

Hypoxemia Following Pulmonary Embolism:

A Dog Model of Altering Regional Perfusion

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We studied the role played by a shift in perfusion to hypoxic lung areas after pulmonary embolism in post embolic hypoxemia. A tracheal divider was used to separate hypoxic (N₂ ventilated) from oxygenated (100 per cent O₂ ventilated) lung in anaesthetized dogs. Relative perfusion was assessed from total ¹³³Xenon (¹³³Xe) exhaled from each lung area after intravenous infusions. When one lung area was ventilated with N₂ and the other with O₂ at a normal Pa_{CO₂} to allow hypoxic pulmonary vasoconstriction (HPV), there was a significant ($P < 0.001$) shift away from the hypoxic side. Starch or blood clots were then infused to produce pulmonary emboli. Starch emboli were distributed predominantly to the oxygenated lung. After blood clot embolization in normocapnic dogs, pulmonary artery pressure increased 15 torr, perfusion to the hypoxic lung increased from 14 ± 2 to 23 ± 1 per cent, and Pa_{O₂} fell from 278 to 186 torr. When the degree of HPV was reduced in another group of dogs by hypocapnea, a similar increase in pulmonary artery pressure (14 torr) created by blood clot embolism did not shift perfusion or create hypoxemia. In all dogs the perfusion shift to hypoxic lung was sufficient to account for all the post embolic hypoxemia. In this dog model, post embolic hypoxemia is explained by preferential distribution of emboli to oxygenated lung followed by perfusion shift to hypoxic lung as the effect of HPV is overcome by pulmonary hypertension. (Key words: Complications: embolism. Embolism: pulmonary. Hypoxia. Lung: blood flow; hypoxic pulmonary vasoconstriction; shunting. Ventilation: shunting.)

HYPOXEMIA is frequently observed after pulmonary embolism. However, there is no general agreement on the physiologic mechanisms involved.

We propose a mechanism that may contribute to the hypoxemia after pulmonary embolism. In the presence of many lung diseases and probably even in normal lungs¹ there are areas that receive less ventilation than others. If alveolar hypoxia is present, the vessels perfusing these areas will be vasoconstricted owing to hypoxic pulmonary vasoconstriction (HPV).²⁻⁴ The distribution of emboli is proportional to perfusion. Therefore, emboli entering the pulmonary circulation will distribute predominantly to well ventilated and thus better perfused lung areas, occluding their vessels. The resulting

redistribution of blood flow exhausts the remaining vascular compliance, the pulmonary arterial pressure (P_{PA}) will rise, attenuate the effect of HPV⁵ and force blood through the vessels perfusing hypoventilated lung. This shunted blood will mix with blood perfusing normal lung, creating hypoxemia.

This hypothesis was tested in a dog model by ventilating one area of lung with nitrogen to create regional alveolar hypoxia. The remaining lung area was ventilated with oxygen. We measured perfusion to each lung area and the change in Pa_{O₂} before and after pulmonary emboli were infused. Since the hypothesis is dependent on the presence of HPV, we repeated the experiment when the degree of HPV was reduced by lowering Pa_{CO₂} through hyperventilation.

Materials and Methods

THE EXPERIMENTAL MODEL

The experiments were carried out on 17 mongrel dogs weighing 25-30 kg. Anesthesia was induced with pentobarbital, 30 mg/kg, intravenously (iv) and maintained with intermittent infusions of pentobarbital and pancuronium bromide (these agents have been shown not to affect HPV⁶). The dogs were intubated through a tracheostomy with a Carlen's double lumen endotracheal tube. The endobronchial end was wedged into a first-order bronchus and sealed by inflating the cuff. While the amount of lung ventilated by each lumen of the double-lumen tube was not critical, it was important that the lung separation be maintained throughout the experiment and remain constant. To assure this, the seal was checked for leaks by ventilating the animal through one lumen while the other was attached to a tube submerged under water, P_{I_{O₂}} was measured by testing gas aspirated from each bronchus during inspiration when nitrogen was in one lung area and oxygen in the other, and the ratio of ventilation to the two lung areas was monitored throughout the experiment. If this ratio changed, as it occasionally did owing to tube movement or cuff leakage, the results were discarded.

