Dependence of pulmonary venous admixture on inspired oxygen fraction and time during regional hypoxia in the rabbit

M. O’NEILL, N. G. VEJLSTRUP, B. NAGYOVA AND K. L. DORRINGTON

Summary

In order to examine the value of assuming constant pulmonary venous admixture with respect to changes in inspired oxygen fraction ($F_{O_2}$) and time during sustained unilateral hypoxia, we studied venous admixture for 6 h in 27 anaesthetized rabbits in which the left lung was filled with liquid, isosmotic with plasma. In one group of 10 rabbits the right lung was ventilated for 6 h with $F_{O_2} = 1$; in a second group of 10 the right lung was ventilated with $F_{O_2} = 1$ for 2.5 h and then with $F_{O_2} = 0.3$ for 3.5 h. A third group was similarly studied by changing from $F_{O_2} = 1$ to $F_{O_2} = 0.5$. We found that hypoxic pulmonary vascular vasoconstriction continued to intensify over 3 h. At 3–6 h, with $F_{O_2} = 0.3$, venous admixture (0.32 ± 0.03) was higher than baseline (0.13 ± 0.01), $t = 0$ min during bilateral oxygenation) by twice the elevation above baseline of the venous admixture (0.22 ± 0.01) in the group with $F_{O_2} = 1$. The finding of a marked increase in venous admixture with decreasing $F_{O_2}$ is discussed in relation to current models of hypoxic pulmonary vasoconstriction. (Br. J. Anaesth. 1995; 75: 603–609)

Key words

Hypoxia, Lung, hypoxia, Oxygen, inspired concentration, Rabbit.

The use of iso-shunt plots in the management of respiratory failure assists prediction of arterial oxygenation during changes in inspired oxygen fraction ($F_{O_2}$) when pulmonary venous admixture may be assumed to remain largely unchanged [1]. An increase in venous admixture after a reduction in $F_{O_2}$ may occur because of intrinsic changes in the hypoxic pulmonary vascular response [2], a broad distribution of ventilation-perfusion mismatch [3], systemic hypoxic stimulation of the extrinsic chemoreceptor reflex to the lung [4] and increases in cardiac output [5]. However, changes in venous admixture with changing $F_{O_2}$ are usually regarded as small if $F_{O_2}$ is maintained above 0.3 and systemic hypoaxaemia is avoided.

This expectation has recently been found to be consistent with a theoretical analysis by Marshall and colleagues of several clinical scenarios in which hypoxic pulmonary vasoconstriction (HPV) is thought to be an important determinant of pulmonary gas exchange [6]. The analysis was based on the dose-response relationship for HPV which has been observed by Marshall and Marshall with in vitro lungs of rats [7] and in vivo lungs of dogs [8] which incorporates a dependence of HPV on both mixed venous $P_{O_2}$ ($P_{V_{O_2}}$) and alveolar $P_{O_2}$ ($P_{A_{O_2}}$). These dose-response relationships were determined using brief 6 min [7] or 10 min [8] exposures to different levels of the stimulus partial pressures.

Because some evidence has accumulated from experiments in rats [9], dogs [10–12], ferrets [13], rabbits [14] and humans [15] that suggests that HPV may have a slow phase of intensification after an initial rapid phase of constriction, we have been concerned to know if the model of Marshall and Marshall predicts the behaviour of the pulmonary circulation after sustained exposure to hypoxia, lasting hours rather than minutes. We hypothesized that pulmonary venous admixture associated with sustained unilateral hypoxia over hours might show a marked dependence on $F_{O_2}$ above 0.3.

