THE EFFECT OF P_{CO_2} ON HYPOXIC PULMONARY VASOCONSTRICTION

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ABSTRACT

Lung areas with a low V/Q ratio cause hypoxaemia. The low alveolar oxygen concentration may cause local hypoxic pulmonary vasoconstriction (HPV) which reduces perfusion, raises the V/Q ratio, and hence reduces the tendency to a low Pa_{O_2}. By changing P_{CO_2}, the HPV response can be altered. We examined this relationship in anaesthetized dogs by using a tracheal divider to separate hypoxic (nitrogen ventilated) from oxygenated (100 per cent oxygen ventilated) lung. Relative perfusion was assessed from total ^{133}Xe exhaled from each lung area after intravenous infusions. When Pa_{CO_2} was changed by changing ventilation, we found that an increasing Pa_{CO_2} increased HPV and also Pa_{O_2}. At a Pa_{CO_2} of 3.3 kPa, HPV was abolished and Pa_{O_2} fell. We also changed Pa_{CO_2} by altering PI_{CO_2} to one or both lung areas while ventilation remained constant throughout the experiment. Again as Pa_{CO_2} increased, HPV and Pa_{O_2} increased. When Pa_{CO_2} fell and end tidal carbon dioxide in the hypoxic lung (PET_{CO_2}) remained elevated (by maintaining PI_{CO_2} in the hypoxic lung and removing CO_2 from the oxygenated lung) HPV was maintained. Thus it is the alveolar concentration of CO_2 in the hypoxic lung which is important in modifying HPV.

We conclude that in this model a low PET_{CO_2} (3.3 kPa) in hypoxic lung will reduce HPV, and will result in more severe hypoxaemia. This may have relevance in both anaesthetized and intensive care unit patients when a higher Pa_{O_2} may be obtained by increasing hypoxic lung PET_{CO_2}. The effect of PET_{CO_2} on Pa_{O_2} will be influenced by other variables, but when hypoventilated or hypoxic lung areas exist, increasing PET_{CO_2} may reinforce hypoxic pulmonary vasoconstriction and thus may increase Pa_{O_2}.

KEY WORDS: LUNG, hypoxic vasoconstriction, carbon dioxide.

RESPIRATORY GAS EXCHANGE depends on the ratio of ventilation to perfusion. A low V/Q ratio and hypoxaemia will result from poorly ventilated lung unless perfusion is also reduced in the same region. Alveolar oxygen concentration helps to match regional perfusion to ventilation through a mechanism of hypoxic pulmonary vasoconstriction (HPV).[1-3]

The mechanism of HPV is still not understood, but several events which occur under anaesthesia are reported to reduce HPV (and therefore to create hypoxaemia). Sykes, *et al.*,[4-7] Benumof and Wahrenbrock,[8] and Bjertnaes[9,10] have found that inhaled anaesthetics reduce HPV. Benumof, *et al.*[11] have found that increased pulmonary vascular pressure can reduce HPV. P_{CO_2} is also known to affect HPV.[11-13]

P_{CO_2} during anaesthesia may be increased, decreased, or normal. If HPV were present and a low P_{CO_2} reduced HPV, the low P_{CO_2} could create hypoxaemia by increasing perfusion to hypoxic lung. P_{CO_2} may also alter Pa_{O_2} through its effect in the alveolar gas equation or by changing the position of the oxyhaemoglobin dissociation curve, cardiac output, or R values. In order to document which effect was dominant we assessed HPV in dogs and observed the effect of altering ventilation and therefore Pa_{CO_2} on both HPV and Pa_{O_2} when one third of the lung was made hypoxic. The relative importance of end tidal and arterial P_{CO_2} changes on HPV were also investigated by altering inspired carbon dioxide to two separate lung areas (one hypoxic, the other oxygenated) while ventilation was unchanged.

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METHODS

The experiments were carried out on 38 mongrel dogs weighing 25–30 kg. The animals were anaesthetized with pentobarbitone 30 $mg \cdot kg^{-1}$ intravenously. Anaesthesia was maintained with intermittent infusions of pentobarbitone and pancurium bromide, as these agents have been shown not to affect HPV.[10] The dogs were intubated through a tracheostomy with a Carlens double lumen tracheal tube, to separate two lung areas. It was important that the lung separation remain constant throughout the experiment. To

be assured of this: (a) the inflated cuff seal was checked for leaks by ventilating the animal through one lumen while the other was attached to a tube submerged under water; (b) $P_{I_{O_2}}$ was measured by testing gas aspirated from each bronchus during inspiration when nitrogen was in one lung and oxygen in the other; and (c) the ratio of ventilation to the two lung areas was monitored throughout the experiment. If this ratio changed, as it occasionally did due to tube movement or cuff leakage, the results were discarded.