The pulmonary artery and a femoral artery were catheterized to monitor pressures continuously. All lines were kept patent by intermittent flushing with physiologic saline; no heparin was used. Arterial

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Received from the Department of Anaesthesia, University of Toronto, St. Michael's Hospital, 30 Bond Street, Toronto, Ontario M5B 1W8. Accepted for publication September 3, 1980. Supported by the York-Toronto Lung Association and the Medical Research Council of Canada.

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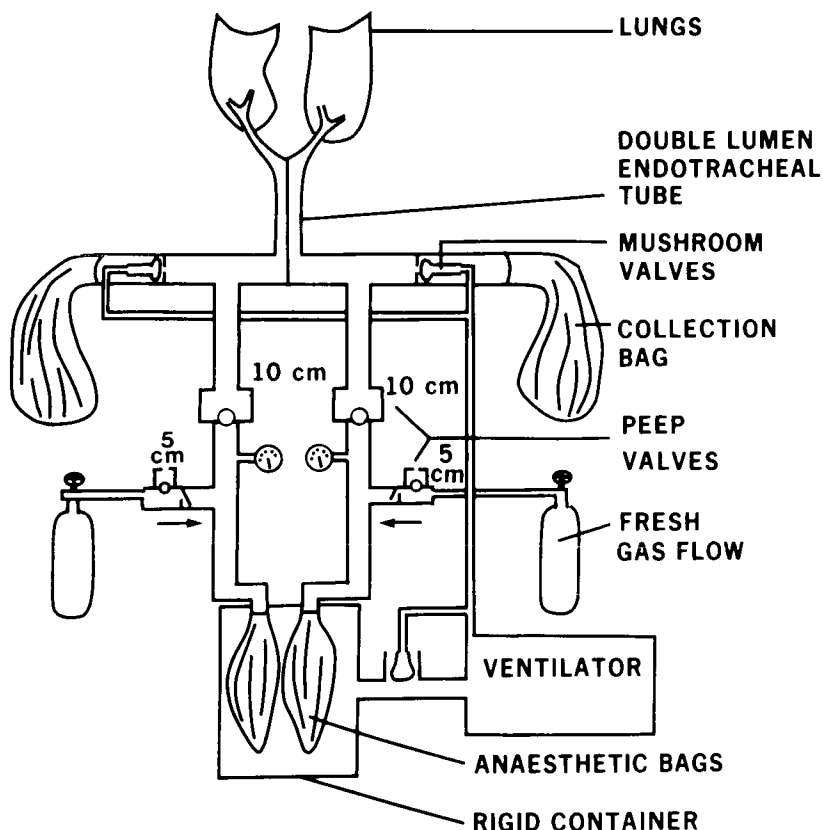


FIG. 1. Schematic representation of secondary ventilator circuit. The circuit allows synchronous isobaric but separate ventilation to both lungs. Note the circuit allows complete separation of inspired and expired gas to each lung. See text for explanation of mechanism.

and mixed venous blood samples were obtained for blood gas analysis, and cardiac output was determined by the thermodilution technique.⁷ An additional large-bore catheter was inserted into the left external jugular vein for injection of xenon dissolved in saline, and emboli.

VENTILATION

Each limb of the Carlen's tube was connected to a secondary ventilator circuit, modified from Sykes *et al.*,⁸ which allowed the lungs to be synchronously but independently ventilated to the same pressure with separate gases (fig. 1). During expiration a known gas fills two anesthetic bags within a rigid container. The 10-cm H₂O PEEP valve remains closed while the bags fill, assuring complete separation of inspired and expired gases. When the bags are full, the rise in pressure closes one-way valves, resulting in venting of the excess gases. During the inspiratory cycle, the volume-cycled ventilator (Ohio 560[®]) forces a volume of gas into the rigid container, opening the 10-cm H₂O PEEP valve and displacing the same volume from the bags into the lungs. The distribution of the 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.