Materials and methods

We induced unilateral hypoxia in the closed-chested anaesthetized rabbit for a period of 6 h, and during this time compared pulmonary shunt in groups undergoing ventilation with two different fractions of $F_{O_2}$: 1 and 0.3. Hypoxia was induced by liquid filling of the left lung, which accounts in the rabbit for approximately 40% of lung tissue. We have shown previously that the response of the pulmonary circulation in the rabbit to liquid filling is similar to the response to nitrogen filling at the same airway pressure [14]. Furthermore, although apnoeic liquid filling of the lung is used infrequently during studies of pulmonary circulation, it is arguably a closer model of conditions in which pulmonary oedema predominates than ventilation of the lung with hypoxic gas mixtures. This method of inducing regional hypoxia also helps to ensure that the contribution to venous admixture from the hypoxic lung is pure shunt and not influenced by extremes of ventilation-perfusion mismatch. In order to minimize effects on the pulmonary circulation of changes in pressure in the hypoxic lung, the lung was filled initially with liquid in a manner designed to replace oxygen with little or no change in lung volume [16], and was then held at a constant distending pressure of 0.3 kPa throughout. Because

M. O’NEILL, N. G. VEJLSTRUP, MD, DPHIL, B. NAGYOVA, MD, K. L. DORRINGTON, DM, DPHIL, FRCAn, University Laboratory of Physiology, Parks Road, Oxford OX1 3PT, UK. Accepted for publication: May 26, 1995.

Correspondence to K.L.D.
of the possibility [4] that our findings in the $P_{O_2} = 0.3$ group could be related to the mild systemic hypoxaemia achieved using that procedure, we studied seven animals using an $P_{O_2}$ of 0.5 where systemic hypoxaemia was absent.

ANAESTHESIA

A Home Office licence was issued for these experiments. Twenty-seven New Zealand White rabbits (2.5–4.1 kg) were premedicated with Hypnorm (fentanyl 0.315 mg ml$^{-1}$, fluanisone 10 mg ml$^{-1}$) 0.3 ml/kg body weight i.m. Anaesthesia was induced with 1–2% halothane in oxygen 3 litre min$^{-1}$ via a face mask connected to an Ayre’s T-piece system. Tracheostomy was performed and a 4.0 or 4.5 mm internal diameter tracheal tube was introduced 1 cm into the trachea. Administration of halothane in oxygen was continued through the tracheal tube while maintaining spontaneous ventilation. Pulse and arterial saturation were monitored on a hind limb using a pulse oximeter (Satlite, Datex). Halothane administration was stopped when surgery was complete and anaesthesia was maintained with an i.v. infusion of Hypnorm 1–2 ml h$^{-1}$ and neuromuscular block produced with alcuronium 1–2 mg h$^{-1}$. Halothane anaesthesia was administered only during the surgical preparation, which lasted 60–90 min. Subsequently, anaesthesia without halothane for a minimum of 90 min preceded the study involving induction of regional hypoxia. In pilot studies the end-tidal halothane concentration was found by mass spectrometry to have decreased to less than 5% of its initial value by 90 min after its withdrawal from the inspired gas. Arterial pressure and heart rate were monitored continuously and autonomic signs observed to ensure that anaesthesia was adequate. Animals were given Hartmann’s solution at a rate of 5 ml kg$^{-1}$ h$^{-1}$. The animals were kept in the supine position throughout the experiment.

PREPARATION

A 19-gauge cannula was inserted in the left carotid artery for measurement of arterial pressure and sampling arterial blood. A 23-gauge cannula was introduced into an ear vein for i.v. infusion. A 4-French gauge umbilical cannula was introduced via the left jugular vein and advanced into the right ventricle or pulmonary artery for sampling mixed venous blood.

The bladder was catheterized and a thermometer was introduced into the rectum. Body temperature was maintained with a warming blanket. After neuromuscular block the rabbits’ lungs were ventilated using a Bear Cub infant ventilator (Bear Medical Systems, Riverside, CA, USA). The ventilator setting was initially: gas flow 8 litre min$^{-1}$, peak pressure 2 kPa, positive end-expiratory pressure (PEEP) 0.3 kPa, I:E ratio 0.5, $P_{O_2}$ 1, rate 14–20 min$^{-1}$. Throughout the experiment the ventilator rate was adjusted to maintain $P_{CO_2}$ between 4.7 and 6.0 kPa; the other variables were held constant. Mean airway pressure was 0.6–0.7 kPa. Ventilator settings for $P_{O_2}$ were confirmed using a gas meter (Normocap OXY, Datex, Finland) that had itself been calibrated with standard gases.

