Proximal pulmonary arterial obstruction decreases the time constant of the pulmonary circulation and increases right ventricular afterload

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Submitted 11 January 2013; accepted in final form 26 March 2013

Pagnamenta A, Vanderpool R, Brimioulle S, Naeije R. Proximal pulmonary arterial obstruction decreases the time constant of the pulmonary circulation and increases right ventricular afterload. J Appl Physiol 114: 1586–1592, 2013. First published March 28, 2013; doi:10.1152/japplphysiol.00033.2013.—The time constant of the pulmonary circulation, or product of pulmonary vascular resistance (PVR) and compliance (Ca), called the RC-time, has been reported to remain constant over a wide range of pressures, etiologies of pulmonary hypertension, and treatments. We wondered if increased wave reflection on proximal pulmonary vascular obstruction, like in operable chronic thromboembolic pulmonary hypertension, might also decrease the RC-time and thereby increase pulse pressure and right ventricular afterload. Pulmonary hypertension of variable severity was induced either by proximal obstruction (pulmonary arterial ensnarement) or distal obstruction (microembolism) eight anesthetized dogs. Pulmonary arterial pressures (Ppa) were measured with high-fidelity micromanometer-tipped catheters, and pulmonary flow with transonic technology. Pulmonary ensnarement increased mean Ppa, PVR, and characteristic impedance, decreased Ca and the RC-time (from 0.46 ± 0.07 to 0.30 ± 0.03 s), and increased the oscillatory component of hydraulic load (Wosc/Wtot) from 25 ± 2 to 29 ± 2%. Pulmonary microembolism increased mean Ppa and PVR, with no significant change in Ca and characteristic impedance, increased RC-time from 0.53 ± 0.09 to 0.74 ± 0.05 s, and decreased Wosc/Wtot from 26 ± 2 to 13 ± 2%. Pulse pressure increased more after pulmonary ensnarement than after microembolism. Concomitant measurements with fluid-filled catheters showed the same functional differences between the two types of pulmonary hypertension, with, however, an underestimation of Wosc. We conclude that pulmonary hypertension caused by proximal vs. distal obstruction is associated with a decreased RC-time and increased pulsatile component of right ventricular hydraulic load.

pulmonary hypertension; pulmonary vascular impedance; pulmonary vascular resistance; pulmonary arterial compliance; Doppler echocardiography; high-fidelity catheter

THE TIME CONSTANT OF THE PULMONARY circulation, or product of pulmonary vascular resistance (PVR) and compliance (Ca), called the RC-time, has been reported to remain constant over a wide range of pressures, etiologies of pulmonary hypertension, and treatments (12, 13, 22). A constant relationship between PVR and Ca implies that Ca becomes a relatively more important determinant of right ventricular (RV) afterload when PVR is normal or only moderately increased (2), and also that RV oscillatory power (Wosc) remains a constant fraction of total power (Wtot), irrespective of pulmonary arterial pressure (Ppa) (21, 23). The only noticeable exception is pulmonary hypertension secondary to left ventricular failure (24). In these patients, RC-time is decreased because of a stiffer pulmonary arterial tree caused by increased pulmonary venous pressure (16).

Proximal pulmonary arterial obstruction has been shown to increase wave reflection, which increases pulse pressure (PP) at any given level of mean Ppa (mPpa) (7, 8, 26). This finding has been confirmed in patients with chronic thromboembolic pulmonary hypertension (CTEPH) (4, 17, 18). Increased wave reflection with disproportionate increase in systolic Ppa (sPpa) relative to mPpa would add to the effects of increased pulmonary arterial stiffness in decreasing calculated Ca and RC-time and thereby increase RV afterload at any given level of PVR (6, 26).

We, therefore, investigated the effects of proximal pulmonary vascular obstruction by pulmonary arterial ensnarement, and of distal pulmonary vascular obstruction by the injection of microbeads in anesthetized dogs. Pulmonary vascular function was quantified in both time and frequency domain using high-fidelity but also standard fluid-filled catheter equipment and trans-thoracic echocardiography, as used in clinical practice to allow for optimal translation. The results show that purely proximal increase in PVR decreases RC-time and increases RV afterload.

