Hypoxic Pulmonary Vasoconstriction in Human Lungs

A Stimulus-Response Study

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Background: A stimulus-response relation between alveolar oxygen tension and pulmonary vascular resistance has been observed in animals. This study investigated this relation in healthy human lungs. The distribution of pulmonary blood flow was measured during unilateral (1) graded hypoxia (fractional concentration of oxygen in inspired gas [FIO₂] = 0.12, 0.08, and 0.05) and contralateral hyperoxia (FIO₂ = 1.0; n = 6); (2) single-step hypoxia (FIO₂ = 0.05) and contralateral hyperoxia (n = 5); and (3) normobaric hyperoxia and contralateral normoxia (FIO₂ = 0.25; n = 6).

Methods: Seventeen patients with healthy lungs were studied during intravenous anesthesia. The lungs were separately and synchronously ventilated. The relative perfusion of each lung was assessed by the inert gas (sulfurhexafluoride) elimination technique.

Results: (1) Unilateral graded hypoxia reduced the perfusion of the hypoxic lung from a mean (±SD) of 52 (2)% of cardiac output (Q̇) during bilateral hyperoxia, to 47 (5)% (P < 0.05), 40 (3)% (P < 0.01), and 30 (8)% (P < 0.001) of Q̇, respectively. There were progressive reductions in the perfusion of the hypoxic lung were all significantly different from each other. (2) Unilateral single-step hypoxia caused a blood flow diversion of the same magnitude as when the lung was previously ventilated with FIO₂ of 0.12 and 0.08. The perfusion of the hypoxic lung was reduced from 46 (9)% of Q̇ (bilateral hyperoxia), to 26 (4)% of Q̇ (P < 0.01). (3) Unilateral hyperoxia did not significantly change the relative blood flow distribution between the two lungs or the pulmonary artery pressure.

Conclusions: A stimulus-response relation between graded hypoxia and blood flow diversion defines hypoxic pulmonary vasoconstriction in the normal human lung. Hyperoxia has no significant effect on vascular resistance in the normal human lung. (Key words: Anesthesiology; intravenous. Lung(s); hypoxia; hypoxia; individual pulmonary blood flow; stimulus-response. Measurement technique: inert gas exchange.)

A stimulus-response relation exists between alveolar oxygen tension (P O₂) and pulmonary vascular resistance.1,3 Graded hypoxia causes progressive increases in pulmonary vascular resistance (hypoxic pulmonary vasoconstriction [HPV]) in anesthetized cats and dogs3 having open-chest procedures and in rat lungs perfused in vitro.5 In contrast to the well-documented hypoxic part of the stimulus-response curve, the results from studies of the acute effect of normobaric hyperoxia on pulmonary vascular resistance are conflicting. Hyperoxia has been reported to cause pulmonary vasodilation,1,4,7,8 to have no effect on pulmonary vascular resistance,2,7,9–11 and indirect evidence suggests that acute normobaric hyperoxia might cause vasoconstriction.12–14

Our aim in this study was to determine whether graded hypoxia causes progressive increases in pulmonary vascular resistance, and whether hyperoxia causes pulmonary vasoconstriction in healthy human lungs.

Patients and Methods

Patients

The study was approved by the local ethics committee at Karolinska Hospital. Entry criteria were that patients were scheduled for elective major abdominal surgery, ages 18 to 60 yr, and no history or clinical evidence of cardiopulmonary disease. The patients were given a detailed description of the study, orally as well as in
writing, before their consent was obtained. Seventeen patients (table 1) divided in three different sets of experiments were studied while they lay supine. There were no complications attributable to the investigation. All patients were interviewed one or several days after the investigation. None experienced awareness.

