Changes in the Pulmonary Circulation after Bronchial Occlusion in Anesthetized Dogs and Cats

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ABSTRACT

The effects of bronchial occlusion on the pulmonary circulation were studied in anesthetized cats and dogs. Immediately after occlusion, blood flow fell rapidly at normal pulmonary arterial pressure (−71% cats, −54% dogs), and in constant flow perfusion experiments, perfusion pressure rose (+50% cats, +28% dogs). These resistance changes were reversed by vasodilator drugs, alkali, or perfusion of the lung with arterial blood. We concluded that an active mechanism, probably an increase in vasomotor tone, was involved; a mechanical process would not be reversed in this way. Pulmonary venous Po2 was the factor most closely related to the increase in resistance. In collapsing “oxygen-filled” lobes, compared with “air-filled” lobes the resistance change was delayed until the pulmonary venous Po2 fell. Hypoventilation and ventilation with hypoxic mixtures causing a fall in pulmonary venous Po2 similar to that due to collapse caused equivalent changes in blood flow. Changes in pH, Pco2 and lung volume played a relatively minor role in resistance changes following collapse. The increase in resistance may be caused by a mechanism regulating ventilation-perfusion ratios in both normal and diseased lung.

ADDITIONAL KEY WORDS

atelectasis hypoxia hypercapnia
pulmonary vascular resistance ventilation-perfusion ratios

There is disagreement on whether there is an increase or a decrease in blood flow through an acutely collapsed lung (1-12). An earlier study from this laboratory showed that, in cats, there is a rapid and profound decrease in blood flow immediately after bronchial occlusion (11). Since blood flow through the fully collapsed lung could be greatly increased by vasodilator drugs, we concluded that an increase in vasomotor tone rather than mechanical obstruction had taken place. This mechanism may be an important factor determining ventilation-perfusion ratios in both normal and diseased lung, so we have made further studies on the effects of bronchial occlusion in cats and dogs. The fall in oxygen tension was found to be the most important factor reducing blood flow through collapsed or poorly ventilated areas of lung.

Methods

Fifty-one cats (1.1 to 4.0 kg) and 45 dogs (6.6 to 21.1 kg) were used. Cats were anesthetized with ethyl chloride and ether followed by chloralose (60 mg/kg iv) or by chloralose alone (100 mg/kg ip) or in a few experiments by pentobarbital (30 mg/kg ip, with further intravenous doses as required); results were similar with the different anesthetics. Dogs were anesthetized with morphine (approximately 1 mg/kg subcutaneously) followed by pentobarbital (25 mg/kg iv). Heparin (1000 units/kg) was given on completion of the dissection.

PROCEDURES COMMON TO ALL EXPERIMENTS

Pressures were measured with electromanometers (Elema) and blood flow with a Wyatt (13)
cannulating electromagnetic flowmeter. An Ever-shed-Vignoles pen recorder with a level response from dc to 20 cps or an ultraviolet light recorder (SE Laboratories) was used. The resistance across the flowmeter head was negligible, and the maximum pressure drop across the cannulas used in cats was < 2 mm Hg (for a saline flow of 100 ml/min) and across those used in dogs was < 2.7 mm Hg (for a saline flow of 200 ml/min). Blood gas tensions and pH were measured with Radiometer (Astrup) electrodes at 37°C. Blood samples were kept on ice until analyzed. Mean systemic blood pressure was recorded from a cannula in either the carotid or femoral artery. In all experiments artificial respiration with 100% O2 was maintained with a Starling Ideal pump. Collapse of the lung was prevented by periodic hyperinflation, or, in a few experiments, by maintaining end-expiratory pressure at 3 to 5 mm Hg. When required, low O2 and high CO2 mixtures were administered from commercial cylinders. Drugs were infused with a Harvard pump.

**PREPARATION 1: MEASUREMENT OF PULMONARY VENOUS BLOOD FLOW**

*Cats.*—In 19 cats the chest was opened by splitting the sternum in the midline, and blood flow was measured in the left lower lobe pulmonary vein; in 15 of these experiments the condition of the lobe, the flow, and the venous pressure were considered satisfactory for the recording of results. The left lower lobe pulmonary vein was cannulated and connected to the left atrium by a loop of polyethylene tubing (approximately 40 to 45 cm long, bore 7.5 mm), which included the flowmeter. Pulmonary venous pressure was measured at the atrial end of the loop by a lateral connection (2.5 mm bore) to a manometer (occasionally with a wide bore needle). The pressure drop across the loop and cannulas was 1.5 mm Hg for a saline flow of 50 ml/min. Pulmonary arterial pressure (which was the natural pressure in this preparation) was measured through a retrograde cannula in a small upper left lobe artery or a small catheter inserted through the wall of the main pulmonary artery. Blood samples were withdrawn from the venous circuit as close to the lung as possible. In most experiments the left lower lobe was separately ventilated with a second small Starling Ideal pump, and in a few of these, intrabronchial pressure was recorded with a high sensitivity electromanometer. The lobe was collapsed either by clamping the ventilating tube from the small pump or by occluding the bronchus with a snare.