Each limb of the Carlens tube was connected to a secondary ventilator circuit, modified from Sykes,[14] which allowed the lungs to be synchronously but independently ventilated to the same pressure with separate gases (see Figure 1 for explanation of mechanism). With this system the gas distribution to the lungs depends on the compliance of the lung to which it is attached and expired gas can be collected separately from each lung area to measure ventilation. In order to maintain oxygenation when nitrogen was used, nitrogen was always ventilated into the smaller lung area and the other lung was ventilated with 100 per cent oxygen. Inspired and end tidal P_{O_2} and P_{CO_2} from each lung were measured intermittently by aspirating gas from a 1.7 mm O.D. catheter situated in the bronchi through the Carlens tube.

To measure the distribution of blood flow to each lung area we used a technique described by Arborelius.[15] ^{133}Xe was dissolved in saline and 1 mc was infused rapidly into a central vein. Because of its low solubility ^{133}Xe diffuses into alveolar gas, and is washed out by ventilation. Immediately following the injection, expired gas from each lung was collected for seven minutes and the volume was measured. A 10 ml sample of mixed expired gas collected from each lung was counted in a scintillation counter to give ^{133}Xe cpm/ml. The ^{133}Xe excreted by each lung area is proportional to its perfusion. Then ^{133}Xe excreted by the hypoxic lung divided by the total ^{133}Xe excreted indicates the proportion of perfusion to the hypoxic lung. The model thus compares the perfusion between any two ventilated lung areas isolated by the insertion of the Carlen's double lumen tube. In our experiments ventilation between the two lung areas remained constant, eliminating its contribution as a source of error.

The pulmonary artery, femoral artery and femoral vein were catheterized to monitor pressures continuously with pressure transducers.

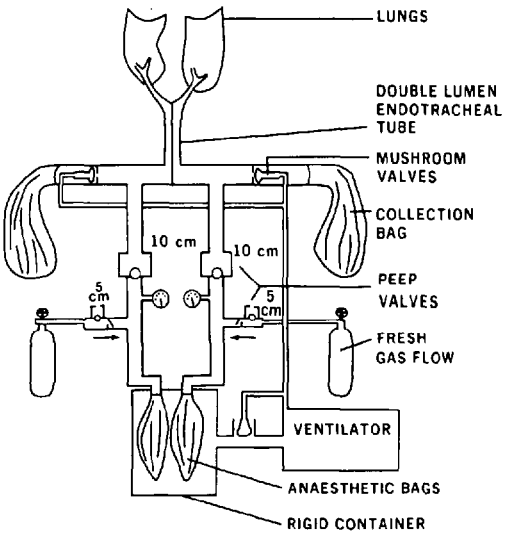

FIGURE 1 Secondary ventilator circuit used to separate inspired and expired gases in each lung. During expiration, a known gas fills two anaesthetic bags within a rigid container. The 10 cm H_2O PEEP valve remains closed while the bags fill. When the bags are full the rise in pressure closes one way valves, resulting in venting of excess fresh gases. During the inspiratory cycle the volume cycled ventilator (OHIO 560) forces a volume of gas into the rigid container, opening the 10 cm H_2O PEEP valve and displacing the same volume from the bags into the lungs. The distribution of gas to the lungs depends on the compliance of the lung to which it is attached. A non-rebreathing mushroom valve synchronized with the primary ventilator circuit prevents contamination of expired gas with inspired gas.

All lines were kept patent by intermittent flushing with physiological saline, and no heparin was used. Arterial and mixed venous blood samples were obtained for blood gas analysis, and cardiac output was determined using the thermodilution principle.[16]

EXPERIMENTAL PROTOCOL

There were two groups of dogs. In the Δ VENTILATION group, measurements were taken at a specific Pa_{CO_2} and with each lung area ventilated with 100 per cent oxygen to remove all HPV. At the same Pa_{CO_2} we then introduced nitrogen into the smaller lung area to create HPV and repeated the measurements. With one lung ventilated with nitrogen and the other with oxygen, Pa_{CO_2} was increased or decreased by changing ventilation. Haemodynamic and respiratory measurements were repeated after $P_{ET_{CO_2}}$ had stabilized (usually between 30 and 90 minutes).

