Reactivity of the Vessels of Collapsed and Ventilated Lungs to Drugs and Hypoxia

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The vessels of the unexpanded foetal lung react more strongly to certain stimuli than those of the expanded foetal or newborn lung; they probably react more strongly than the vessels of adult lungs. Thus acetylcholine and histamine caused profound vasodilatation in unexpanded foetal lungs and comparatively weak dilatation in expanded foetal lungs. Noradrenaline caused a high degree of vasoconstriction in the lungs of immature foetal lambs but only small effects have been observed in the adult lungs of other species.

The vascular resistance of unexpanded foetal lungs is frequently high compared with that of ventilated foetal lungs but this is mainly due to vascular tone.

The question arises as to whether similar differences in reactivity and pulmonary vascular resistance exist between the aerated and nonaerated adult lung. In the present study the circulation through the collapsed and ventilated adult cat lung has been studied using hypoxia and a variety of pharmacological substances as testing agents. Preliminary reports of this work have been published elsewhere.

Methods

Cats were anaesthetised with ethyl chloride or ether and chloralose (60 mg/kg iv). For some experiments in which isolated lungs were perfused chloralose was given alone intraperitoneally (100 mg/kg at 50°C). The chest was opened in the midline and the lungs were ventilated with O₂ from a Starling Ideal pump. It was necessary to use oxygen not only to ensure rapid collapse of the lungs but also to keep the cat in good condition when only one lung was being ventilated.

Two polyethylene tubes were connected through a T-piece to the respiration pump; the distal end of the left-hand tube was curved laterally and a piece of foam rubber was tied round its tip. These tubes were inserted into the trachea so that the left one became wedged in the left bronchus; when this tube was occluded the left lung collapsed and the right one continued to be ventilated.

Blood pressures were measured with inductance manometers (Elena); outputs were led to Evershed-Vignoles recorders having a frequency response flat to 20 cycles/sec. Systemic pressure was sometimes recorded with a mercury manometer and left atrial pressure with a saline manometer. After completion of the dissection, heparin (Boots Pure Drug Company, 10 mg/kg iv) was given to prevent blood coagulation. Pulmonary blood flow was measured with a Wyatt electromagnetic flowmeter or, in a few experiments, with a bubble flowmeter. The flowmeter was inserted either into a loop of polyethylene tubing connecting the two ends of the left pulmonary artery or into a loop connecting the central end of a carotid artery to the distal end of the left pulmonary artery. In the latter instance the pressure in the carotid loop was reduced to 10 to 15 mm Hg by means of an adjustable clip and pulmonary arterial pressure was measured distal to this clip. By this means the flow and pressure in the pulmonary artery could be altered at will.

Pulmonary vascular resistance was defined as the quotient of pulmonary arterial pressure minus left atrial pressure (mm Hg) and pulmonary blood flow (ml/min). Comparisons of resistance were always made at constant blood flow in order to avoid passive changes in resistance caused by changes in the diameter of the vessels; in addition pressure/flow diagrams were constructed. Denervation of the lungs was performed by cutting the vagosympathetic trunks in the neck and removing the stellate ganglia and sympathetic trunks and ganglia in the thorax to a level at least 1 cm caudal to the hilum of the lung on both sides.

In the experiments involving the use of low oxygen mixtures (7.9 to 10.8%) blood oxygen saturation was measured by a modification of the Barcroft-Haldane method, or by a spectrophotometric method.

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Blood pO₂ was measured with a Clark type (Radiometer) oxygen electrode.

Lung perfusions were done at constant flow with a Dale-Schuster pump and an artificial lung in which blood was equilibrated with different gas mixtures. Great difficulty was at first experienced in perfusing collapsed lungs because high pressures were often needed to start the perfusion and the lungs often became oedematous. This difficulty was overcome as follows: the left lung was collapsed and a ligature was placed but not tied round the hilum of the right lung which was being ventilated. The cat was bled out, the main pulmonary artery and left atrium were cannulated and the perfusion of both lungs was started. No blood which had been standing more than five minutes was used. After the perfusion had been going for one-half to one hour, the hilum of the right lung was tied and the left lung alone was perfused in situ. The values for pressure and flow were then usually similar to those found in vivo and there was no oedema; only experiments of this type were included.

