Partitioning of Pulmonary Vascular Resistance in Primary Pulmonary Hypertension

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Objectives. This study sought to determine the site of increased pulmonary vascular resistance (PVR) in primary pulmonary hypertension by standard bedside hemodynamic evaluation.

Background. The measurement of pulmonary vascular pressures at several levels of flow (Q) allows the discrimination between active and passive, flow-dependent changes in mean pulmonary artery pressure (Ppa), and may detect the presence of an increased pulmonary vascular closing pressure. The determination of a capillary pressure (Pc') from the analysis of a Ppa decay curve after balloon occlusion allows the partitioning of PVR in an arterial and a (capillary + venous) segment. These approaches have not been reported in primary pulmonary hypertension.

Methods. Ppa and Pc' were measured at baseline and after an increase in Q induced either by exercise or by an infusion of dobutamine, at a dosage up to 8 μg/kg body weight per min, in 11 patients with primary pulmonary hypertension. Reversibility of pulmonary hypertension was assessed by the inhalation of 20 ppm nitric oxide (NO), and, in 6 patients, by an infusion of prostacyclin.

Results. At baseline, Ppa was 52 ± 3 mm Hg (mean value ± SE), Q 2.2 ± 0.2 liters/min per m², and Pc' 29 ± 3 mm Hg. Dobutamine did not affect Pc' and allowed the calculation of an averaged extrapolated pressure intercept of Ppa/Q plots of 34 mm Hg. Inhaled NO had no effect. Prostacyclin decreased Pc' and PVR. Exercise increased Pc' to 40 ± 3 mm Hg but did not affect PVR.

Conclusions. These findings are compatible with a major increase of resistance and reactivity at the periphery of the pulmonary arterial tree.

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Nitric oxide (NO) was supplied from a pure NO source tank (Oxydrique, Machelein, Belgium) and delivered through a face mask. The inspired fraction of NO was monitored by chemiluminescence after calibration against standard NO concentration (Model 42 chemiluminescence NO-NO2-NOx analyzer, Thermo Environmental Instruments Inc.). The pulmonary vascular pressure signals were sampled at 200 Hz using an analog/digital converter (RTI 800, Analog Device) and stored and analyzed on a personal computer. \( P_c' \) was computed in duplicate from the \( P_{pa} \) decay curves after extrapolation to 150 ms after the instant of occlusion (To) of a single exponential fitting of the \( P_{pa} \) decay curve between 200 ms (\( T_{200} \)) and 2,000 ms (\( T_{2000} \)) after the occlusion, with secondary adjustment for mean \( P_{pa} \).

Figure 1. Typical pulmonary artery single-occlusion recording to estimate effective \( P_c' \) by the extrapolation to 150 ms after the instant of occlusion (To) of a single exponential fitting of the \( P_{pa} \) decay curve between 200 ms (\( T_{200} \)) and 2,000 ms (\( T_{2000} \)) after the occlusion, with secondary adjustment for mean \( P_{pa} \).
Results

The main hemodynamic and blood gas measurements are summarized in Table 1. At baseline, the hemodynamic and blood gas profile of the patients was similar to that of previously reported large series of patients with primary pulmonary hypertension (9), with very high Ppa, moderately high Pra, normal Ppao, decreased Q, respiratory alkalosis, moderate arterial hypoxemia and decreased mixed venous partial pressure of oxygen (P\textsubscript{O}\textsubscript{2}). P\text{'}c was markedly elevated, to a mean value of 29 mm Hg.

Exercise increased Q by an average of 0.9 liter/min per m\textsuperscript{2}, increased all vascular pressures including P\text{'}c and decreased mixed venous P\textsubscript{O}\textsubscript{2}. P\text{'}c increased more than Ppao (by an average of 11 and 5 mm Hg, respectively). Pooled exercise-induced Ppa/Q relations had a slope of 15 mm Hg/liter per min and a Pi of 34 mm Hg (Fig. 2).

Dobutamine at the dose of 8 \mu g/kg per min increased Q by an average of 0.6 liter/min per m\textsuperscript{2}, but had no effect on blood gases or vascular pressures, except for slight decreases in Psa, Pra and PVR.

Pooled dobutamine-induced relations had a slope of 8.3 mm Hg/liter per min and a Pi of 34 mm Hg (Fig. 2).

NO 20 ppm had no effect on pulmonary hemodynamics or blood gases. Individual changes in Ppa and in PVR associated with inhaled NO ranged respectively from +3 to −10 mm Hg and from +258 to −408 dynes/cm\textsuperscript{5}m\textsuperscript{2}.