In the inspired carbon dioxide group, Pa_{CO_2} was

altered by adding or removing inspired carbon dioxide to one or both lung areas while ventilation stayed constant throughout the experiment. Again, measurements were taken when haemodynamic and respiratory variables had stabilized (30 to 90 minutes).

Results are expressed as mean ± S.E.M. Differences were assessed using unpaired and paired Student's 't' test. Regression equations and correlations were determined using the method of least squares. $P < 0.05$ was considered significant.[17] In this paper changes are only referred to if they are significant.

Results

Throughout these experiments we found no significant changes in cardiac output or pulmonary artery pressure. Since these variables did not change we have equated decreased perfusion to hypoxic lung with an increase in HPV. The percentage of lung made hypoxic was 32 ± 2 per cent of total, measured by ventilation.

Δ Ventilation Group

In Figure 2 we plot the Pa_{CO_2} at which nitrogen was introduced into one lung against the resulting decreased perfusion to that hypoxic lung (or HPV). Each point represents one dog. An increasing Pa_{CO_2} increases HPV. Up to a Pa_{CO_2} of 6.7 kPa (50 mm Hg) HPV is enhanced. At a Pa_{CO_2} of 3.3 kPa (25 mm Hg) HPV is abolished.

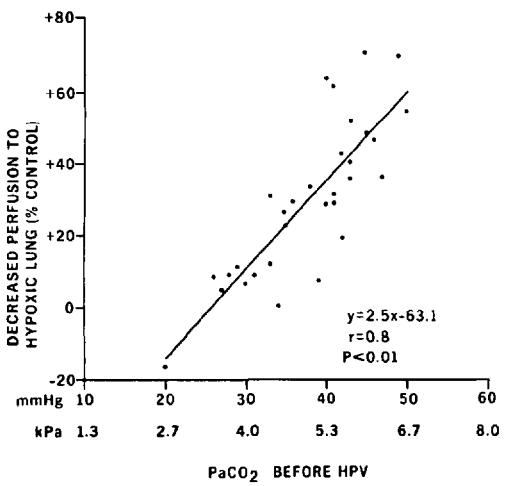

FIGURE 2 Pa_{CO_2} before ventilating one lung area with nitrogen (before HPV) is plotted against the decreased perfusion to the hypoxic lung ventilated with nitrogen (HPV). The change in perfusion created by nitrogen ventilation is expressed as a percentage of the control value to normalize the data for hypoxic lung segment size.

The same results are found if arterial or venous pH are plotted against the decreased perfusion created by hypoxia (HPV[% CONT.] = −190 pHa + 1500, $r = -0.7$, $p < 0.01$). We can make no comment about the effects of metabolic alterations in pH, since pH was only altered by changing Pa_{CO_2}.

After HPV was in place we altered ventilation and Pa_{CO_2}, and followed shifts in perfusion between hypoxic and hyperoxic lung areas (Figure 3). A plot similar to Figure 2 is obtained. At Pa_{CO_2} values above 7.3 kPa (55 mm Hg) there still seems to be no plateauing of the effect of Pa_{CO_2} on HPV. There is more scatter here and the regression line is not as steep. HPV is not abolished until Pa_{CO_2} values of 2 kPa (15 mm Hg).

A low Pa_{CO_2} increased perfusion to the hypoxic lung (Figures 2 and 3). The greater the perfusion to the hypoxic lung, the lower the Pa_{O_2} ($\Delta Pa_{O_2} = -10.9\Delta$ perfusion to hypoxic lung +4.2, $r = -0.8$, $p < 0.01$). As Pa_{CO_2} increased by decreasing ventilation, Pa_{O_2} increased (Figure 4). When ventilation was increased and Pa_{CO_2} reduced, HPV was reduced (Figures 2 and 3), perfusion shifted to hypoxic lung, and Pa_{O_2} fell (Figure 4).