METHODS

Preparation. Eight mongrel dogs (mean weight 30 kg; range, 19–48 kg) were included in the present study, which was approved by the Committee on the Care and Use of Animals in Research of the Brussels Free University School of Medicine. Anesthesia was induced with propofol (10 mg/kg), and thereafter the dogs were anesthetized with α-chloralose (20 mg/h) and repeated morphine boluses (0.1 mg/kg) and paralyzed with pancuronium bromide (0.2 mg·kg−1·h−1) to maintain anesthesia and apnea. The dogs were ventilated (Elena 900 B servo-ventilator, Siemens Elema, Solna, Sweden) via a cuffed endotracheal tube in the volume control mode. The inspired O2 fraction was 0.4. The respiratory rate was 10 breaths/min, the tidal volume was 15–25 ml/kg, adjusted to maintain arterial PCO2 between 35 and 45 Torr, and the positive end-expiratory pressure was 5 cmH2O. Periodic deep inspirations were administered to prevent atelectasis formation. Body temperature was maintained at 36–38°C using an electric heating pad. When metabolic acidosis occurred, it was corrected with a slow infusion of sodium bicarbonate. Physiological saline was infused at 300 ml/h, with rate adaptation to maintain right and left ventricular filling pressures and blood pressure within normal limits.

A balloon-tipped flow-directed pulmonary catheter (model 131H-7F; Baxter Edwards, Irvine, CA) was inserted in the main pulmonary artery through the left external jugular vein for measurements of mPpa, sPpa, and diastolic Ppa (dpPpa), right atrial pressure, cardiac output (Q), central temperature, and for mixed venous blood sampling. A polyethylene catheter was inserted in the abdominal aorta via
the right femoral artery for measurements of systemic arterial pressure (Psa) and for arterial blood sampling. In all of the animals, left lateral thoracotomy in the fourth intercostal space was performed. The tip of a Swan-Ganz catheter (model 131H-7F; Baxter Edwards, Irvine, CA) was inserted in the left atrium via the atrial appendage to measure left atrial pressure (Pla). A 16- to 24-mm no-constricting ultrasonic flow probe (T101, Transonic Systems, Ithaca, NY) was positioned around the main pulmonary artery for the measurement of instantaneous pulmonary Q. The transonic flowmeter system is linear to 60 Hz, with a flat amplitude response to 35 Hz. A 5F high-fidelity manometer-tipped catheter (model SC 350, Millar Instruments, Houston, TX) was introduced through the RV into the main pulmonary artery, and its tip was positioned just distal to the flow probe for the measurement of the instantaneous Ppa. The frequency response of the micromanometer system is flat beyond 200 Hz. The chest was tightly closed, and some large inspirations were then performed to reexpand the lungs, but no attempt was made to restore a negative pleural pressure.

**Measurements.** Heart rate (HR) was determined from a continuously monitored electrocardiographic lead. Ppa and pulmonary arterial flows were measured with the high-fidelity micromanometer-tipped catheters and the ultrasonic flow probe, respectively. Psa, Pla, and also Ppa were measured using Gould Statham P50 transducers (Gould, Oxnard, CA). The vascular pressure and flow signals were displayed by using a monitoring system (Sirecust 404, Siemens, Erlangen, Germany) and recorded on a six-channel Gould recorder (model 2600S, Gould, Instruments Division, Cleveland, OH). The pressure transducers of fluid-filled catheters were zero referenced at midchest, and vascular pressures were obtained at end expiration. Mean Q was measured using the thermodilution technique as a mean of at least three successive measurements (CO-set, Baxter; Edwards, Santa Ana, CA). Instantaneous Q was measured using the ultrasonic flow probe. The zero Q from the ultrasonic flow probe was adjusted to the end-diastolic value, assumed to be zero. The instantaneous pulmonary pressures and flow signals were sampled at 200 Hz using an analog-to-digital converter (RTI 800, Analog Device), stored, and analyzed on a personal computer. Instantaneous pulmonary flow was also measured by transthoracic Doppler echocardiography using a 3.5-MHz probe (SONOS 2000, Palo Alto, CA) with the dog in a lateral position. Pulsed-Doppler velocity was recorded in the RV outflow tract using the short-axis parasternal view, as previously described (10). Sampling frequency and gain setting were optimized to obtain the best flow-velocity envelope. All transthoracic Doppler echocardiographies were performed by the same investigator (A. Pagnamenta). Ppa and flow signals were recorded after the Swan-Ganz catheter was withdrawn to the same position as the high-fidelity catheter, as close as possible to the pulsed Doppler pulmonary artery flow-velocity sampling site. The signals were visually checked for quality and then were synchronized by an ECG artifact and recorded on a paper of 100 mm/s using the built-in printing system of the echocardiograph. Pressure and flow-velocity were “manually” scanned (UnGraph for Windows, Biosoft, Cambridge, UK), digitized at a paper velocity of 100 mm/s using the built-in printing system of the echocardiograph. Instantaneous pulmonary and flow signals were sampled for PVZ calculations. Thereafter, the same measurements were repeated during the following conditions:

