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STIMULUS–RESPONSE CURVES FOR THE PULMONARY VASCULAR BED TO HYPOXIA AND HYPERCAPNIA

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SUMMARY

1. In anaesthetized open-chest cats and dogs, blood flow and gas tensions were measured in a circuit inserted into a pulmonary vein while ventilating the lobe which it drained with low O_2 and high CO_2 mixtures.

2. Both hypoxic and hypercapnic mixtures caused a reduction in blood flow from the lobe.

3. Stimulus–response curves relating blood flow to pulmonary venous P_{O_2} and P_{CO_2} were obtained. Those for hypoxia were usually asymptotic in shape; the curves became steep below 100 torr and flow sometimes fell to zero. The mean reduction in blood flow for every 20 torr fall in P_{O_2} was 15·7 % in cats and 11·8 % in dogs. Those for hypercapnia were steep at first but levelled out at high P_{CO_2} values; the maximum reduction in flow was 40–60 % as vasoconstriction was only observed over a limited P_{CO_2} range.

4. Hypoventilation of the lobe led to a reduction in blood flow. This was mainly attributable to hypoxia though other factors such as hypercapnia may sometimes have contributed.

5. Total occlusion of the bronchus of an O_2-filled lobe caused blood flow to fall in two phases. The first phase could be attributed to a rise in P_{CO_2} and the second to a fall in P_{O_2}.

6. The results confirm the hypothesis that hypoxia is an important factor regulating local blood flow in relation to local ventilation.

INTRODUCTION

Euler & Liljestrand (1946) suggested that local blood flow in the lung was regulated according to local ventilation through the vasoconstrictor action of hypoxia and hypercapnia. Subsequent work has shown that both stimuli constrict pulmonary vessels (Fishman, 1961; Duke &

Lee, 1963) although the effect of CO_2 is probably mediated through a reduction in blood pH (Barer, Howard & McCurrie, 1967); the CO_2 molecule itself may in some circumstances cause dilatation (Viles & Shepherd, 1968; Shaw, 1970). Both gases play a role in determining the blood flow through foetal and new-born lungs (Dawes, 1968) and hypoxia may cause pulmonary hypertension at high altitude (Hultgren & Grover, 1968) and in lung disease (Abraham, Cole, Green, Hedworth-Whitty, Clarke & Bishop, 1969). Yet the original hypothesis that O_2 and CO_2 tensions control ventilation-perfusion ratios in the normal adult lung remains unproven. To establish this, it must be shown that a substantial reduction in local blood flow follows underventilation of part of a lung. In previous work we showed that occlusion of a bronchus led to a profound fall in blood flow through the affected lobe. The pulmonary venous O_2 tension seemed to be the important controlling factor (Barer, 1966*a*; Barer, Howard, McCurrie & Shaw, 1969). The aims of the present study were, first, to establish the stimulus–response relationship between blood flow and alveolar O_2 and CO_2 tensions in a single lobe (blood flow, P_{O_2} and P_{CO_2} were measured in a single pulmonary vein); and secondly, to compare the blood flow changes caused by bronchial occlusion and hypoventilation with the stimulus–response curves to see if they could be wholly explained in terms of hypoxia and hypercapnia. Preliminary reports of some of this work have been published (Barer, Howard & Shaw, 1970; Barer, Howard, McCurrie & Shaw, 1970).

METHODS

Twenty-six cats (1·5–3·9 kg) were anaesthetized with chloralose (100 mg/kg I.P.). Ten dogs (9·7–17·1 kg) were anaesthetized with pentobarbitone (25 mg/kg I.V.) after premedication with morphine (1 mg/kg subcutaneously). Heparin (1000 u./kg) was given after completing the dissection. Blood pressures were measured with electromanometers (Elema–Schönander) and blood flow with a Wyatt (1961) cannulated electromagnetic flowmeter. Results were recorded using an ultra-violet light recorder (S.E. Laboratories). Blood gas tensions were measured with either Radiometer (Astrup) or E.I.L. electrodes at 37° C. Blood samples were kept upon ice for a short time until analysed. Positive pressure ventilation was maintained through a tracheal cannula with a Starling Ideal pump. The control gas was 100 % O_2; collapse of the lung was prevented by periodic hyperinflations. Systemic blood pressure was recorded from the femoral or carotid artery. Mean pressures only were recorded. For the Figures, records of pressure and flow were traced, as photographs of the ultra-violet recorder paper were unsatisfactory.

