RC-TIME CONSTANT OF SINGLE LUNG EQUALS THAT OF BOTH LUNGS TOGETHER: A STUDY IN CHRONIC THROMBOEMBOLIC PULMONARY HYPERTENSION


ABSTRACT

The product of resistance, R, and compliance, C, (RC-time) of the entire pulmonary circulation is constant. It is unknown if this constancy holds for individual lungs. We determined R and C in individual lungs in CTEPH patients where resistances differ between both lungs. Also, the contribution of the proximal pulmonary arteries (PA) to total lung compliance was assessed.

Patients (n=23) were referred for the evaluation of CTEPH. Pressure was measured by right heart catheterization, and flows in the main, left and right PA, by MRI. Total, left and right lung resistances were calculated as mean pressure divided by mean flow. Total, left and right lung compliances were assessed by the pulse pressure method. Proximal compliances were derived from cross-sectional area change ΔA and systolic-diastolic pressure difference ΔP (ΔA/ΔP) in main, left and right PA, multiplied by vessel length. The lung with the lowest blood flow was defined “Low-Flow” (LF), the contralateral lung “High-Flow” (HF).

Total resistance was 0.57±0.28mmHg∙s/ml, and resistances of LF and HF lungs were 1.57±0.2 vs. 1.00±0.1mmHg∙s/ml, respectively, p<0.0001. Total compliance was 1.22±1.1ml/mmHg, and compliances of LF and HF lung were 0.47±0.11 and 0.62±0.12ml/mmHg respectively, p=0.01). Total RC-time was 0.49±0.2s, and RC-times for the LF and HF lung were 0.45±0.2 and 0.45±0.1s respectively, not different. Proximal arterial compliance, given by the sum of main, right and left PA compliances, was only 19% of total lung compliance.

The RC-time of a single lung equals that of both lungs together, and pulmonary arterial compliance comes largely from the distal vasculature.
INTRODUCTION

In contrast to the systemic circulation, in the pulmonary circulation compliance and resistance were shown to be inversely related in health and in various types of pulmonary hypertension i.e., their product, RC-time, is constant for both lungs together. This means that in patients with low resistance, compliance is high and vice versa. Why resistance and compliance are coupled in the total pulmonary arterial system, is not clear. Two possible explanations exist: 1) The constant RC-time is an intrinsic property of each lung, similar to what is found to both lungs together. 2) The lungs, hemodynamically acting in parallel, may compensate for each other's changes, i.e., with increased resistance in one lung, the compliance in the other lung increases with the overall RC-time unaltered, but with different RC-times in the two lungs.

Also in contrast with the systemic arterial system, where compliance is mainly located in the (proximal) aorta, it is not known how compliance of the pulmonary arterial tree is distributed over the system. If explanation 1 is more likely, it is to be expected that the pulmonary arterial compliance is distributed over the whole pulmonary arterial bed, and it does not matter which part of a lung is obstructed. If in a lung segment the resistance increases by a partially obstructing clot than automatically the compliance of this same segment will be lost and the RC product will remain about the same.

To investigate the RC-time in individual lungs we studied a group of chronic thromboembolic pulmonary hypertension (CTEPH) patients with different resistances between left and right lung. To obtain resistances and compliances we measured main pulmonary artery (PA) pressure (right heart catheterization) and flows and diameters in the main PA, left and right PA (MRI). To determine the contribution of proximal arteries to total arterial compliance we determined area compliance of the main and left and right PA with their lengths to derive proximal volume compliance. This last test should provide information on the distribution of compliance over the pulmonary vascular bed: Is it mainly from the proximal arteries (as in the systemic circulation), or more equally distributed? If a more equal distribution were found, then this provides a mechanism for the constancy of RC-time in each lung, irrespective of the degree of obstruction.

METHODS

Patient population

Twenty three patients suspected for CTEPH were referred to our hospital for a diagnostic work up between March 2008 and December 2008. All patients had a documented history of pulmonary embolism, a high probability V/Q scan and echocardiographic evidence for pulmonary hypertension.
The study protocol was approved by the institutional ethics committee, and informed consent was obtained from all subjects.

All patients underwent, as part of the diagnostic procedure, pulmonary angiography to assess the operability of the thromboembolic lesions according to current guidelines. Pressure was measured with a fluid-filled, single-lumen, 7-Fr or 5-Fr Grollman catheter (Cordis, Roden, the Netherlands) in the main PA. Four patients turned out to have no pulmonary hypertension and were considered as ‘normals’. Thus data are presented of 19 patients plus four ‘normals’.