MEASUREMENT OF LUNG VOLUMES AND OXYGEN CONSUMPTION

The total volume of both lungs was measured at end-expiratory pressure 0 kPa (functional residual capacity) and 0.3 kPa using the helium dilution technique with a thermal conductivity helium meter (P. K. Morgan, Chatham, UK). The fraction of lung volume associated with the left lung was estimated by assuming it to be equal to the fraction of apnoeic oxygen uptake associated with the left lung in comparison with both lungs. (This method could underestimatethe fraction of lung isolated because carbon dioxide in the isolated lung reaches venous levels, which in turn could cause slight vasoconstriction.) To measure the fractional oxygen uptake, a 7-French gauge balloon-tipped catheter was inserted into the tracheal tube via a Y-connector. The catheter was connected to an oxygen supply at a pressure of 0.6 kPa with a calibrated bobbin flowmeter connected in series. The balloon was inflated in the tracheal tube at the end of expiration. The rabbit’s oxygen consumption was measured as the steady state flow of oxygen through the flowmeter. The rate of oxygen uptake of the apnoeic left lung at 0.6 kPa was then measured after deflating the balloon, advancing the catheter into the left main bronchus, and reinflating the balloon, as explained below. The rate of oxygen uptake by the left lung was also measured at a pressure of 0.3 kPa (see below).

BRONCHIAL ISOLATION OF STUDY LUNG

The 7-French gauge balloon-tipped catheter was advanced into the left main bronchus. The catheter was shaped to pass easily into the left main bronchus. By inflating the balloon the airways of the left lung were isolated. Care was needed to position the balloon within 1 cm from the carina, because the left upper lobe bronchus in the rabbit leaves the left main bronchus at this distance from the carina. Correct positioning of the catheter was confirmed by observing chest movements, auscultation, blood-gas sampling, and measurement of oxygen uptake. The position was confirmed at post mortem.

LIQUID INSTILLATION INTO THE STUDY LUNG

A fresh solution of glucose 10 mmol litre$^{-1}$ and blue Dextran 1 mmol litre$^{-1}$ was made isosmotic with the arterial plasma of the study animal using sodium chloride. In some experiments amiloride and phloridzin (both 1 mmol litre$^{-1}$) were included in the solution as part of a separate study of lung liquid balance. These drugs were found to have no effect on venous admixture, and their presence or absence is not considered further in this article.

Having measured the rate of oxygen uptake to the apnoeic left lung at the study pressure of 0.3 kPa (see above), and having measured the volume of the left lung at that inflation pressure (see above), the liquid instillate was injected manually into the left
main bronchial catheter at the same flow as the oxygen uptake to achieve filling to the measured lung volume. Typically a volume of liquid of 10–20 ml was injected over 1–2 min. Ventilation of the lung with oxygen alone for at least 90 min preceded instillation of liquid. The reason for filling the lung in this way was to achieve displacement of oxygen by liquid with little or no change in lung volume, and consequently no stretching of pulmonary vessels.

Immediately after instillation of liquid, the bronchial catheter was connected to a reservoir of the instillate. The liquid level in the reservoir was kept at a height of 3 cm above the manubrium for 6 h to maintain a constant distending pressure of 0.3 kPa.

At post mortem the pleural cavity was examined for leakage of blue instillate, and the lung was inspected by eye for regions of persistent gas filling of alveoli. In no case was pleural leakage or a deficiency of liquid filling found.

MEASUREMENT OF CARDIAC OUTPUT AND PULMONARY VENOUS ADMIXTURE

Cardiac output was measured before and after 6 h of liquid filling of the lung using the Fick principle. Apnoeic oxygen uptake measurements for the whole animal were made at the same time at which arterial and mixed venous blood samples were obtained for measurement of pH, \( P_{O_2} \) and \( P_{CO_2} \) (1306 blood gas analyser, Instrumentation Laboratory, Italy) and measurement of haemoglobin concentration (Hb (mmol litre\(^{-1}\)) of oxygen binding sites; OSM3 Hemoximeter, Radiometer, Denmark). The oxygen concentrations in arterial (\( C_aO_2 \)) and mixed venous (\( C_vO_2 \)) blood samples were calculated using these measurements and the following published variables for the rabbit [17]: Hill coefficient 2.91; \( P_50 = 4.66 \text{kPa} \) at \( P_{CO_2} = 5.33 \text{kPa} \) and \( pH = 7.40 \); Bohr shift \( \Delta pH = -0.427 \text{ kPa} \) and \( 0.0041 \Delta P_{CO_2} \). The equations for fractional arterial oxygen saturation (\( S_aO_2 \)) and (\( C_aO_2 \)) used were as follows:

