO is 77% of total power and thus total power equals 1/0.77 = 1.3 times mean power.

Mean power relates to mean pressure and therefore to pulmonary vascular resistance. Oscillatory power relates to pulse pressure and thus to arterial compliance. As a consequence the present study emphasizes that both resistance and arterial compliance are important determinants of the load on the right heart as shown before by Lankhaar et al.

We report that approximately 23% of total RV hydraulic power is devoted to producing pulsatile blood flow in non-PH individuals and that this proportion remains this high in IPAH. Previous studies who have investigated the external hydraulic power of the RV in humans showed various values for the fraction of oscillatory power, but all these studies except one had in common that this fraction was higher than in the systemic circulation. Milnor et al. showed that the oscillatory power is about one-third of total power in ‘normal’ subjects (33%, n=3) and that the oscillatory power fraction was reduced to 24% in 7 patients with PH. A possible explanation may be that Milnor calculated flow from the differential pressure using Womersley’s oscillatory flow theory, thus based on a very small pressure difference and estimates of vessel diameter. We suspect that this indirect flow determination may lead to the differences, especially since Laskey et al. using measured velocity calculated into flow via thermodilution reports data close to ours. The different values in patients may also be that Milnor described patients with PH secondary to left heart failure, which can influence hydraulic
power of the RV differently from patients with PAH.\textsuperscript{19} In addition, this latter seems also to be supported by Kussmaul’s study showing only an oscillatory power fraction of 16\% in patients with PH secondary to congestive left heart failure. A more recent study from Laskey et al. reported an oscillatory power fraction in healthy individuals of 24\%,\textsuperscript{5} which is in agreement with our results. Laskey’s study, however, showed that the oscillatory power fraction was decreased to 14\% in PAH patients, while the ratio of pulse pressure to mean pressure remained about 1, as in our present results (see appendix). Therefore we cannot explain this difference.

The study of Weinberg et al. showed an oscillatory power fraction of only 7\% in ‘healthy’ individuals and 5\% in pulmonary hypertensive patients.\textsuperscript{17} This seems to be in conflict with the fact that this oscillatory power fraction is even lower than described in the systemic circulation, while oscillations play a much larger role in the pulmonary circulation. A possible explanation for this large difference is may be the pediatric population studied with other etiology of pulmonary hypertension than the adult IPAH patients.

In experimental studies using dogs in whom PH was induced by beads of various sizes\textsuperscript{20–22}, PA constriction\textsuperscript{20} or autologous clots\textsuperscript{23,24} and by monocrotaline, MCT\textsuperscript{25} all showed a reduced oscillatory power fraction compared to normal. These observations are not in agreement with the results of this study where we show a constant oscillatory power fraction. However, the data are acute, except for MCT, and obtained under anesthesia, and pressure relations as in Fig 2 are not given or do not seem present. If the oscillatory power ratio would decrease in PH this could be interpreted as an increase in efficiency.

By means of standard catheterization one can obtain pressure and flow (Cardiac Output). From these data we can calculate the pulmonary vascular resistance, thereby characterizing the arterial load only. Calculation of external hydraulic power from the same (mean) pressure and flow data includes the cardiac effects, since hydraulic power depends not only on the mechanical properties of the arterial tree but also on the ability of the ventricle to do external work. Although power does not characterize the heart alone it gives information about the status of the heart. For instance, when in RV failure resistance remains constant, and power is decreased, cardiac function is different due to a decrease in muscle contractility (or muscle mass). Since the central role of the right ventricle in PAH is more and more recognized, there is a rationale to further explore this approach.

Because we show proportionality, i.e. that total power is always 1.30 times mean power, it suffices to measure mean pressure and CO, using routine right heart catheterization.

