PULMONARY EMBOLISM DISTRIBUTION TO VENTILATED AND UNVENTILATED LUNGS IN THE DOG: A CAUSE OF HYPOXAEMIA

YAHAYA Z. KADIRI, J. COLIN KAY, KALMAN KOVACS AND WILLIAM H. NOBLE

ABSTRACT

To examine a possible mechanism which could cause arterial hypoxaemia following pulmonary embolism, we collapsed and did not ventilate one lung in each of eleven dogs, to produce hypoxic pulmonary vasoconstriction. In five dogs (Starch Group), Pa_{O_2} fell from 10 to 7.7 kPa (76.2 to 58.4 torr) as shunt fraction (Q_s/Q_t) rose from 19 to 31 per cent. Mean pulmonary artery pressure (PFA), Pa_{CO_2} and V_D/V_T remained constant. Starch emboli (63–74 μ) were then injected. PFA increased significantly and Pa_{O_2} dropped further to 5 kPa (37.8 torr) as Q_s/Q_t rose to 57 per cent. V_D/V_T increased and Pa_{CO_2} remained constant. Microscopic examination of the lungs showed that three times as many emboli went to the ventilated lung compared to the unventilated lung. Six dogs (Blood Clot Group) received ^{51}Cr labelled autologous blood clot. Changes after emboli in PFA, Pa_{O_2} , Q_s/Q_t , Pa_{CO_2} and V_D/V_T were similar to the results in the Starch group. ^{125}I serum albumin was then injected and the dogs were sacrificed. The lungs were homogenized separately and the ^{51}Cr and ^{125}I counted. The ^{51}Cr counts indicated 66 per cent of the blood clot emboli went to the ventilated lung. Following embolization, the ^{125}I counts suggested a shift in perfusion to the unventilated lung. We conclude from these results that emboli are preferentially distributed to ventilated lung. After embolization PFA increases. At least in this pulmonary embolism model the increased PFA may overcome hypoxic pulmonary vasoconstriction, redistribute blood to non-ventilated lung and create arterial hypoxaemia.

VARIOUS HYPOTHESES have been advanced to explain the hypoxaemia that occurs following pulmonary embolism. These include bronchoconstriction,¹⁻³ opening of arterio-venous anastomoses in the embolised lung,⁴ impairment of diffusion^{5,6} pulmonary oedema⁷ and ventilation perfusion abnormalities.⁸⁻¹⁰ However, none of these hypotheses are universally accepted.

The hypothesis we propose is that areas of the lung with reduced ventilation, hypoxic pulmonary vasoconstriction and, therefore, reduced perfusion, should not receive emboli. The emboli should go to the well ventilated and perfused lung. The resulting pulmonary hypertension should shift blood flow to the poorly ventilated lung and, therefore, create hypoxaemia. To test this hypothesis we determined, first, the distribution of emboli in the lung when a portion of it

is not ventilated and, secondly, the distribution of pulmonary blood flow after pulmonary embolism. We found that emboli are preferentially distributed to the vasculature of well ventilated lung and that, following embolism, pulmonary hypertension occurs, redistributing pulmonary blood flow to unventilated lung and contributing to immediate arterial hypoxaemia.

MATERIALS AND METHODS

Eleven mongrel dogs weighing between 15–25 kg were anaesthetised with intravenous pentobarbitone (Nembutal®) 30 mg·kg⁻¹. Pentobarbitone was chosen because it does not reduce hypoxic pulmonary vasoconstriction.¹¹ A tracheostomy was done and the trachea was intubated with a double lumen Carlen's tube which was connected to a Lloyd low-resistance non-rebreathing valve. All studies were done with the animal supine and breathing room air spontaneously. Anaesthesia was maintained with intermittent doses of pentobarbitone 23–50 mg as required to achieve light anaesthesia. The femoral artery and vein, pulmonary artery and left atrium were catheterised without opening the chest, to monitor pressures continuously.¹² All lines were kept patent by intermittent flushing with physiological saline and no heparin was used.