1. After ensnarement of the right-end left pulmonary arteries distal to the intravascular catheter tips, at two different Ppa levels: mPpa of 22 mmHg and mPpa of 27 mmHg. Attempts at higher Ppa caused too much hemodynamic instability and were thus omitted. Care was taken to avoid proximal pulmonary artery tree distortion by the ensnarement.

2. At baseline 2: after waiting sufficient time to be sure that there was no residual effect of proximal constriction assessed by a return of HR, Psa, and Ppa values to baseline levels.

3. One to three grams of 100-μm glass beads (Sigma, St. Louis, MO) were then slowly administered into the right atrium in around 20 min. The embolization was carried out until mPpa reached 35 mmHg and then stopped, allowing mPpa to stabilize in 20–30 min at a value around 25 mmHg. A second embolization was carried out until mPpa reached 45 mmHg and then stopped, allowing mPpa to stabilize in 20–30 min at a value around 35 mmHg.

**Statistics.** Results are expressed as mean values ± SE. Hemodynamic data and blood-gas results were analyzed by a repeated-measures analysis of variance. When the F-ratio of the analysis of variance reached a P < 0.05 critical level, modified t-tests were used to compare two different situations (27). A P critical level < 0.05 of the modified t-tests was accepted as indicating statistical significance. PVZ calculated using the fluid-filled catheter and echocardiography and PVZ calculated with the high-fidelity catheter and ultrasonic flow probe were compared by correlation analysis and by Bland-Altman agreement analysis by calculating the bias (mean of the difference between the two methods) and the 95% limits of agreement (2 standard deviations around the mean difference) (1).

**RESULTS**

Effect of pulmonary artery ensnarement and microembolization on pulmonary hemodynamics. See Table 1. Progressive ensnarement increased mPpa and HR, decreased Q, while Pla remained unchanged. Ensnarement increased mPpa with a proportional increase in sPpa (1.8 × mPpa) and a small effect on dPpa (0.3 × mPpa) pressure (Fig. 1). All measurements returned to baseline after relief of ensnarement, with the exception of a slight decrease in Pla, which was compensated for by fluid-filling. There were no significant differences between the two baselines. Progressive microembolization and microembolization increased mPpa, HR, and Pla, decreased Psa, and Q remained unchanged. Acute microembolism increased mPpa with an increase in sPpa that was proportionally less than after ensnarement (1.3 × mPpa), while dPpa increased more (0.8 × mPpa). This resulted in a larger PP in the ensnare-
Table 1. Steady hemodynamic data in eight dogs at baseline, two levels of progressive ensnarement of the pulmonary arteries, a second baseline, and two levels of progressive microembolization of the distal pulmonary circulation