**Dogs.*—In 16 dogs a similar circuit was constructed after opening the chest through the 4th left intercostal space and dividing the mediastinal barer; in 12 of these, conditions were considered satisfactory for recording of results. Cannulation of the left lower lobe vein was difficult in dogs because of its short length and multiple radicals so that in seven of the experiments it was cannulated through the left atrium. The blood was returned into either the jugular vein or the right atrium (approached through a right intercostal opening). The pressure drop across the circuit was 3.2 mm Hg for a flow (saline) of 200 ml/min. The left lower lobe was not separately ventilated in dogs; the bronchus was intermittently occluded with a snare.

**PREPARATION 2: MEASUREMENT OF PULMONARY ARTERIAL BLOOD FLOW AND PERFUSION ALTERNATELY WITH VENOUS AND ARTERIAL BLOOD**

In five cats the chest was opened by splitting the sternum in the midline, and left pulmonary arterial flow and pressure were measured in a loop of polyethylene tubing connecting the main and the left pulmonary arteries (probably beyond the main pressure receptors); right pulmonary arterial flow was not affected. A side tube connected this loop to a carotid artery. At intervals, the venous blood supply to the left lung was occluded, the side tube was opened and the lobe was supplied with arterial blood; a gate clip kept the pressure at which the lobe received blood the same as it had been previously. The lungs were ventilated with a double tube. The right-hand tube remained in the trachea and the left-hand one, whose tip was surrounded by a cushion of foam rubber, was firmly wedged into the left bronchus; occlusion of the left tube led to collapse of the left lung while ventilation of the remaining lung continued through the right tube. Thus, in this preparation, the bronchial circulation remained intact.

**PREPARATION 3: PERFUSION OF THE LEFT LOWER LOBE WITH ARTERIAL OR VENOUS BLOOD AT A CONSTANT RATE OF FLOW**

*Cats.*—In 23 cats the chest was opened by splitting the sternum in the midline, and the left lower lobe pulmonary artery was perfused at a constant rate of flow with a Marlow roller pump, using blood drawn alternately from the right atrium (occasionally the inferior vena cava) or a carotid artery. A rate of flow was chosen which gave a pressure within the normal range for the pulmonary artery in an open-chest cat (14). Results were accepted in only those experiments (15) in which the lobe of lung was of normal appearance and the inflow pressure was normal for the rate of flow. Pulmonary arterial pressure and flow were recorded in the circuit, and left atrial pressure was recorded from a small cannula inserted into the atrial appendage. A clip in the circuit was used to reduce the oscillations produced by the pump. In some experiments the
left lower lobe was separately ventilated with a small Starling Ideal pump, and in these, collapse was caused by clamping the ventilating tube. In other experiments, the bronchus was occluded with a snare. Blood samples were taken from the circuit.

Dogs.—In 26 dogs the chest was opened on each side through an opening in the 4th intercostal space (occasionally through a transverse split in the sternum), and the left lower lobe was perfused with either arterial or venous blood from a Marlow pump, as in the cat experiments. Conditions were satisfactory in 20 experiments. Arterial blood was drawn from the right atrium; a heat exchanger at 38°C and an oscillation-damping chamber were included in the circuit. The left lower lobe bronchus was occluded with a snare. Sodium bicarbonate (2.5% or 5%) was occasionally perfused into a vein to correct low pH.

Pressure-Flow Diagrams: Four States of the Lobe.—In this preparation, when the lobe was perfused at a constant rate of flow, increases in perfusion pressure in the circuit (left atrial pressure unaltered) indicated an increase in pulmonary vascular resistance. Regulation of the pump allowed flow to be varied over a wide range and pressure-flow diagrams to be plotted. The lobe was studied in four states: (1) ventilated, perfused with arterial blood (called ventilated-arterial); (2) ventilated, perfused with venous blood (ventilated-venous); (3) collapsed, perfused with venous blood (collapsed-venous); (4) collapsed, perfused with arterial blood (collapsed-arterial). Collapse of the lung could be achieved only with venous blood because the lung gases were not absorbed during perfusion with arterial blood.

STATISTICS
Regression coefficients of the pressure drop across the lung vs. blood flow were calculated by the method of least squares. Standard errors are given after mean values.

DRUGS
The following drugs were used: acetylcholine perchlorate (British Drug Houses), theophylline ethylene diamine (TED aminophylline, Martin-dale Samoore), phen tolamine (Regitine, CIBA), bretylium (Darenthin, Wellcome Research Laboratory).

MEASUREMENT OF PULMONARY VASCULAR RESISTANCE
Pulmonary vascular pressures were referred to the anteroposterial midpoint of the left atrium and were measured at end-expiration. At this time hydrostatic forces, which have important effects on pulmonary pressure and flow (16), were minimal, since the vertical height of the test lobe was only 4 to 5 cm in dogs and less in cats. The pulmonary arterial pressure (whether natural or controlled) was higher than the top of the lung at end-expiration. The left atrial pressure was not controlled (mean value in 25 experiments 3.0 ± 0.4 mm Hg) but was greater than alveolar pressure throughout the lung in almost all experiments. Thus flow was assumed, initially, to take place under non-waterfall conditions and to depend on the difference between pulmonary arterial and left atrial pressure (17, 18). For this reason and to permit comparison between different animals (with different left atrial pressures), we used the difference between pulmonary arterial pressure and left atrial pressure in our pressure-flow diagrams and in calculating regression coefficients. However, during certain procedures (see below) an increase in vascular tone might have caused flow to take place under waterfall conditions (15) and to be independent of left atrial pressure; this situation was suggested by parallel shifts in the pressure-flow diagrams (see below). Conditions were such as to minimize changes in left atrial pressure which, in the non-waterfall state, may alter pulmonary vascular resistance (19). Such changes as took place are given in the figure legends.