Description of circuit

Cats. The chest was opened by splitting the sternum in the mid line; the left lower lobe vein was cannulated and connected by a loop of polyethylene (which included the flowmeter) to a second cannula in the left atrium. A small section of rubber tubing was inserted close to the pulmonary venous cannula for taking samples and a side arm was used for recording pulmonary venous pressure (PVP). The resistance

of the circuit was low (1·5 torr pressure drop for a saline flow of 50 ml./min). Mean blood flow from the lobe for all experiments was 42·3 ± 3·5 (S.E.) ml./min, which is reasonable when compared with a total pulmonary flow of 114 ± 20·6 ml./kg. min measured in open-chest cats (Barer & Nüsser, 1957). 'Natural' pulmonary artery pressure (PAP) was measured from a small cannula inserted through the wall of the main pulmonary artery. The left lower lobe was ventilated separately with a second Starling Ideal pump through a cannula tied into its bronchus. Thus bronchial artery blood flow was occluded; the bronchial nerve supply was probably also damaged. (Occasionally a subsidiary posterior bronchus joined the lobe distal to the cannula; it was discovered when intrabronchial pressure and pulmonary venous P_{O_2} failed to fall after occlusion of the main bronchus indicating that collateral ventilation was taking place.) The gas mixtures used were, 100, 30, 21, 18, 12, 10 and 5 % O_2 in N_2 and pure N_2; 5, 10 and 15 % (occasionally higher) CO_2 in O_2. In nineteen experiments the condition of the lobe and the rate and stability of blood flow were considered satisfactory for recording results.

Dogs. The procedure was similar except that the chest was occasionally opened through the right third and left fourth intercostal spaces instead of the mid line. The left lower lobe vein was difficult to cannulate owing to its short length and multiple radicles and had to be entered via the left atrium. The tip of the cannula was tied into the vein and the circuit drained into the right atrium. The pressure drop across the circuit was 3·2 torr for a saline flow of 200 ml./min. Mean blood flow from the lobe in all experiments was 234·8 ± 41·2 ml./min. PAP was measured through a retrograde cannula in an upper lobe artery. The position of the venous cannula was critical for obtaining a stable flow and it was more difficult in the dog to get an acceptable preparation. Conditions were considered satisfactory for recording results in seven dogs.

Stimulus–response curve measurement

Blood flow, expressed as a % of the control value before the test, was plotted against pulmonary venous P_{O_2} or P_{CO_2} to give stimulus–response curves. The plotting of flow as a % enabled measurements at different times in the same animal (when PAP might have varied) and in different animals to be compared.

When PAP in the main pulmonary artery and blood flow from the lobe were stable a pulmonary venous blood sample was taken. The control ventilating gas was 100 % O_2, occasionally air. The O_2 concentration of the lobar ventilating gas was then reduced in a stepwise manner; before each change a stable rate of blood flow was achieved and a blood sample taken. The same procedure was followed with increasing CO_2 concentrations. In the cat only, removal of 1 ml. blood for gas analysis often caused a small reduction in PAP and blood flow which was rectified by small injections of dextran (0·5–1·5 ml. I.V.).

The circuit did not permit control of PAP which usually rose slightly during hypoxia and hypercapnia thereby reducing the fall in blood flow to a small extent. This particular circuit was chosen in preference to a perfusion method in which PAP could be controlled because it enabled local blood flow and gas tensions to be measured simultaneously after local changes in ventilation. The lobe received its normal pulsatile blood supply. The pulmonary venous blood was not diluted by bronchial flow as the latter was occluded in tying in the bronchial cannula; pulmonary venous gas tensions were therefore assumed to be close to alveolar gas tensions.

Two factors sometimes caused errors in measuring the curves, viz. the occasional uncompensated fall in blood flow after taking blood samples (cats only) and an occasional downward drift in PAP. Stimulus–response curves have only been included in which these errors were small. In cats, the mean fall in blood flow due to sampling while measuring a whole curve (changing from 100 % O_2 in steps to N_2, or

from 100 % O_2 to 15 % CO_2 in O_2) was 3·8 ± 1·0 % of the maximum fall in blood flow due to the greatest stimulus; the greatest fall in PAP was 1·6 torr. In dogs, conditions were less stable and PAP often fell gradually. This would slightly exaggerate the total effect of the stimulus but not the shape of the curve; each new gas concentration was associated with a clear stepwise change in flow unrelated to a change in PAP. The PAP fell by less than 2·3 torr in all but one dog (in this the PAP fell by 3·5 torr during hypoxia and 5·0 torr during hypercapnia). Owing to technical difficulties the dog results are less reliable quantitatively than those in cats but provide valuable qualitative confirmation.

Statistics

Standard errors are given after means. Regression lines (b) and correlation coefficients (r) were calculated.