\[
S_{aO_2} = \frac{(P_{aO_2})^{2.91}}{(P_{aO_2})^{2.91} + (P_{50})^{2.91}},
\]

\[
(C_{aO_2}) = Hb \cdot S_{aO_2} + \alpha \cdot P_{aO_2},
\]

where \( \alpha \), the solubility of oxygen in blood, was taken to be 0.0102 mmol litre\(^{-1}\)kPa\(^{-1}\) at standard temperature and pressure. Corresponding equations were used for mixed venous blood.

Pulmonary venous admixture was also calculated on the basis of the oxygen concentrations estimated for arterial and mixed venous blood. We used the classical shunt equation [18], as follows:

\[\text{venous admixture} = \left( C_{CO_2} - C_{aO_2} \right) / \left( C_{CO_2} - C_{vO_2} \right)\]

where \( C_{CO_2} \) = concentration of oxygen in end-capillary blood. To calculate \( C_{CO_2} \) we assumed for the lung ventilated with 30–100% oxygen an end-capillary haemoglobin saturation of 1 and an end-capillary oxygen partial pressures (\( P_{cO_2} \)) calculated from the alveolar gas equation [18]:

\[P_{cO_2} = P_{aO_2} - P_{CO_2}(1 - F_{O_2}(a - R))/R\]

where the respiratory exchange ratio was assumed to be 0.8. As \( P_{cO_2} \) decreased in response to a reduction in \( P_{aO_2} \) to 0.3, the assumption that the end-capillary oxygen saturation, \( S_{CO_2} \) remains 1 will be slightly in error. Though \( S_{CO_2} \) cannot be calculated precisely because of our lack of knowledge of \( P_50 \) for end-capillary blood, we estimate that it does not decrease to less than 0.99, and that the resulting error in the calculation of venous admixture is small.

PROCEDURE FOR INSPIRED OXYGEN FRACTION

In 10 animals the \( P_{FI O_2} \), ventilating the right lung was held constant at 1 for 6 h. This group acted as a control in which any changes in pulmonary shunt with time could be observed. In 10 animals \( P_{FI O_2} \) was held at 1 for 2.5 h and then changed abruptly to 0.3 for 3.5 h. In seven animals \( P_{FI O_2} \) was held at 1 for between 2 and 3 h and changed abruptly to 0.5 for the remainder of the 6-h experimental period.

STATISTICAL ANALYSIS

All data are presented as mean (SEM) unless otherwise indicated. Analysis of variance (ANOVA, Minotab 8.1) was used to compare data from the three study groups and unpaired t tests were used to compare between-group means. Significance was regarded as present at \( P < 0.05 \).

Results

All animals survived the study period and had liquid filling of the left lung confirmed at post mortem. Mean rectal temperature was 38.9 °C, at which oxygen consumption was 7.6 (0.2) ml (STPD) min\(^{-1}\)kg body weight. The fraction of oxygen uptake occurring in the left lung was 0.37 (0.02), which we take to be a low estimate of the fraction of functional lung tissue present in the left lung for the reason given above. The lung volumes measured at 0 (FRC) and 0.3 kPa were, respectively, 9.7 (0.6) and 14.2 (0.6) ml/kg body weight. Cardiac output measurements were available in 23 animals; at \( t = 0 \) cardiac output was 151 (5) ml min\(^{-1}\)kg body weight and at \( t = 6 \) h 186 (9) ml min\(^{-1}\)kg body weight. There was no significant difference in cardiac output between the three groups at either 0 or 6 h.