<table>
<thead>
<tr>
<th>Variables</th>
<th>Baseline 1</th>
<th>Ensnarement 1</th>
<th>Ensnarement 2</th>
<th>Baseline 2</th>
<th>Embolization 1</th>
<th>Embolization 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR, beats/min</td>
<td>138 ± 8</td>
<td>151 ± 6</td>
<td>157 ± 6*</td>
<td>127 ± 10</td>
<td>164 ± 7†</td>
<td>157 ± 3†</td>
</tr>
<tr>
<td>Psa, mmHg</td>
<td>118 ± 7</td>
<td>120 ± 6</td>
<td>124 ± 6</td>
<td>120 ± 7</td>
<td>107 ± 10†</td>
<td>109 ± 10†</td>
</tr>
<tr>
<td>mPpa, mmHg</td>
<td>17 ± 2</td>
<td>22 ± 2*</td>
<td>27 ± 2*</td>
<td>17 ± 2</td>
<td>26 ± 1†</td>
<td>33 ± 4†</td>
</tr>
<tr>
<td>sPpa, mmHg</td>
<td>28 ± 4</td>
<td>38 ± 6</td>
<td>44 ± 5*</td>
<td>27 ± 3</td>
<td>33 ± 1†</td>
<td>44 ± 7†</td>
</tr>
<tr>
<td>dPpa, mmHg</td>
<td>11 ± 2</td>
<td>12 ± 1</td>
<td>11 ± 1</td>
<td>10 ± 2</td>
<td>19 ± 1†</td>
<td>26 ± 3†</td>
</tr>
<tr>
<td>Pla, mmHg</td>
<td>7 ± 2</td>
<td>6 ± 2</td>
<td>8 ± 2</td>
<td>5 ± 2</td>
<td>8 ± 2†</td>
<td>9 ± 2†</td>
</tr>
<tr>
<td>Q, l/min 1·m−2</td>
<td>4.5 ± 0.9</td>
<td>3.8 ± 0.6</td>
<td>3.6 ± 0.6*</td>
<td>3.4 ± 0.6</td>
<td>3.2 ± 0.4</td>
<td>3.5 ± 0.5</td>
</tr>
<tr>
<td>SV, ml</td>
<td>33 ± 4</td>
<td>25 ± 3</td>
<td>20 ± 1*</td>
<td>27 ± 3</td>
<td>21 ± 2</td>
<td>24 ± 3</td>
</tr>
<tr>
<td>Ca, ml/mmHg</td>
<td>2.1 ± 0.2</td>
<td>1.1 ± 0.1*</td>
<td>0.7 ± 0.1*</td>
<td>1.9 ± 0.3</td>
<td>1.6 ± 0.2</td>
<td>1.8 ± 0.6</td>
</tr>
<tr>
<td>RC-time, s</td>
<td>0.46 ± 0.07</td>
<td>0.35 ± 0.03</td>
<td>0.30 ± 0.03*</td>
<td>0.53 ± 0.09</td>
<td>0.74 ± 0.05</td>
<td>0.83 ± 0.12†</td>
</tr>
</tbody>
</table>

Values are means ± SE; n = 8 dogs. HR, heart rate; Psa, mean systemic arterial pressure; mPpa, mean pulmonary arterial pressure; sPpa, systolic pulmonary arterial pressure; dPpa, diastolic pulmonary arterial pressure; Pla, left atrial pressure; Q, cardiac output; SV, stroke volume; Ca, compliance; RC, pulmonary vascular resistance-Ca. *P < 0.05 compared with baseline 1. †P < 0.05 compared with baseline 2.

Fig. 1. Correlation between systolic mean pulmonary arterial pressure (mPpa) and diastolic mPpa in pulmonary hypertension induced by proximal obstruction (ensnarement) and distal obstruction (microembolism).

Fig. 2. The inverse relationship between compliance (Ca) and total pulmonary vascular resistance (TPVR) calculated from Millar-measured pressures (Ca = RC-time/TPVR). In the ensnarement model, the RC-time is decreased (0.39 s, $R^2 = 0.61$, $P = 0.001$) compared with the microembolization model (0.61 s, $R^2 = 0.41$, $P = 0.004$).

With progressive ensnarement, SV decreased from 33 to 20 ml as a result of decreased Q and increased HR. Microembolization increased HR, but, with no change in Q, there was no significant change in SV. The result was that, with progressive ensnarement, Ca decreased but stayed approximately the same with microembolism (Table 1). The RC-time decreased with ensnarement and increased with microembolism (Fig. 2).