RESULTS

Hypoxia

Ventilation of the left lower lobe with decreasing O_2 concentrations led to stepwise decreases in blood flow (Fig .1 *A*) in all experiments. Flow stabilized at each new O_2 concentration. PAP usually increased slightly (0·4 ± 0·41 (S.E.) torr in cats and 0·2 ± 0·76 torr in dogs). PVP usually fell as flow diminished ($-0·4 \pm 0·18$ torr in cats and $-0·4 \pm 0·43$ torr in dogs). There were few exceptions to this pattern but in one cat, blood flow fell sharply at each new O_2 concentration then rose and finally stabilized at an intermediate value. In another, flow fell with air and 12 % O_2 but rose to greater than the control level with 5 % O_2. In three dogs, flow fell with progressive hypoxia but rose slightly or failed to fall further with N_2. These few observations might indicate a dilator mechanism which occasionally counteracts hypoxic vasoconstriction.

On returning to 100 % O_2 blood flow returned rapidly to normal when it had been moderately reduced by the stimulus. When it had been reduced to very low levels, it rose rapidly to 30–60 % of control values and then continued to climb slowly; a small intravenous injection of dextran, briefly raising PAP, accelerated the restoration of flow.

Stimulus–response curves in cats. A typical stimulus–response curve is shown in Fig. 1 *B* and the curves from all experiments in Fig. 2. There was a small but definite fall in flow when P_{O_2} was reduced from 500 to 100 torr. Below 100 torr the rate of fall of blood flow increased sharply and at very low P_{O_2} values, the rate of flow was often very low or zero. Two curves in which the control gas was air are shown in Fig. 2; they fall parallel to the other curves. Thus the shape of the stimulus–response curve in the cat is usually asymptotic with the sharp inflexion in the normal physiological range (P_{O_2} of 80–100 torr). Below 100 torr the response was nearly linear and the slope of the regression line was 0·785 % per torr. Thus the mean decline in flow was 15·7 % for every 20 torr fall in P_{O_2} below 100 torr. In a few curves there was some flattening at low P_{O_2} values (Fig. 1 *B*). Curves

were easily repeatable in most experiments and points measured with single gas mixtures usually fitted well; occasionally slight differences may have indicated a change in sensitivity.

In the control state, lobar venous P_{CO_2} was often low (Fig. 6). This was probably due to the small dead space of the ventilating tube to the lobe compared to its normal tracheal connexions. In later experiments the

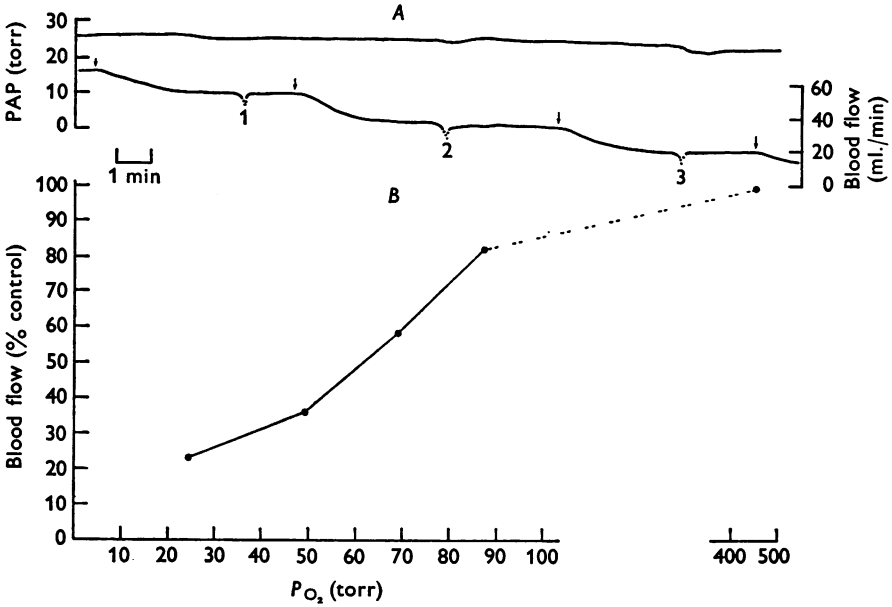

Fig. 1. Hypoxia. Cat: 2·2 kg, chloralose.

A. Tracing of part of pulmonary venous blood flow from left lower lobe and PAP record; at arrows ventilation with a lower O_2 mixture. Samples taken at equilibrium (1, 2, 3).