In six of the patients, (three of them 6 to 12 months after the initial study) an infusion of prostacyclin 4 to 10 ng/kg per min had no effect on blood gases, Ppa, Pra or Ppao, but decreased P\text{'}c, PVR and Psa and increased Q (Table 2). Individual changes in Ppa and PVR ranged respectively from +5 to −16 mm Hg and from −310 to −1,288 dynes/cm\textsuperscript{5}m\textsuperscript{2}.

The effects of dobutamine in these 6 patients were the same as in the group of 11 patients (not shown).

Discussion

The present results show that in severe primary pulmonary hypertension, both Pi and P\text{'}c are increased, suggesting that the main site of increased resistance is at the periphery of the pulmonary arterial tree, and possibly is a cause of an increased closing pressure.

Exercise-induced Ppa/Q relations. Ppa/Q relations, with Q increased by exercise, had a lower Pi and a higher slope than

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Table 1. Hemodynamic and Blood Gas Responses to Exercise, Dobutamine and Nitric Oxide in 11 Patients With Primary Pulmonary Hypertension

<table>
<thead>
<tr>
<th>Variables Baseline</th>
<th>Exercise</th>
<th>Dobutamine</th>
<th>Nitric Oxide</th>
</tr>
</thead>
<tbody>
<tr>
<td>Q (liter/min per m\textsuperscript{2})</td>
<td>2.2 ± 0.2</td>
<td>5.1 ± 0.4</td>
<td>2.8 ± 0.2</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>82 ± 2</td>
<td>102 ± 8</td>
<td>91 ± 4</td>
</tr>
<tr>
<td>Psa (mm Hg)</td>
<td>102 ± 4</td>
<td>118 ± 8</td>
<td>92 ± 4</td>
</tr>
<tr>
<td>PVR</td>
<td>1,841 ± 240</td>
<td>1,717 ± 231</td>
<td>1,560 ± 216</td>
</tr>
<tr>
<td>(dynes/cm\textsuperscript{5}m\textsuperscript{2})</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ppa (mm Hg)</td>
<td>52 ± 3</td>
<td>67 ± 2</td>
<td>56 ± 4</td>
</tr>
<tr>
<td>P'c (mm Hg)</td>
<td>29 ± 3</td>
<td>40 ± 3</td>
<td>29 ± 4</td>
</tr>
<tr>
<td>Ppao (mm Hg)</td>
<td>10 ± 1</td>
<td>15 ± 2</td>
<td>10 ± 1</td>
</tr>
<tr>
<td>Pra (mm Hg)</td>
<td>8 ± 2</td>
<td>15 ± 2</td>
<td>5 ± 2</td>
</tr>
<tr>
<td>pHa</td>
<td>7.47 ± 0.01</td>
<td>7.46 ± 0.01</td>
<td>7.49 ± 0.01</td>
</tr>
<tr>
<td>Pao\textsubscript{2} (mm Hg)</td>
<td>64 ± 4</td>
<td>60 ± 5</td>
<td>68 ± 4</td>
</tr>
<tr>
<td>PacO\textsubscript{2} (mm Hg)</td>
<td>28 ± 1</td>
<td>26 ± 1</td>
<td>26 ± 1</td>
</tr>
<tr>
<td>PVo\textsubscript{2} (mm Hg)</td>
<td>35 ± 2</td>
<td>28 ± 3</td>
<td>37 ± 1</td>
</tr>
</tbody>
</table>

*Values are expressed as mean value ± SE. †p < 0.05, ‡p < 0.01, §p < 0.001 versus baseline. Dobutamine was infused at the dose of 8 \mu g/kg per min, and nitric oxide inhaled at the dose of 20 ppm. P\textsubscript{aCO}\textsubscript{2} = arterial P\textsubscript{CO}\textsubscript{2}; P\textsubscript{aO}\textsubscript{2} = arterial P\textsubscript{O}\textsubscript{2}; P\text{'}c = effective pulmonary capillary pressure; pHa = arterial pH; Ppa = mean pulmonary artery pressure; Ppao = occluded Ppa; Pra = right atrial pressure; Psa = mean systemic arterial pressure; PVo\textsubscript{2} = mixed venous P\textsubscript{O}\textsubscript{2}; PVR = pulmonary vascular resistance; Q = cardiac output.
Increased Pi are due to an increased resistance of small order pulmonary vessels, which are not a feature of primary pulmonary hypertension (9). Several studies have shown that the arterial occlusion technique may overestimate the effective Pc' as determined by the isogravimetric method or the double occlusion technique in diseased lungs (3). Obstruction of small resistive arteries with 100-μm glass beads increases Pc' without changes in capillary pressure as measured by isogravimetry or by the double arterial and venous occlusion technique (22,23). Hakim and Kelly (4) compared pressure measurements with micropuncture, a small retrograde catheter and arterial and venous occlusion in isolated perfused dogs lungs and found that the arterial occlusion technique measures pressure in vessels of a diameter between 50 and 900 μm, probably on average ~100 μm. We hypothesized that an infusion of dobutamine would increase Q, which was more likely than exercise to allow us to construct passive Ppa/Q plots, on the basis of previous animal work suggesting that low dose dobutamine does not affect pulmonary vascular tone (12). Infusing dobutamine to increase Q led to Ppa/Q plots with a very high Pi. An increased Pi can be explained by a pulmonary vascular closing pressure acting as an effective outflow pressure higher than left atrial pressure (estimated by Ppao) (5–7). There is an alternative viscoelastic model (18) that explains a Pi that is higher than left atrial pressure by a pulmonary vascular closing pressure acting as an effective outflow pressure (17). There is an alternative viscoelastic model (18) that explains a Pi that is higher than left atrial pressure (estimated by Ppao) (5–7). This model explained a Pi that is higher than left atrial pressure by an increase in resistance and compliance of small order pulmonary vessels. We modified this model to provide for a parallel structure of the pulmonary vascular bed at the level of small resistance arteries, corresponding to inhomogeneous distribution of obstruction and showed that it still predicts that a monoeponential fitting gives a reasonable approximation of the Ppa decay curve (21). Applied to intact normal dogs, the modified model allowed the calculation of a (capillary + venous) component of PVR ~25%, somewhat lower than in several previous studies using different methods of analysis (21). It is thus unlikely that in the present study the method of analysis of the Ppa decay curve would have overestimated Pc'.