Arterial and mixed venous blood samples were

Yahaya Z. Kadiri, M.D., F.R.C.P.(C), J. Colin Kay, A.I.M.L.T., William H. Noble, M.D., F.R.C.P.(C), Department of Anaesthesia, and Kalman Kovacs, M.D., Ph.D., F.R.C.P.(C), Department of Pathology, The University of Toronto and St. Michael's Hospital, Toronto, Ontario.

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Address for reprints: Dr. William H. Noble, M.D., F.R.C.P.(C), Department of Anaesthesia, St. Michael's Hospital, 30 Bond Street, Toronto, Ontario, M5B 1W8.

TABLE 1

	Number Emboli/Field	Lung Tissue Counts	Emboli/Tissue Ratio
Ventilated Lung	21.7 ± 0.8	18.4 ± 0.3	1.2 ± 0.04
Unventilated Lung	11.1 ± 0.5	27.8 ± 0.7	0.4 ± 0.02
P Value	<0.001	<0.001	<0.001

Mean ± 1 SEM (n = 5). P value indicates significance of difference between values for ventilated and unventilated lung.

measurements were repeated. One millicurie of ^{125}I tagged serum albumin (RISA) was then infused rapidly and the animal was sacrificed within five minutes. The hilum were clamped and the lungs were removed quickly, examined, weighed and homogenized separately. Weighed aliquots of homogenates from ventilated and unventilated lung were taken and counted for ^{51}Cr and ^{125}I radio-activity. Radioactive counts obtained were taken as indicative of blood clot distribution (^{51}Cr) to ventilated and unventilated lung.

Data were evaluated statistically using the Student's "t" test for paired data and independent groups. If $P < 0.05$ the changes were considered significant.¹⁸

RESULTS

Starch Group

Both gross and microscopic examinations confirmed that we were successful in creating an area of atelectasis in all dogs. Since there are more capillaries and lung tissue per microscopic field in the unventilated collapsed lung than in the ventilated lung, a false impression of distribution of emboli results (Figure 1a & 1b). To eliminate this, we calculated a ratio of emboli count to lung tissue count per field. Thus, the higher the ratio, the more starch micro-emboli in the specimen. Table I details our results.

Twice as many emboli went to the ventilated lung compared to the unventilated lung. There was more lung tissue per field in the unventilated collapsed lung (higher lung tissue counts, Table I). We corrected for the amount of lung tissue and therefore capillaries in the lung by calculating an emboli to lung tissue ratio. This showed three times as many emboli went to the ventilated lung compared to the unventilated lung (Table I). The differences are highly significant. These results suggest that emboli are preferentially distributed to the better perfused ventilated lung, presum-

FIGURE 2 Blood gas, Vd/Vt and Qs/Qt changes and control values at times of measurement in the Starch group of dogs. Mean ± SEM, n = 5. P values indicate significance of change from previous value. NS = not significant change from previous value. Control measurements were made over two hours to ensure a stable state. Values with unventilated lung represent stable state after bronchial occlusion. Measurements after embolisation within 10 minutes.

ably as a result of hypoxic pulmonary vasoconstriction in the unventilated lung.^{19,20}

Following establishment of an unventilated lung, arterial oxygen tension (PaO_2) dropped significantly from control value of 10.1 ± 0.3 kPa (76.2 ± 2.1 torr) to 7.8 ± 0.5 kPa (58.4 ± 3.6 torr) while Qs/Qt rose from 18.6 ± 3.3 to 31.2 ± 3.7 per cent (Figure 2). Arterial carbon dioxide tension (PaCO_2) and Vd/Vt did not change significantly. After embolization PaO_2 dropped further to 5.0 ± 0.4 kPa (37.8 ± 2.6 torr) within 10 minutes. Qs/Qt rose to $57.1 \pm 3.1\%$, Vd/Vt increased from 55.9

obtained for blood gas analysis; mixed expired gas was collected and analysed for oxygen and carbon dioxide concentrations. Cardiac output ($\dot{Q}$) was determined using the thermodilution principle.¹³ The shunt fraction (Q_s/Q_t),¹⁴ dead space to tidal volume ratio (V_D/V_T)¹⁵ and pulmonary vascular resistance (PVR)¹⁶ were calculated. At the end of each experiment the animal was sacrificed by injecting 40 mmol of KCl. The chest was opened, both hila were clamped quickly and the lungs were removed, examined, weighed and biopsied or homogenized.