Effect of pulmonary artery ensnarement and microembolization on PVZ. See Table 2. There were no significant differences in the baseline measurements before and after progressive ensnarement. Progressive ensnarement increased $Z_0$, $Z_1$, and $Z_C$, with no change in the Ph1. Wtot increased with unchanged Wosc/Wtot. Progressive microembolization increased $Z_0$ and had no effect on $Z_1$ and $Z_C$. The first minimum frequency of the PVZ spectrum shifted toward higher frequencies. The Ph1 decreased, and Wtot increased, but Wosc/Wtot decreased.

Contrasted effects of ensnarement and microembolism on PVZ spectra of three animals at the same severity of pulmonary hypertension ($Z_0$) with marked increase in the ratios of pressure and flow moduli over the entire range of the spectrum are illustrated in Fig. 3.
tion, and that this is associated with an increased RV afterload. The results also show that the hemodynamic effects of proximal vs. distal increase in PVR can be evaluated with a clinically acceptable approximation using fluid-filled catheters and Doppler echocardiography.

The present results are in keeping with previous reports. Furuno et al. (8) showed that, at the same increase in Ppa, pulmonary artery banding compared with microembolism affects pulmonary pressure and flow waves by an increased PP, late systolic peaking of pressure, and midsystolic deceleration of flow, all aspects explained by earlier return of the first reflected wave on forward wave. Similar results were reported by Wauthy et al. (26) in three different animal species. Elzinga et al. (6) showed that isolated decrease in Ca at unchanged PVR increased RV systolic pressure with late systolic peaking and increased PP. Calvin et al. (3) showed that a proximal pulmonary arterial obstruction increased both Z0 and ZC, whereas, with a distal obstruction, ZC remains unchanged or decreased. Because ZC is a ratio between inerterance and Ca, the decrease of ZC in pulmonary hypertension on distal small arteriolar obstruction was tentatively explained by a compensatory dilatation of the proximal arterial tree (3). Fitzpatrick and Grant (7) showed that pulmonary arterial ensnarement increased both Z0 and ZC and decreased Ca, while the application of positive end-expiratory pressure to compress peripheral vessels, and thus increased peripheral resistance, increased Z0 but had negligible effects on ZC and Ca. In the present experiments, ZC increased after pulmonary arterial ensnarement and was unchanged after microembolism, but with directional changes in Ca. The reason why Ca was preserved in microembolic pulmonary hypertension is unclear. Even though the mPpa in these animals increased to 30–35 mmHg, this did not appear sufficient to affect the slope of diameter-pressure relationships. Active neurohumoral mechanisms contributing to the observed changes cannot be excluded, even though this has been explored in only one study, which showed a decrease in Zc during pulmonary arterial ensnarement after the administration of the serotonin receptor blocker ketanserine (7). Decreased Ca and increased ZC in pulmonary arterial banding can be explained by the combined effects of mechanical interference of the maneuver and wave reflection on proximal constriction.

In the present experiments, increased mPpa and PVR were accompanied by an increase in total pulmonary arterial hydraulic work, indicating increased RV afterload. However, the pulsatile component of hydraulic work increased after pulmonary arterial ensnarement and decreased after microembolism. A faster HR could have decreased the pulsatile component of hydraulic work (15). However, there were no significant differences in HR between our two pulmonary hypertension models. Thus increased pulsatile hydraulic work after ensnarement is to be explained by contrasting changes in low- and high-frequency impedance and associated changes in Ca.

The RC-time was markedly shorter in “proximal” pulmonary hypertension as a model of operable CTEPH, compared with “distal” pulmonary hypertension as a model of PAH. This is in contrast to clinical studies that reported constant RC-time and oscillatory component of hydraulic load independently of type of pulmonary hypertension (21, 23). These differences between experimental and clinical pulmonary hypertension

Table 2. Pulsatile hemodynamics at baseline, two levels of progressive ensnarement of the pulmonary arteries, a second baseline, and two levels of progressive microembolization of the distal pulmonary circulation