Figure 1 compares the arterial oxygen partial pressure for the \( P_{FI O_2} = 1 \) group and the \( P_{FI O_2} = 0.3 \)
In both groups there was an initial decrease in \( P_{aO_2} \) on filling of the left lung with liquid and a gradual increase in \( P_{aO_2} \) over most of the succeeding 150 min. In the \( P_{fO_2}/H_11005 \) 1 group, \( P_{aO_2} \) increased little after t/\( H_11005 \) 150 min; in the \( P_{fO_2}/H_11005 \) 0.3 group, \( P_{aO_2} \) decreased rapidly to approximately 9 kPa and remained at that level for the duration of the study. Error bars were so close after 150 min in this group that they are not visible in figure 1.

Figure 2 shows the mixed venous oxygen partial pressures in the \( P_{fO_2}/H_11005 \) 1 group and in the \( P_{fO_2}/H_11005 \) 0.3 group. In the \( P_{fO_2}/H_11005 \) 1 group the initial filling of the left lung resulted in a decrease in \( P_{vO_2} \) of approximately 1.3 kPa, followed by a gradual restoration to the baseline value of approximately 6.6 kPa after 200 min. In the \( P_{fO_2}/H_11005 \) 0.3 group the trend was similar up to the time when \( P_{fO_2} \) was changed from 1 to 0.3, at which point the \( P_{vO_2} \) decreased abruptly to approximately 4.6 kPa and stayed at that level for 3.5 h.

Figure 3 shows the venous admixture in the \( P_{fO_2}/H_11005 \) 1 group and in the \( P_{fO_2}/H_11005 \) 0.3 group. At t = 0 the baseline venous admixture for all 20 animals was 0.128 (0.004). Immediately after liquid filling of the left lung the maximal venous admixtures were obtained between 3 and 5 min, during which time the average value for all 20 animals was 0.335 (0.016). After 5 min venous admixture declined in both groups to approximately 0.22 at 150 min. In the \( P_{fO_2}/H_11005 \) 1 group venous admixture changed little after 150 min; in the \( P_{fO_2}/H_11005 \) 0.3 group an increase in venous admixture from 0.221 (0.016) at 150 min to a peak of 0.383 (0.043) at 160 min was induced by the change in \( P_{fO_2} \) from 1 to 0.3 at 150 min. After 200 min venous admixture remained fairly constant in the \( P_{fO_2}/H_11005 \) 0.3 group.

Figure 4 shows the pulmonary artery pressures in the \( P_{fO_2}/H_11005 \) 1 group and in the \( P_{fO_2}/H_11005 \) 0.3 group, The figure shows that small changes in pulmonary artery pressure accompanied the substantial changes in venous admixture seen in figure 3.

In view of the near constancy of all measured variables during the period 200–360 min, and to facilitate modelling of HPV during this period, we elected to average variables for each animal from the half hourly measurements during this time window. These data are presented in table 1 for both the \( P_{fO_2}/H_11005 \) 1 and \( P_{fO_2}/H_11005 \) 0.3 groups. Also included in table 1 are data for the \( P_{fO_2}/H_11005 \) 0.5 group in which \( P_{aO_2} \) of 14.6 kPa permitted us to examine the effect of \( P_{fO_2} \) on venous admixture while avoiding the mild systemic hypoxaemia of the \( P_{fO_2}/H_11005 \) 0.3 group, in which \( P_{aO_2} \) was 8.84 kPa.

Discussion

The first question we have examined is whether or not changes in inspired oxygen fraction in rabbits in
The effects of different inspired oxygen concentrations by to be of clinical importance if they were to occur to admixture which were large (table 1, fig. 3) and likely admixture. We observed differences in venous lung tissue, led to substantial changes in venous level of oxygen in approximately 40% of which there is sustained hypoxia, at the mixed 

The second question we have asked is whether or not the dependence of venous admixture on $P_{O_2}$ is predictable from our current knowledge of the pulmonary circulation. The dose–response relationship for HPV has recently been reviewed, in a clinical context by Marshall and colleagues [2, 6] who have computed the changes in venous admixture which are to be anticipated in a wide range of conditions, including that of 40% pulmonary atelectasis (fig. 1), which is directly equivalent to the hypoxic insult in the experiments reported here. The model of Marshall uses a stimulus $P_2O_2$ for HPV which is a function of both $P_{O_2}$ and $P_{O_3}$, and a stimulus–response relationship which is sigmoidal with a 50% response at a stimulus $P_2O_2$ (the $P_{50}$) of 4.0 kPa in rat lungs [7] and 5.3 kPa in dog lungs [8].