Pulmonary vascular resistance was defined in two ways: (1) $R_1$ is the ratio of the difference between pulmonary arterial pressure and left atrial pressure to volume of blood flow. This ratio was measured and compared only at equal rates of blood flow in any one animal. (2) $R_2$ is the slope of the relation between flow and the difference of pulmonary arterial and left atrial pressures.
In the range of measurements made in this work there appeared to be a linear relation between pulmonary arterial-left atrial pressure difference and blood flow so that $R_2$ was a constant. The difference between $R_1$ and $R_2$ is illustrated in Figure 1. A point on the line AB has a different $R_1$ from a point (at equal flow) on CD but $R_2$ is the same in both cases. ED has a different $R_2$ from AB and CD. Changes in the diameter of resistance vessels will alter both $R_1$ and $R_2$. Changes in either the surrounding pressure or the tone of collapsible vessels may alter $R_1$ alone, causing parallel shifts in the pressure/flow diagrams (15, 17, 20).

**FIGURE 2**

Records of pulmonary venous blood flow after bronchial occlusion. A: Dog, 8.9 kg, ventilated with 100% O$_2$ (morphine and pentobarbital). Traces of pulmonary venous blood flow and pulmonary arterial pressure (PAP). The bronchus was occluded at the vertical arrow; note two-phase fall in blood flow (horizontal arrows). B: Dog, 13.4 kg, ventilated with 100% O$_2$ (morphine and pentobarbital). Traces of femoral arterial pressure (FP) pulmonary venous blood flow, PAP and left atrial pressure (LAP). Bronchus occluded at arrow at a lower lung volume than in A. C: Same dog as B, ventilated with air. Bronchus occluded at large arrow.

Pulmonary venous blood samples taken at small arrows:

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Tracings B and C darkened for photography. Vertical lines = 10 seconds.
Results

PREPARATION I
Changes in Pulmonary Venous Blood Flow during Collapse of a Lung

Occlusion of the left lower lobe bronchus was followed by a rapid fall in pulmonary venous blood flow from this lobe in 15 cats and 12 dogs (Figs. 2 and 3). This effect could be obtained repeatedly. Changes in flow were small or absent in an additional four cats and four dogs, but in all these there was either some technical failure or evidence of pulmonary edema. The timing of the decrease in venous blood flow depended on whether the lobe was full of air or oxygen at the moment of bronchial occlusion.

Lobe Ventilated with Oxygen before Occlusion.—Bronchial occlusion at end-inspiration in O₂-filled lobes was followed by two phases

![Figure 3](attachment:image.png)

**FIGURE 3**
Pulmonary venous blood flow after bronchial occlusion in O₂- and air-filled lobes of a dog, 8.9 kg (morphine and pentobarbital). Tracings show pulmonary venous blood flow and pulmonary arterial pressure. Pulmonary venous pressure in the circuit was constant in A but fell by 3 mm Hg in B and C. Horizontal bar = 1 minute. Small artifacts in flow trace when samples are taken. Blood samples at small arrows, gas tensions in mm Hg. A: Ventilated with 100% O₂. Bronchus occluded at end-inspiration at thick arrow. Blood flow falls in two phases (second begins just before fourth sample). B: Ventilated with 100% O₂. Bronchus occluded at end-expiration at thick arrow. C: Ventilated with air. Bronchus occluded at first thick arrow; lung volume still high at second thick arrow. Bronchus released and flow rises rapidly to right of record.

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of change (Figs. 2A and 3A). In the first phase, lung volume and intrabronchial pressure fell rapidly as $O_2$ was absorbed. Pulmonary venous pH fell and $P_{CO_2}$ rose but $P_{O_2}$ remained high. In most animals there was a simultaneous small fall in blood flow (to 83 ± 3.5% of control values); in the rest (20%) it remained constant. The second phase began when, at low lung volume, solid patches appeared on the lung surface and rapidly coalesced until the lung resembled liver. At this time the $P_{O_2}$ of venous blood from the lobe began to fall, and blood flow declined rapidly to a low level; pH began to rise again and $P_{CO_2}$ to fall. The mean blood flow at the lowest level was 29.1 ± 5.3% of control values in cats and 46.0 ± 5.6% in dogs. No tests were continued for more than 15 minutes. Pulmonary arterial pressure rose slightly after bronchial occlusion in many but not all experiments, and the rise was sometimes delayed until the second phase. Pulmonary venous pressure sometimes declined but never increased. Thus the fall in blood flow could not be attributed to changes in either pressure.

When the bronchus of an $O_2$-filled lobe was occluded in expiration, the first phase was shortened or absent. The main fall in blood flow again took place when the venous blood from the lobe became deoxygenated. There was also a reversal in the trend of pH and $P_{CO_2}$ values in venous blood in later samples (legends, Figs. 2B and 3B).