MEASUREMENT OF PERFUSION

To measure the distribution of blood flow to each lung, we used a technique described by Arborelius.⁹

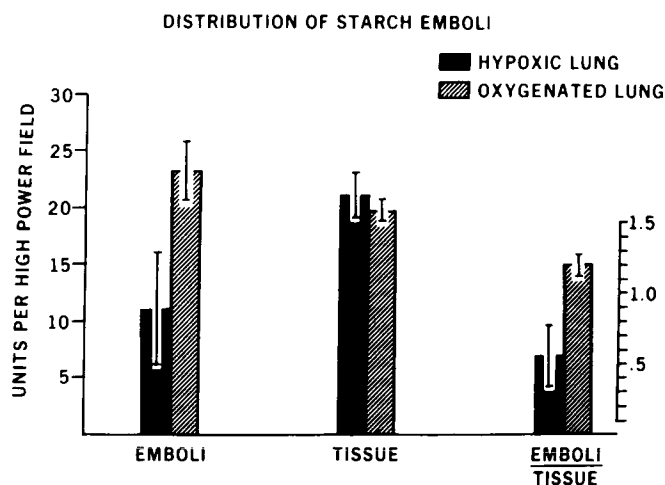


FIG. 2. Distribution of emboli to hypoxic and oxygenated lung (EMBOLI). Distribution of tissue counts between oxygenated and hypoxic lung (TISSUE). EMBOLI/TISSUE ratio in oxygenated and hypoxic lung.