The following drugs were used and doses of those marked with an asterisk were calculated in terms of the base:—adrenaline hydrochloride;* tyramine hydrochloride;* theophylline ethylenediamine;* histamine acid phosphate;* acetylcholine perchlorate;* reserpine (Serpasil, Ciba); dibenamine hydrochloride; phenoxybenzamine (Dybenyline, Smith Kline and French, England); dopamine hydrochloride;* guanethidine (Ismelin, Ciba); lysergic acid diethylamide, referred to as LSD. (Delysid, Sandoz); 5-hydroxytryptamine creatinine sulphate,* referred to as 5HT; and mepyramine maleate (May and Baker).

Results

CHANGES IN THE PULMONARY CIRCULATION WHEN A LUNG IS COLLAPSED

When the left lung was collapsed by occluding the tube inserted into the left bronchus it became gas-free in from one to five minutes. The blood flow through the lung, measured in a loop in the left pulmonary artery, began to diminish within a few seconds of stopping ventilation and after about ten minutes became relatively constant at a low level (fig. 1A); in 12 cats the mean rate of blood flow at this time was 35 ± 4.4 (SE)$ of the initial level, though a further very gradual decline was often observed. In most cats pulmonary arterial pressure rose slightly during collapse of a lung; there was no constant change in left atrial pressure. Similar changes to those just described took place in two cats in which the lungs had been denervated. Figure 2 shows that during collapse the pressure/flow diagram is shifted towards the pressure axis; there is therefore an increase in pulmonary vascular resistance. Once a lung was completely airless, high intratracheal pressures (20 to 40 mm Hg) were required to reinflate it but once it was reinflated, ventila-

FIGURE 1

A. Diminution in rate of blood flow during collapse of a lung. Left bronchus occluded at arrow. B. Re-expansion of lung. Ventilation started at arrow but lung did not re-expand until after period of ventilation at high pressure. As soon as it expanded rate of blood flow again increased. Rate of flow higher than in A because a dose of theophylline ethylenediamine had been given in interval between A and B. Upper record: intratracheal pressure. Lower record: blood flow measured in loop in left pulmonary artery. Cat, 2.5 kg, chloralose.

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tion could be continued at low pressures (fig. 1B).

**ACTION OF VASODILATOR DRUGS ON COLLAPSED AND VENTILATED LUNGS**

To determine whether the increased vascular resistance of collapsed lungs was due to mechanical causes or to increased vascular tone, several vasodilator drugs were injected directly into the pulmonary artery. Isopropyl-noradrenaline (4 to 8.3 µg in 3 cats) and theophylline ethylenediamine (9 to 17.5 mg in 6 cats) consistently caused vasodilation in collapsed lungs (fig. 3). Adrenaline (0.3 to 1 µg in 5 cats) also usually caused vasodilation (fig. 3). Small doses of acetylcholine (0.75 to 15 µg in 4 cats) and, occasionally, small doses of histamine (0.4 to 1.8 µg in 2 cats) caused vasodilation but larger doses of these drugs caused vasoconstriction as did occasional doses of adrenaline. Figure 4 shows a threefold increase in blood flow through a collapsed lung after doses of acetylcholine and even larger increases have been observed. There is therefore increased vascular tone in a collapsed lung.

**FIGURE 2**

Pressure/flow diagrams of left lung during ventilation, collapse and re-expansion. Cat, 1.4 kg, chloralose.

**FIGURE 3**

Vasodilation in collapsed lungs (perfused from a carotid artery). Cat, 4.6 kg, chloralose. Injections at arrows into the pulmonary artery as follows: 1) 5.5 µg adrenaline. 2) 8.3 µg isopropyl-noradrenaline.

Upper record: pulmonary arterial pressure. Lower record: pulmonary blood flow.

**FIGURE 4**

Vasodilatation caused by acetylcholine in collapsed and ventilated lung. Injections at arrows into left pulmonary artery as follows: 1) acetylcholine 0.75 µg. 2) left bronchus occluded, lung collapses, blood flow diminishes. 3) acetylcholine 0.75 µg. 4) acetylcholine 1.5 µg. 5) acetylcholine 7.5 µg. 6) acetylcholine 15 µg.

Upper record: pulmonary arterial pressure. Lower record: blood flow measured in loop in left pulmonary artery. Cat, 2.5 kg, chloralose.
The action of these drugs on the vessels of ventilated lungs was neither qualitatively nor quantitatively different from their action in collapsed lungs except that the dilator effect of small doses of histamine was not observed in ventilated lungs.