MRI protocol
Within 24 hours before or after pulmonary angiography and right heart catheterization patients received MRI scan for the purpose of this study. MRI was performed 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 by MRI, using phase contrast flow quantification in the main, left and right PA. This imaging was performed during breath-hold 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 = $240 \times 320$ mm$^2$, matrix size = $140 \times 256$, echo time = 4.8 ms, repetition time = 11 ms, temporal resolution = 22 ms, flip angle = 25°.

After the three flow measurements were acquired, a phantom was imaged with identical imaging parameters, to serve as correction for the background phase error in the main, left and right PA.

**Cross-sectional area measurements**
The image plane for measuring area change (mm$^2$) was chosen orthogonal in the middle of the main, right and left PA as previously published. The magnitude images, as obtained with the above-mentioned flow measurements, were used to measure the arteries’ cross sectional areas at peak systole (maximal area) and end-diastole (minimal area), see Figure 1. The vessel cross-section could accurately be delineated through all phases of the cardiac cycle and was obtained by automatic delineation of the vessel wall (main, left and right PA) with in-house developed software in MATLAB 7.0, R14 (The Mathworks, Natick, MA) based on a study of Li et al.

**Data analysis**
Resistances. Total pulmonary resistance (TPR) was calculated from mean PA pressure, and mean flow in main PA. The resistances of individual lungs were calculated from the mean PA pressure divided by the mean flow to that lung. Thus
we assume that the pressure in the MPA is identical to the pressures in the proximal left and proximal right PA. The resistance in right and left lung were summed (as parallel resistances) and compared with the total resistance measured in the MPA.

**Compliances.** Total arterial compliance (i.e., compliance of both lungs together, Ct) was assessed with the pulse pressure method (PPM). The PPM uses the two-element Windkessel model with flow waveform and resistance as inputs to estimate the compliance value that best predicts systolic and diastolic pressures. This method has been shown to produce more accurate data than the calculations on the basis of the 3-element Windkessel. Compliances of the individual lungs were also assessed with the PPM with the resistance and flow waveform of the individual lungs as input variables.

In each patient we defined the lung with the lowest pulmonary blood flow as ‘Low Flow’ (LF) lung, and the other lung as ‘High Flow’ (HF) lung.

Fig 1. Minimal and maximal area of main, right and left PA. Top panel: Transversal MRI of main PA. Middle panel: Cross-section of right PA. Bottom panel: Cross-section of left PA. In all panels the arrow in the first image show the minimal area and in the second image the maximal area of the pulmonary artery.
Local compliances
From the area variation between systole and diastole, ΔA, and the Pulse Pressure, ΔP, we calculated (local) area compliance $C_A = \frac{\Delta A}{\Delta P}$. Area Compliance, $C_A$, times artery length gives local volume compliance, $C$, of the main, left and right PA. Artery length was assumed to be 2 cm for the main PA, and 3 cm for right as well as left PA, based on measurements in a subset of patients. Total proximal volume compliance was taken as the sum of the three compliances of the main, left and right PA.

For each patient the product of resistance and compliance, RC-time, was calculated for the both lungs together, as well as for the LF and the HF lung separately.

Statistics
Values presented are means ± SD. The group averages were compared using one way analysis of variance with a Bonferroni multiple comparison adjustment. An association between meanPAP and $C_A$, was explored using simple linear regression. A p value < 0.05 was considered statistically significant.

RESULTS
We studied 19 patients with confirmed CTEPH and 4 with angiographic lesions but without PH (CTE-nonPH). The gender was equally distributed between male and female. The PH patients had pulmonary hypertension with a mean pulmonary artery pressure (meanPAP) of 40 ± 12 mmHg (range 28-63 mmHg), and a Cardiac Index (CI) of 2.7 ± 0.5 L/min/m$^2$. The 4 non-PH patients had a meanPAP of 16 ± 2 mmHg (range 15-19), and a CI of 3.7 ± 0.6 L/min/m$^2$. Table 1 summarizes the baseline pulmonary hemodynamics of both groups.

Examples of flows in main, right and left pulmonary artery are shown in Figure 2.

The LF lung with the smallest flow had the highest resistance and this resistance was significantly higher than in the HF lung. The averaged resistance data are presented in Fig 3a, 1.57 ± 0.2 vs. 1.00 ± 0.1 mmHg·s/ml, $p < 0.0001$. The parallel addition of the resistances of the HF and LF lung was 0.57 ± 0.28 mmHg·s/ml, when plotted as a function of measured total resistance, the relation is tight with a slope not different from unity (Fig 3b, $r^2 = 0.94$, $p < 0.0001$). This proves that the sum of resistances of individual lungs equals total resistance.