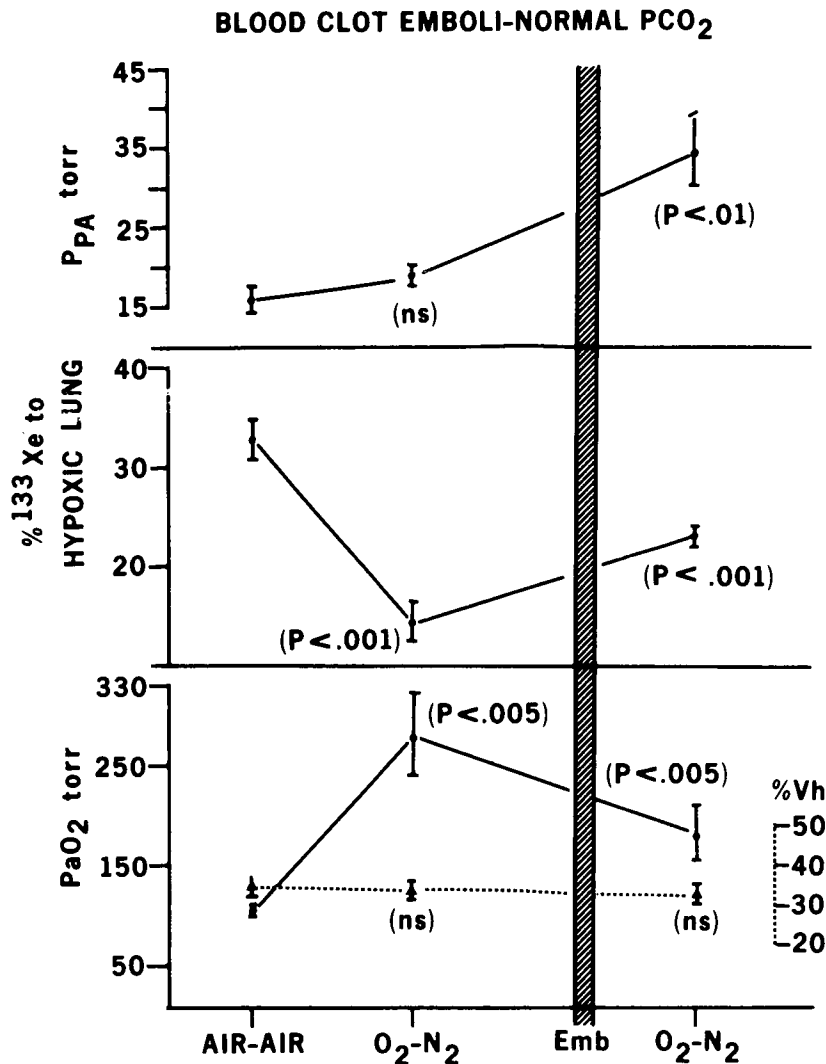


FIG. 3. Changes in P_{PA} , per cent perfusion to hypoxic lung, P_{aO_2} and per cent ventilation to hypoxic lung (per cent V_h , dashed line) in the three phases of the experiment: air both lungs (Air-Air); 100 per cent O_2 one lung, 100 per cent N_2 the other lung (O_2-N_2) and after blood clot embolism, in the normocapnic group of dogs.

^{133}Xe was dissolved in saline and 1 mc rapidly infused into the left jugular vein. Because of its low blood solubility, xenon diffuses into the alveolar gas and is washed out by ventilation. Immediately following the injection, expired gas from each lung was collected for 7 min, and the volume 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 of gas. Total xenon excreted by each lung was calculated as the volume of gas excreted multiplied by ^{133}Xe cpm/ml. The ^{133}Xe excreted by each lung area is proportional to its perfusion and the ^{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.

To study microemboli and blood clot emboli, dogs were divided into two main groups. One group re-

ceived starch microemboli; the other received blood clot emboli. The group receiving blood clot were further divided into normocapnic and hypocapnic groups. The hypocapnic group was created, through hyperventilation, in order to reduce the degree of HPV.¹⁰ The relative distribution of blood flow to each lung was measured. We simultaneously monitored cardiac output and pressures and blood gas values during ventilation of each lung with air (Air-Air). One lung was then ventilated with oxygen, the other with nitrogen (O_2-N_2) for at least 90 min to allow stabilization of HPV,¹⁰ and the measurements repeated. The dogs then received emboli within 5 min of this measurement. All measurements were again repeated within 5 min of embolization.

STARCH GROUP

Seven dogs were rapidly infused with a single bolus of starch particles ($63-74\mu$) in a dose of 0.1-0.15 g/kg