**ACTION OF VASOCONSTRICTOR DRUGS ON COLLAPSED AND VENTILATED LUNGS**

When injected or infused into the pulmonary artery 5HT caused profound vasoconstriction which was similar in magnitude in collapsed and ventilated lungs. The pressure/flow curve was shifted towards the pressure axis (Fig. 5B shows a typical effect; 4 cats received infusions of 3.7 to 9.8 μg/kg/min). The effect of a single dose is illustrated in figure 11 (6 cats received doses of 2 to 4 μg).

Doses of histamine also usually (with the exceptions recorded above) caused a large increase in pulmonary arterial pressure at constant blood flow in both collapsed and ventilated lungs (0.7 to 18 μg in 7 cats); in collapsed lungs these doses sometimes caused a total arrest of blood flow.

Pulmonary vasoconstriction was observed during infusions of noradrenaline into the pulmonary artery in both collapsed and ventilated lungs if the dose was not so high as to cause a big rise in left atrial pressure. In 6 out of 10 cats a definite shift in the pressure/flow diagram towards the pressure axis was observed during infusions (0.5 to 5.4 μg/kg/min in 5 collapsed and 5 ventilated lungs) but this was smaller than the shift caused by 5HT. Figure 5A shows a typical example. In no individual cat was the increase in the regression coefficient significant at the 5% level. The degree of shift was reduced after measuring points at a high level of flow presumably because this reduced the concentration of noradrenaline in the lungs. In the other four cats there was no measurable shift in the pressure/flow diagram but most of the points lay to the right of the controls. The effect of single doses of noradrenaline given into the pulmonary artery was complex; there was a rise in pulmonary artery pressure, pulmonary blood flow and left atrial pressure but the pulmonary arterial pressure usually remained raised when the other parameters had returned to normal, indicating vasoconstriction.

Dopamine (single doses of 4 to 330 μg and infusions of 35 μg/kg/min in 4 cats) and tyramine (8 μg to 1.6 mg in 3 cats) also caused vasoconstriction when injected into the pulmonary artery in both collapsed and ventilated lungs. Slightly larger effects were seen than after noradrenaline, but larger doses could be given without causing a rise in left atrial pressure. The ratio of the rise in pulmonary pressure to the rise in systemic pressure after a dose of dopamine or tyramine was higher than after a dose of noradrenaline.

**EFFECT OF HYPOXIA ON COLLAPSED AND VENTILATED LUNGS**

Experiments on Intact Cats

In 40 cats the left lung was collapsed and
Pulmonary vascular constriction during hypoxia in collapsed lungs and the effect of adrenalectomy in a normal cat and another treated with reserpine.  
A: cat, 4.1 kg, chloralose. Periods of hypoxia (breathing 10% O₂, between arrows) before and after adrenalectomy in a control cat. B: cat, 2 kg, chloralose. Periods of hypoxia (between arrows) before and after adrenalectomy in a reserpinised cat (5 mg/kg for 2 days). Adrenalectomy at large arrows.

Upper record in each cat, pulmonary arterial pressure: no significant change in left atrial pressure. Lower record in each cat, blood flow to collapsed left lung in carotid-pulmonary loop: kept constant. The left pulmonary artery was perfused with blood from a carotid artery. When the right lung was ventilated with 10% O₂ (instead of O₂) for four to five minutes, there was vasoc constriction in the unventilated left lung. At a constant rate of blood flow the pulmonary arterial pressure rose rapidly and remained raised until the 10% O₂ was discontinued (fig. 6A). Left atrial pressure usually rose slightly (1 to 3 mm Hg). The mean increase in pulmonary arterial pressure minus left atrial pressure during hypoxia at a constant rate of pulmonary blood flow was 54.3 ± 5.9 (SE)%. Repeated tests with 10% oxygen in the same animal produced a similar rise in pulmonary arterial pressure every time. Figure 7 shows pressure/flow diagrams before and during hypoxia and is typical of eight experiments. During hypoxia the intercept on the pressure axis increased by a mean of 3.9 mm Hg (77.5%), the limits being 1.2 to 5.2 mm Hg (26 to 198%). The regression coefficient also increased; the difference between the regression coefficient during control and hypoxic periods was significant at the 5% level or less in all but two of the eight experiments and in these there was a wide scatter in the points measured.