Anesthesia

Figure 1 shows the experimental design. Premedication consisted of morphine (0.15 mg/kg) and scopolamine (0.006 mg/kg) given intramuscularly 1 h before anesthesia. Before induction of anesthesia, the patients were given 2-5 mg midazolam intravenously and they were connected to electrocardiograph and pulse oximeter equipment. Electrocardiograph, oxygen saturation, and inspiratory and end-tidal concentrations of oxygen and carbon dioxide were monitored continuously (Datex AS/3® Anaesthesia Monitor, Datex Engstrom, Helsinki, Finland) during the entire experiment. Anesthesia was induced by thiopental (5 mg/kg). Pancuronium bromide (0.1 mg/kg) was given for muscle relaxation, and fentanyl (0.1-0.2 mg) was given for analgesia. Intubation was performed with a double-lumen, left-sided endobronchial catheter (Portex Twin Lumen Tube, size 5 or 6; Sims Portex, Keene, NH). The position of the endobronchial tube was checked by fluoroscopy and by inflating each lung separately while auscultating the breath sounds. The absence of leaks from the lungs was considered satisfactory if one lung at a time could keep a constant positive end-expiratory pressure of 10 cm water. The different and persistent fractions of expired oxygen during unilateral hypoxia or hyperoxia was regarded as proof of separation between the lungs. Low and similar peak airway pressures in both lungs were considered signs of unobstructed gas flow through the endobronchial tube.

Anesthesia was maintained during the experiment with repeated intravenous doses of thiopental (50 mg), midazolam (1-2 mg), and fentanyl (0.05 mg) if systemic arterial pressures increased 20% above the initial control value. Pancuronium bromide (1-2 mg) was given if peak airway pressures increased 20% above the initial control value.

![Fig. 1. The experimental design. HR = heart rate, MaP = mean systemic arterial pressure, MPaP = mean pulmonary arterial pressure, PcwP = pulmonary capillary wedge pressure, and SF₆ = sulfurhexafluoride.](image-url)
Ventilation
After anesthesia was induced, paralysis ensued, and the trachea was intubated, the double-lumen tube was connected to a specially designed Engström ventilator with two separate bag-in-box circuits and pressure-operated non-rebreathing valves. Compressed air was delivered to both bag-in-box chambers by the same piston. The respiratory frequency (12 breaths/min) in the two circuits was synchronous with an inspiration/expiration ratio of 1:2. Each circuit was fed from independent flow meters, which allowed individual gas mixtures to be supplied to the two lungs. The expired gas volumes from each lung were measured by a spirometer (Gould, Godart expiograph; Gould, Godort, Bilthoven, The Netherlands) and sampled separately in two bags. The lungs were ventilated with equally large tidal volumes to obtain an arterial carbon dioxide tension (P_{a\text{CO}_2}) of 34–35 mmHg. All gas volumes were converted to the volumes at body temperature, ambient pressure, and saturated with water vapor.

Hemodynamics
Two peripheral venous catheters were inserted, one to infuse inert gas and catheters to infuse anesthetic agents. The left radial artery was cannulated for pressure recordings and blood sampling. All pressures were recorded with pressure transducers (Gould Statham P23, Gould Statham Instruments Inc., Hato Rey, Puerto Rico), the signal being fed into an amplifier (Hellige GMBH, Freiburg, Germany). The transducers were calibrated against a saline manometer positioned at the mid-thoracic level and zeroed against atmospheric pressure.

Regional Perfusion
To assess the relative perfusion to the two lungs and the cardiac output, a poorly soluble gas, sulfur hexafluoride, in saline was infused at a constant rate (3 ml/min). Mixed expired gas was collected from each lung under steady-state conditions, and the tracer gas concentrations were measured by gas chromatography (Hewlett-Packard gas chromatograph 5890, Palo Alto, CA). The ratio between the amount of exhaled sulfur hexafluoride from the two lungs was assumed to reflect their perfusion ratio.\textsuperscript{15,16} The reliability of the method has been confirmed in animal experiments.\textsuperscript{17} The method is described in detail elsewhere.\textsuperscript{16,18,19} The arterial and mixed venous oxygen tensions (P_{a\text{O}_2}, and P_{v\text{O}_2}), P_{a\text{CO}_2}, pH, and arterial oxygen saturation (S_{a\text{O}_2}) were measured by standard techniques (ABM 300, Radiometer Medical A/S, Bronshøj, Denmark).

Cardiac Output
A triple-lumen, thermistor-tipped, balloon catheter (Swan-Ganz 7-Fr) was introduced percutaneously into the right subclavian vein, and the tip of the catheter was advanced to the right middle pulmonary artery during fluoroscopy and electrocardiographic and pressure monitoring. Cardiac output (Q) was measured by thermodilution and calculated from the elimination of sulfur hexafluoride. The results from the two methods were compared using the Bland Altman plot.\textsuperscript{20} The mean (SD) difference was −0.1 (0.7) l/min.

