Time course and pattern of pulmonary flow distribution following unilateral airway occlusion in sheep

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1. Unilateral bronchial occlusion causes ipsilateral hypoxic pulmonary vasoconstriction, which shifts blood flow towards the other lung. We studied the time course of flow diversion following acute bronchial occlusion, and the temporal effect of the latter on blood gases and vertical distribution of blood flow within the two lungs.

2. Serial infusions of radioactive or fluorescent microspheres were given to each of seven adult standing sheep before, during occlusion of the left mainstem bronchus for up to 6 min, and after release of occlusion. Pulmonary and systemic arterial pressures were recorded continuously and arterial and mixed venous blood gases were determined intermittently. Post-mortem, the lungs were inflated, dried and cut into slices. Relative blood flow at the time of infusion was expressed as the weight-normalized intensity of each tracer in each slice or lung divided by the weight-normalized intensity in the two lungs.

3. Within 30 s, 1 min and 2 min after onset of occlusion, flow in the occluded lung had decreased to 68-84% (range), 51-78% and 43-79% respectively, of the initial value. In the contralateral lung, flow increased by 10-24%, 14-37% and 23-37% respectively. The distribution of flow along the gravitational axis within each lung varied widely between animals, both before and during occlusion. The during-occlusion profiles in the occluded lung differed from those in the non-occluded lung. In either lung, during-occlusion profiles could not be predicted with certainty from the pre-occlusion profiles. Two minutes post-occlusion, inter- and intra-lung flow distribution were nearly the same as before occlusion. Arterial oxygen tension fell in the first minute of occlusion, but never below 7.5 kPa, and increased slowly thereafter. Arterial carbon dioxide tension increased slightly throughout the occlusion period. No appreciable changes in systemic or pulmonary artery pressure were observed. Post-occlusion, arterial oxygen tension was still sub-normal, while carbon dioxide tension continued to increase.

4. We conclude that acute unilateral bronchial occlusion diverts blood flow within 30 s towards the contralateral lung. This rapidly occurring flow diversion prevents the development of severe arterial hypoxaemia. The variable and largely unpredictable distribution of blood flow in the hyperperfused non-occluded lung might explain some of the gas-exchange abnormalities observed in physiologically hyperfused lungs and in patients with one hyperperfused lung.

INTRODUCTION

Unilateral alveolar hypoxia increases ipsilateral vascular resistance [1]. This leads to a shift in pulmonary perfusion towards the other lung [2]. In several studies, bronchial occlusion has been used to induce alveolar hypoxia. One minute after occlusion of the right lung in dogs, flow in that lung had decreased by 19-59%, with only a moderate decrease in arterial oxygen tension [3]. In a study on single lung function in healthy subjects, in whom the occlusion lasted for several minutes, the arterial oxygen saturation rarely fell below 90% [4]. These observations suggest that the shift in pulmonary perfusion towards the other lung must occur very shortly after the onset of occlusion. The exact time course of flow diversion induced by unilateral bronchial occlusion is not known. In a recent study, flow diversion was present 80 s after occlusion of the left lower lobe [5]. Several studies have focused on the regional distribution of pulmonary flow in hypoxic lungs. In global hypoxia, the non-dependent zones received the larger part of redistributed blood [6]. In unilateral hypoxia, the diverted flow in supine subjects increased evenly in the cranial and caudal parts of the lung, while the reduction in flow in the hypoxic lung was more pronounced in the caudal parts [7]. In another study, diverted flow in supine subjects was preferentially distributed cranially [5]. Little is known about the distribution of perfusion along the gravitational axis in unilateral hypoxia. In

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Abbreviations: FRC, functional residual capacity; V/Q, ventilation-perfusion ratio.
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the present study, we occluded one mainstem bronchus in standing sheep with the purpose of examining: (a) the time course of flow diversion, (b) the temporal effect of such occlusion on blood gases and (c) the pattern of pulmonary blood flow redistribution along the gravitational axis in both the occluded and the non-occluded lung.

MATERIAL AND METHODS

Animals

Seven adult sheep, weighing 40–60 kg, were studied. The study protocol was approved by the local Animal Experimentation Committee.