Effect of hypoxaemia and phenoxybenzamine on pulmonary vascular resistance in collapsed lungs. Cat, 4.0 kg, chloralose. Pressure/flow diagrams during control periods (●), hypoxaemia (●), and after phenoxybenzamine (○; 5 mg/kg/IV). Regression coefficients; control, 0.1752; hypoxaemia, 0.3493; after phenoxybenzamine, 0.133. Difference between control and hypoxaeemic period significant (P < 0.05) and also difference between control and after phenoxybenzamine (P < 0.001).
The increase in pulmonary vascular resistance during periods of hypoxia was observed after acute bilateral denervation of the lungs in three cats (table 1). The effect of hypoxia was also undiminished in four cats in which the adrenal glands were removed and there was no definite change in pulmonary vascular resistance (fig. 6A and table 1).

In nine cats, with both lungs ventilated, breathing 10% O$_2$ also caused an increase in pulmonary vascular resistance which was similar in time course and magnitude to that which took place in collapsed lungs. The mean increase in pulmonary arterial pressure minus left atrial pressure at constant blood flow was 55 ± 16.3 (SE)%.

The mean oxygen saturation of the carotid arterial blood during ventilation with 10% O$_2$

**TABLE 1**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Number of lungs* and state</th>
<th>Pulmonary arterial pressure minus left atrial pressure† (constant blood flow)</th>
<th>Per cent change</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Control</td>
<td>Hypoxemia</td>
</tr>
<tr>
<td>1. Control</td>
<td>9C</td>
<td>12.48±0.13</td>
<td>16.82±1.41</td>
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<tr>
<td>Dibenamine</td>
<td></td>
<td>10.46±0.98</td>
<td>9.81±1.01</td>
</tr>
<tr>
<td>2. Control</td>
<td>6C,5V§</td>
<td>10.04±1.04</td>
<td>14.55±1.14</td>
</tr>
<tr>
<td>Phenoxybenzamine</td>
<td></td>
<td>9.12±0.46</td>
<td>9.38±0.79</td>
</tr>
<tr>
<td>3. Ventilated</td>
<td>8V</td>
<td>12.14±1.17</td>
<td>18.34±2.77</td>
</tr>
<tr>
<td>4. Denervated</td>
<td>3C</td>
<td>12.5</td>
<td>20.1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>10.1</td>
<td>13.1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>13.9</td>
<td>17.1</td>
</tr>
<tr>
<td>5. Control Adrenalectomy</td>
<td>1C</td>
<td>6.2</td>
<td>9.9</td>
</tr>
<tr>
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<td></td>
<td>6.3</td>
<td>13.6</td>
</tr>
<tr>
<td>Control Adrenalectomy</td>
<td>1C</td>
<td>7.3</td>
<td>22.5</td>
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<td></td>
<td>7.7</td>
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</tr>
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<td>1C</td>
<td>13</td>
<td>17.7</td>
</tr>
<tr>
<td>Control Adrenalectomy</td>
<td></td>
<td>12.3</td>
<td>17.6</td>
</tr>
<tr>
<td>6. Guanethidine</td>
<td>1C</td>
<td>8.2</td>
<td>14</td>
</tr>
<tr>
<td>Control Guanethidine</td>
<td></td>
<td>11.5</td>
<td>13.9</td>
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<tr>
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<td>1C</td>
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<td>11</td>
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<tr>
<td>Guanethidine</td>
<td></td>
<td>10.2</td>
<td>12.4</td>
</tr>
</tbody>
</table>

*C: collapsed; V: ventilated.
†Mean values are given ± standard error where numbers are greater than 6, otherwise individual values.
Blood flow kept constant in control and hypoxaemic periods and after drugs (except in a very few experiments where not possible owing to fall in systemic pressure after drug).
§Includes two cats with denervated lungs and one which had had mepyramine.
Includes one cat which had had LSD, one which had had reserpine and one which had had the adrenal glands removed.
Doses: dibenamine, 5 to 10 mg/kg; phenoxybenzamine, 5 to 10 mg/kg; guanethidine, 10 mg/kg.

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in six cats was 62% (range 34 to 77) and there was no systematic difference between the three cats with collapsed and the three with ventilated lungs. In ten further cats with venti-
lated lungs the pO$_2$ of the arterial blood during hypoxia was 34.3 ± 3.7 (SE)mm Hg.