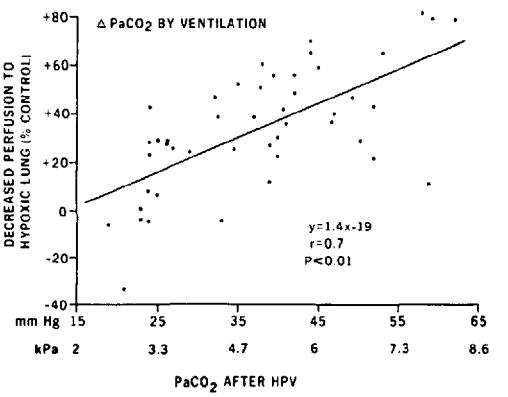

FIGURE 3 While the smaller lung segment was ventilated continuously with nitrogen and the other with 100 per cent oxygen, Pa_{CO_2} was altered by changing ventilation. These changes in Pa_{CO_2} occurred after HPV was present. The new Pa_{CO_2} (Pa_{CO_2} after HPV) is plotted on the x axis. The y axis represents HPV and is the change in perfusion to the hypoxic lung from the oxygenated control state to the nitrogen ventilated new Pa_{CO_2} state expressed as a percentage of the oxygenated control perfusion. The combination of nitrogen ventilated lung and the new Pa_{CO_2} level almost always decreased perfusion to the hypoxic lung (increased HPV) since most values are above the 0 level. When perfusion to the hypoxic lung increased (five times) Pa_{CO_2} was always at low levels.

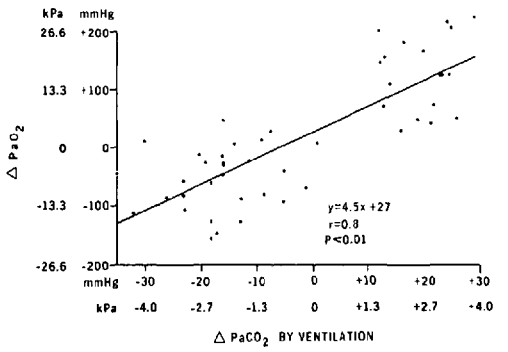

FIGURE 4 The changes in Pa_{CO_2} created by ventilation changes are plotted against the resulting changes in Pa_{O_2} while the smaller lung segment was ventilated continuously with nitrogen and the other with 100 per cent oxygen. Although there would appear to be two groups of data, the same dogs appear in both groups, and the grouping results from the alternate raising and lowering of Pa_{CO_2}.

Data from Figures 2, 3 and 4 are all from the same dogs.

To examine whether these changes in Pa_{O_2} achieved by altering Pa_{CO_2} could have been influenced by ventilation per se rather than Pa_{CO_2} we held ventilation constant in the inspired carbon dioxide group while Pa_{CO_2} was altered by changing the inspired carbon dioxide.

INSPIRED CARBON DIOXIDE GROUP

The same sequence was followed in every dog in this group, and is presented in Table I. Initially (measurement #1) both lungs were hyperventilated with 100 per cent oxygen to an arterial Pa_{CO_2} of 2.9 kPa (22 mm Hg) to remove HPV. Carbon dioxide (5–9 per cent) was then introduced into the larger lung area that was to remain oxygenated throughout the experiment, until Pa_{CO_2} was just above 5.3 kPa (40 mm Hg) (measurement #2). This resulted in a small but significant shift in perfusion towards the lung receiving inspired carbon dioxide. Nitrogen was then introduced into the other smaller lung area (measurement #3, Table I) without altering the inspired carbon dioxide concentration. HPV occurred, as there was an 18 per cent shift in perfusion away from the nitrogen lung. This shift in perfusion away from hypoxic lung increased dead space, lowered the $P_{ET_{CO_2}}$ in that lung (3.7 to 3.1 kPa), and since the perfusion was shifted to the inspired carbon dioxide lung, Pa_{CO_2} rose (5.7 to 6.4 kPa). These changes resulted in a Pa_{O_2} of 9.6 kPa (72 mm Hg).

Over the next three measurements (#4, 5 and 6) carbon dioxide was added, removed, and added again to the hypoxic lung. As both Pa_{CO_2} and hypoxic lung $P_{ET_{CO_2}}$ increased, HPV was increased and Pa_{O_2} increased. When P_{CO_2} fell, HPV was reduced.

Measurement #7 was taken when inspired carbon dioxide was removed from the oxygenated lung and left in the hypoxic lung. Since the hypoxic lung area was the smaller area, Pa_{CO_2} fell to 4.7 kPa (35 mm Hg) while hypoxic lung $P_{ET_{CO_2}}$ was maintained at 5.7 kPa (43 mm Hg). In spite of the reduced Pa_{CO_2}, HPV and Pa_{O_2} did not significantly change.

With no inspired carbon dioxide in either lung (measurement #8) Pa_{CO_2} returned to 2.9 kPa (22 mm Hg), HPV was reduced, and Pa_{O_2} fell to 9.4 kPa (71 mm Hg). When carbon dioxide was added to both lung areas again (measurement #9) HPV was enhanced and Pa_{O_2} rose to 15.6 kPa (117 mm Hg).