There were two groups of dogs. One group received starch micro-emboli, to mimic small vessel obstruction. The other group received blood clot emboli, to obstruct larger vessels and to release chemical substances which may play a role in hypoxaemia after pulmonary embolism. Four control measurements of hemodynamic, blood gas and mixed expired gas values were made over two hours in both groups to determine if the preparation was stable. An unventilated portion of lung was created by extracting gas from the lung with a large syringe and clamping off the corresponding lumen of the Carlen's tube. In the starch group the left lung was clamped in four dogs and the right lung in one dog. In the blood clot group the left lung was clamped in five dogs and the right lung in one dog. The right lung was clamped in two dogs to demonstrate that embolic distribution was not the result of anatomical differences between right and left lungs. Measurements were repeated until a stable condition was reached. The dogs were then treated as follows.

Starch Group

Five dogs were rapidly infused with a single bolus of starch micro-emboli (63–74 μ size) in a dose of 0.1 g/kg through an external jugular venous line. This dose was chosen because it resulted in significant increases of pulmonary artery pressure and yet did not kill the dogs. Measurements were repeated within ten minutes and the animal was sacrificed. On removing the lungs, biopsies of ventilated and unventilated lung were taken at the same horizontal level and fixed in formalin. Serial sections were cut from the biopsies and twenty-five sections from each set stained by the Periodic-Acid-Schiff (PAS) technique. The slides were examined microscopically (magnification $\times 100$). Five random fields were selected and the number of starch particles within the confines of a grid (Leitz Wetzlar Microscopes, Germany) were counted for each field

Fig. 1a

Fig. 1b

FIGURE 1 (a) and (b) Biopsy sections from (a) ventilated and (b) unventilated lung following embolisation with starch particles (63–74 μ size). Stained by Periodic-Acid-Schiff technique. (Magnified 100X). X – starch particle, Y – cross-hair of grid overlying lung tissue. For details of counting, see text.

(Figures 1a & 1b). The cross-hairs of the grid lying over lung tissue were also counted and related to the emboli counted in that field. A ratio of emboli count to lung tissue count was calculated for each set.

Blood Clot Group

Six dogs were rapidly infused with autologous blood clots in which the red cells had been labelled with radio-active chromium (^{51}Cr). Blood was taken from the dog the day before the experiment, citrated, and equilibrated with ^{51}Cr . Calcium chloride was then added to create the blood clot. Before infusion the large clots were fragmented into finer ones (average size 5 mm $\times$ 2 mm). 10–20 ml of this clot (mean 13.7 ml) were rapidly infused to increase the mean pulmonary artery pressure (PPA) to about 5 kPa (40 torr). The haemodynamic, blood gas and expired gas

FIGURE 3 Haemodynamic changes and control values at times of measurement in the Starch Group of dogs. Mean $\pm$ 1 SEM $n = 5$. P values indicate significance of change from previous values. For time of observations see Figure 2.

± 3.0 per cent to 73.8 ± 3.9 per cent and P_{aCO_2} did not change. Thus, there was a marked rise in V_D/V_T and the animals hyperventilated to compensate for the rise and maintained their P_{aCO_2} .