Surgery

General anaesthesia was achieved with pentobarbitone (10–20 mg/kg in total), infused through a catheter in the left jugular vein. A Swan-Ganz 7 Fr catheter with a thermodilution port 30 cm from the tip was inserted into the other jugular vein and directed into the pulmonary artery. The position of the tip and the thermodilution port, from which mixed venous blood was to be drawn, was controlled by a pressure transducer coupled to a multichannel recorder (Gould 2300 S Recorder, Bilthoven, The Netherlands). The level of the right aurium was taken as the zero reference point for pulmonary artery pressure. Via a catheter in the carotid artery, arterial blood was drawn and systemic blood pressure recorded. The animal was then tracheotomized and an endotracheal tube (Ø 10 mm, Mallinckrodt Laboratories, Athlone, Ireland), lubricated with xilocaine gel, was inserted into the trachea. The distal end was positioned just above the orifice of the right upper lobe, which in the sheep originates approximately 5 cm above the carina. The cuff was inflated to secure the tube in that position. After completion of surgery, heparin 5000 units were given subcutaneously. The animal was allowed to wake up and remained standing in a barred wagon for the remaining experiment. Heparin, 2500 units, was given every 90 min thereafter. The skin area around the tracheostomy was sprayed regularly with xilocaine.

Airway occlusion

Under guidance of a fibreoptic bronchoscope (Olympus BF OC10, Tokyo, Japan) in the endotracheal tube, we instilled 1–2 ml of oxybuprocaine into the distal trachea and the same amount in the left mainstem bronchus. A Fogarty 8/10 Fr venous thrombectomy catheter (American Edwards Laboratories, Santa Ana, CA, U.S.A.), 80 cm long and with an inflatable balloon, was advanced into the left main bronchus. The balloon had a maximum diameter of 19 mm and a maximum capacity of 4 ml of fluid. We placed the balloon, covered with xilocain gel, as distal as possible in the mainstem bronchus and inflated it with saline until it occluded the airway completely. We checked the position of the balloon during several tidal breaths before deflating it, and repeated the inflation/deflation procedure if necessary to adjust the position of the balloon and the volume of instilled saline. The catheter with deflated balloon was then fixed to the endotracheal tube and the bronchoscope was removed.

Blood flow tracers

In sheep 1–5, we used up to six (109Cd, 57Co, 51Cr, 103Ru, 95Nb, 46Sc) radioactively labelled microspheres (Ø = 15.5 ± 0.1 µm, NEN, Boston, MA, U.S.A.). The microsphere suspension was prepared and infused at a constant rate [8]. In sheep 6–7, the microspheres were labelled with six different fluorochromes (blue, green, yellow-green, orange, red, crimson, Fluosphores®, Ø = 15 µm, Molecular Probes, Eugene, OR, U.S.A.). It has been shown that the number of trapped microspheres in a piece of lung correlates closely to the pulmonary flow through that piece [9], and that the recovery of infused fluorescent-labelled microspheres is similar to that of radioactively labelled ones [10].

Experimental procedure

The animals breathed room air throughout the experiments. The order of infused microsphere suspensions was randomized. In sheep 1, 2 and 3 (Group A), we infused five suspensions. Each infusion required 15 s. The first infusion was given 3–10 min before occlusion of the mainstem bronchus. The next three suspensions were infused 2, 4 and 6 min respectively after the onset of occlusion. Inflation of the balloon required less than 10 s. Time zero was defined as the time of complete occlusion. The balloon was deflated just after the fourth infusion. The final suspension was infused 5 min after the occlusion had been lifted. Arterial blood samples were drawn at the same five time points as the infusions and analysed within 15 s (Radiometer ABL30, Copenhagen, Denmark). In sheep 4–7 (group B), we infused six suspensions of microspheres, the first before occlusion and the next ones 15–30, 45–60, 75–90 and 105–120 s respectively after the onset of occlusion. The airway remained occluded for another 3 min. The final suspension was given 2 min after the occlusion had been lifted. In this group, paired samples of arterial and mixed venous blood were drawn every 30 s, the first pair within 15 s after the airway had been occluded. Each sample was drawn in approximately 10 s. Arterial and venous sampling was repeated every 30 s until the sixth suspension had been infused (16 paired samples in total). The samples were stored on ice and analysed after the end of each experiment. Sys-
temic and pulmonary artery pressure were recorded continuously throughout each experiment.

Sheep 2 coughed the balloon into the trachea after 3 min of occlusion, but the balloon was repositioned in the left mainstem bronchus and reinflated within 30 s. In sheep 3, only two of the planned three suspensions were infused during the occlusion. In sheep 6, only four of the planned six suspensions were infused: one before, the other ones during occlusion.