For measurements of cardiac output by thermodilution, the thermal indicator was 10 ml of 5% glucose at 0–2°C injected into the right atrium. The first measurement was ignored and cardiac output was derived from the mean of the three consecutive measurements (CO, SVO\textsubscript{2} computer, Abbot Laboratories, North Chicago, IL).

Blood Flow Diversion and Changes in Perfusion Pressure
Blood flow diversion was calculated according to the method of Marshall and Marshall\textsuperscript{21} as: (\dot{Q}_{SN} − \dot{Q}_{SH})/\dot{Q}_{SN}, where \dot{Q}_{SN} = blood flow rate to the test segment during normoxia (fractional concentration of oxygen in inspired gas [F_{\text{O}_2}] > 0.21), and \dot{Q}_{SH} = blood flow rate to the test segment during hypoxia (F_{\text{O}_2} = 0.0–0.1). (If \dot{Q} during hypoxia does not equal \dot{Q} during normoxia, each term should be divided by the corresponding \dot{Q}.)

Changes in perfusion pressure were calculated\textsuperscript{21} as P_{H}/P_{SN} where P_{H} = perfusion pressure (mean pulmonary artery pressure − mean pulmonary artery occlusion pressure) during hypoxia to the test segment, and P_{SN} = perfusion pressure during normoxia.

Experimental Protocol
Three sets of experiments were made. In all three the left lung was used as the test lung and exposed to hypoxic (F_{\text{O}_2} = 1.0), normoxic (F_{\text{O}_2} = 0.25, balance nitrogen), or hypoxic (F_{\text{O}_2} = 0.12, 0.08 or 0.05, balance nitrogen) inspired gas mixtures. The right lung was used as the control lung and was ventilated with either normoxic or hyperoxic gas. All references to time include 10 min of measurements at the end of each ventilator setting, before any change in inhaled gas composition.

Set I. Study of the Effect of Unilateral Inhalation of Graded Hypoxic Gas Mixtures during Contralateral Hyperoxia. Patients 1–6. Both lungs were first ventilated with 100% oxygen for 40 min. While the right lung continuously was ventilated with 100%
oxygen, the left lung was rendered hypoxic, first by ventilation with 12%, then 8%, and finally 5% oxygen, balance nitrogen. Each hypoxic period was maintained for 25 min. Between the hypoxic periods, both lungs were ventilated with 100% oxygen for 15 min.

Set II. Study of the Effect of Unilateral Single-Step Inhalation of the Hypoxic Gas Mixture during Contralateral Hyperoxia. Patients 7-11. To determine whether the repeated periods of hypoxia (12% and 8% oxygen) preceding the hypoxic ventilation with 5% oxygen had any influence on the magnitude of the blood flow diversion, five separate patients were exposed to 40 min of bilateral hyperoxia immediately followed by 25 min of hypoxic ventilation of the left lung with 5% oxygen.

Set III. Study of the Effect of Unilateral Inhalation of 100% Oxygen during Contralateral Normoxia. Patients 12-17. Both lungs were ventilated with 25% oxygen for 40 min. To determine whether hyperoxia causes pulmonary vasoconstriction, the left lung was ventilated with 100% oxygen for 25 min while the right lung was continuously ventilated with 25% oxygen. Finally, both lungs were again ventilated with 25% oxygen for 25 min.

Statistics
Data in the text, tables, and figures are presented as means (SD). A two-way analysis of variance was applied to each continuous variable to disclose any differences between various measurement periods within each set of experiments. The patients (random) and the measurement periods (fixed) comprised the two block factors. In all analysis of variance tests, residual variance was used as the test factor and Fisher’s least-significant difference method was used as the post hoc test. A probability value less than 0.05 was accepted as significant. Probability values were corrected for multiple comparisons in the least-significant difference test. All analyses were performed with the SOLO Statistical System (version 4.0; BMDP Statistical Software, Los Angeles, CA).

Results

General Findings
No or only minor changes were seen in cardiac output and in systemic artery pressures (tables 2-4). Recording of pulmonary artery pressures did not disclose any effect of unilateral hyperoxia and only a slight effect of unilateral hypoxia. The oxygenation of arterial and mixed venous blood was, as expected, reduced during unilateral hypoxia and increased during unilateral hyperoxia. We do not address these results in the article.