**Isolated Perfused Lungs**

Pulmonary vasoconstriction has frequently been demonstrated during hypoxia (or more usually anoxia) in isolated, perfused, venti-
lated lungs. In five out of ten satisfactory preparations of isolated, collapsed lungs per-
fused at a constant rate of blood flow (for criteria see Methods), there was an increase in pulmonary arterial pressure when the per-
fusing blood was rendered hypoxaemic by changing the gas in the artificial lung from 95% O$_2$ and 5% CO$_2$ to 95% N$_2$ and 5% CO$_2$ in the other five lungs there was no effect. The rise in pressure when present was unequivocal (9 to 48%) and was observed several times (fig. 8). In three of the preparations pressure/flow diagrams were constructed and they were shifted towards the pressure axis during hypoxia as they were in the intact cats.

These experiments and those of other work-
ers on ventilated lungs show that there is some mechanism within the lung itself which can cause pulmonary vasoconstriction during hy-
poxia—perhaps the release of a vasoconstric-
tor substance. The next section describes ex-
periments designed to test the possibility that one of the pulmonary vasoconstrictor sub-
stances described above might be respon-
sible for the pulmonary vasoconstriction of hypoxia.

**EFFECT OF INHIBITORS OF VASOCONSTRICTOR DRUGS ON PULMONARY VASOCONSTRICTION DURING HYPOXIA (IN BOTH COLLAPSED AND VENTILATED LUNGS)**

**Catecholamine Inhibitors**

Dibenamine was given to cats with both collapsed and ventilated lungs in doses (5 to 10 mg/kg intravenously) which reversed or abolished the vasoconstrictor effect of nor-
adrenaline and tyramine on the pulmonary circulation. The pulmonary arterial pressure rose briefly but after 15 to 30 minutes it was lower than it had been initially for the same rate of blood flow; dibenamine therefore caused a decrease in pulmonary vascular re-
sistance (table 2). The pressure/flow diagram was also shifted towards the flow axis. Eleven cats (2 with ventilated lungs, 7 with collapsed lungs and 2 with collapsed denervated lungs) were subjected to periods of hypoxia before and after administration of dibenamine. In every cat pulmonary vasoconstriction during hypoxia was abolished or greatly reduced and in some cats there was actually pulmonary vasodilatation during hypoxia after dibena-
mime; the maximum effect was reached in about 30 minutes. Table 1 shows the mean

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*FIGURE 8*

Pulmonary vasoconstriction during anoxia in an isolated perfused collapsed lung. Cat, 2.8 kg, chloralose. The lung was gassed in 95% O$_2$ and 5% CO$_2$, except during the periods shown by the horizontal lines when it was gassed with 95% N$_2$ and 5% CO$_2$.

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changes in pulmonary vascular resistance (pulmonary arterial-left atrial pressure at constant blood flow) during hypoxia before and after dibenamine.

Phenoxybenzamine was given to another series of cats with both collapsed and ventilated lungs in doses (5 to 10 mg/kg intravenously) which reversed or abolished the pulmonary vasoconstrictor effect of noradrenaline. As after dibenamine, there was a brief increase in pulmonary vascular resistance followed, in 17 out of 21 cats, by a permanent decrease (table 2). Figure 7 shows that the pressure/flow diagram was shifted towards the flow axis after phenoxybenzamine and is typical of the four experiments in which this was measured; the decrease in the regression coefficient was significant at the 5% level or more in all four experiments but changes in the intercept were variable. Figure 9 shows a typical example of eleven experiments in which the effect of hypoxia in the lung vessels was tested before and after phenoxybenzamine. In every experiment the pulmonary vasoconstriction which accompanied hypoxia was abolished or greatly reduced 15 to 30 minutes after phenoxybenzamine. The mean changes in pulmonary vascular resistance during hypoxia before and after phenoxybenzamine are shown in table 1.

Sixteen cats were given reserpine for two or three days before the experiment (2 to 3 doses of 0.8 to 5 mg/kg intraperitoneally); the cats were kept at 21 ± 1.5°C. They had a low systemic blood pressure, heart rate and rectal temperature (31 to 37°C) and required only small amounts of volatile anaesthetic to cause respiratory arrest; however, with care,
they could be kept alive under chloralose anaesthesia for several hours and subjected to repeated tests with hypoxia. There was no significant difference between the pulmonary vascular resistance of the reserpinised cats and a control group. Comparing groups in which rates of blood flow were similar (controls 25.2 ± 0.8, (SE) ml/min and treated 24.7 ± 0.9) the difference in pressure across the pulmonary circulation was similar (pulmonary arterial minus left atrial pressure for controls, 12.8 ± 1.2 (SE) mm Hg; and for treated cats, 11.1 ± 0.93).