$P\bar{P}A$ did not change when an unventilated lung was created (Figure 3) but, following embolism, a significant rise from 2.9 ± 0.1 kPa (21.5 ± 0.5 torr) to 4.2 ± 0.3 kPa (31.6 ± 1.9 torr) occurred. Changes in mean left atrial pressure (P_{LA}) and $\dot{Q}$ were not significant. However, PVR rose significantly from 397.3 ± 39.2 dynes·sec·cm⁻⁵ with an unventilated lung to 654.5 ± 101.1 dynes·sec·cm⁻⁵ after embolism. This data shows that the rapid fall in P_{aO_2} following embolism occurs simultaneously with increases in $P\bar{P}A$ and PVR.

Blood Clot Group

^{51}Cr distribution indicates that 66.2 ± 3.2 per cent of the ^{51}Cr tagged clot emboli went to the ventilated lung. The ventilated lung weighed 53.8 ± 1.9 per cent of total lung weight.

After blood clot was in the pulmonary vascu-

FIGURE 4 Blood gas, V_D/V_T and Q_s/Q_t changes and control values at times of measurement in the Blood Group of dogs. Mean $\pm$ 1 SEM, $n = 5$. P values indicate significance of change from previous value. For time of observations see Figure 2.

lature only 49.1 ± 4.1 per cent of the ^{125}I albumen labelled blood volume was in the ventilated lung.

While $P\bar{P}A$ rose immediately after blood clot emboli it was not as stable as in the starch group and tended to drift downward. The peak elevation in $P\bar{P}A$ was to 5.9 ± 0.4 kPa (44 ± 3 mm Hg) from 2.9 ± 0.3 kPa (22 ± 2 mm Hg) after the unventilated lung was established. Otherwise changes in blood gas, V_D/V_T and Q_s/Q_t (Figure 4) and haemodynamic variables were similar to those obtained in the starch group.

DISCUSSION

This study demonstrates that starch micro-emboli and small blood clot pulmonary emboli are preferentially distributed to the vasculature of ventilated lung.

Alveolar hypoxia is a well known cause of vasoconstriction of contiguous pulmonary vasculature.¹⁹⁻²¹ This is a normal protective reflex designed to "divert blood flow away from unventilated lung units"²⁰ so as to improve the matching of ventilation to perfusion ($\dot{V}/\dot{Q}$) in the lung.²¹ While on a weight basis we would have expected 53.8 per cent of blood clots to go to the ventilated lung, ^{51}Cr distribution indicates that 66.2 per cent went to ventilated lung. This should be compared to Hales, *et al.*,²⁰ who observed a reduction of

16.8 per cent of $\dot{Q}$ in flow to a lung rendered hypoxic by unilateral ventilation with nitrogen in the supine position. This suggests that emboli are distributed to the lung with the highest flow and is supported by Malik and van der Zee's²² observation that dependent lung zones (with better perfusion) receive most pulmonary emboli.

However, the hypoxic pulmonary vasoconstriction response to alveolar hypoxia can be blunted in the presence of an increase in $\overline{PFA}$.²³ Pulmonary hypertension results from pulmonary embolism.¹⁷ Our studies confirm that this occurs. The pulmonary hypertension will tend to overcome the hypoxic pulmonary vasoconstriction and re-open the vessels of the hypoxic lung since there is an inverse relationship between $\overline{PFA}$ and the hypoxic response of the pulmonary vasculature.²³ After blood clot emboli ¹²⁵I indicates 49.1 per cent of total lung blood is in the ventilated lung. This is not conclusive but is evidence suggesting that blood flow has shifted away from ventilated lung (before clot 66.2 per cent of flow; after clot 49.1 per cent of blood volume) and to the unventilated lung. Redistribution of blood flow may be due to the increase in $\overline{PFA}$ overcoming the hypoxic pulmonary vasoconstriction in the unventilated lung and could account for the rise in Q_s/Q_t and the drop in Pa_{O_2} observed after embolism in our experiments.