In 10 consecutive experiments (six cats and four dogs) the ($H^+$) in venous blood from the test lobe was $10^{-9} \times 45.9 \pm 0.29$ in the control period; it rose to $10^{-9} \times 70.3 \pm 0.35$ in phase 1 and fell to $10^{-4} \times 37.8 \pm 0.44$ in phase 2 (the values for the two phases were significantly different at 5%). $P_{CO_2}$ was 27.1 ± 2.3 mm Hg in the control period; it rose to 48.9 ± 3.5 in phase 1 and fell to 41.1 ± 3.1 in phase 2 (difference not significant). $P_{O_2}$ in the control period was 453 ± 23.9 mm Hg and in phase 1 was 400.5 ± 24.1 (difference not significant); it fell to 41.6 ± 2.3 in phase 2. Thus the smaller decline in blood flow in phase 1 was associated with large changes in pH and $P_{CO_2}$ but no change in $P_{O_2}$. The second larger decline in flow in phase 2 accompanied a large fall in $P_{O_2}$; at this time pH and $P_{CO_2}$ were returning toward normal.

**Lobe Ventilated with Air before Bronchial Occlusion.**—When the lobe was ventilated with air prior to bronchial occlusion (in the dog, since the lobe was not separately ventilated, the rest of the lung was also ventilated with air), two phases in the decline of blood flow were not seen (Figs. 2C and 3C). There was an immediate fall in pH and $P_{O_2}$ and rise in $P_{CO_2}$ in blood from the test lobe; simultaneously, blood flow decreased rapidly. The decrease in flow was well advanced before the intrabronchial pressure had fallen to zero. Lung volume declined slightly, but at the lowest level of blood flow a substantial amount of gas (presumably mainly $N_2$ and $CO_2$) was still present in the lobe. The mean blood flow at the lowest level was $27.0 \pm 8.8\%$ of control values in eight cats and $52.3 \pm 4.5\%$ in four dogs. In dogs, but not in cats, the decline in flow was less when the lobe was full of air than when it was full of $O_2$ (Fig. 2B and C). Changes in pulmonary arterial and venous pressures were similar to those observed in the $O_2$-filled lobes. A reversal in the trend of pH and $P_{CO_2}$ values was again seen in samples taken some minutes after occlusion (legend, Fig. 2C). When the bronchus of an air-filled lobe was occluded in expiration the changes which followed were more rapid but otherwise similar to those which followed occlusion in inspiration.

**Comparison of the Effects of Bronchial Occlusion in $O_2$- and Air-Filled Lobes.**—In both $O_2$- and air-filled lobes the main decline in blood flow after bronchial occlusion was not related either to lung volume or to intrabronchial pressure. In the air-filled lobe, blood flow declined while intrabronchial pressure was still positive and the lobe still contained much gas; in the $O_2$-filled lobe it declined when the lobe was at a very low volume and the intrabronchial pressure was zero (Fig. 4A).

The major fall in blood flow after bronchial occlusion always coincided with a fall in pulmonary venous $P_{O_2}$. In the air-filled lobes this began to fall immediately after occlusion.
A: Pulmonary venous blood flow and intrabronchial pressure during pulmonary collapse in a cat, 3.0 kg (chloralose). Blood flow expressed as percent of control value before each test. Intrabronchial pressure falls to zero after bronchial occlusion but is unrelated to the fall in blood flow as the curves are different for the oxygen- (●) and air- (▲) filled lobes. B: Relation between pulmonary blood flow and pulmonary venous $\text{PO}_2$ during pulmonary collapse, in a cat, 3.0 kg, ventilated with low $\text{O}_2$ mixtures and hypoventilation.

Pulmonary venous blood flow is related to pulmonary venous $\text{PO}_2$, whether the latter is reduced by collapse of the $\text{O}_2$-filled (●) or air-filled (▲) lobe, ventilation of the lobe with 10% or 12% $\text{O}_2$ (○), hypoventilation of the lobe by reducing the pump stroke (■), or ventilating the lobe with 10% $\text{CO}_2$ in $\text{N}_2$ (●). No change in pulmonary venous pressure. Initial flow 43 ml/min. Range of PAP values (mm Hg): ● 21.4 to 22.7; ▲ 18.6 to 20.7; ○ 20.0 to 22.4; □ 21.0 to 22.4; ● 22.0.

(Fig. 3C) but in the $\text{O}_2$-filled lobes the fall was often delayed for several minutes until the reservoir of $\text{O}_2$ in the lungs had been absorbed (Fig. 3A). In Figure 5 we have plotted the relation between pulmonary venous $\text{PO}_2$ and blood flow as a percent of control values before each test, in both $\text{O}_2$- and air-filled lobes, for three dog and five cat experiments. In both species there is a relation between blood flow and $\text{PO}_2$ when the latter falls below normal arterial values. In cats there was no major change in flow until the
Po$_2$ fell below 100 mm Hg (small reductions above this level were in phase 1 in O$_2$-filled lobes); below this level blood flow fell steeply and the relation was highly significant ($P < 0.001$). There was no consistent difference between points obtained from air- and O$_2$-filled lobes. In the three dogs blood flow began to decline at a rather lower Po$_2$ than in cats and in the air-filled lobes was greater at any given Po$_2$ than in the O$_2$-filled lobes; this may have been solely due to the fact that, in dogs ventilated with air, the Po$_2$ was already low and may have affected the control flow.