I. Effect of Unilateral Inhalation of Graded Hypoxic Gas Mixtures during Contralateral Hyperoxia
During the initial control period of bilateral hyperoxia, 52 (2%) of cardiac output perfused the left lung and 48 (2%) perfused the right lung (fig 2, table 2). Hypoxic ventilation of the left lung with 12%, 8%, and 5% oxygen, respectively, reduced the perfusion of the left lung to 47 (5%) (P > 0.05), 40 (3%) (P < 0.01), and 30 (8%) (P < 0.001) of cardiac output. The relative blood flow to the left lung during the three different periods of graded hypoxic ventilation were all significantly different from each other.

II. Effect of Unilateral Single-Step Inhalation of Hypoxic Gas Mixture during Contralateral Hyperoxia
During bilateral hyperoxia, 46 (9%) of cardiac output perfused the left lung and 54 (9%) perfused the right lung (table 3). Ventilation of the left lung with 5% oxygen significantly (P < 0.01) reduced the perfusion of this lung to 26 (4%) of cardiac output.

III. Effect of Unilateral Inhalation of 100% Oxygen during Contralateral Normoxia
During the initial control period of bilateral normoxia, 49 (3%) of cardiac output perfused the left lung and 51 (3%) the right lung (table 4). Neither the increase in F\textsubscript{O\textsubscript{2}} to the left lung from 0.25 to 1.0 nor the decrease from 1.0 to 0.25 caused any significant change in pulmonary artery pressure, or in the perfusion distribution between the two lungs.

Discussion
Our results show a stimulus-response relation between graded hypoxia and blood flow diversion, which is consistent with other reports of a stimulus-response relation between alveolar oxygen tension and pulmonary vascular resistance.\textsuperscript{24-26}

Hypoxic Pulmonary Vasoconstriction and P\textsubscript{a}O\textsubscript{2}
Mixed venous oxygen tension also influences pulmonary vascular resistance.\textsuperscript{22-21} The relative roles of P\textsubscript{a}O\textsubscript{2}

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Table 2. Mean (SD) Effects of Unilateral Inhalation of Graded Hypoxic Gas Mixtures during Contralateral Hyperoxia in Patients 1–6

<table>
<thead>
<tr>
<th>DCP</th>
<th>P Value</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7 (n = 5)</th>
</tr>
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<tbody>
<tr>
<td>Time (min)</td>
<td>40</td>
<td>25</td>
<td>15</td>
<td>25</td>
<td>15</td>
<td>25</td>
<td>15</td>
<td></td>
</tr>
<tr>
<td>F\textsubscript{O}2,RL</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>F\textsubscript{O}2,LL</td>
<td>1.0</td>
<td>0.12</td>
<td>1.0</td>
<td>0.08</td>
<td>1.0</td>
<td>0.05</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>Q\textsubscript{L}/Q\textsubscript{O} (%)</td>
<td>&lt;0.0000</td>
<td>52 (2)</td>
<td>47 (5)</td>
<td>53 (9)</td>
<td>40† (3)</td>
<td>48 (3)</td>
<td>30† (8)</td>
<td>45† (2)</td>
</tr>
<tr>
<td>Q\textsubscript{ESP} (L/min)</td>
<td>0.0959</td>
<td>4.4 (0.8)</td>
<td>4.3 (0.9)</td>
<td>4.0 (0.9)</td>
<td>4.1 (0.9)</td>
<td>4.0 (1.1)</td>
<td>4.0 (1.1)</td>
<td>3.7 (1.2)</td>
</tr>
<tr>
<td>MaP (mmHg)</td>
<td>0.2632</td>
<td>76 (3)</td>
<td>73 (12)</td>
<td>74 (12)</td>
<td>72 (13)</td>
<td>76 (12)</td>
<td>69 (14)</td>
<td>74 (16)</td>
</tr>
<tr>
<td>MPaP (mmHg)</td>
<td>0.2208</td>
<td>12 (3)</td>
<td>12 (2)</td>
<td>12 (1)</td>
<td>14 (3)</td>
<td>12 (1)</td>
<td>13 (2)</td>
<td>12 (1)</td>
</tr>
<tr>
<td>Pcwp (mmHg)</td>
<td>0.6524</td>
<td>7 (3)</td>
<td>5 (2)</td>
<td>5 (2)</td>
<td>7 (2)</td>
<td>7 (2)</td>
<td>8 (1)</td>
<td>8 (2)</td>
</tr>
<tr>
<td>SaO\textsubscript{2} (%)</td>
<td>0.0432</td>
<td>99.9 (0.0)</td>
<td>99.1 (1.4)</td>
<td>99.9 (0.0)</td>
<td>98.3 (2.4)</td>
<td>99.9 (0.0)</td>
<td>97.9† (3.1)</td>
<td>99.0 (0.0)</td>
</tr>
<tr>
<td>Pa\textsubscript{O}2 (mmHg)</td>
<td>&lt;0.0000</td>
<td>465 (93)</td>
<td>217† (73)</td>
<td>482 (104)</td>
<td>167† (74)</td>
<td>492 (93)</td>
<td>155† (72)</td>
<td>510 (50)</td>
</tr>
<tr>
<td>Pa\textsubscript{O}2 (mmHg)</td>
<td>&lt;0.0000</td>
<td>62 (18)</td>
<td>48† (10)</td>
<td>54† (10)</td>
<td>43† (5)</td>
<td>56† (9)</td>
<td>42† (6)</td>
<td>51† (8)</td>
</tr>
<tr>
<td>Pa\textsubscript{CO}2 (mmHg)</td>
<td>0.6160</td>
<td>38 (5)</td>
<td>37 (5)</td>
<td>37 (6)</td>
<td>36 (6)</td>
<td>35 (9)</td>
<td>37 (6)</td>
<td>36 (8)</td>
</tr>
<tr>
<td>Cet\textsubscript{CO}2,LL (%)</td>
<td>0.0002</td>
<td>4.4 (0.4)</td>
<td>4.2 (0.3)</td>
<td>4.1 (0.3)</td>
<td>4.0† (0.4)</td>
<td>4.1† (0.4)</td>
<td>3.6† (0.2)</td>
<td>4.1 (0.3)</td>
</tr>
</tbody>
</table>