A comparison of measurements #7 and #9 again indicates that when $P_{ET_{CO_2}}$ in the hypoxic lung is held constant but Pa_{CO_2} altered by changing inspired carbon dioxide in the oxygenated lung, HPV and Pa_{O_2} do not change.

A comparison of measurements #4 and #9 indicates HPV and Pa_{O_2} are increased with repeated applications of the same amount of carbon dioxide.

There were no significant changes in $\dot{Q}$ or $\overline{P_{PA}}$ at any time during this experiment (lower portion, Table I).

Since hypoxic lung alveolar carbon dioxide seems important (measurement #7, Table I), we plot the changes in $P_{ET_{CO_2}}$ in the hypoxic lung created either by changing inspired carbon dioxide or ventilation against the shift in perfusion to the hypoxic lung (Figure 5). The two regression

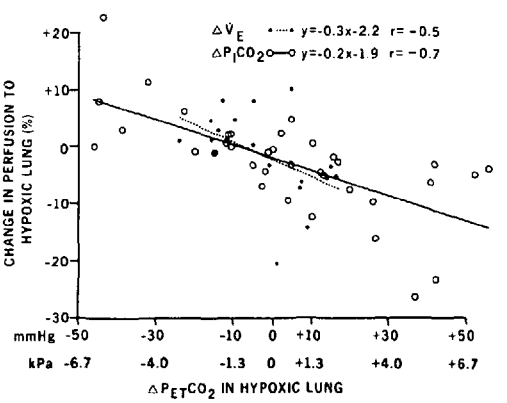

FIGURE 5 The change in end tidal P_{CO_2} ($P_{ET_{CO_2}}$) from the hypoxic lung, created either by changing ventilation ($\Delta \dot{V}E$) or by changing inspired P_{CO_2} ($P_{I_{CO_2}}$) is plotted against the resulting change in perfusion to the hypoxic lung.

TABLE I

CHANGES CREATED BY ALTERING INSPIRED CARBON DIOXIDE (CO_2) WITH CONSTANT VENTILATION

Measurement No.	1	2	3	4	5	6	7	8	9
Inspired gases:									
Hypoxic lung-	O_2	O_2	N_2	N_2/CO_2	N_2	N_2/CO_2	N_2/CO_2	N_2	N_2/CO_2
Oxygenated lung-	O_2	O_2/CO_2	O_2/CO_2	O_2/CO_2	O_2/CO_2	O_2	O_2	O_2	O_2/CO_2
Pa_{CO_2} kPa	2.9 ± 0.1	5.7 ± 0.3	6.4 ± 0.3	7.8 ± 0.9	7.0 ± 0.4	7.8 ± 0.8	4.7 ± 0.4	2.9 ± 0.1	8.0 ± 1.1
Hypoxic lung $P_{ET_{CO_2}}$ kPa	2.4 ± 0.1	3.7 ± 0.1	3.1 ± 0.1	6.0 ± 0.9	2.8 ± 0.3	5.7 ± 0.8	5.7 ± 0.5	1.6 ± 0.1	5.7 ± 1.1
HPV %*	0	6 ± 2	18 ± 6	40 ± 11	31 ± 11	51 ± 9	54 ± 11	30 ± 8	58 ± 10
Pa_{O_2} kPa	66.4 ± 6.9	66.4 ± 6.9	9.6 ± 1.2	12.0 ± 2.0	11.4 ± 1.9	13.7 ± 2.4	15.9 ± 4.7	9.4 ± 1.5	15.6 ± 2.8
$\dot{Q}$ l/min	2.6 ± 0.2	2.9 ± 0.3	2.7 ± 0.2	2.7 ± 0.4	2.5 ± 0.3	2.2 ± 0.4	2.3 ± 0.4	—	2.5 ± 0.4
P_{PA} kPa	2.3 ± 0.1	2.3 ± 0.1	2.8 ± 0.1	2.8 ± 0.1	2.7 ± 0.3	2.8 ± 0.3	2.7 ± 0.1	2.9 ± 0.1	3.2 ± 0.4

*HPV % refers to the per cent shift in perfusion away from the hypoxic lung area.

lines are not different and indicate that as hypoxic lung $P_{ET_{CO_2}}$ increases, HPV is enhanced.

Discussion

Our results indicate that P_{CO_2} affects HPV by determining the maximum HPV that can be achieved, or by modifying existing HPV. By enhancing HPV a high P_{CO_2} may improve oxygenation. A low P_{CO_2} may reduce HPV, and therefore oxygenation.