Sample values:	P_{O_2} (torr)	P_{CO_2} (torr)	pH
Control 100 % O_2 (before trace)	440	28·5	7·425
(1) Air	87	29	7·450
(2) 12 % O_2 in N_2	69	26·5	7·350
(3) 5 % O_2 in N_2	49	23	7·415
(off trace) 100 % N_2	24·5	19	7·605

Initial blood flow 62·3 ml./min, PVP fell by 0·4 torr.

B. Stimulus–response curve for hypoxia calculated from observations shown in *A*.

tube was lengthened, P_{CO_2} values were more normal and results were similar. P_{CO_2} values decreased as hypoxia increased.

Stimulus–response curves in dogs. The shape of the curves was similar to those found in cats (Figs. 3*A* and 7*B*) but they mostly lay to the left of the cat curves; maximum flow reduction was less and P_{CO_2} values were higher than in the cat (25–47 torr). The slope of the regression line for P_{O_2} values

less than 100 torr was 0·592 % per torr indicating an 11·8 % reduction in flow for every 20 torr fall in P_{O_2}. We are unsure as to whether these differences were due to technical difficulties in the dog preparation or a real species difference.

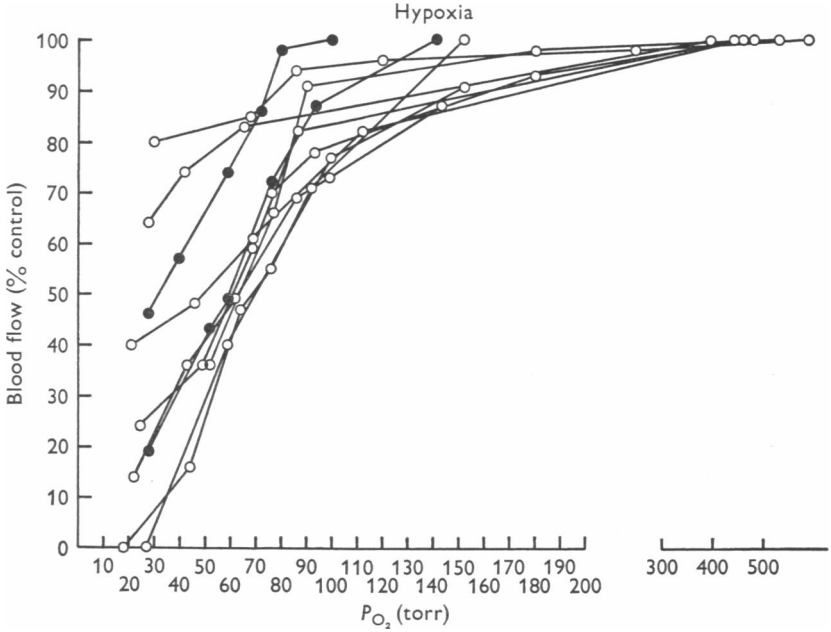

Fig. 2. Stimulus–response curves for hypoxia, eleven cat experiments. ○, control ventilation with 100 % O_2 (in a few no control P_{O_2} was measured). ●, control ventilation with air. For all values of P_{O_2} of 100 torr or less: $b = 0{\cdot}785$ %/torr; $r = 0{\cdot}750$; $P < 0{\cdot}001$.

Hypercapnia

In cats, ventilating the left lower lobe with increasing concentrations of CO_2 in O_2, caused a fall in blood flow with the first steps; thereafter there were smaller decreases, no change or small increases in flow (Fig. 4*A*). In dogs, there was usually a small fall in blood flow at all CO_2 concentrations. PAP rose slightly in cats ($+1{\cdot}2 \pm 0{\cdot}52$ torr) and fell slightly in dogs ($-1{\cdot}5 \pm 0{\cdot}66$ torr); PVP fell ($-0{\cdot}7 \pm 0{\cdot}21$ torr in cats; $-0{\cdot}5 \pm 0{\cdot}31$ torr in dogs). In some experiments at each change of CO_2 concentration blood flow fell sharply but then rose to an intermediate value. As samples were not taken at both the lowest and equilibrium values it is impossible to be sure whether 'adaptation' or transient changes in P_{CO_2} had occurred.

On returning to 100 % O_2 after hypercapnia, control levels of blood flow were rapidly restored.