P values for data collection periods (DCP) from two-way analysis of variance.
* Significantly different between two periods of hypoxic stimulation.
† Significantly different from the initial control value.

and P\textsubscript{O}2 on pulmonary vascular resistance were quantitated by Marshall et al. in rat lungs perfused in vitro\textsuperscript{22} and in anesthetized dogs having open-chest procedures.\textsuperscript{3} They showed that the pressor response to hypoxia can be predicted with precision when both P\textsubscript{a}O\textsubscript{2} and P\textsubscript{O}2 are known. In in vivo studies, F\textsubscript{O}2 can be controlled, but P\textsubscript{O}2 cannot be. Mixed venous oxygen tension regulates the lower limit of alveolar oxygen tension. We chose a F\textsubscript{O}2 of 0.05 as the lower limit for unilateral hypoxic ventilation during contralateral hyperoxia, which resulted in a mean P\textsubscript{O}2 of 42–48

Table 3. Mean (SD) Effects of Unilateral Single Step Hypoxia (F\textsubscript{O}2 = 0.05), during Contralateral Hyperoxia in Patients 7–11

<table>
<thead>
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<th>DCP</th>
<th>P Value</th>
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<tbody>
<tr>
<td>Time (min)</td>
<td>40</td>
<td>25</td>
<td>25</td>
</tr>
<tr>
<td>F\textsubscript{O}2,RL</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>F\textsubscript{O}2,LL</td>
<td>1.0</td>
<td>0.05</td>
<td>0.05</td>
</tr>
<tr>
<td>Q\textsubscript{L}/Q\textsubscript{O} (%)</td>
<td>0.0019</td>
<td>46 (9)</td>
<td>26′ (4)</td>
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<tr>
<td>Q\textsubscript{ESP} (L/min)</td>
<td>0.8008</td>
<td>4.2 (0.6)</td>
<td>4.3 (1.4)</td>
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<tr>
<td>MaP (mmHg)</td>
<td>0.4314</td>
<td>63 (6)</td>
<td>65 (10)</td>
</tr>
<tr>
<td>MPaP (mmHg)</td>
<td>0.0249</td>
<td>11 (4)</td>
<td>12′ (5)</td>
</tr>
<tr>
<td>Pcwp (mmHg)</td>
<td>0.1778</td>
<td>7 (4)</td>
<td>7 (4)</td>
</tr>
<tr>
<td>SaO\textsubscript{2} (%)</td>
<td>0.2162</td>
<td>99.9 (0.1)</td>
<td>98.7 (1.6)</td>
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<tr>
<td>Pa\textsubscript{O}2 (mmHg)</td>
<td>0.0037</td>
<td>433 (19)</td>
<td>166′ (46)</td>
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<tr>
<td>Pa\textsubscript{CO}2 (mmHg)</td>
<td>0.0092</td>
<td>54 (5)</td>
<td>48′ (4)</td>
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<tr>
<td>Pa\textsubscript{CO}2 (mmHg)</td>
<td>0.0119</td>
<td>41 (4)</td>
<td>44′ (5)</td>
</tr>
<tr>
<td>Cet\textsubscript{CO}2,LL (%)</td>
<td>0.0002</td>
<td>4.8 (0.4)</td>
<td>4.1′ (0.4)</td>
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</table>