<table>
<thead>
<tr>
<th>Variables</th>
<th>Baseline 1</th>
<th>Ensnarement 1</th>
<th>Ensnarement 2</th>
<th>Baseline 2</th>
<th>Embolization 1</th>
<th>Embolization 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Z0, dyn·s·cm⁻³·m⁻²</td>
<td>376 ± 52</td>
<td>498 ± 31</td>
<td>655 ± 53*</td>
<td>436 ± 69</td>
<td>712 ± 79†</td>
<td>864 ± 171†</td>
</tr>
<tr>
<td>Z1, dyn·s·cm⁻³·m⁻²</td>
<td>85 ± 9</td>
<td>176 ± 18*</td>
<td>362 ± 31*</td>
<td>86 ± 11</td>
<td>66 ± 5</td>
<td>110 ± 23</td>
</tr>
<tr>
<td>ZC, dyn·s·cm⁻³·m⁻²</td>
<td>113 ± 8</td>
<td>181 ± 15*</td>
<td>267 ± 11*</td>
<td>108 ± 8</td>
<td>89 ± 7</td>
<td>95 ± 15</td>
</tr>
<tr>
<td>Ph1, rad</td>
<td>0.07 ± 0.11</td>
<td>0.07 ± 0.08</td>
<td>0.07 ± 0.09</td>
<td>0.06 ± 0.11</td>
<td>−0.29 ± 0.16†</td>
<td>−0.67 ± 0.09†</td>
</tr>
<tr>
<td>Wtot, mW/m²</td>
<td>264 ± 72</td>
<td>290 ± 83</td>
<td>326 ± 56*</td>
<td>175 ± 44</td>
<td>230 ± 36</td>
<td>308 ± 6†</td>
</tr>
<tr>
<td>Wosc/Wtot, %</td>
<td>25 ± 2</td>
<td>28 ± 2</td>
<td>29 ± 2*</td>
<td>26 ± 2</td>
<td>16 ± 2†</td>
<td>14 ± 2†</td>
</tr>
</tbody>
</table>

Values are means ± SE; n = 8 dogs. Z0, 0-Hz impedance (total resistance); Z1, first harmonic impedance; ZC, characteristic impedance; Ph1, first harmonic phase angle; Wtot, total hydraulic work; Wosc/Wtot, oscillatory hydraulic work-to-total hydraulic work ratio.*P < 0.05 compared with baseline 1. †P < 0.05 compared with baseline 2.

Fig. 3. Average impedance (Z) spectra in 3 dogs at baseline and with identical or very close 0-Hz impedance (Z0) after induction of pulmonary hypertension with either ensnarement or microembolism. Ensnarement shifted the entire impedance spectrum to higher ratios of pressure and flow moduli. Vertical and horizontal bars indicate SE.
may be explained by better control of the site of obstruction in the present experiments, while pulmonary vasculopathy in CTEPH tends to spread over the entire pulmonary arterial tree (9). It may be noted that there was a longer RC-time at baseline before the injection of microbeads. This may be related to previous ensnarement, even though care was taken to observe return of HR, mPpa, and $Q$ to baseline. The RC-time number is a product of two ratios and, therefore, sensitive to small changes in either one of its several components, in relation to incompletely recovered stability or unnoticed changes in depth of anesthesia. Pla after ensnarement and before microbead injection was decreased, by an average of 2 mmHg within limits of normal, illustrating imperfect maintenance of hemodynamic stability by fluid loading. However, such a small decrease in Pla without other hemodynamic alterations would be unlikely to affect the RC-time. We, therefore, believe that the difference in RC-time between the two pulmonary hypertension models is true, as it was enhanced over time with progressive increase in pulmonary pressures.

$sPpa$, $dPpa$, and $mPpa$ are tightly correlated, with simple formulas to predict one from another that seem applicable to any type of pulmonary hypertension (5). This remains true only if $Ca$ is predictable at any level of PVR and RC-time remains constant. A recent study reported on a decreased RC-time in heart failure (24), which is explained by increased pulmonary wedge pressure causing a decrease in $Ca$ at any level of PVR (16). The present results report on exclusive proximal obstruction as another cause of decreased RC-time and show the associated increase in PP and oscillatory arterial hydraulic work. Previously reported equations to predict mPpa from sPpa, which are used in Doppler echocardiographic studies of the pulmonary circulation, have to be used with great caution in case of decreased $Ca$ or increased $Z_C$.