Figure 10 compares the magnitude of the increase in pulmonary arterial pressure minus left atrial pressure at constant blood flow during hypoxia in the 16 treated cats (14 with collapsed, 2 with ventilated lungs) with that in the 40 control cats. A much higher proportion of the treated cats (one quarter) than of the control group showed no increase or a very small increase in pulmonary arterial pressure during hypoxia. The magnitude of the increase in successive tests was also more variable in the treated group; thus, there might be no response to the first test but large responses to later tests.

In eight cats attempts were made to restore the stores of catecholamines in reserpinised cats with prolonged infusions of dopamine (2.7 and 2.9 mg in 2 cats) or noradrenaline (112 μg to 2 mg in six cats). In one cat the response to hypoxia, which had been negligible in three tests before dopamine was infused, increased steadily for one and one-fourth hour afterwards. In a second cat the size of the response increased progressively after a noradrenaline infusion, but in the other six cats the results were inconclusive because the animals did not survive long enough after the infusions for repeated tests with hypoxia to be made.

Guanethidine was given to five cats with collapsed lungs (10 mg/kg intravenously in 4 and 15 mg the previous day intraperitoneally in the 5th) and usually caused a rise in pulmonary vascular resistance (table 2). In three cats pulmonary vasoconstriction during hypoxia was reduced or abolished one to one and one-half hours after guanethidine, in one cat it was increased and in the fifth (pretreated) there was a small response which was reduced further by another dose of guanethidine (table 1).

An Inhibitor of 5-hydroxytryptamine
Lysergic acid diethylamide (LSD) was given to three cats with collapsed lungs in doses (100 to 200 mg/kg intravenously) which led to a reversal of the pulmonary vasoconstrictor effect of 5-hydroxytryptamine (5HT). The pulmonary vascular resistance was increased in contrast to the decrease which followed dibenamine and phenoxybenzamine. The effect of hypoxia remained undiminished (fig. 11).

An Antihistaminic Drug
Mepyramine was given to four cats with

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FIGURE 11

Effect of 5HT on vessels of collapsed lungs before and after LSD and the effect of LSD on pulmonary vasoconstriction during hypoxia. Cat, 2.4 kg, chloralose. A: rise in pulmonary arterial pressure during hypoxia (caused by ventilating right lung with 10% O\textsubscript{2}) shown by arrows and effect of 5HT (4.1 μg) into pulmonary artery immediately after this. B: rise in pulmonary arterial pressure during second period of hypoxia 13 minutes after LSD (100 μg/kg IV) and reversed effect of same dose of 5HT on pulmonary vessels directly afterwards. Upper record: pulmonary arterial pressure. Lower record: pulmonary blood flow in carotid-pulmonary loop (kept constant). Left atrial pressure did not change significantly.

collapsed lungs in doses (1 to 3 mg/kg intravenously) which reversed or abolished the pulmonary vasoconstrictor effect of histamine (one cat showed pulmonary vasodilatation after a large dose of histamine and this also was abolished by mepyramine). It had no constant effect on pulmonary vascular resistance. In two of the four cats the pulmonary vasoconstrictor effect of hypoxia was undiminished 50 to 60 minutes after mepyramine; in the other two cats tests at 12 and 14 minutes after mepyramine showed a definite but somewhat reduced response.

Discussion

COMPARISON OF THE CIRCULATION THROUGH COLLAPSED AND VENTILATED LUNGS

This study has shown that in the adult cat pulmonary vascular resistance is much higher in the collapsed than in the ventilated lung. This change is not due to an extrinsic nervous mechanism nor is it due wholly to mechanical factors because vasodilator drugs were able greatly to increase blood flow through collapsed lungs. Vascular tone is therefore increased.

A possible but unproven cause of this increase in tone is that the whole pulmonary vascular bed is perfused with mixed venous blood when a lung is collapsed, so that parts of the bed are exposed to a pO\textsubscript{2} much lower than that in the ventilated lung. When the pO\textsubscript{2} of the blood perfusing a collapsed lung was reduced from arterial to venous levels (in the carotid loop experiments) there was a large increase in pulmonary vascular resistance comparable in magnitude to that observed when a lung collapses (compare figs. 2 and 7).