Processing of the lungs

At the end of each experiment, the animal was killed by exsanguination under light pentobarbitone anaesthesia. The lungs were excised, inflated with air to their approximate total lung capacity (pressure 30 cm H₂O) and were dried for up to 1 week until constant weight. They were cut in approximately 1 cm thick slices perpendicular to the gravitational axis at the time of microsphere infusion. Each slice was weighed and cut into small pieces which were placed in small plastic tubes. Tissue from bronchi larger than 3 mm in diameter was not included in the samples. The radioactivity was determined in a gamma counter (Cobra, Autogamma 5002, Packard, Chicago, IL, U.S.A.). Background activity was subtracted and thereafter the tracers were separated by matrix inversion and corrected for decay (Compusphere, Packard). The samples with fluorescent microspheres were soaked in known volumes of ethoxyethylacetate and shaken overnight to ensure complete extraction of the fluorochromes. The intensity of fluorescence was determined in a spectrophotometer (Perkin-Elmer LS50B, Beaconsfield, U.K.). Before separation by matrix inversion, all intensities were corrected for the small and constant contribution from ethoxyethylacetate itself.

Analysis

The flow in each slice (at the time of infusion of a given tracer) was first determined as activity/intensity per gram by taking the total count of the tracer in that slice divided by slice weight. It was then expressed as a fraction (relative flow) of the weight-normalized activity of both lungs. The latter was calculated as the total count of the tracer in both lungs divided by the summed weight of both lungs. The relative flow in the right and left lung was calculated in a similar way. A relative flow value of 1 signified that the weight-normalized flow through that slice or that lung was equal to the weight-normalized flow of both lungs.

The number of entrapped microspheres in a piece of tissue follows a Poisson distribution, as does the radioactivity emitted from them [11]. In each slice, except the small dorsal and ventral slices, the number of microspheres exceeded 400. The counting error of the radioactivity was negligible. This gives a standard error of measured flow in each lung of 5% or less, and a less than 1% error in a single lung.

RESULTS

Fig. 1 shows that occlusion led to a substantial flow reduction (in relative terms) in the ipsilateral lung within 2 min in group A (left panel), and that the reduction was clearly present already during the very first measurement (15–30 s) in group B animals (right panel). In group A, inter-lung distribution of

![Graph showing relative flow in sheep lungs before, during and after occlusion.](image-url)
flow was relatively stable during the remaining occlusion period and had returned to baseline conditions at the 5 min measuring point after deflation of the balloon. In group B, ipsilateral flow continued to decrease after the first 30 s of occlusion. At 2 min post-occlusion, flow had nearly returned to baseline values in these animals.

Fig. 2 shows the vertical (dorsal to sternal) perfusion profiles in the left and right lungs of all animals pre-occlusion, and when the occlusion had lasted 4 min in group A (left panels) and 1 min in group B (right panels). Before occlusion, there was a wide inter-animal variability in vertical perfusion profiles, but usually no variability between the left and right lungs. The profiles during occlusion did not show any consistent pattern. Between animals, they differed with respect to the pre-occlusion profiles and to the profile in the other lung. In some animals, flow in the non-occluded lung increased more in non-dependent than in dependent lung zones, in others the reverse was true. Flow in the occluded lung showed a similar variable pattern.

Fig. 2. Vertical profiles of relative flow in sheep lungs. Left panel: left lung (triangles) and right lung (squares) in group A sheep before (open symbols) and after 4 min occlusion of the left lung (closed symbols). Right panel: left and right lung in group B sheep before and after 45–60 s occlusion of the left lung. Symbols as in left panel. Relative flow = ratio of weight-normalized activity/intensity in each lung slice to weight-normalized activity in both lungs.
Fig. 3 shows all perfusion profiles for two animals (sheep 1 and 7). In each animal, the distribution of flow remained remarkably constant during occlusion. The perfusion profiles before occlusion and after the occlusion had been lifted were also quite similar. The experiments illustrated are representative for all animals. Fig. 4 shows that the lowest arterial oxygen tension was present at the first measuring point during occlusion in group A (2 min), whereas it was present at the second measuring point in group B (45–60 s). In three of four animals in group B, arterial carbon dioxide tension fell

![Sheep 1](image1)

![Sheep 7](image2)

**Fig. 3.** Vertical profiles of relative flow in left lung (left panel) and right lung (right panel) of sheep 1 and 7 before and after occlusion of left lung (open symbols) compared with profiles during occlusion (closed symbols)

![Sheep 1-3](image3)

![Sheep 4-7](image4)

**Fig. 4.** Arterial oxygen and carbon dioxide tension in sheep lungs. Left: arterial oxygen (closed symbols) and carbon dioxide tension (open symbols) in group A sheep before, during occlusion of the left lung for 6 min, and 5 min post-occlusion. Right: arterial oxygen and carbon dioxide tension in group B sheep before, during occlusion of the left lung for 5 min, and 2 min post-occlusion.
immediately when the airway was occluded, but increased slightly thereafter and also after balloon deflation. Mean mixed venous oxygen tension decreased by 0.3 kPa during occlusion. Occlusion led to a small but transient rise in mean pulmonary artery pressure (0–4 cm H2O). Systemic pressure varied between 125 and 90 mmHg (mean), but did not change due to occlusion.