BLOOD CLOT EMBOLI-LOW PCO₂

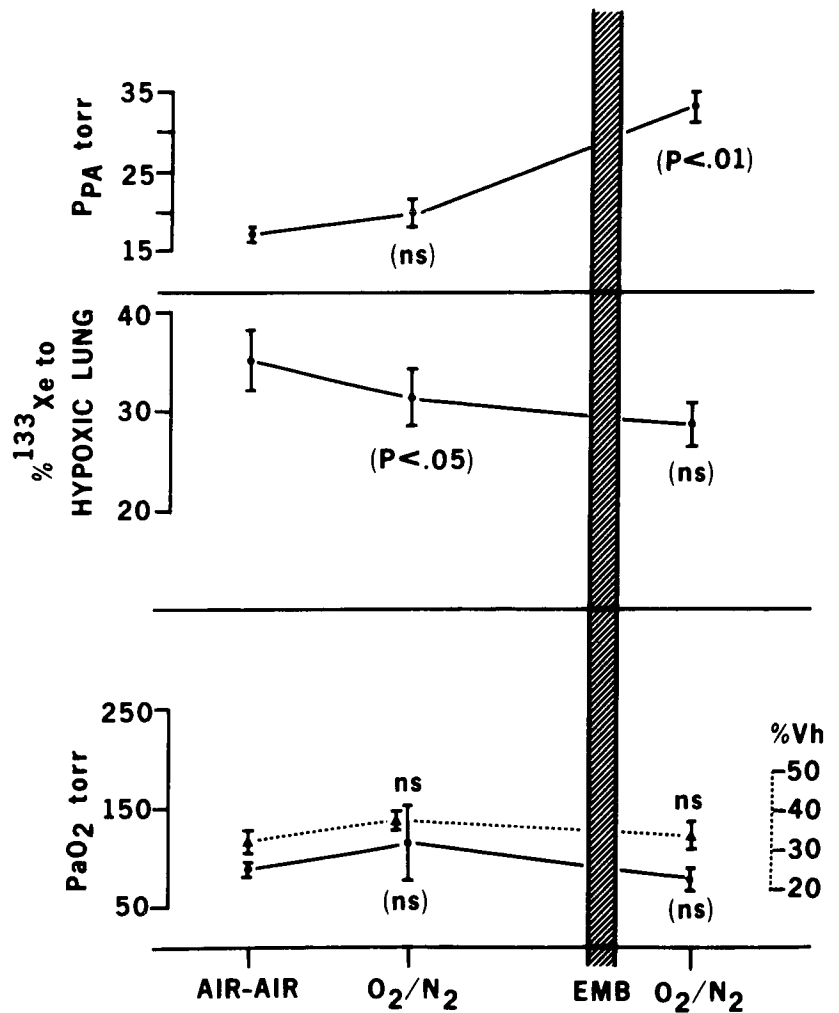


FIG. 4. Changes in P_{PA}, per cent perfusion to hypoxic lung, Pa_{o₂} and per cent V_h (dashed line) in the three phases of the experiment in the hypocapnic blood clot group of dogs.

through an external jugular vein. Measurements were repeated within 5 min after embolization, and the animal sacrificed. Biopsies were taken from hypoxic and oxygenated lung areas at the same level and fixed in formalin. Sections from the biopsies were stained with PAS (Periodic Acid Schiff) and examined microscopically (magnification × 100). Using techniques described by Weibel¹¹, the total number of emboli within the confines of a grid were counted. In order to relate the emboli to tissue density, the cross hair intersections lying over lung tissue were also counted. This allowed us to calculate a ratio of emboli count to lung tissue count for oxygenated and hypoxic lung tissue.

BLOOD CLOT GROUP

Autologous blood clots were prepared by allowing a 100-ml sample of the dog's blood to clot for 2 hours. Large clots were then forced through the nozzle of a

20-ml syringe, creating clots of approximately 5 × 2 mm in size. Five normocapnic dogs were rapidly infused with 0.8 ml/kg of these clots, through an external jugular vein, and five hyperventilated hypocapnic dogs received 1.14 ml/kg in order to achieve the same increase in P_{PA} in both groups. Measurements were repeated within 5 min of embolization, and the animal sacrificed.

Results are expressed as mean ± SEM. Differences were assessed using unpaired and paired Student's *t* tests. Regression equations and correlations were determined using the method of least squares. *P* < 0.05 was considered significant.¹²

Results

STARCH EMBOLI, NORMAL PaCO₂ (SEVEN DOGS)

The distribution of starch emboli differed in oxygenated and hypoxic lung areas (fig. 2). Twice as many

HYPOXIA FOLLOWING PULMONARY EMBOLISM:

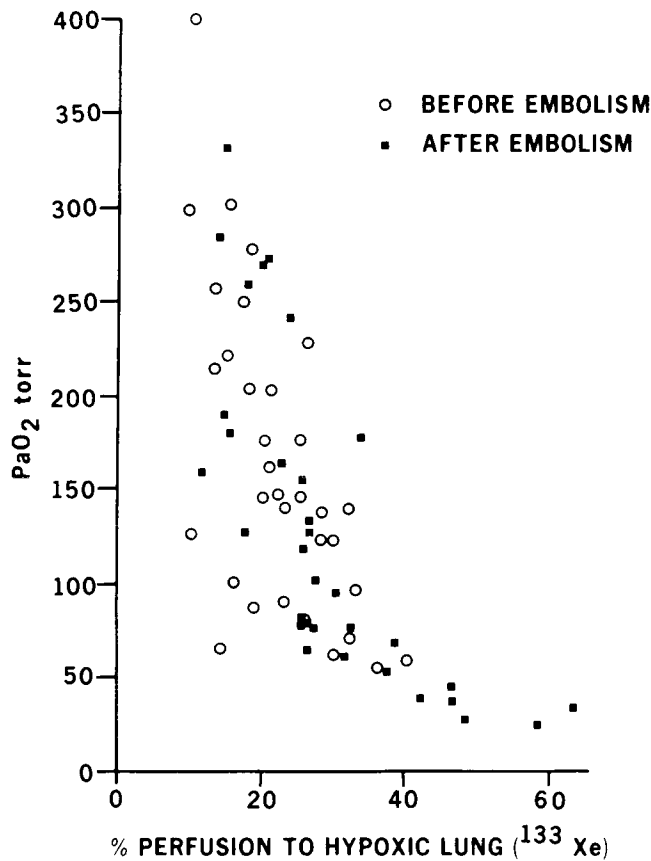


FIG. 5. Per cent perfusion to the hypoxic lung, as measured by the ^{133}Xe technique is plotted against PaO_2 both before and after emboli in all groups of dogs. Every ^{133}Xe measurement while on $\text{O}_2\text{-N}_2$ is included.

emboli/unit tissue went to well oxygenated as to hypoxic lung areas. There was no evidence of atelectasis in the hypoxic lung areas, as the tissue counts/field were the same as in the oxygenated lung. Since the physiologic changes were in the same direction in the dogs embolized with starch or blood clot at normal PaCO_2 levels, we shall present only physiologic data from dogs receiving blood clots.

BLOOD CLOT, NORMAL PaCO_2 (FIVE DOGS)

At normocapnic ventilation ($\text{PaCO}_2 42.6 \pm 1.2$ torr), the smaller lung was ventilated with nitrogen ($\text{P}_{\text{I}\text{O}_2} < 25$ torr) and the rest of the lung with oxygen ($\text{P}_{\text{I}\text{O}_2} > 650$ torr). This resulted in a drop in perfusion to the hypoxic lung from 32.8 ± 1.8 (Air-Air) to $14.4 \pm 2.2\%$ ($\text{N}_2\text{-O}_2$; $P < 0.001$) and a rise in PaO_2 from 85.4 ± 5.2 to 278 ± 40 torr ($P < 0.005$; fig. 3). There was no significant change of P_{PA} or in per cent ventilation to the hypoxic lung area (per cent V_h) at this point.

After embolization P_{PA} rose from 19.4 ± 0.9 to 34.4 ± 4.3 torr ($P < 0.01$); there was a shift in perfusion back to the hypoxic lung, 14.4 ± 2.2 to $23.0 \pm 1.4\%$ ($P < 0.001$), and a concomitant drop in PaO_2 from 278 ± 40 to 186 ± 34 torr ($P < 0.005$). There was no change in per cent V_h . The cardiac output did not change significantly after one lung area was made hypoxic or after pulmonary emboli were infused. P_{PA} tended to fall with time after embolization, so all measurements were made within 5 min.

BLOOD CLOT, LOW PaCO_2 (FIVE DOGS)

These dogs were hyperventilated to a mean PaCO_2 of 30.4 ± 1.0 torr. Then the smaller lung was made hypoxic ($\text{P}_{\text{I}\text{O}_2} < 25$ torr, and the rest of the lung was ventilated with 100 per cent O_2 ($\text{P}_{\text{I}\text{O}_2} > 650$ torr). There was a shift of perfusion away from the hypoxic lung, 34.6 ± 3.5 (Air-Air) to 31.4 ± 3.0 per cent ($\text{N}_2\text{-O}_2$; $P < 0.05$; fig. 4). PaO_2 , P_{PA} and per cent V_h remained unchanged. After embolization there was a rise in P_{PA} comparable to that in the normocapnic blood clot group. However, unlike the normocapnic dogs, there was no shift in perfusion or drop in PaO_2 . There was again no significant change in \dot{Q} (cardiac output) or per cent V_h after embolism.

Discussion

In our model both alveolar hypoxia and infusion of emboli caused shifts in lung perfusion.

We postulate that the mechanisms involved in the shifts in perfusion are as follows: HPV increases the vascular resistance in the hypoxic lung, decreasing its perfusion, hence protecting it from embolization (fig. 2). The emboli act as fixed obstructions, predominantly in the oxygenated lung. As the cardiac output stayed constant, blood was redirected through the hypoxic lung. The increase in P_{PA} attenuated the effect of HPV⁵ and increased the perfusion through the constricted pulmonary vascular bed.