A feature of their model is that changes in $P_{O_2}$ above 0.3 produce only small changes in venous admixture in the presence of a fixed percentage of lung exposed only to the mixed venous $P_{O_2}$, because $P_{50}$ is so much lower than the alveolar oxygen partial pressure in the ventilated lung. For the case of 40% atelectasis, Marshall and colleagues computed the changes in venous admixture with changing $P_{O_2}$ for the homogeneous ventilated lung and, for the ventilated lung displaying a distribution of ventilation–perfusion ratios. In both cases the model predicted a similar small reduction in venous admixture on reducing $P_{O_2}$ from 1 to 0.3. Increases in venous admixture with decreasing $P_{O_2}$ that are attributable to a broad distribution in ventilation–perfusion ratios are most marked at values of $P_{O_2}$ less than 0.3 [3, 6]. This is an important observation in relation to our experimental model, because although the contribution to venous admixture from our liquid-filled lung must have been pure shunt, some of the contribution to venous admixture from the right lung may have resulted from areas of lung with low ratios of ventilation to perfusion. As baseline venous admixture in the supine rabbit was 0.128, and as the right lung contributes approximately 60% of lung tissue, up to approximately 0.077 of the venous admixture in the period after liquid instillation may have been contributed by areas of low ventilation–perfusion ratio rather than pure shunt. However, it has been

### Table 1 Mean (±sd) blood-gas variables, arterial oxygen concentration ($C_{O_2}$) mixed venous oxygen content ($C_{O_2v}$) venous admixture and pulmonary artery pressure (PAP) for the time window 200–360 min for three levels of $P_{O_2}$ during unilateral liquid filling of the left lung of the rabbit. Cardiac output (CO) was measured at 360 min. $P$ values were determined by ANOVA between the three groups

<table>
<thead>
<tr>
<th>$P_{O_2}$</th>
<th>1</th>
<th>0.5</th>
<th>0.3</th>
<th>P</th>
</tr>
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<tbody>
<tr>
<td>$n$</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$P_{O_2}$ (kPa)</td>
<td>39.6 (2.3)</td>
<td>14.6 (0.99)</td>
<td>8.84 (0.39)</td>
<td>0.000</td>
</tr>
<tr>
<td>$P_{CO_2}$ (kPa)</td>
<td>4.99 (0.15)</td>
<td>5.16 (0.26)</td>
<td>5.05 (0.13)</td>
<td>0.706</td>
</tr>
<tr>
<td>$P_{O_2}$ (kPa)</td>
<td>6.62 (0.18)</td>
<td>5.50 (0.21)</td>
<td>4.04 (0.17)</td>
<td>0.000</td>
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<tr>
<td>$P_{CO_2}$ (kPa)</td>
<td>6.22 (0.21)</td>
<td>6.45 (0.23)</td>
<td>6.22 (0.17)</td>
<td>0.707</td>
</tr>
<tr>
<td>pH</td>
<td>7.31 (0.01)</td>
<td>7.28 (0.02)</td>
<td>7.23 (0.01)</td>
<td>0.152</td>
</tr>
<tr>
<td>$C_{O_2v}$ (mmol litre$^{-1}$)</td>
<td>5.68 (0.11)</td>
<td>5.39 (0.15)</td>
<td>4.30 (0.21)</td>
<td>0.000</td>
</tr>
<tr>
<td>$C_{O_2}$ (mmol litre$^{-1}$)</td>
<td>3.80 (0.12)</td>
<td>3.38 (0.16)</td>
<td>2.43 (0.20)</td>
<td>0.000</td>
</tr>
<tr>
<td>Venous admixture</td>
<td>0.218 (0.015)</td>
<td>0.290 (0.025)</td>
<td>0.32 (0.026)</td>
<td>0.007</td>
</tr>
<tr>
<td>PAP (kPa)</td>
<td>2.15 (0.14)</td>
<td>2.39 (0.11)</td>
<td>2.14 (0.10)</td>
<td>0.331</td>
</tr>
<tr>
<td>CO (ml min$^{-1}$/kg body weight)</td>
<td>193 (10)</td>
<td>167 (9)</td>
<td>188 (22)</td>
<td>0.605</td>
</tr>
</tbody>
</table>