**DISCUSSION**

There were two major findings in this study. First, acute unilateral bronchial occlusion led to a substantial decrease in ipsilateral perfusion already within half a minute, and consequently, a corresponding increase in the other lung. Secondly, the arterial oxygen tension reached its lowest value within the first minute of occlusion, after which it rose gradually. A third finding was that the vertical perfusion profiles varied considerably between animals, both without and during occlusion. During-occlusion profiles in a single lung showed little resemblance to the profile in the other lung. They usually also differed from the pre-occlusion profiles in the same lung. In the hypoperfused lung, there was no tendency for flow to increase more (or less) in the uppermost than in the dependent zones, nor was there a tendency for flow in the occluded lung to decrease more (or less) in either zone.

Hypoxic pulmonary vasoconstriction is an important regulating mechanism in maintaining adequate ventilation–perfusion relationships [12]. In isolated rat and rabbit lungs, pulmonary vascular pressure increased within 30 s after hypoxia had been induced [13–15]. In dogs, ipsilateral flow decreased to 41–81% of the baseline value within 1 min after onset of occlusion [3]. In humans, flow diversion has usually been measured at a single time point during the hypoxic period [7, 16]. The earliest observation point appears to be at 80 s [5], at which time flow was reduced to half its initial value. There are few published data on serial measurements of flow diversion. In open-chest cats, occlusion of the left lung led within 1 min to a more than 10% decrease in flow, with a nadir in flow after 5 min [17]. The latter observations, and ours, seem to confirm the findings in isolated lungs, in which pulmonary artery pressure responses to hypoxia were observed within 30 s [13]. In a recent study, 90% of the fall in alveolar oxygen tension had taken place within 30 s after onset of occlusion [5]. In our study, microspheres were infused 15–30 s after the airway had been occluded. The transit time from the jugular vein to the small pulmonary arteries is only a few seconds. Since relatively more of these microspheres were found in the right lung, the vasoconstrictor mechanism must have been activated very rapidly after the onset of occlusion.

The kinetics of the vasoconstrictor response has been reported to depend on the rate of change of alveolar PO2 [13]. The magnitude of the blood flow reduction in a hypoxic lung depends on the intensity of the hypoxic stimulus (alveolar oxygen tension), but is also inversely related to mixed venous oxygen tension and to the size of the hypoxic segment [18]. The left lung in this study composed 37–45% of the whole lung. If we assume that alveolar oxygen tension during occlusion equalled mixed venous oxygen tension (4.5 kPa), the flow in the left lung should, according to [18], decrease by 48–52% (SEM 8.4). In our study, the decrease at the end of occlusion varied from 34 to 56%, values that fit well within the predicted range.

The classical concept that regional distribution of perfusion is largely determined by gravity [19], in particular at high volumes [20], has recently been challenged in several reports [9, 21, 22]. The present study confirms that there exists a spectrum of perfusion profiles along the gravitational axis. Interestingly, the during-occlusion profiles in each single lung could not be predicted with certainty from its pre-occlusion profile, nor from the occlusion profile of the other lung (Fig. 2). However, several methodological factors may account for some of the observed variability. First, we were unable to control the volume at which the left lung was occluded, but the small range of possible occlusion volumes [functional residual capacity (FRC) to FRC + tidal volume] makes this factor unimportant. Secondly, microspheres infused into the bronchial artery of sheep led to a long-lasting dilatation of this vessel [23]. Even if the pulmonary artery should behave similarly (unpublished observations from our laboratory suggest that this is not the case), vasodilatation alone could not explain the differences between and within each lung. Moreover, the fact that consecutive during-occlusion profiles in one lung remained constant (Fig. 3) makes it unlikely that microsphere-induced vasodilatation took place. Thirdly, the animals had undergone major surgery and might have been under physical and emotional stress. Again, the consistency of the individual flow profiles, both without and during occlusion, and the stable within-animal arterial blood pressure speak against stress-induced changes during the measurement period. On the other hand, constant within-animal, but different between-animal stress, might have contributed to the inter-animal variability. Finally, the decrease in volume of the left lung due to absorption of oxygen during occlusion was probably too small to have influenced the temporal distribution of blood flow in that lung.