The compliance was lower in the LF lung as compared with the HF lung (Fig 3c, 0.47 ± 0.11 vs. 0.62 ± 0.12 ml/mmHg, $p = 0.01$). Again, the sum of individual compliances was compared with total arterial compliance (1.22 ± 1.1 ml/mmHg), and it is tightly related (Fig 3d, $r^2 = 0.99$, $p < 0.0001$). This proves that the sum of compliances of individual lungs equals total arterial compliance.
Table 1. Baseline parameters of patients with CTEPH (n=19) and CTE-nonPH (n=4). Values presented as mean ± SD.

<table>
<thead>
<tr>
<th>Variable</th>
<th>CTEPH</th>
<th>CTE-nonPH</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>mean ± SD</td>
<td>range</td>
</tr>
<tr>
<td>Age (yrs)</td>
<td>60 ± 12</td>
<td>23 – 77</td>
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<td>female/ male ratio (n)</td>
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<td>-</td>
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<td>Functional class NYHA (n)</td>
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<td>-</td>
</tr>
<tr>
<td>RAP (mmHg)</td>
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<td>2 – 17</td>
</tr>
<tr>
<td>meanPAP (mmHg)</td>
<td>40 ± 12</td>
<td>28 – 63</td>
</tr>
<tr>
<td>TPR (mmHg•s•ml⁻¹)</td>
<td>0.64 ± 0.28</td>
<td>0.31 – 1.13</td>
</tr>
<tr>
<td>Cardiac index (L/min/m²)</td>
<td>2.7 ± 0.5</td>
<td>1.8 – 3.7</td>
</tr>
<tr>
<td>SvO₂ (%)</td>
<td>62.8 ± 8.5</td>
<td>45 – 72</td>
</tr>
</tbody>
</table>

NYHA denotes New York Heart Association; RAP, right atrial pressure; mPAP, mean pulmonary artery pressure; TPR, total pulmonary resistance; SvO₂, mixed venous oxygen saturation. Note: 1 mmHg•s•ml⁻¹ = 1.33 × 10⁻³ dyne•s•cm⁻⁵.

Relation resistance and compliance

The total resistance was inversely related with total compliance of both lungs together (r² = 0.81). The average RC-time was 0.49 s ± 0.15 (Fig 4a). The resistance and compliance in the LF and the HF lung were also inversely related (r² = 0.63 and r² = 0.85, respectively; Fig 4b and c). The average RC-time for the LF and the HF lung were 0.45 ± 0.15 s and 0.45 ± 0.14 s respectively, and were not different (p = NS, Fig 5). RC-times of individual lungs were also not different from total RC-time (both lungs together, p = NS).

Fig 2. Example of flow in the main, right and left PA. In this example the flow measured in the right PA is less than the flow in the left PA.
Relation diameter and area compliance with pressure

To investigate how much the 3 most proximal vessels contribute to total compliance we derived area compliances and multiplied them with vessel length. The proximal arterial volume compliance, of the main, right and left PA were 0.056 ± 0.02, 0.048 ± 0.03 and 0.049 ± 0.02 ml/mmHg respectively. Their sum, i.e. total proximal arterial compliance, equals 0.152 ± 0.003 ml/mmHg, and is 19% of total arterial volume compliance (0.804 ± 0.29 ml/mmHg).

The proximal compliance was 15 ± 3 % of total compliance in the non-PH and 19 ± 6 % of total compliance in the CTEPH patients (p = NS).

Volume compliance of the main, left and right PA (or actually main, HF and LF PA) showed all three the same inverse relation with meanPAP (Fig 6).

Fig 3. A: the resistance in the right, left and both lungs (total) were measured and compared. B: the sum of the left and right lung were summed as parallel resistances and compared with the resistance measured in the main PA (thus for both lungs). C: the compliance of individual lungs and both lungs compared. D: the sum of the compliances of individual lungs compared with total compliance (both lungs). * P < 0.01 and ** P < 0.001
Fig 4. The relationship between resistance and compliance (determined by pulse pressure method) of both lungs (total) A, in the lung with highest flow (thus less resistance) B, and the lung with lowest flow (thus higher resistance) C.

Fig 5. The product of resistance and compliance (i.e. RC-time) of both lungs (total), the lung with the lowest flow and highest flow. There was no statistical significant difference between these RC-times.
DISCUSSION

The present study shows that the product of resistance and compliance, RC, is similar in each lung, whether the vascular bed is more (Low flow) or less (High flow) affected, and in both lungs together. The similar RC-time constant per lung implies an intrinsic phenomenon, and that changes in one lung do not compensate for the other. In other words, each lung has a reciprocal relation between resistance and compliance, regardless of the magnitude of resistance in a lung. To the best of our knowledge this is the first study where resistance and compliance are measured within single lungs and both lungs together in healthy individuals and pulmonary hypertensive patients.