To accept these results, the experimental model used must be examined. The vasoconstrictor response to hypoxia varies in potency from one species to another. At a $P_{a_{CO_2}}$ of 5.3 kPa (40 mm Hg) induction of hypoxia decreased perfusion to hypoxic lung by 40 per cent (Figure 2). This order of magnitude correlates well with previously reported studies showing reduction of perfusion to hypoxic lung performed on isolated lungs (53 per cent),[11] open chest dogs (40–56 per cent),[18] and humans (27–62 per cent).[9]

The lung separation technique, using a Carlen's double lumen tube, results in a variable amount of separation (hypoxic lung as percentage of total, mean 32 ± 2 per cent, measured by ventilation). Since there were no significant changes in $\overline{P_{PA}}$ or $\dot{Q}$ during these experiments, the small variability (S.E. 2 per cent) of lung separation was not critical.[19] However, the lung separation must remain constant throughout the experiment. We were assured of constancy because of the care taken in sealing the cuff, checking the $P_{I_{O_2}}$ to each lung area, and finally discarding any results that indicated the ratio of ventilation to the two lung areas was changing. The advantage of the technique is that a thoracotomy involving surgery on airways and their neurovascular bundles is not required, and all hypoxic lung area is brought together so that measurements of gas exchange and perfusion can be made.

The ^{133}Xe technique used to measure perfusion requires perfect separation between two lung areas, could be influenced by changes in ventilation and does not give absolute, but only proportional, flow. The first two problems were dealt with by the checks on lung separation listed above. The third problem did not apply since, for this study, we only needed proportional flow.

Pure nitrogen ventilation of the hypoxic lung is different than hypoventilation. Oxygen will be removed from pulmonary arterial blood in the lung ventilated with nitrogen, resulting in a decrease in $P_{a_{O_2}}$. Oxygen removal is a factor common to both low and high P_{CO_2} phases of the experiment and therefore should not be a problem. Nitrogen ventilation lowers the alveolar carbon dioxide in the hypoxic lung as perfusion is reduced because of HPV. This is different than a low V/Q region where $P_{ET_{CO_2}}$ may be increased. These experiments began with $P_{ET_{CO_2}}$ from both lung areas not significantly different. Once nitrogen was introduced, $P_{ET_{CO_2}}$ from the hypoxic lung was reduced. Certainly this must influence the results, for measurement #7 in Table I indicates that alveolar P_{CO_2} is important in determining how much HPV is present when alveolar and arterial P_{CO_2} are changed in opposite directions. However, Figure 6 also indicates there are no significant differences between our results whether the P_{CO_2} is altered by ventilation or by changing inspired carbon dioxide levels. There are also no differences whether $P_{ET_{CO_2}}$ or $P_{a_{CO_2}}$ are plotted against HPV (Figure 6). This consistency in our findings (Figure 6) indicates that arterial and alveolar P_{CO_2} influence each other. However alveolar carbon dioxide exerts the main control over HPV (Table I).

We examined the possibility that the effects of P_{CO_2} on HPV are different before and after HPV is induced. A comparison of the slopes of Figures 2 and 3 is suggestive, but they are not significantly different.

Another factor which could influence HPV is pressure in the pulmonary vascular bed.[11,19] Pulmonary artery pressures were not significantly altered by any of the manoeuvres undertaken.

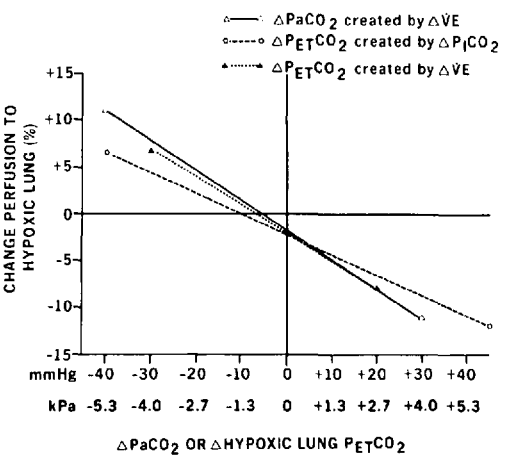

FIGURE 6 The changes in (Δ) $P_{a_{CO_2}}$ or hypoxic lung $P_{ET_{CO_2}}$ created by altering ventilation ($\Delta\dot{V}E$) or inspired carbon dioxide ($\Delta P_{I_{CO_2}}$) are plotted against the change in perfusion to the hypoxic lung. There are no significant differences between the regression lines.

Cardiac output was not significantly changed despite large swings in P_{CO_2}. This could be accounted for by the variability of response to changes in P_{CO_2} between dogs. Since neither pulmonary artery pressure nor cardiac output changed significantly with changing P_{CO_2}, alterations in HPV must have been created by P_{CO_2} itself.