Comparison of the Effects of Bronchial Occlusion with Those of Hypoventilation and Ventilating with High CO$_2$ and Low O$_2$ Mixtures

The left lower lobe was separately ventilated with different gas mixtures and the effects were compared with those of collapsing the lobe. In five of seven cats ventilation of the lobe with 10% or 12% O$_2$ in N$_2$ caused a similar fall in venous blood flow to that...
observed in the collapsing lobe when the venous Po2 had reached a similar level. In the other two cats the reduction in blood flow was less than during collapse. Ventilation of the lobe with 6.5% CO2 + 6% O2 in N2 caused a reduction in blood flow comparable to that caused by collapse in both of two cats. On the other hand ventilation of the lobe with 10% CO2 in N2 caused a lesser reduction in flow than collapse in six cats. Hypoventilation of the lobe caused by reducing the pump stroke progressively until pulmonary venous blood became desaturated also led to a fall in blood flow comparable to that following collapse (five cats). Figure 4B shows an experiment in which several of these tests were made. There is a very clear relation between blood flow and pulmonary venous Po2 (below 100 mm Hg) when the latter is reduced by various means. Pulmonary arterial pressure varied slightly between tests in these experiments (the range is given in the legend to Fig. 4). An attempt was made to allow for this by expressing blood flow as a percent of control values; in no test was there a fall in pulmonary arterial pressure which could have caused the decline in flow.

PREPARATION 2

Changes in Pulmonary Arterial Blood Flow during Collapse of a Lung and the Effect of Perfusing a Collapsed Lung with Arterial Blood

In all of five cats bronchial occlusion (internal) led to a rapid fall in blood flow; a typical example is shown in Figure 6. In three of the cats two phases of decline in flow were detected, the second coinciding with the appearance of solid patches on the lung. Mean blood flow was 22.4 ± 8.2 ml/min of control values at the lowest level. Changes in pulmonary arterial pressure were small (maximum change was a rise of 3 mm Hg), and those in left atrial pressure were negligible. In four of the cats the left lung was supplied intermittently with arterial blood at the same pressure as its normal venous blood supply. This caused no change in the left lung before occlusion, but in the collapsed lung it caused a rise in blood flow to normal or nearly normal
Collapse of a lung perfused at constant flow. The effects of perfusing with arterial blood and of NaHCO₃; cat, 2.0 kg (pentobarbital). Blood flow constant throughout (36 ml/min), left atrial pressure constant. **Top:** bronchial occlusion and changing perfusate from venous to arterial blood (brief intervals before second blood pH and before second arterial blood). **Bottom:** later in experiment, during an infusion of bicarbonate (0.35, 3.2 ml/min) there is a trivial rise in pulmonary arterial pressure (PAP) following collapse, although the lung became solid within 5 minutes of occluding the bronchus. pH values in perfusing blood are given. Left atrial pressure, 2 mm Hg rising to 6 mm Hg briefly during infusion.

**PREPARATION 3**

Changes in Pulmonary Vascular Resistance after Bronchial Occlusion and Their Reversal by Vasodilators and Perfusion with Arterial Blood

**Cats.**—When the lung was perfused with mixed venous instead of arterial blood at a constant flow rate there was a rise in pulmonary arterial pressure in 15 of 16 cats. In nine of these, this pressure declined from the peak value but always remained higher than when the lung was perfused with arterial blood. Occlusion of the bronchus of the left lower lobe perfused with venous blood led to collapse and solidification of the lobe as before and to a rapid further rise in pulmonary arterial pressure (15 of 18 cats). The mean pulmonary arterial pressure rose from 18.1 ± 1.0 to 26.8 ± 1.5 mm Hg. In eight cats, it then declined from its peak value but remained above the value for the ventilated-venous state. When the solid lung was then perfused with arterial blood, the pressure fell rapidly until it was equal to, or only slightly greater than, that measured in the ventilated arterial state. The lobe changed color but there was no perceptible change in volume which might have indicated a return of gases to the alveoli (even in some experiments when the lobe was perfused with arterial blood for several hours). Changing the perfusate back to venous blood resulted in a rise in pulmonary arterial pressure as great or greater than that observed when the lobe was collapsed (Fig. 7, upper record). All these changes could be repeated many times.

Bretylium (20 mg/kg) failed to influence the changes caused by collapse of a lobe or changing from arterial to venous blood in three cats. Atropine likewise had no effect in three cats (0.2, 0.6 and 1.1 mg/kg).

In six cats, infusions of sodium bicarbonate (2.4 to 18.3 mM iv) reduced or delayed the
rise in pulmonary arterial pressure which followed collapse, or change from arterial to venous blood, or both (Fig. 7, lower record). Phentolamine similarly delayed or reduced these responses in two cats (0.6 and 1.0 mg into the pulmonary circuit).