The rise in V_D/V_T could not have accounted for the hypoxaemia since the animals maintained their Pa_{CO_2} levels constant by hyperventilating. Pulmonary oedema has been mentioned as a cause of hypoxaemia in pulmonary embolism.⁷ Saldeen²⁴ suggested that pulmonary oedema, as a cause of hypoxaemia in micro-embolism syndrome, occurs late in the course. We agree with Malik and van der Zee²⁵ that pulmonary oedema can not account for the rapidity of the fall seen in Pa_{O_2} . In our dogs, arterial desaturation occurred within five minutes of embolization (starch or blood clots). Lung water accumulation sufficient to account for the magnitude of drop in Pa_{O_2} seen in our dogs would require a longer time to develop.²⁶ If pulmonary oedema occurs, we do not believe, like others,^{7,24,25} that it is cardiogenic in origin since after embolism our $\overline{PFA}$ values were maintained at control levels.

There can be no doubt that bronchoconstriction occurs after pulmonary embolism.¹⁻³ Various broncho-active substances such as serotonin from degraded platelets,²⁷ prostaglandins from various embolized material,^{24,28,29} and histamine³⁰ have been incriminated. Where does the bronchoconstriction occur? If it occurs in the

embolized lung, and there is evidence for this,³¹ it will improve $\dot{V}/\dot{Q}$ matching.²¹ However, if it occurs in the non-embolized lung, hypoxaemia will result. While this experiment does not exclude the possibility of broncho-constriction aggravating hypoxaemia after pulmonary embolism, or the effects of substances released in altering hypoxic pulmonary vasoconstriction, it demonstrates that hypoxaemia may be accounted for by emboli going preferentially to well-ventilated lung and perfusion then shifting to unventilated lung.

Our findings could be extrapolated to human pulmonary embolism. In disease, mismatch of ventilation and perfusion in different lung units may be marked.²¹ Patients with cardiorespiratory diseases²¹ have a wide scatter of $\dot{V}/\dot{Q}$ ratios. This could mean zero $\dot{V}/\dot{Q}$ (atelectatic), low $\dot{V}/\dot{Q}$ (shunt) or low $\dot{V}$ and $\dot{Q}$ areas in the lungs. Such patients (eg. post-operative, bedridden, congestive heart failure and obese) are most at risk of having pulmonary embolism.³² If emboli are preferentially distributed to ventilated lung units and following this, blood flow is redistributed to unventilated or poorly ventilated lung units, it would appear that elimination of poorly ventilated units (e.g. by application of continuous positive pressure ventilation) would be beneficial. The augmented blood flow to these areas after embolism would then be better matched by the increased ventilation leading to an improvement in Pa_{O_2} . Caldini⁹ first suggested the beneficial effects of CPPV in improving Pa_{O_2} after pulmonary embolism. Application of CPPV may also improve oxygenation if hypoxemia is due to bronchoconstriction.

The role of redistribution of pulmonary blood flow in creating hypoxaemia is further supported by examining the literature.^{9,10,33}

Verstappen,³³ using oxygen gas emboli found that shunt increased by only 1.5 per cent after emboli while breathing high inspired oxygen but increased by 19 per cent after oxygen gas embol while breathing room air. To account for the increased shunt while breathing air they suggested that low $\dot{V}/\dot{Q}$ areas had an increased perfusion after oxygen gas emboli. Dantzker,¹⁰ using blood clot pulmonary emboli concluded that $\dot{V}/\dot{Q}$ abnormalities could account for almost all of the arterial hypoxaemia after pulmonary emboli. Re-examining their Figure 3 is of interest. Lobar blood flow is plotted against time before and after embolization. The five lobes with the highest blood flow (> 30 per cent of $\dot{Q}$) also have the largest reduction in lobar blood flow at twenty

FIGURE 5 Two Compartment lung with blood flow and ventilation (litres/min) matched in the top panel. In the middle panel, flow to the smaller compartment is reduced by 90 per cent. In the bottom panel, flow to the larger compartment is reduced by 50 per cent. The changes in the $\dot{V}_A/\dot{Q}$ ratios, the P_{O_2} and the P_{CO_2} of each compartment are shown along with the resulting mixed arterial P_{O_2} and P_{CO_2} . In each case the P_{O_2} and P_{CO_2} of mixed venous blood are assumed to be (5.32 and 5.99 kPa (40 and 45 mm Hg), respectively (Reproduced by Dantzker, *et al.*, *Circ. Research* 42: 92-103, 1978. By kind permission of the authors and the American Heart Association, Inc.).

minutes after embolization to < 15 per cent of $\dot{Q}$. These articles support a hypothesis of blood flow redistribution to account for arterial hypoxaemia after pulmonary embolism.