Instantaneous pulmonary arterial flow velocity can be measured by transthoracic pulsed Doppler echocardiography and converted into volume flow using a conversion factor obtained by conventional thermodilution $Q$ measurement (10, 11). It has been generally assumed that the frequency response of fluid-filled thermodilution Swan-Ganz catheters that are used for routine right heart catheterization would be insufficient for accurate instantaneous pressure measurements, especially at high HRs like in the present study (25). However, the present results confirm that realistic pressure and flow measurements to be used in the calculation of PVZ can be obtained using simple
bedside fluid-filled catheter and transthoracic Doppler technology. But there are a few limitations. In the present study, there was a poor accuracy for the Ph1 and for the oscillatory hydraulic work. This observation is due to the time latency in pressure recording inherent in fluid-filled catheters compared with high-fidelity micromanometer-tipped catheters. The parameters that have been found to be important for the characterization of the pulmonary circulation (Zc, PVR, and Ca) were sufficiently measured.

The PVZ comparison with the two methods presented here was made in dogs and not in humans. Previous studies have shown canine and human PVZ spectra are remarkably similar except for body size-related differences in the high-frequency impedance of humans (19). Given that PVZ is more descriptive of the pulmonary circulation, it is interesting there are only a few reports on the PVZ spectra in humans (20). This is likely due to the difficulty of placement of the high-fidelity micromanometer-tipped catheter in the pulmonary artery and cost. However, as we show in this paper, it is possible to measure meaningful PVZ magnitudes using tools that are commonly used in reference pulmonary hypertension centers. A limited number of clinical studies that have used fluid-filled catheters and echocardiography to measure PVZ have demonstrated sensitivity to pharmacological interventions (10, 11) and, in one pediatric study (11), prognostic relevance.

To what extent the ensnarement of the pulmonary arteries and microembolism are realistic models of CTEPH and PAH is not exactly known. Successful pulmonary endarterectomy does not always reverse pulmonary hemodynamics to normal, indicating more widespread vasculopathy than generally assumed (8). Pulmonary arterial hypertension may be associated with secondary proximal arterial remodeling. Therefore, caution should be exerted in the clinical extrapolation of the present results.

![Graphs showing linear regression and Bland-Altman analysis for impedance metrics.](image)

**Table 3. Linear regression and Bland-Altman analysis for impedance metrics obtained with the high-fidelity and fluid-filled catheter methodology**

<table>
<thead>
<tr>
<th>Variables</th>
<th>Regression</th>
<th>Bland-Altman</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Slope</td>
<td>R²</td>
</tr>
<tr>
<td>Z₀, dyn·s·cm⁻⁵·m⁻²</td>
<td>0.90</td>
<td>0.99</td>
</tr>
<tr>
<td>Ph1, rad</td>
<td>0.41</td>
<td>0.34</td>
</tr>
<tr>
<td>Ws, mW/m²</td>
<td>0.93</td>
<td>0.95</td>
</tr>
<tr>
<td>Wosc, mW/m²</td>
<td>1.81</td>
<td>0.6</td>
</tr>
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</table>

Ws, steady hydraulic power.
In conclusion, the site of increased PVR in pulmonary hypertension affects the time constant of the pulmonary circulation. Purely proximal obstruction like in purely operable CTEPH may be added to heart failure as a cause of shortened RC-time and relative increase in RV afterload.

ACKNOWLEDGMENTS

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GRANTS

The study was supported by Grant 3.4637.09 from the “Fonds de la Recherche Scientifique Medicale,” Belgium. A. Pagnamenta was supported by the Lega polmonare ticinese (Lugano, Switzerland), the Fondazione Dr. PL Recherche Scientifique Medicale,” Belgium. A. Pagnamenta was supported by a Marie Curie postdoctoral grant from the European Respiratory Society.

DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the author(s).

AUTHOR CONTRIBUTIONS


REFERENCES