Stimulus–response curves in cats. Fig. 4*B* shows a single curve and Fig. 5 those from all experiments. As P_{CO_2} increased, flow fell sharply at first

and then flattened out or actually rose. These changes were independent of the initial P_{CO_2} and the increases in flow sometimes seen at high P_{CO_2} values were not due to pressure changes. The maximum change was less than that encountered with hypoxia. Plots of pH against flow were similar in shape to the CO_2 curves. Within the normal physiological range (40–46 torr P_{CO_2}) the effect on flow was small and variable being either an increase or decrease. During the steep part of the curve (below

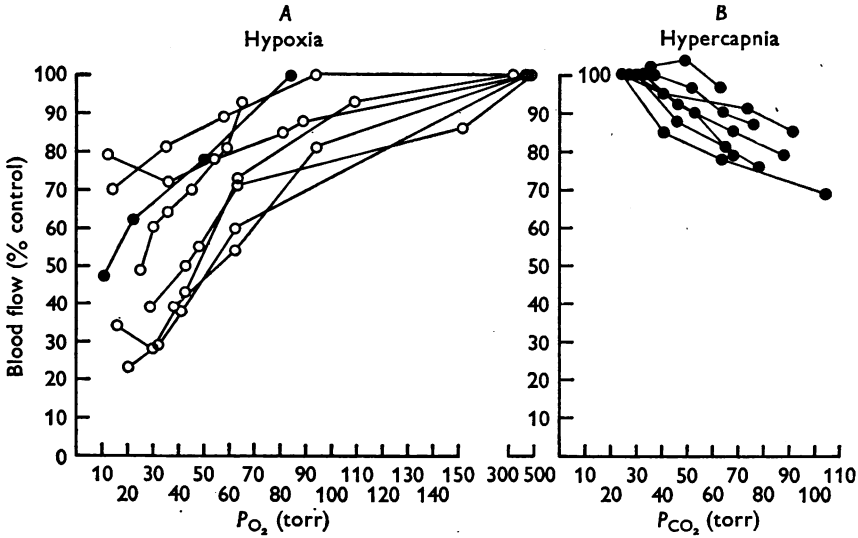

Fig. 3. *A*. Stimulus–response curves for hypoxia (eight tests from five dog experiments). ○, control ventilation with 100 % O_2. ●, control ventilation with air. For all P_{O_2} values of 100 torr or less: b = 0·592 %/torr; r = 0·652, $P < 0·001$.

B. Stimulus–response curves for hypercapnia (seven tests from four dog experiments). b = − 0·350 %/torr; r = − 0·814, $P < 0·001$.

55 torr) the relationship was nearly linear; the slope of the regression line was 0·969 % per torr. Thus a rise in P_{CO_2} of 20 torr would cause a 19·4 % fall in blood flow.

Stimulus–response curves in dogs. These differed from the cat curves in that the initial fall in blood flow was less steep (Fig. 3*B*), the levelling out at high P_{CO_2} values was less marked and no increases in flow were observed within the range of gas tensions studied. The slope of the regression line was 0·35 % per torr. Thus dog pulmonary vessels may be less sensitive to CO_2 than cat vessels.

In both species the effect of CO_2 was studied at high oxygen concentrations. The action of increasing hypercapnia in the presence of hypoxia remains to be studied.

Autonomic blockade

In two cats bretylium (20 mg/kg I.V.) and atropine (1 mg/kg I.V.) did not alter the response to hypoxia; in a third cat the response was slightly diminished. In one cat the effect of hypercapnia was unchanged, and in another it was slightly diminished after similar doses of bretylium and atropine.

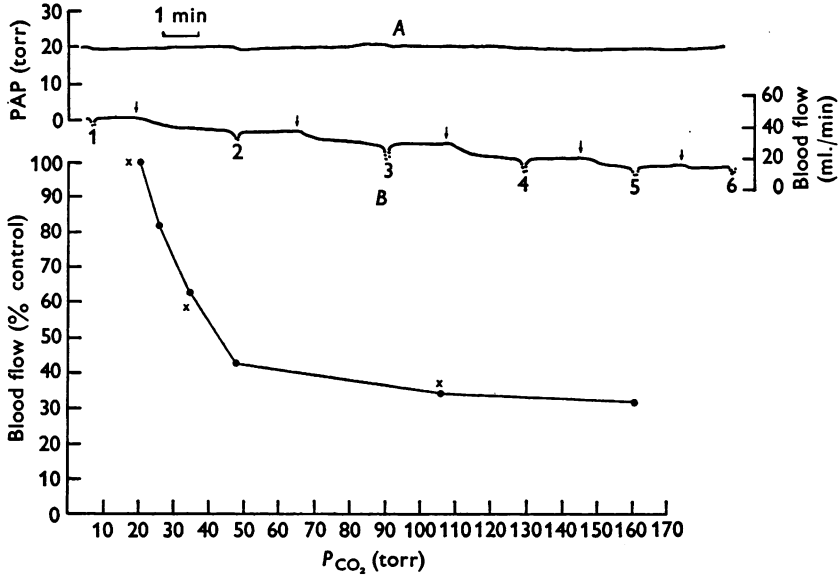

Fig. 4. Hypercapnia. Cat: 2·6 kg, chloralose.