Perfusion shifts after pulmonary embolization to increase $\dot{V}/\dot{Q}$ abnormalities and create hypoxaemia may also occur in normal lungs. In normal upright lungs, significant differences in perfusion, ventilation and $\dot{V}/\dot{Q}$ ratios exist between the apex and base.³⁴ Therefore areas of low $\dot{V}$ and $\dot{Q}$ exist ($\dot{V}/\dot{Q} = 1$). Our data would suggest well perfused areas would be embolized, shifting perfusion to low $\dot{V}$ and $\dot{Q}$ areas, increasing $\dot{Q}$ and lowering $\dot{V}/\dot{Q}$ to create hypoxaemia. Figure 5, taken from Dantzker,¹⁰ illustrates how this might occur in patients with normal $\dot{V}/\dot{Q}$ ratios. Although the middle and bottom panels of Figure 5 must co-exist, our evidence that 75 per cent of starch (Table I) and 66 per cent of blood clot emboli are preferentially distributed to the well ventilated lung indicates that the bottom panel of Figure 5 is a likely mechanism of hypoxaemia after pulmonary embolism. The remaining 25-33

per cent of emboli going to poorly ventilated lung will contribute minimally to arterial hypoxaemia (middle panel).

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RÉSUMÉ

Dans le but d'étudier un mécanisme possible de l'hypoxémie artérielle lors de l'embolie pulmonaire, nous avons collabé unilatéralement sans le ventiler un poulmon de façon à produire de la vasoconstriction pulmonaire hypoxique sur onze chiens. Pour cinq animaux (groupe amidon) la Pa_{O_2} est tombée de 10 à 7.7 kPa (72.2 à 58.4 torr) alors que le shunt (Q_s/Q_t) est passé de 19 à 31 pour cent. La pression moyenne de l'artère pulmonaire (PFA), la Pa_{CO_2} et le V_p/V_t sont demeurés constants. Des embolies d'amidon (63-74 μ) furent alors injectées. La PFA s'accrut de façon significative et la Pa_{O_2} chuta davantage à 5 kPa (37.8 torr) avec une augmentation du shunt à 57 pour cent. Le V_p/V_t s'éleva et la Pa_{CO_2} demeura constante. L'examen microscopique des poulmons a montré que trois fois plus d'embolies ont atteint le poulmon ventilé comparativement au poulmon collabé. Six chiens (groupe caillots sanguins) ont reçu des caillots de sang autologue marqués au ^{51}Cr . Les changements après embolisation ont été les mêmes que pour le groupe amidon en ce qui concerne la PFA, la Pa_{O_2} , le Q_s/Q_t , la Pa_{CO_2} et le V_p/V_t . De la sérum-albumine marquée (^{125}I) fut alors injectée et les chiens sacrifiés. On procéda par la suite à une homogénéisation séparée des poulmons avec comptage du ^{51}Cr et du ^{125}I . Le comptage du ^{125}I a montré que 66 pour cent des embolies par caillots se sont distribuées au poulmon ventilé. Après embolisation, le compte du ^{125}I laisse supposer un déplacement de la perfusion vers le poulmon non ventilé. A partir de ces données, nous concluons que les embolies se sont distribuées de façon préférentielle au poulmon ventilé. Après embolisation, la pression moyenne de l'artère pulmonaire a montré une augmentation qui pourrait, du moins sur notre modèle, forcer la vasoconstriction hypoxique, redistribuer le sang au poulmon non ventilé et ainsi causer de l'hypoxémie.