We found a small but significant six per cent shift in perfusion to the lung area with increased inspired carbon dioxide when both lungs were oxygenated (measurement #2, Table I). Whether this resulted from vasoconstriction in the non-carbon dioxide lung, or vasodilation in the carbon dioxide lung is speculative.

HPV and Pa_{O_2} were always at their highest at the end of the day, sometimes at lower P_{CO_2} levels than seen previously (see Table I). This finding might be explained by a potentiation of HPV by repeated changes in P_{CO_2}. Pirlo and Benumof[20] have found HPV enhanced by repeated intermittent hypoxic challenges. The first hypoxic challenge only reduced hypoxic lung perfusion by 31.8 ± 5.9 per cent, while each successive hypoxic challenge increased the perfusion shift away from the hypoxic lung until a plateau perfusion shift of 59 per cent was reached at the fifth to eighth hypoxic challenges. Our findings and those of Pirlo and Benumof[20] might indicate that HPV is mediated through an inducible mechanism.

Factors other than HPV changes might have contributed to the change in Pa_{O_2}. For example, changes in Pa_{CO_2} may alter $\dot{Q}$, shift the oxyhaemoglobin curve, and alter R. These changes, together with HPV changes, may contribute to the alterations in Pa_{O_2}. Measurement #7 in Table I makes this unlikely. Pa_{CO_2} has fallen, but because hypoxic lung alveolar carbon dioxide is maintained by inspired carbon dioxide, HPV, and Pa_{O_2} are unchanged.

In order to maintain adequate oxygenation for dog survival it was necessary to ventilate the larger lung area with 100 per cent oxygen. This may influence the results. The effect of P_{CO_2} on the oxyhaemoglobin dissociation curve will not change oxygen saturation at very high P_{O_2} levels. At lower P_{O_2} levels, on a steeper portion of the oxyhaemoglobin dissociation curve, reducing P_{CO_2} may increase oxyhaemoglobin saturation from the oxygenated lung because of a leftward shift in the oxyhaemoglobin dissociation curve. This might partially compensate for the reduced HPV associated with the low P_{CO_2}. However, with an $F_{I_{O_2}}$ of 0.21 a well ventilated alveolus will have a P_{O_2} above 13.3 kPa (100 mm Hg) and haemoglobin would be almost fully saturated at P_{CO_2} levels of 2.66 kPa (20 mm Hg). Therefore at $F_{I_{O_2}}$ 0.21 in the non-hypoxic lung the magnitude of our Pa_{O_2} changes should not be reduced.

The alveolar gas equation states $P_{A_{O_2}}$ will decrease with a high $P_{A_{CO_2}}$. Our findings include this factor and indicate that in spite of the alveolar gas equation, HPV enhancement with a high Pa_{CO_2} increases Pa_{O_2}. Measurements 7 and 9 in Table I indicate how important HPV is. Pa_{CO_2} has increased from 4.7 kPa to 8 kPa (35 to 60 mm Hg) and should have reduced Pa_{O_2} by a similar amount, but HPV and Pa_{O_2} did not change significantly.

These findings together with the fact that there is no significant change in $\dot{Q}$, indicate that the changes in Pa_{O_2} in this experiment were the result of changes in HPV created by hypoxic lung $P_{ET_{CO_2}}$ alterations.

In patients undergoing anaesthesia, three factors (other than ancillary drugs) might influence HPV. These are: inhaled anaesthetics;[8-10,4-6] intravascular pulmonary pressures;[11,19] and carbon dioxide levels. Intravenous anaesthetics do not seem as important.[8-10] While we have no comparative data, a literature search suggests that P_{CO_2} may be the most important, over inhaled anaesthetic level and pulmonary vascular pressures, in influencing HPV. For example, Benumof and Wahrenbrock[11] decreased HPV in dogs by 30 per cent by lowering Pa_{CO_2} from 5.3 kPa to 2.7 kPa (40 to 20 mm Hg). At a Pa_{CO_2} of 5.3 kPa (40 mm Hg) the same decrease in HPV did not occur until left atrial pressures were elevated to 2.9 kPa (22 mm Hg). They also found that fluroxene would not achieve this reduction in HPV until levels greater than 2 MAC. Isoflurane reduced HPV by 30 per cent at 3 MAC while nitrous oxide could not achieve this reduction and halothane did not impede HPV.[8] Sykes *et al.* found similar data with nitrous oxide.[6] Sykes *et al.* found that one per cent trichlorethylene reduced HPV by 24 per cent,[4] and five per cent diethyl ether reduced HPV by 28 per cent.[5] Bjertnaes[9] found that halothane decreased HPV by 20 per cent while diethyl ether decreased HPV by 30 per cent. These papers and our results suggest it is P_{CO_2} that must be critically controlled if HPV is to be enhanced under anaesthesia or in an intensive care unit setting.