To summarize, our findings have the following implications: A) Hydraulic power based on mean pressure and flow underestimates total hydraulic power by about 33\% in the pulmonary circulation, which is considerably larger than in the systemic circulation; B) Due to the proportionality in hydraulic power components (oscillatory power is 23\% of total power), we can derive total power from mean
PA pressure and CO only by multiplying mean power with 1.33; C) Treatment with vasodilators in IPAH will decrease total hydraulic power which is beneficial, however the fraction of ‘useless’ oscillatory power will remain at the same high value (23%). Lankhaar et al.\textsuperscript{14} showed that pulmonary arterial compliance contributes importantly to RV load. Therefore, it would be of great interest to evaluate the possibility to decrease the oscillatory power fraction by increasing the PA compliance selectively in PAH. This will make the RV work more efficient in respect to its arterial load by pumping blood to the pulmonary circulation at a lower energy cost.

For studies aiming to understand and treat patients with right heart failure these implications are relevant to consider, because the response of the RV to its arterial load is apparently different from its systemic counterpart, regarding their difference in hydraulic power components and pressure relations. Accordingly, treatment of right heart failure secondary to PH needs another approach than in left heart failure secondary to systemic hypertension.

Limitations

We could not include completely healthy asymptomatic individuals, due to ethical issues. Although the pressures of our non-PH patients are slightly higher than reported by Kovacs et al.,\textsuperscript{26} they all have mean pulmonary artery pressures less than 25 mmHg. Since truly normal individuals fall on the same proportional relation between systolic and mean pressure (Syyed et al.\textsuperscript{12}) there is no reason to expect that in healthy patients the power ratio will be different. The found constant oscillatory power fraction in this group of subjects, appears based on the proportionality of systolic and mean pressure (Fig. 2 and appendix). Since this proportionality has been reported by others as well in larger groups (Syyed et al. and Chemla et al.\textsuperscript{11,12}) suggests that the same power fraction will be found in healthy subjects.

The recordings of pressure and flow were not simultaneously measured introducing potentially the chance of pressure and flow measurements were performed in different hemodynamic states. However, since we performed MRI within 12 hours before or after catheterization we think this effect to be small. In addition, we made sure that included patients had a heart rate during catheterization which was less than 5% different from during MRI measurement. The pressure wave form obtained by fluid filled catheters can be distorted by the dynamic response of the catheter. However, if used properly (flushing etc.) errors are small and reliable pressure curves can be obtained, especially since the pulmonary artery pressure does not contain high frequencies.

In conclusion, in this study we found that in analogy to the proportionality of pulse pressure with mean pressure the oscillatory power fraction is similar (~23%) in non-PH and disease.
REFERENCE LIST


Mathematical basis of proportional power

We show here that the oscillatory power fraction (relation of oscillatory power and total power) is based on the proportional relation between mean pressure and systolic pressure.\textsuperscript{11,12}

Using equation 1, integrating over the ejection period and assuming that pressure in systole is constant gives:

$$\text{Power}_{\text{tot}} = \frac{1}{T} \cdot P_{s} \cdot \int Q(t) \times dt = \frac{1}{T} \cdot P_{s} \cdot SV = P_{s} \cdot CO,$$

(4)

with $P_{s}$ is systolic pulmonary artery pressure and $SV$ is Stroke Volume.

Oscillatory power is the difference between total and mean power (see equation 3), and the ratio of oscillatory and total power equals:

$$\frac{P_{s} \cdot CO - P_{m} \cdot CO}{P_{s} \cdot CO} = 1 - \frac{P_{m}}{P_{s}}.$$  

(5)

The ratio $P_{m} / P_{s}$ reported in this study is constant, that is $1/1.54$, therefore the fraction oscillatory power is $1 - 1/1.54 = 1 - 0.65 = 0.35$.

The assumption that pressure equals systolic pressure during ejection gives an overestimation of the total power. Therefore in a number of patients we determined the ratio peak systolic pressure over mean systolic pressure (determined over the ejection period) and found $\sim 1.2$. Using this correction factor we obtain $1 - 1.2 \cdot P_{m} / P_{s} = 1 - 1.2 \cdot 0.65 = 0.22$, a value close to what we find experimentally.