Dogs.—Similar experiments were performed in 26 dogs, and conditions were satisfactory for the recording of results in 20. There was no change in pulmonary arterial pressure on changing from the ventilated-arterial to the ventilated-venous state (unlike in cats) but it rose steeply when the lung was collapsed while perfused with venous blood from 17.9 ± 1.3 to 23.2 ± 1.5 mm Hg. There was no decline in pressure from the peak value, but on perfusing the lung with arterial blood, the pulmonary arterial pressure fell nearly or completely to control values (Fig. 8). There was no change in this pressure when the lung was collapsed in three dogs in which conditions were satisfactory and in three others found to have pulmonary edema.

In the collapsed dog lung, both theophylline ethylene diamine (1 to 13 mg/min into perfusing circuit in 4 dogs) and acetylcholine (20 μg/min in 1 dog) reduced pulmonary arterial pressure nearly or completely to control values (Fig. 8).

Comparison of Resistance Values (R₁) and Pressure-Flow Diagrams in the Four States of the Lung.—Pressure-flow diagrams were measured in all four states of the lung in six cats (Fig. 9A and C). Since all points were measured at equilibrium they represent a minimal response. The change in the P-F curve from the ventilated-arterial to the ventilated-venous state was associated with a change in slope or intercept or both; an even greater change occurred when the lobe was collapsed while perfused with venous blood, but the curve for the collapsed lung supplied with arterial blood was usually superimposed, or nearly so, on the curve for the ventilated lung supplied with arterial blood (Fig. 9A and C). In general, when there was a large change on changing from the ventilated-arterial to the ventilated-venous state, there was a small change on changing from the ventilated-venous to the collapsed-venous state and vice versa. In some of the experiments, changes in the curves were limited to an intercept change producing parallel shifts in the curves (Fig. 9C). Figure 10 shows the regression coefficients and intercepts for the four states of the lobe in all experiments.

In dogs, pressure-flow diagrams also showed changes in both slope and intercept (Fig. 9B) but a higher proportion than in cats showed a large change in intercept and a small or absent change in slope. Changes in slope and intercept for all four states of the lobe in all experiments are shown in Figure 10.

To take into account changes in both slope and intercept, R₁(ΔPAP/LAP/Q) was measured at points of equal flow (in each experiment) in all four states of the lobe. In 10 cats the mean R₁ values for the ventilated-arterial, ventilated-venous, collapsed-venous and collapsed-arterial states were, respective-
Pressure-flow diagrams of ventilated and collapsed lungs perfused with venous or arterial blood. Left lower lobe perfused with Marlow pump. • = ventilated-arterial; o = ventilated-venous; □ = collapsed-venous; △ = repeat collapsed-venous; ▲ = collapsed-arterial; ◊ = re-expanded-arterial.

A: Cat, 2.8 kg (chloralose); bretylium, 20 mg/kg, given 20 minutes before. Left atrial pressure (LAP): • = 2.7 to 3.4; o = 0.9 to 1.9; □ = 1.8 to 2.5; ▲ = 2.5 to 3.8 mm Hg. B: Dog, 10.4 kg (morphine and pentobarbital). LAP: • = 2.2 to 3.6; o = 2.2 to 3.6; □ = 2.2 to 2.9; ▲ = 4.3; ◊ = 2.9 to 3.6; ◊ = 5.0 mm Hg. C: Cat, 3.0 kg (pentobarbital). LAP: 1.9 to 2.6 mm Hg throughout. • and o show change in intercept only. In no instance did the small changes in LAP account for the shifts in the pressure-flow diagrams. PAP = pulmonary arterial pressure.

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Regression coefficients and intercepts for pressure-flow diagrams of ventilated and collapsed lungs perfused with arterial or venous blood. Top: 12 dog experiments. Bottom: 14 cat experiments.

calculated from the regression equations. Values for $R_1$ for ventilated-arterial, ventilated-venous, collapsed-venous, and collapsed-arterial were, respectively, $0.139 \pm 0.01, 0.139 \pm 0.01, 0.212 \pm 0.01$ and $0.171 \pm 0.02$. The values for ventilated-arterial and ventilated-venous $R_1$ were the same; ventilated-venous was significantly different from collapsed-venous ($P < 0.001$); collapsed-arterial was not significantly different from ventilated-arterial ($P > 0.05$).
Vasodilatation in Collapsed Lungs

Since several groups of workers have reported increases in blood flow on collapse of a lung (7, 9, 12), we have looked closely for evidence of vasodilatation during collapse in our experiments. In no experiment in which the lobe was normal have we observed an increase in flow in preparation 1 or a decrease in pulmonary arterial pressure in preparation 3 as a lobe was collapsed; very small increases in flow were observed occasionally in lobes which were obviously edematous. However, in a very few tests in which pulmonary venous blood flow was measured (four tests in two dogs and one cat, out of a total of 143 tests in this group of experiments), we noticed that after the lung was fully collapsed and the blood flow had fallen to a low level, the flow gradually crept back toward control values although there had been no changes in pulmonary arterial or venous pressure to account for this. In the cat, the systemic blood pressure was low and in one of the dogs the intratracheal pressure had been slowly rising, but no other unusual features were noticed. These few observations may point to an unknown mechanism which antagonizes the effects of collapse we have described.