Certain similarities and equally marked differences between the adult collapsed lung and the foetal lung emerged. The change in vascular resistance when an adult lung collapsed was comparable in magnitude but opposite in sign to that observed when the lung of a foetal lamb was ventilated for the first time. In both cases the greater vascular resistance in the unaerated state was attributable more to increased vascular tone than to mechanical factors. The vessels of both foetal and adult collapsed lungs dilated in response to doses of acetylcholine and histamine but the effects in the foetus were probably greater and in the adult lung there was no difference in reactivity in the aerated or nonaerated state. Vasocostriction was greater in foetal vessels during infusions of noradrenaline than in adult collapsed (or ventilated) lungs. Both foetal and adult lung vessels constricted during hypoxia in both the aerated and nonaerated state; in the unexpanded foetal lung there was evidence for sympathetic vasomotor tone but no such evidence exists for the adult cat lung. Both adult collapsed lungs and unexpanded foetal lungs required high pressures to initiate ventilation presumably in order to overcome high surface tension in the alveoli.

EFFECT OF HYPOXIA IN THE COLLAPSED AND VENTILATED ADULT CAT LUNG

The vessels of the cat lung constricted sim-
ilarly in response to hypoxia whether the lung was ventilated or collapsed. The vessels of isolated perfused collapsed lungs constricted during anoxia in the same way as has been shown many times for the vessels of isolated perfused ventilated lungs. Thus the underlying mechanism must be at least in part a local one. This does not exclude the possibility that under certain circumstances nervous impulses and adrenal or other secretions may contribute to the effects of hypoxia on the pulmonary circulation. The lesser sensitivity of the isolated lung vessels as compared to the lung vessels in the intact animal may be due to the impairment of some mechanism or the depletion of some store of vasoconstrictor substance during the death of the animal and preparation of its lungs for perfusion.

**ACTION OF VASOCONSTRICTOR SUBSTANCES COMPARED WITH THE ACTION OF HYPOXIA ON THE PULMONARY CIRCULATION IN COLLAPSED AND VENTILATED LUNGS**

In order to test the hypothesis that a local release of a vasoconstrictor substance might be responsible for the pulmonary vasoconstriction of hypoxia, the actions of 5HT, histamine and catecholamines (all of which have been isolated from lungs) were compared with the action of hypoxia. All three substances caused pulmonary vasoconstriction under the conditions of these experiments and there was no difference between their action on collapsed and ventilated lungs. 5HT and histamine caused profound pulmonary vasoconstriction comparable in magnitude to that observed during hypoxia. A small but definite vasoconstriction was observed during infusions of noradrenaline; dopamine and tyramine (which is believed to act by releasing noradrenaline) had rather greater effects. Other workers have also observed that noradrenaline causes a small degree of pulmonary vasoconstriction which is frequently obscured by its effects on the systemic circulation. In man, Goldring et al. found that the whole effect of noradrenaline on the pulmonary circulation could be accounted for by the rise in left atrial pressure which it caused. A rise in left atrial pressure leads to pulmonary vasodilatation which might counteract any vasoconstrictor effect.