Effects of inhaled NO and intravenous prostacyclin. In the present study, pulmonary hypertension was on average not reversible with inhaled NO. Sitbon et al. (11) showed in a series of 35 patients with primary pulmonary hypertension that changes in PVR during NO inhalation or prostacyclin infusion are closely correlated, and that a maximum pulmonary vasodilation can be obtained with 10 ppm NO. However, in six of our patients unresponsive to 20 ppm inhaled NO, prostacyclin decreased PVR by 29% (range 18% to 41%). This change occurred without significant changes in Ppa, but with a decrease in Pc', indicating that the decrease in PVR was not just an artifact caused by increased Q (5–7), but truly corresponded to a decreased pulmonary vascular tone. Nevertheless, none of our patients was a "high responder" to prostacyclin, as defined by a >50% decrease in PVR (20). Such a response to prostacyclin was observed in only 9 of 91 patients with primary pulmonary hypertension in a recent study (20).
therefore believe that Pc' in our patients reflects an increased pressure in small resistive arteries and arterioles, rather than an increased pressure in capillaries. It is of interest that prostacyclin in our patients decreased Pc', compatible with an acute effect at the main site of increased resistance.

Histologic studies have shown that primary pulmonary hypertension is primarily a disease of the small muscular pulmonary arteries and arterioles that are <500 to 1,000 μm in diameter (8). These vessels present with various combinations of medial hypertrophy, concentric or eccentric intimal fibrosis and more complex arteritis, plexiform or dilation lesions, with, in 30% of cases, in situ thrombosis (8). Both increased Pi and Pc' in our patients suggest that these lesions are not associated with structural changes important enough to increase resistance of larger diameter pulmonary arteries. In addition, increased Pc' at exercise appear entirely explained by exercise-induced vasoconstriction at the site of small resistive arteries. Previous histologic studies have also shown that 10% of patients with primary pulmonary hypertension present with pulmonary veno-occlusive disease (8). These patients are difficult to distinguish clinically from those with a precapillary pathologic process. In our series, a histologic examination of the lungs could be obtained in one of the female patients after a heart–lung transplantation. The examination disclosed no venous abnormalities in this patient whose Ppa/Q plots and Pc' did not deviate from the average values of the group as a whole. In addition, because of the relative rarity of pulmonary veno-occlusive disease, we believe it unlikely that the increased Pc' in the present study could have been explained by an increase in venous resistance.

Appetite suppressant drugs. Pulmonary hypertension in eight of our patients was associated with the intake of appetite suppressant drugs, mainly fenfluramines. The association between the intake of these drugs and primary pulmonary hypertension was recently established by a Western European case control study (24). The clinical course and histologic pattern in patients with fenfluramine-associated pulmonary hypertension do not appear different from those of the other patients with primary pulmonary hypertension (25). It is thus unlikely that Ppa/Q characteristics and Pc' determinations in our patients would have been affected by previous intake of fenfluramines.

Conclusions. A recent study reported on the use of pulmonary artery pressure waveform analysis for the differential diagnosis of proximal versus distal obstruction of the pulmonary arterial tree in severe pulmonary hypertension (26). The present report shows that standard bedside hemodynamic evaluation with measurements at variable cardiac output and analysis of pulmonary artery occlusion pressure decay curves allow for an identification and quantification of increased distal small arteries and arterioles resistance.

Marie-Thérèse Gautier helped in the preparation of this report.

References