P values for data collection periods (DCP) from two-way analysis of variance.
* Significantly different from the initial control value.

Table 4. Mean (SD) Effects of Unilateral Inhalation of 100% Oxygen during Contralateral Normoxia in Patients 12–17

<table>
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<th>P Value</th>
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<td>25</td>
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<tr>
<td>F\textsubscript{O}2,RL</td>
<td>0.25</td>
<td>0.25</td>
<td>0.25</td>
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<tr>
<td>F\textsubscript{O}2,LL</td>
<td>0.25</td>
<td>1.0</td>
<td>0.25</td>
</tr>
<tr>
<td>Q\textsubscript{L}/Q\textsubscript{O} (%)</td>
<td>0.8842</td>
<td>49 (3)</td>
<td>49 (2)</td>
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<tr>
<td>Q\textsubscript{ESP} (L/min)</td>
<td>0.9869</td>
<td>4.8 (1.1)</td>
<td>4.9 (1.2)</td>
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<tr>
<td>MaP (mmHg)</td>
<td>0.2183</td>
<td>65 (6)</td>
<td>66 (7)</td>
</tr>
<tr>
<td>MPaP (mmHg)</td>
<td>0.4889</td>
<td>11 (3)</td>
<td>10 (2)</td>
</tr>
<tr>
<td>Pcwp (mmHg)</td>
<td>0.9457</td>
<td>8 (2)</td>
<td>8 (2)</td>
</tr>
<tr>
<td>SaO\textsubscript{2} (%)</td>
<td>&lt;0.0000</td>
<td>98.3 (0.6)</td>
<td>99.7° (0.1)</td>
</tr>
<tr>
<td>Pa\textsubscript{O}2 (mmHg)</td>
<td>&lt;0.0000</td>
<td>113 (19)</td>
<td>255′ (24)</td>
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<tr>
<td>Pa\textsubscript{CO}2 (mmHg)</td>
<td>0.0002</td>
<td>41 (3)</td>
<td>45′ (3)</td>
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<tr>
<td>Pa\textsubscript{CO}2 (mmHg)</td>
<td>0.5609</td>
<td>38 (4)</td>
<td>38 (3)</td>
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<tr>
<td>Cet\textsubscript{CO}2,LL (%)</td>
<td>0.0202</td>
<td>4.8 (0.3)</td>
<td>4.6′ (0.2)</td>
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P values for data collection periods (DCP) from two-way analysis of variance.
* Significantly different from the initial and final control values.
mmHg (tables 2 and 3). Based on the calculations of Marshall et al., the slight reductions of P\textsubscript{a}O\textsubscript{2} during hypoxic ventilation in our study can be assumed to make only a minor contribution to the blood flow diversion compared with the dominating part played by the reductions of P\textsubscript{a}O\textsubscript{2}.

**Hypoxic Pulmonary Vasoconstriction and P\textsubscript{a}O\textsubscript{2}**

*In vivo*, the systemic P\textsubscript{a}O\textsubscript{2} affects pulmonary vascular tone through the bronchial arteries, which supply the vasa vasorum of pulmonary vessels down to about 500 \( \mu \)m in diameter. These large pulmonary arteries constrict only in the event of systemic hypoxemia. In our study, the redistribution of pulmonary blood flow to the hypoxic lung prevented systemic hypoxemia. The single lowest P\textsubscript{a}O\textsubscript{2} (62 mmHg) and Sa\textsubscript{O}\textsubscript{2} (92%) values were observed in case 6 during ventilation with 5% oxygen. The redistribution of pulmonary blood flow thus can be assumed to be due to constriction of small pulmonary arteries only.