Discussion

BRONCHIAL OCCLUSION IN OPEN- AND CLOSED- CHEST PREPARATIONS

In the two species studied, bronchial occlusion led to a rapid increase in pulmonary vascular resistance, confirming results of earlier workers who used open-chest preparations or studied man during thoracic surgery (1-3, 5, 6, 8, 10). Results in closed-chest preparations have been less consistent. In dogs, Moore (4) found a decrease in blood flow but more recently, Niden (9), Elebute et al. (7), and Anand and Marshall (12) all reported an increase in the first few hours after bronchial occlusion. All but Moore used the shunt equation to calculate blood flow. There are a number of sources of error in this procedure, but it is significant that similar conclusions were reached using three widely differing techniques. The possibility must therefore be considered that the basic vasoconstrictor mechanism described in the present work may, in the intact animal, be antagonized by other factors. The low intrapleural pressures observed (9, 12) might, by increasing transmural pressure, have dilated vessels in opposition to any increase in active tension in their walls. Low systemic arterial PO₂ values were also recorded (7, 12) and might have excited chemoreceptor reflexes affecting the pulmonary circulation (21), or caused the release of catecholamines; both adrenaline and noradrenaline may cause pulmonary vasodilatation when there is high vascular tone (11, 12). Systemic hypoxemia did not occur in our experiments because the remaining lobes were usually well ventilated with O₂ or air. We noticed no common feature in the very few tests in which flow through the collapsed lobe gradually returned toward normal.

ACTIVE INCREASE IN PULMONARY VASCULAR RESISTANCE FOLLOWING BRONCHIAL OCCLUSION

The increase in pulmonary vascular resistance after bronchial occlusion in our studies is an active process probably mediated through an increase in vasomotor tone. The evidence for this conclusion is that the high vascular resistance was reversed by perfusing the lung with arterial blood and by acetylcholine, theophylline ethylene diamine, NaHCO₃, and phentolamine. An increase in resistance of mechanical origin could not be reversed in this way. All these agents cause pulmonary vasodilatation (11, 23, 24). In addition, phentolamine inhibits the pulmonary vasoconstrictor action of hypoxia in the cat (23) and alkalis reduce the sensitivity of the lung vessels to hypoxia (25-27). Woodson et al. (8) also showed a decrease in resistance when a collapsed lung was perfused with arterial instead of venous blood. The reduction was less than in our experiments but exact comparison is not possible since, in their experiments, perfusion pressures were not identical for arterial and venous bloods. An alternative explanation for the effect of arterial blood must be considered. When arterial blood is substituted for mixed venous blood, the oxygen tension in the perfusate will be higher than in the alveolar gas and...
backward diffusion might occur, increasing the alveolar volume slightly. Burton and Patel (28) and Thomas et al. (29) found an increase in pulmonary vascular resistance at low lung volume which could presumably be reversed by a small increase in lung volume. As lung volume could not be measured in our experiments, it is not possible categorically to refute this idea, but indirect evidence suggests that gas does not enter alveoli during perfusion with arterial blood. Firstly, no visible change in volume takes place after several hours of perfusion of the collapsed lobe with arterial blood. Secondly, the collapsed lobes became solid and required intrabronchial pressure of 20 to 30 mm Hg to reexpand them. The high pressure requirement probably results from surface tension effects, and the same force would be required before gas could enter the alveoli from the bloodstream. We therefore think that arterial blood reduces the vascular resistance of collapsed lungs by causing vasodilatation.

RELATION BETWEEN VASCULAR RESISTANCE IN THE COLLAPSED LOBE AND PULMONARY VENOUS PO2

The active increase in pulmonary vascular resistance might be due to a nervous mechanism, or to the local vasoconstrictor action of hypoxia, hypercapnia, or pH. In the cat a nervous mechanism was excluded by denervation experiments (11) and by autonomic blockade. In both cats and dogs we have found a close relation between pulmonary venous blood flow and pulmonary venous oxygen tension in several types of experiment, during collapse of a lobe (filled with either air or O2), ventilation with low O2 mixtures, and hypventilation.

Hypoxia is probably the stimulus causing vasoconstriction and hence a rise in pulmonary vascular resistance in all these tests. Previous work has shown that pressure-flow diagrams obtained during ventilation with low O2 mixtures and during collapse of a lung are similar (11). After bronchial occlusion the PO2 distal to the occlusion falls and must affect just those vessels which are stimulated by ventilation with low O2 mixtures. These will include capillaries, veins, and probably also precapillary vessels, since these are affected by alveolar gas tensions (30). When collapse of the lobe is complete, all pulmonary vessels are exposed to venous blood. However, not all workers have found comparable increases in resistance during hypoxia and during collapse (2, 8, 9).