Our experimental model allows us to measure both ventilation and perfusion to a lung area in an intact animal. Ventilation with pure nitrogen is different than hypoventilation. Hypoventilated lung areas have an elevated alveolar P_{CO_2} as well as hypoxia. Ventilation with N_2 washes out CO_2 from the hypoxic lung.¹⁰ The low alveolar P_{CO_2} decreases the vasoconstriction response to hypoxia.¹⁰ Therefore, our model underestimates the shift in perfusion created by hypoventilation and should influence distribution.

In our normocapnic dogs, induction of hypoxia decreased perfusion to that lung area to less than half (fig. 3). This order of magnitude correlates well with previously reported studies showing reduction of perfusion to hypoxic lung performed on isolated lungs

(54 per cent),¹⁰ open chest dogs (40–56 per cent,¹³ and humans.¹⁴

In essence, all the blood perfusing the hypoxic lung can be considered shunted blood. When we switched to O₂–N₂ the Pa_{O₂} rose because the larger lung area was ventilated with 100 per cent O₂. After embolization with either starch or blood clot in the normal Pa_{CO₂} groups, there was an increased perfusion of the hypoxic lung and a drop in Pa_{O₂}.

The question arises, to what extent does such a perfusion shift account for hypoxemia after embolism? We postulate that HPV plays a central role in the mechanism of hypoxemia. Abolishing HPV should equalize perfusion and, hence, embolic distribution between the hypoxic and oxygenated lung areas. Even with a rise in P_{PA}, there should be no shift in perfusion. If blood clot emboli produce shunting by any mechanism other than a shift in perfusion, hypoxemia should still result. Since attenuating HPV with drugs would likely affect various cardiopulmonary parameters, we abolished HPV by hyperventilation. Without HPV there was a larger blood flow to the hypoxic lung, and thus a lower Pa_{O₂} compared to the normal Pa_{CO₂} group (fig. 3 and 4). The lung vasculature was also more compliant and thus required a larger amount of clot (1.14 ml/kg *vs.* 0.8 ml/kg) to achieve an equal P_{PA} rise. Despite the larger dose of clot, and an equivalent rise in P_{PA}, there was only a 3 per cent shift in perfusion after embolism and no drop in Pa_{O₂}. If embolization causes a shunting of blood by any other mechanism than shifting perfusion, the Pa_{O₂} for any given per cent perfusion of hypoxic lung should be lower after embolization. In figure 5, we graphed the Pa_{O₂} *vs.* per cent perfusion of the hypoxic lung both pre- and post-embolization. In every dog the shift in perfusion corresponded to the change in Pa_{O₂} in an appropriate direction. The pre- and post-embolization points are indistinguishable. Therefore, in this experimental model the shift of perfusion after embolization is sufficient to account for all the hypoxemia.

We chose specific-sized emboli which are different than variable-sized clinical emboli. In defense of our model, two very different-sized emboli behaved in the same way. Although the differences between this dog model and clinical pulmonary emboli do not allow us to extrapolate directly to the clinical situation, this model allowed recognition of a mechanism of hypoxemia after pulmonary embolism, which the complex clinical situation does not.

In patients who have areas of hypoventilation, HPV, and a sufficient rise in P_{PA} to overcome the effect of HPV, our model would predict that blood flow should redistribute to hypoventilated lungs producing hypoxemia. In support of this, McIntyre and Sasahara¹⁵

noted that their patients showed an inverse relationship between post-embolic P_{PA} and Pa_{O₂}.

The results of this study indicate that in our model the hypoxemia that occurs after pulmonary embolism is predominantly due to the attenuation of the effect of HPV by the pulmonary hypertension which occurs after pulmonary embolization. There is evidence in the literature^{15–17} that this mechanism could also account, at least in part, for hypoxemia after pulmonary embolism in patients.

The authors thank G. Caskennette, E. Janssen and C. Mindorff for their valuable technical assistance, Dr. J. Obdrzalek for his valuable suggestions regarding the use of ¹³³Xenon to measure lung perfusion, and Dr. K. Kovacs for his help with the pathological studies.

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