### Table 2 Venous admixture computed from the model of hypoxic pulmonary vasoconstriction of Marshall and Marshall [7] using the measured $P_{O_2}$ values for the 100% and 30% oxygen groups (see fig. 2, table 1). Two alternative methods have been used to incorporate the baseline venous admixture of 0.128 observed during bilateral oxygenation: (A) the venous admixture arises from a region of lung exposed only to mixed venous blood (e.g. atelectatic lung), that it is distributed between the two lungs in proportion to the ratio of functional lung tissue (40% left, 60% right), and that it displays HPV; (B) the venous admixture is pure shunt that carries a fixed fraction of the cardiac output under all circumstances. The bracketed numbers represent the fraction of cardiac output perfusing the tissue accounting for the baseline venous admixture. $\Delta VA\% = $ percentage difference in venous admixture for the period 200–360 min between the conditions $P_{O_2} = 1$ and $P_{O_2} = 0.3$. For other details of the calculation see text

<table>
<thead>
<tr>
<th></th>
<th>Model A</th>
<th>Model B</th>
<th>Measured venous admixture</th>
</tr>
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</table>
|                  | Responsive baseline shunt | Fixed baseline Shunt | Ve
|                  | Measured venous admixture | shunt | admixture |
|                  |         |         | $t = 3–5$ min | 0.381 | 0.379 | 0.335 (0.016) |
|                  |         |         | (0.131) | (0.128) |         |         |
|                  |         |         | $t = 200–360$ min | 0.412 | 0.402 | 0.218 (0.015) |
|                  |         |         | (0.143) | (0.128) |         |         |
|                  |         |         | $t = 200–360$ min | 0.377 | 0.375 | 0.320 (0.026) |
|                  |         |         | (0.130) | (0.128) |         |         |
|                  |         |         | $P_{O_2} = 0.3$ | 0.152 | 0.349 | 0.757 |
|                  |         |         | (0.130) | (0.128) |         |         |
|                  |         |         | $\Delta VA\%$ | −8.5 | −6.7 | +46.8 |
shown that much of the venous admixture that arises as a consequence of anaesthesia in the supine position is pure shunt associated with dependent atelectasis [21]. We conclude that by far the greatest contribution to venous admixture in both groups in the interval 150–360 min was pure pulmonary shunt.

We have repeated the calculation of Marshall and colleagues [6, 7] here for the case of homogeneous lung for precise direct comparison with our experimental findings. The results are shown in table 2. The precise characteristics we have used in the model of Marshall are as follows: a stimulus–response relationship as derived for the rat (17], equation 1) with P50 = 4.04 kPa; a linear pressure–flow relationship; a maximum vessel resistance caused by HPV which equals 3.15 times the value in the absence of a response [8]; PVo2 as measured from mixed venous blood samples (fig. 2, table 1); PAO2 was calculated from the alveolar gas equation to be 88 and 22 kPa, respectively, for the cases FAO2 = 1.0, 0.3. Furthermore, it has been necessary to model the baseline venous admixture which we observed during oxygenation of both lungs (fig. 3). This averaged 0.128 for the 10 animals whose lungs were ventilated at FAO2 = 1.0 and 0.3. In table 2, model A is the prediction of the model of Marshall and colleagues if the baseline venous admixture is assumed to arise from a constant region of lung tissue that is exposed only to mixed venous PO2 is distributed between left and right, respectively, in the proportions 0.4 : 0.6, and displays HPV according to the same dose–response relationship as the rest of the lung. Model A predicts a decrease in venous admixture of 8.5 % of changing FAO2 from 1 to 0.3. In table 2, model B is the prediction in the event that baseline venous admixture is pure shunt that remains a fixed proportion of cardiac output. Model B predicts a reduction in venous admixture of 6.7 % on changing FAO2 from 1 to 0.3. Table 2 shows that the measured change in venous admixture corresponding to the specified change in FAO2 is an increase of 46.8 %. Possible reasons for the discrepancy between measured and predicted changes in venous admixture are considered below.