In contrast to the close relation between blood flow and pulmonary venous PO2 there was no clear association between blood flow and pulmonary venous PCO2 and pH although both these latter factors can cause changes in pulmonary vascular resistance. Acidemia and hypercapnia both increase pulmonary vascular resistance in cats, but the effect of CO2 is less than that of fixed acids for a given change in pH (24); there is evidence that CO2 may also have a dilator action opposing the effect of the fall in pH which it causes (31). Occlusion of oxygen-filled lobes enabled the effects of changes in PCO2 and pH to be separated from those of changes in PO2. During the first phase while PO2 was constant, PCO2 was increasing and pH was falling; blood flow fell by a relatively small amount or not at all. The main reduction in flow occurred when the pulmonary venous PO2 fell sharply in phase 2. At this time PCO2 was falling and pH rising, so neither could have been the principal cause of the rise in resistance; they might, however, have contributed, since acidemia has been shown to enhance the action of hypoxia (25-27). PCO2 and pH changes might have caused the fall in blood flow in phase 1. The cause of the reversal of PCO2 and pH values toward normal in phase 2 is not known; it could be due to an improvement in overall gas exchange due to the reduced shunt of venous blood through the collapsed lung.

ROLE OF MECHANICAL FACTORS AND LUNG VOLUME

Although hypoxic vasoconstriction is probably the main cause of the increased vascular resistance in the collapsed lung, the participation of mechanical factors cannot be excluded. In isolated lungs, both Burton and Patel (28) and Thomas et al. (29) found evidence for increased vascular resistance at low lung volume, which they attributed to mechanical factors. There is also evidence that in the fully
expanded lung the pressure round certain extra-alveolar vessels is below atmospheric (and pleural) pressure, thereby increasing their transmural pressure and diameter (32, 33). Thus release of vessels from this tethering effect, especially in the presence of vascular tone, could be a cause of increased vascular resistance in the collapsed lung. West et al. (34) considered this factor responsible for the high critical closing pressure they observed in isolated perfused collapsed lungs compared with ventilated lung, but a low blood Po2 could also have contributed to their findings.

Our results suggest that although mechanical factors may contribute to the increased vascular resistance of the collapsed lung, their importance is overshadowed by an active mechanism. This evidence rests on the inability to correlate the reduction in blood flow with lung volume and the close correlation obtained between blood flow and pulmonary venous Po2. The circumstances under which mechanical factors contribute to pulmonary vascular resistance needs to be studied further. Phase 1, for example, of the two-phase decline in flow noted during collapse of O2-filled lobes could be due to a mechanical cause. The greater reduction in flow in collapsing O2-filled lobes as compared with air-filled lobes sometimes noted (especially in dogs) might also be mechanical in origin, because the former lobes reached a lower volume.

NATURE OF THE INCREASED RESISTANCE IN COLLAPSED LUNGS

Pressure-flow diagrams obtained in these experiments showed changes in slope and intercept. In the laboratory, changes in intercept are observed in model circuits containing collapsible tubes which function as Starling resistors; parallel curves are produced by altering the surrounding pressure of the collapsible portion (20). Flow then takes place under sluice or waterfall conditions and the effective pressure driving fluid through the circuit becomes inflow pressure minus surrounding pressure of the collapsible portion rather than the pressure difference across the whole circuit (16, 17). Certain pulmonary vessels have been shown to act like Starling resistors when alveolar pressure is raised (16, 35), and it has been suggested that small vessels in a state of tone may also behave in this way (18). In these circumstances the pressure difference causing blood flow through the lungs is no longer pulmonary arterial pressure minus left atrial pressure but pulmonary arterial pressure minus alveolar pressure or minus the pressure at the end of the vessels in a state of tone. The outlet pressure for vessels in a state of tone cannot be measured but pressure-flow diagrams may indicate when this state of affairs exists (20). The parallel shifts in pressure-flow diagrams seen in some of our experiments could be interpreted as indicating the presence in the collapsed lung of vessels with resistor properties.

RE-EXPANSION OF COLLAPSED LUNGS

The lung collapsed while ventilated with air could easily be reexpanded because it contained unabsorbed gases. The completely solid lung collapsed while ventilated with O2 required intrabronchial pressures of 20 to 30 mm Hg fully to reexpand it. Blood flow returned toward normal in both cases as soon as ventilation was restored, but it often failed to reach control values until the pulmonary arterial pressure had been momentarily raised with intravenous dextran. This was not necessary in the constant-flow perfusion experiments. One explanation is that, during collapse, certain vessels were actually closed due to increased tone (closure could not occur in the constant-flow experiments). The cause of the increased tone, a fall in Po2 for example, might not be removed until flow was reestablished. Stagnation of blood cells at low rates of flow is another possible explanation.

Conclusion

Collapse of a lung causes an increase in pulmonary vascular resistance by an active mechanism, probably mediated through a fall in Po2 in vessels normally exposed to either arterial blood or alveolar oxygen tensions. These experiments do not indicate which vessels actually constrict. The same mechanism may control ventilation-perfusion bal-
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ance in the normal lung, as first suggested by von Euler and Liljestrand (36). In intact animals this active reversible mechanism may be antagonized by other factors, mechanical, reflex or hormonal. If our results are applicable to man they could explain why some patients with large areas of collapsed lung have normal arterial blood gas tensions but others are severely hypoxic. In the first group, active vasoconstriction diverts blood away from collapsed areas; in the second group, it is antagonized by some dilator mechanism. These mechanisms may be further obscured in the clinical setting by the potentiating effect of acidemia on the effects of hypoxia (25-27), varying sensitivity of patients to hypoxia (37), and the dilator effect of some drugs such as aminophylline given as treatment (38).

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