A. Tracing of blood flow and PAP record; at arrows ventilation with a higher CO_2 mixture. Samples taken at equilibrium (1–6).

Sample values:	P_{O_2} (torr)	P_{CO_2} (torr)	pH
(1) 100 % O_2	480	20	7·490
(2) Approx. 2 % CO_2 in O_2	470	25·5	7·350
(3) 5 % CO_2 in O_2	440	34	7·280
(4) 10 % CO_2 in O_2	460	47·5	7·275
(5) > 10 % CO_2 in O_2	400	105	6·905
(6) ⩾ 10 % CO_2 in O_2	495	160	6·795

Initial blood flow 37·0 ml./min, PVP fell 2·0 torr.

B. Stimulus–response curve for hypercapnia calculated from observations shown in *A* (●).

(×) One control point plus two points measured during the first phase fall in flow after bronchial occlusion later in the same experiment.

Sample values:	P_{O_2} (torr)	P_{CO_2} (torr)	pH
Control	480	17	7·385
First phase fall in blood flow	390	33·5	7·190
	400	105	6·905

Initial flow 21·1 ml./min, PAP rose 2·0, PVP rose 0·7 torr.

Hypoventilation

This was produced by a progressive reduction of the respiratory stroke volume to the lobe, in three cats and two dogs. Air was used as the ventilating gas since O_2 caused collapse of the lobe. In all animals blood flow fell at each reduction of the stroke volume. Pulmonary venous P_{O_2} during hypoventilation was plotted against pulmonary venous blood flow (% control) and the curves were similar to those found during hypoxia (Figs. 6 and 7*B*). The 100% O_2 point was taken as control so that the first

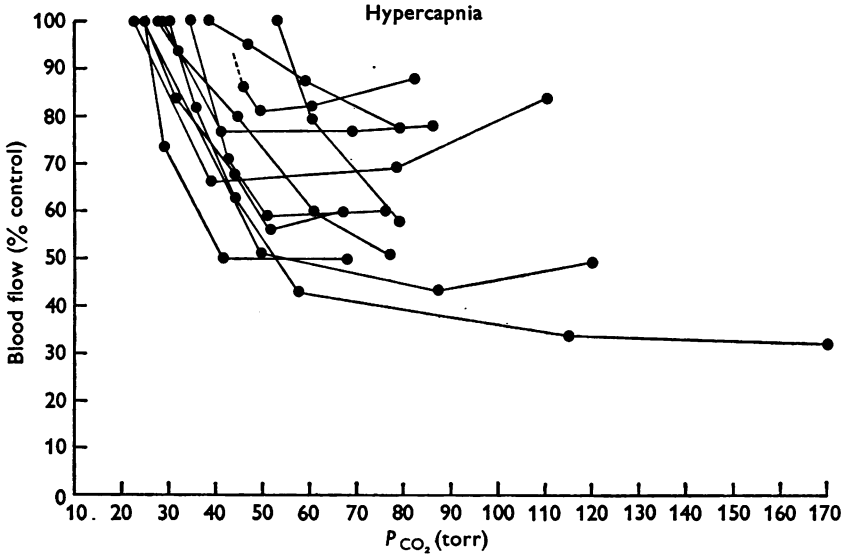

Fig. 5. Stimulus–response curves for hypercapnia, eleven cat experiments. On one curve, the control ventilation was with air and this point is not shown. For all P_{CO_2} values below 55 torr: $b = -0{\cdot}969\%$/torr; $r = -0{\cdot}607$, $P < 0{\cdot}001$.

reduction in flow was due to changing from O_2 to air and subsequent reductions were due to lowering the pump stroke. P_{CO_2} rose at each reduction of the pump stroke but the flow changes were too great to be accounted for by hypercapnia. In three experiments, which included those shown in Figs. 6 and 7*B*, the points measured during hypoventilation lay parallel but to the right of the hypoxia curve and in two (one cat and one dog) they were superimposed. Thus hypoxia could be the main cause of the fall in flow through underventilated lung but there may be an additional factor.