The average product of R and C (i.e. RC-time), which describes the exponential decay of the PAP during diastole, in our study is 0.49 s. Other studies have reported constant RC-times in healthy subjects, Idiopathic Pulmonary Arterial Hypertension (IPAH) and CTEPH, but the values of RC-time differ. The main reason for the differences is the way compliance is derived. Reuben et al. found a constant RC-time of 0.38 s obtained with the exponential decay of the diastolic pulmonary artery pressure wave method. Other studies have shown that the various ways to estimate volume compliance may differ by more than 50%, with the Pulse Pressure method giving the smallest compliance values and thus the shortest RC-times. If we use the compliance estimates reported by Lankhaar obtained with the PPM the average RC-time is ~0.42 s, a value close to the one found in our present study.

Therefore, we conclude, on the basis of the similar RC-times of single and both lungs, that the constant RC-time is an intrinsic property of each lung.

It has been shown on many occasions that increased intravascular pressure distends the arteries and causes increased stiffness of arteries due to their nonlinear distensibility. The observation in this study that area compliance was similarly related to mean pressure in left and right (or ‘HF’ and ‘LF’) pulmonary artery, results from the fact that proximal pulmonary arteries are exposed to the same pressure and material properties are assumed equal.

Fig 6. The correlation between meanPAP and volume compliance in the Main, High-flow and Low-flow pulmonary artery. P value is < 0.0001 of the three slopes.
Both total arterial compliance and area compliance decrease with increasing pressure. Thus in patients with increased pressure compliance is decreased. This may, in part explain our findings that with increased resistance compliance is decreased. Another, speculative, explanation could be that functional removal of part of the arterial system, a consequence of vessel obstruction and/or hypoxic vasoconstriction, also causes a decrease in compliance along with an increase of resistance.

The latter part of the explanation is consistent with our observation that pulmonary compliance is distributed over the distal pulmonary vascular bed. This is a characteristic that differs from the systemic circulation where compliance is mainly located in the proximal aorta. To explore the distribution of compliance we measured the local area compliances of right and left PA with MRI as previously described by others. By multiplying the area compliance with the length we obtain volume compliance of the proximal vessels. Interestingly, the contribution of proximal compliance to overall pulmonary arterial compliance was small (19%). Thus we conclude that an important part of the compliance is located in the pulmonary arteries distal to the proximal left and right pulmonary artery.

Patel et al. have shown that approximately one third of the stroke volume can be stored in the main pulmonary artery, which means that two third of the stroke volume can be stored in the more distal pulmonary arteries, also suggesting that a large part of the total compliance is distributed over the pulmonary arterial vasculature. Normal pulmonary arteries have thinner walls than their systemic counterparts, therefore it has been suggested that the vascular distensibility extends to medium sized arteries of 1mm size, and hence probably contribute to total arterial compliance. This seems also to be confirmed by the study of Engelberg and DuBois, who studied the pressure-volume characteristics of different anatomical portions of the vascular bed in isolated rabbit lungs. Their results showed an almost equal distribution of compliance over the entire arterial vascular bed. In addition, the study of Wiener et al., who studied the pressure and flow propagation in the pulmonary circulation of a dog, also seems to confirm this. They used a model of the pulmonary system to calculate, among other things, the compliance of each arterial segment from the main PA down to the capillary level. Their results demonstrate that the major part of total compliance is present in the arterioles and precapillary arteries. Furthermore, other studies have also shown that the distensibility (fractional diameter change mmHg) of pulmonary arteries is constant and independent of size and location in the pulmonary circulation. These studies all support the hypothesis that compliance is distributed over the entire pulmonary circulation, even in the pre-capillary vessels. However, this distribution of compliance in the human pulmonary arterial system needs further research.

Thus with considerable compliance located in the distal pulmonary arterial system, we can explain that the RC-time is constant in the pulmonary circulation in all categories of patients with PH and over a wide range of resistances; in other words, resistance and compliance are inseparably connected to each other, because they share the same distribution over the pulmonary vascular bed.
Limitations

A limitation of this study is that pressure and flow were not measured simultaneously. Potentially this can result in pressure and flow measurements in different hemodynamic states. We think this effect to be small, since we performed the MRI within 24 hours after or before catheterization. Also the difference in heart rate between MRI and right heart catheterization during pulmonary angiography was less than 5%.

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.

We used main pulmonary artery pressure for left and right artery pressure as well. The distance between these locations is so small that errors differences in pressure are negligible. Womersley's theory states that the longitudinal impedance predicts the pressure difference between two close sites and this impedance is extremely small.\(^{36}\)

In conclusion, we have shown that the RC-time constant applies for each lung separately in CTEPH, despite differences in resistances. This is consistent with our observation that the pulmonary vasculature distal to the main, right and left PA contributes for an important part to total arterial compliance.

REFERENCE LIST

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