Since the arterial partial pressure of CO2 during occlusion remained nearly the same as before occlusion, the ventilation in the non-occluded hyperperfused lung must have increased during occlusion. The difference between pre- and during-occlusion perfusion profiles in that lung implies that significant ventilation/perfusion mismatch might exist if the increased ventilation was not accompanied by ventilation profiles that match the hyperperfusion pro-
files. The findings that: (a) exercise in healthy individuals increased ventilation–perfusion ratio (V/Q) mismatch [24], (b) that ipsilateral hyperperfusion, induced by clamping the contralateral pulmonary artery, did the same [25], and (c) that bronchial occlusion-induced increase in ventilation did not match the increased perfusion [26], suggest that regional distribution of hyperperfusion and hyperventilation may differ in the same lung.

At least two clinical conditions bear some resemblance to our experimental setup: pneumonecтомized patients and patients with a single transplanted lung. We have found no data from man on regional perfusion and ventilation after pneumonectomy. In pneumonecтомized dogs, significant ventilation–perfusion mismatch was found in the remaining lung, together with other functional disturbances after 2 months [27]. Patients with single lung transplants have reduced maximal oxygen uptake and lower arterial oxygen saturation than those with bilateral grafts [28]. Moreover, in four of nine patients 10–23 months post-transplantation, and in whom the single transplanted lung received three-quarters of the total perfusion, regional perfusion in the upper third of that lung was larger than in healthy controls [29]. The increased apical perfusion could not be predicted from the perfusion in the remaining native lung. The authors speculated that the wasted apical perfusion might be due to vascular disease, caused either by allograft preservation, reperfusion, rejection or medication. We think that their observations may be explained by our findings: unpredictable perfusion profiles, not necessarily matched by identical ventilation profiles, when blood is diverted from the native to the transplanted lung. Whether experimental or clinical unilateral hypoxia is followed by a second phase of hypoxic vasoconstriction, this time in the hyperperfused lung, with the purpose of ‘fine-tuning’ the augmented flow to the increased ventilation in that lung, remains unknown. The short occlusion period in the present study allows no conclusion in that respect.

According to the modified shunt equation [30], and assuming that the left lungs received 41% of the total pulmonary blood flow, arterial oxygen tension would have fallen below 6 kPa if no flow diversion had taken place. During the first minute of occlusion, the combined effect of resident-inspired oxygen in the occluded lung and the already occurring flow diversion at that time may explain why it fell to just below 8 kPa (Fig. 4). After 1 min of occlusion, no alveolar reservoir exists [26]. The gradual increase in oxygen tension in this study was presumably due to continuously increasing blood flow in the ventilating lung. Such rapid compensation mechanisms probably exist in humans as well, and could explain why oxygen saturation remained above 90% in nearly all healthy subjects in previous unilateral occlusion studies [4]. It is doubtful, however, whether this also would occur in patients with bronchial or parenchymal lung disease, who may have used some or all of their compensatory reserves. We cannot explain why arterial carbon dioxide tension also gradually increased to above baseline in the 5 min post-occlusion period. Although not specifically alluded to in their papers, the same phenomenon has been observed by others [17, 31]. Possible mechanisms include reversal of previous hyperventilation and the combined effect of venous admixture, previous anaesthesia and an occlusion-induced hypomobility of the other hemithorax [32].

Unilateral hypoxia induced by bronchial occlusion differs in at least three ways from the model in which both lungs are ventilated, but one of them with a hypoxic gas mixture. First, occlusion increases ipsilateral alveolar carbon dioxide tension, which potentiates hypoxic vasoconstriction [2, 33]. Secondly, and depending on the lung volume at which occlusion took place, mean airway pressure distal to the balloon may have been positive and hence facilitated diversion of flow towards the other lung [34]. Finally, the mainstem bronchus may receive a large portion of its blood supply from the pulmonary circulation [35]. Although ventilation with positive end-expiratory pressure did not influence this portion of the blood supply [36], the direct pressure of the balloon on the mucosa could increase the pulmonary vascular resistance on that side. The fast response observed by us may therefore not have relevance to other forms of unilateral hypoxia. This is in agreement with the fact that in the reports with the in vivo earliest diversion of flow, occlusion was used to induce hypoxia [3,6, 17].

In conclusion, we have demonstrated that unilateral occlusion results in a rapid diversion of flow to the other lung, thereby preventing severe arterial hypoxaemia within 1 min. However, the relative hyperperfusion in the ventilating lung was accompanied by flow profiles that often were quite different from those without occlusion. The dispersion of these hyperperfusion profiles, if not matched by ventilation, might explain some observed abnormalities of gas exchange in patients with hyperperfused lungs, including pneumonecтомized and single lung transplanted patients.

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