**Hypoxic Pulmonary Vasoconstriction and Hypoxic Segment Size**

Marshall and Marshall\textsuperscript{21} have shown that the increase in pulmonary perfusion pressure and the diversion of blood flow are related to the size of the hypoxic lung segment. If the hypoxic segment equaled one lung, the blood flow diversion was found to be 40% and the increase in perfusion pressure 30%. This resulted in a relative perfusion of 30% of cardiac output to the hypoxic segment, instead of approximately 50%, which would be anticipated in the absence of HPV. In our study, hypoxic stimulation with 5% oxygen resulted in a blood flow diversion of 42–43% and a 25% increase in perfusion pressure, compared with the initial control period of bilateral hyperoxia, close to the values predicted by Marshall and Marshall.

**Hypoxic Pulmonary Vasoconstriction and Repeated Hypoxic Provocations**

Several authors have tested the hypothesis that HPV is potentiated by repeated periods of hypoxia. Early studies by Unger et al., Pirlo et al., and Benumof confirmed it. Later, neither Chen et al., nor Bindsley et al.\textsuperscript{18} found any evidence of potentiation of HPV by repeated periods of hypoxia.

In patients 1–6, the blood flow diversion from the left lung during hypoxic ventilation with 5% oxygen was 42%, compared with the perfusion to the left lung during the initial control period of bilateral hyperoxia. To ensure that this blood flow diversion was a true stimulus-response effect caused by the gradual decrease in F\textsubscript{1}O\textsubscript{2}, and not the effect of repeated periods of hypoxia (12, 8, and 5% oxygen), five separate patients (cases 7–11) were exposed to bilateral hyperoxia, followed by single-step hypoxic ventilation of the left lung with 5% oxygen. The relative perfusion of the left lung was reduced by 43% compared with the perfusion during bilateral hyperoxia, coinciding closely with the 42% reduction in cases 1–6. This indicates that the reduction...
in relative blood flow during ventilation with 5% oxygen was not affected by the preceding periods of hypoxic ventilation with 12 and 8% oxygen.

**Hypoxic Pulmonary Vasoconstriction and Time**

The prevailing opinion is that HPV has a rapid onset with no potentiation over time.\(^\text{10}\) Using the same experimental model as in the present study, Carlsson et al.\(^\text{19}\) found that ventilation with 5% oxygen resulted in a fully developed diversion of blood flow away from the hypoxic to the hyperoxic lung within 15 min. Between 15 and 60 min of hypoxic exposure, the relative blood flow between the two lungs remained constant. A similar time course was found in anesthetized dogs having open-chest procedures\(^\text{33}\), in awake sheep,\(^\text{10}\) and in anesthetized sheep and newborn lambs.\(^\text{7}\) Recently Vejlstrup et al.\(^\text{32}\) found that unilateral hypoxic pulmonary vasoconstriction in the intact rabbit had a fast phase lasting a few minutes and a slow phase lasting many hours, and that the release of HPV similarly showed both rapid and slow phases. With the purpose of keeping anesthesia time within acceptable limits, we decided to restrict each period of hypoxia to 15 min plus 10 min for measurements, and each control period of bilateral hyperoxia, in between the hypoxic periods, to 5 min plus 10 min for measurements. This decision was supported by the results from (to our knowledge) the only study in humans on HPV and time\(^\text{19}\) and by the fact that we found no significant differences between the initial control period of bilateral hyperoxia and the control periods of bilateral hyperoxia between the hypoxic periods.

**Hypoxia and Pulmonary Vascular Resistance**

The results from studies of the hypoxic part of the stimulus-response curve are conflicting. Hypoxia has been reported to cause pulmonary vasodilation,\(^\text{1,4,7,8}\) to have no effect on pulmonary vascular resistance,\(^\text{2,7,9-11}\) and indirect evidence suggests that acute normobaric hypoxia might cause vasoconstriction.\(^\text{12-14}\) In our study, ventilation of the left lung with 100% oxygen during contralateral normoxia neither resulted in measurable changes in the distribution of relative blood flow nor changed the pulmonary arterial pressure (table 4). Our results are consistent with previous reports indicating that the stimulus-response curve is flat in the hypoxic interval.\(^\text{2,9-11}\)

Based on the results of this study, we conclude that a stimulus-response relation between graded hypoxia and blood flow diversion defines hypoxic pulmonary vasoconstriction in the normal human lung, and that normobaric hyperoxia has no significant acute effect on vascular resistance in the normal human lung.

**References**

GRADED ALVEOLAR OXYGEN TENSION