One important possibility is that changes in systemic FO2 cause differential chemoreceptor-mediated dilatation of hypoxic lung, and consequently an increase in shunt [22]. Levitzky, Newell and Dutton [23] showed in anaesthetised dogs with left lung atelectasis that an increase in the fraction of blood flow perfusing the left lung from 0.26 to 0.37 that occurred with a change in FAO2 in the right lung from 1 to 0.21 was abolished by surgical sinoaortic denervation. In the study the time permitted for equilibration of HPV was 10–20 min. The decrease in FAO2 was associated with a reduction in arterial PO2 from 12.4 to 6.7 kPa. Levitzky, Newell and Button later showed a similar response in awake closed-chest dogs but found interpretation difficult because of large differences in cardiac output and arterial PCO2 between intact and denervated animals [4]. In our study arterial PO2 decreased to 8.84 kPa in the group whose lungs were ventilated to FAO2 = 0.3. It is possible that this level of hypoxia could induce a similar reflex redistribution of blood flow to that seen by Levitzky, Newell and Button. To explore this possibility further we have included in table 1 data for seven animals in which FO2 was lowered to 0.5 in the experiment. In this group arterial PO2 remained at a normoxic value (14.6 kPa) and yet shunt was still substantially higher (by 33 %) than ventilation with FAO2 = 1. If a chemoreflex is responsible for the observed higher shunts in the groups with FAO2 = 0.3 or 0.5 then the effect would appear to be present even at arterial normoxia. If this were to occur in humans, the model of Marshall and colleagues [2, 6] would be unable to predict the results of clinical oxygen therapy even when arterial hypoxia is avoided.

A second possibility is that differences in cardiac output between ventilation with FAO2 = 1 and 0.3 could generate differences in shunt. The mechanisms of this effect remains obscure. In a study in pigs subjected to unilateral oleic acid oedema, Freden and colleagues [5] were unable to demonstrate redistribution of blood flow between lobes, but they raised the possibility of redistribution within the oedematous lobe. In our experiment two factors make it unlikely that changes in cardiac output could account for the changes in shunt. First, cardiac output measured at 360 min (table 1) did not differ between groups. Second, in this model of unilateral hypoxia the liquid-filled lung was exposed uniformly to mixed venous PO2 such that any redistribution of blood flow within the hypoxic lung could not induce a change in shunt in the manner entertained by Freden and colleagues [5].

A third possibility is that the hypoxic vasoconstriction that occurs under sustained hypoxia differs fundamentally from the HPV modelled by Marshall and colleagues on the basis of brief exposures to hypoxia, and that a new dose–response relationship is required to account for the changes in venous admixture during sustained hypoxia. A striking feature of figure 3 is the marked reduction in venous admixture which occurs after the 10 min period in which many workers have made measurements with the aim of quantifying the HPV response. However, the time course of HPV remains controversial. Some studies of sustained hypoxia have shown little [24] or no [25, 26] intensification of HPV after 15 min of exposure to hypoxia; other studies have shown marked intensification over times in excess of 60 min [10, 11, 13–15, 19, 27] or even a response consisting of two phases, the first lasting for 10–20 min and the second developing over more than 60 min [9, 12]. The finding by Leach and colleagues [9] that these two phases of constriction differ in their dependence on an intact epithelium, gives rise to the speculation that the phases may differ in their relative sensitivity to mixed venous and alveolar oxygen tensions. It follows that a dose–response relationship for HPV derived from brief exposures to hypoxia over minutes may not be applicable to HPV resulting from sustained hypoxia over hours.

One of the difficulties of looking for gradual changes in the pulmonary circulation over times of several hours is the need to avoid gradual changes in variables which can modulate HPV and in the viability of the preparation used. In vivo experiments...
may have the advantage of prolonged physiological stability in contrast with isolated lung or vessel experiments, but changes in the level of anaesthesia might conceivably lead to changes in HPV. Because of the known effect of inhalation anaesthetic agents in depressing HPV [28] we waited at least 90 min after a period of surgical anaesthesia until end-tidal halothane levels decreased to low values, changes which are unlikely to account for the time course in venous admixture we observed. What remains unknown, however, is whether or not changing levels of i.v. anaesthesia could influence HPV in our preparation.

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References