**EFFECT OF VASOCONSTRICTOR ANTAGONISTS ON PULMONARY VASOCONSTRICTION DURING HYPOXIA**

In the present study the use of LSD or mepyramine failed to implicate either 5HT or histamine in the genesis of the pulmonary vasoconstriction of hypoxia but two lines of evidence suggested that catecholamines might be involved. Firstly, dibenamine and phenoxybenzamine, shown in other circumstances to antagonise catecholamine compounds predominantly but not exclusively, abolished or reduced greatly the power of the lung vessels to constrict during hypoxia. Secondly, these substances reduced pulmonary vascular resistance, suggesting that the agent responsible for pulmonary vasoconstriction during hypoxia might also maintain a degree of vascular tone in the lungs. However, the possibility that these substances are acting in a nonspecific manner cannot yet be excluded. For example, phenoxybenzamine reduced the pulmonary vasoconstrictor effect of 5HT and histamine on the lungs as well as the effect of catecholamines. Nevertheless, it did not render the lung vessels totally unreactive since it was shown (in 7 cats) that the lung vessels still constricted during hypercapnia at a time when they no longer constricted during hypoxia. Nisell noted that hypoxia no longer caused vasoconstriction in two isolated perfused lung preparations after doses of dibenamine. Lloyd found that phenoxybenzamine reduced the pressor response to hypoxia in isolated dogs lungs and Halmagyi et al. found that dibenamine reduced pulmonary vascular resistance in lungs of dogs. In the present study guanethidine appeared also to reduce the pulmonary vasoconstriction of hypoxia, although Bishop et al. found that it did not reduce the pulmonary pressor effect of hypoxia in human beings. In one quarter of the cats treated with reserpine the pulmonary vasoconstriction of hypoxia was reduced or abolished; nevertheless, a nonspecific effect cannot be excluded and there was insufficient evidence to demonstrate the return of the hypoxic effect after infusions of cate-
COMPARISON OF COLLAPSED AND VENTILATED LUNGS

cholamines. It was perhaps significant that adrenalectomy sometimes reduced the pulmonary pressor response to hypoxia in reserpinised animals. The observation that removal of a source of catecholamines reduced an apparently normal response suggests that catecholamines may have been the cause of this response. In control animals adrenalectomy did not diminish the effect of hypoxia on the lung vessels, perhaps because the lungs contained sufficient stores of a vasoconstrictor substance.

Taken together, the results of experiments using inhibitor drugs point more strongly to catecholamines than to either of the other two substances tested as possible mediators in the response of the lung vessels to hypoxia. This cannot be regarded as more than a suggestion at the present time especially because of the known unreliability of pharmacological inhibitors and because of the discrepancy between the degrees of pulmonary vasoconstriction caused by catecholamines and by hypoxia. Goldring et al. also considered this hypothesis; they concluded that there was no positive evidence for it because they could not reproduce the effect of hypoxia on the pulmonary circulation in human beings with infusions of noradrenaline; the effect of hypoxia was also not abolished in five dogs treated with reserpine. These results are not incompatible with those obtained in the present study but they emphasize the difficulties and the need for further evidence.

Summary

1. In anaesthetised cats the left lung was collapsed by obstructing a ventilating tube which had been wedged into the left bronchus. If the cat had been ventilated with oxygen beforehand, the lung became gas-free in one to five minutes.

2. Blood flow to the left lung diminished rapidly as the lung collapsed and in about ten minutes was reduced by about 65%. Pulmonary vascular resistance increased greatly and these changes persisted after denervation of the lungs.

3. Vascular resistance of collapsed lungs could be reduced substantially by several drugs (acetylcholine, small doses of histamine, theophylline ethylenediamine, isopropyladrenaline, adrenaline) so that it must depend to some extent on increased vascular tone.

4. Vessels of collapsed lungs constricted when the oxygen saturation of the blood reaching them was reduced. This was demonstrated in vivo both before and after denervation of the lungs and after adrenalectomy and also in isolated perfused lungs. This effect is large enough to account for the changes in the pulmonary circulation which follow collapse of a lung. The time course and magnitude of the pulmonary vasoconstriction which took place during hypoxia were similar in collapsed and ventilated lungs.

5. The effects of a number of naturally occurring vasoconstrictor substances on the pulmonary circulation were compared with the effect of hypoxia. Noradrenaline caused weak but definite vasoconstriction of the pulmonary vessels, in a majority of cats; dopamine and tyramine had a more powerful constrictor effect and 5-hydroxytryptamine a much more powerful effect. Doses of histamine also usually caused pulmonary vasoconstriction.

6. Dibenamine and phenoxybenzamine reduced greatly or abolished the pulmonary vasoconstriction which accompanies hypoxia in collapsed or ventilated lungs. Guanethidine sometimes reduced or abolished it. Dibenamine and phenoxybenzamine reduced pulmonary vascular resistance. Pulmonary vasoconstriction during hypoxia was less frequently observed in cats treated with reserpine than in normal cats.

7. Lysergic acid diethylamide did not alter the pulmonary vasoconstrictor effect of hypoxia in doses which reversed the pulmonary vasoconstrictor action of 5-hydroxytryptamine. Mepyramine did not abolish (but may have sometimes diminished) the effect of hypoxia on the pulmonary vessels, in doses which reversed or abolished the pulmonary vasoconstrictor effect of histamine.
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