Total bronchial occlusion leading to collapse of a lobe

In previous work, blood flow to a lobe was shown to decline rapidly after bronchial occlusion (Barer *et al.* 1969). When the lobe was ventilated

with O_2 and the bronchus was occluded in the inspiratory phase, the main decline in flow was delayed for several minutes until the store of O_2 in the lung was absorbed. During this first phase blood flow fell by a small

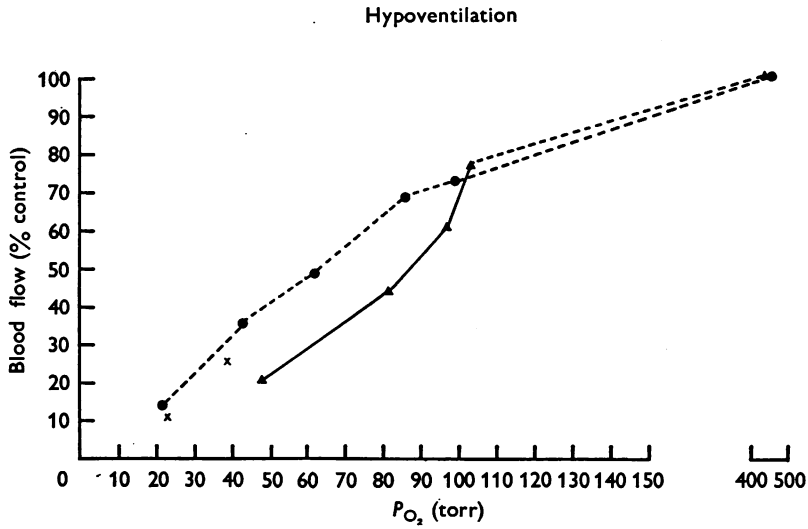

Fig. 6. Hypoventilation compared with hypoxia. Cat: 3·2 kg, chloralose. Curve for hypoventilation ▲——▲.

Sample values:	P_{O_2} (torr)	P_{CO_2} (torr)	pH
100 % O_2	400	—	—
Air	103	11	7·450
Stroke of ventilating pump reduced 3 times	97	14	7·395
	82	17	7·305
	48	25	7·240

Initial blood flow 43·1 ml./min, PAP rose 3·0, PVP fell 0·6 torr.
Stimulus–response curve for hypoxia ●---●.

Sample values:	P_{O_2} (torr)	P_{CO_2} (torr)	pH
100 % O_2	400	—	—
30 % O_2 in N_2	143	11·5	7·530
Air	99	10	7·560
18 % O_2 in N_2	86	10·5	7·440
10 % O_2 in N_2	62	10	7·670
Approx. 5 % O_2 in N_2	43	10	7·630
100 % N_2	22	10	7·730

Initial blood flow 48·7 ml./min, PAP rose 2·3, PVP fell 0·7 torr.
(×) Two points measured during the second phase fall in flow after bronchial occlusion.

Sample values

P_{O_2} (torr)	P_{CO_2} (torr)	pH
39	16·5	7·260
23·5	24	7·240

Initial blood flow 43·1 ml./min, PAP rose 2·6, PVP fell 1·3 torr.

amount to an equilibrium level (occasionally this fall was absent). During the second phase blood flow fell sharply to a new low level as pulmonary venous P_{O_2} fell rapidly. We considered that the first phase was due to hypercapnia and the second to hypoxia as P_{CO_2} changes precede P_{O_2} changes in the O_2-filled lobe. The present work provided an opportunity to test these hypotheses by enabling points measured after bronchial occlusion to be fitted to the hypoxia and hypercapnia stimulus–response curves. A typical trace of blood flow after bronchial occlusion in an O_2-filled lobe in a dog is shown in Fig. 7*A*. The two phases of decline in blood flow are clearly seen. Points measured at, or near, equilibrium in phases 1 and 2 (samples 1 and 4) are plotted on the hypercapnia curve (Fig. 7*C*) and hypoxia curve (Fig. 7*B*) for the same animal. An equally good correspondence was found in thirteen other animals. Points measured during periods of rapid changes sometimes fitted less well. Fig. 6 shows two points measured in the second phase fall in blood flow in a cat.

Fig. 8 relates blood flow changes after bronchial occlusion to those occurring during hypoxia and hypercapnia in all experiments (nine cats, five dogs). On the left, blood flow in the first phase after bronchial occlusion is compared with blood flow during hypercapnia in the same animal (read from the stimulus–response curve at the same P_{CO_2}). There is a close linear relationship (correlation coefficient $r = 0{\cdot}926$, $P < 0{\cdot}001$). On the right is plotted the relationship between blood flow in the second phase after bronchial occlusion and that during hypoxia in the same animal (read from the stimulus–response curves at the same P_{O_2}). There is again a close linear relationship ($r = 0{\cdot}829$, $P < 0{\cdot}001$). The rather greater scatter may be attributable to the greater variations in PAP in these tests.