The importance of these findings to the anaesthetist is found in Figure 4. An increase of Pa_{CO_2} increased Pa_{O_2} in these dogs with HPV present. This finding correlates well with the increased

HPV or perfusion shifts away from hypoxic lung found at a high Pa_{CO_2} (Figures 2 and 3). We must emphasize that this does not mean that a higher Pa_{CO_2} will always increase Pa_{O_2}. Only when hypoxic pulmonary vasoconstriction exists and can respond to P_{CO_2}, will increasing Pa_{CO_2} increase Pa_{O_2}. This experiment in dogs has allowed us to dissect out an effect of P_{CO_2} on both HPV and Pa_{CO_2} in a way that the complex clinical situation does not permit. One must take care in applying these results to patients. For example, HPV may not exist in some patients, or may not respond to Pa_{CO_2} changes if $P_{ET_{CO_2}}$ in the hypoxic lung is not changing. P_{CO_2} also has many other effects than those on HPV, which may be more important in determining the optimum P_{CO_2} for a patient.

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20. PIRLO, A. & BENUMOF, J.L. Hypoxic pulmonary vasoconstriction and intermittent hypoxia. Anesthesiology suppl. *53*: 5380 (1980) Abstract.

RÉSUMÉ

Les zones pulmonaires dont le rapport V/Q est bas produisent de l'hypoxémie. La baisse de concentration de l'oxygène alvéolaire par contre entraine de la vasoconstriction hypoxique locale, ce qui a pour effet de diminuer la perfusion, améliorer le rapport V/Q et ainsi diminuer la tendance à l'hypoxémie. En modifiant la P_{CO_2}, on peut altérer la vasoconstriction hypoxique pulmonaire. Nous avons examiné cette relation sur des chiens anesthésiés en utilisant une cloison trachéale qui séparait un poumon rendu hypoxique par ventilation à l'azote, d'un poumon oxygéné avec 100 pour cent d'oxygène. La perfusion relative a été évaluée par la mesure du ^{133}Xe expiré par chaque poumon après injection intraveineuse.

Lorsqu'on a modifié la Pa_{CO_2} en changeant la ventilation, nous avons trouvé qu'une augmentation de la Pa_{CO_2} augmentait la vasoconstriction pulmonaire hypoxique et ainsi la Pa_{O_2}. A une Pa_{CO_2} de 3.3 kPa, la vasoconstriction hypoxique pulmonaire a été abolie et la Pa_{O_2} s'est abaissée. Nous avons modifié aussi la Pa_{CO_2} en changeant la PI_{CO_2} pour un ou les deux poumons alors que la ventilation demeurait constante pendant l'expérience: encore là, lorsque la Pa_{CO_2} a augmenté, la vasoconstriction hypoxique pulmonaire et la Pa_{O_2} ont aussi augmenté. Lorsque la Pa_{CO_2} s'est abaissée et que la mesure du CO_2 du poumon hypoxique en fin d'expiration (PET_{CO_2}) est demeuré élevée (en maintenant la PI_{CO_2} dans le poumon hypoxique et en retirant le CO_2 du poumon oxygéné) la vasoconstriction hypoxique a été maintenue. On peut en conclure que c'est la concentration alvéolaire de CO_2 dans le poumon hypoxique qui permet de modifier la vasoconstriction hypoxique.

Nous avons conclu que sur ce modèle une PET_{CO_2} basse (3.3 kPa) va diminuer la vasoconstriction pulmonaire hypoxique sur le poumon hypoxique et va ainsi augmenter la gravité de l'hypoxémie. Ceci peut avoir de l'importance chez le malade sous anesthésie et aux soins intensifs où une augmentation de la PET_{CO_2} du poumon hypoxique permettra d'obtenir une Pa_{O_2} plus élevée. L'influence de la PET_{CO_2} sur la Pa_{CO_2} peut être modifiée par d'autres facteurs variables mais quand il existe des zones hypoventilées ou hypoxiques, l'augmentation de la PET_{CO_2} peut augmenter la vasoconstriction hypoxique et par le fait même augmenter la Pa_{O_2}.