DISCUSSION

In 1951, Duke observed vasoconstriction in isolated perfused cat lungs when the O_2 concentration of the ventilating gas mixture was reduced to 15% or less; an inverse relationship was shown between inspired P_{O_2} (0–120 torr) and the % increase in PAP at constant blood flow. In 1953, Rahn & Bahnson calculated the proportion of blood flowing to the right and left lungs after ventilation of the left lung with low O_2 mixtures. Maximum diversion of flow from the left to the right lung occurred when the left alveolar P_{O_2} fell from 120 to 60 torr. There was also a significant change in flow to the left lung when its alveolar P_{O_2} fell from 158 to 120 torr. Hauge & Staub (1969) measured arterial blood flow to a lobe of lung receiving its normal blood supply while ventilating it with different gas mixtures. A stepwise decrease in blood flow occurred as the O_2 concentration was reduced. The relation between calculated pulmonary vascular

resistance and the O_2 concentration of the ventilating gas was curvilinear; resistance increased steeply when the O_2 concentration was reduced below 10%. We have confirmed and extended these observations in two species. Although the technique did not exclude participation of local or reflex nervous activity in the response to local hypoxia and hypercapnia, the tests after autonomic blockade indicated that at least the greater part of the effects was caused by local non-nervous mechanisms. During hypoxia it

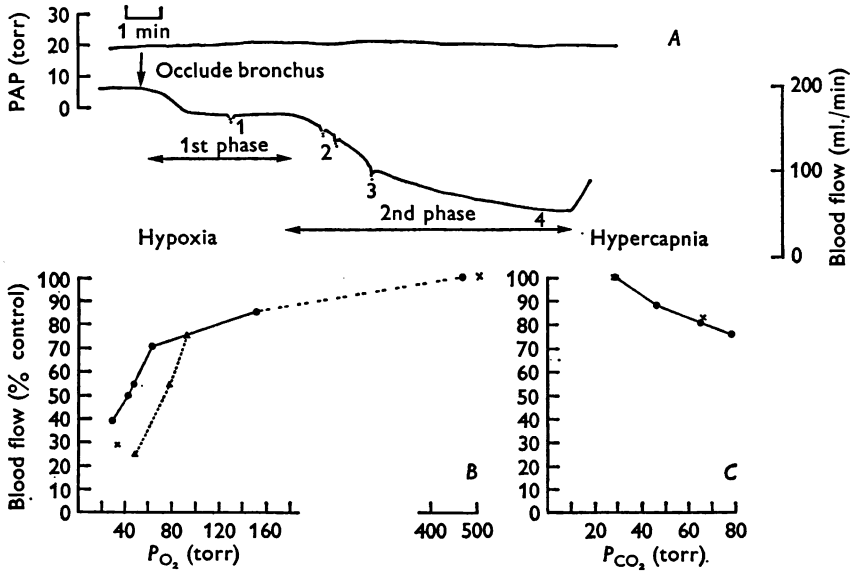

Fig. 7. For legend see opposite page.

is the reduction in alveolar O_2 tension which initiates vasoconstriction (although changes in P_{O_2} in pre-alveolar vessels may also be effective (Bergofsky, 1969)). In our experiments the gas tensions in pulmonary venous blood were probably close to alveolar gas tensions as the diluting effect of bronchial venous blood was avoided. There was an inverse relationship between P_{O_2} and local blood flow; a measurable decrease in flow took place when P_{O_2} fell from 500 to 100 torr. Below 100 torr flow fell steeply but there may have been some levelling off at very low P_{O_2} values. A fall in P_{O_2} from a normal pulmonary venous value (100 torr) to a normal pulmonary arterial value (40 torr) decreased blood flow by 47%. Thus adjustments in blood flow would be expected to occur in any region in which venous blood was incompletely oxygenated in its passage through the lung. Blood would be diverted to better ventilated areas and in the poorly ventilated region the slower flow rate would facilitate equilibration between alveolar gas and capillary blood.

The stimulus–response curves to hypercapnia differed from those to hypoxia in that the flow flattened out at high P_{CO_2} values and the total reduction in flow was rarely more than 50 % of control values. A rise in P_{CO_2} from a normal pulmonary venous (40 torr) to a normal pulmonary arterial value (46 torr) caused at most a 6 % fall in blood flow. Thus the

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Legend to Fig. 7.

Fig. 7. The effect of bronchial occlusion compared with the effects of hypoxia and hypercapnia. Dog: 17·1 kg., morphia and pentobarbitone.

A. Occlusion of an O_2-filled lobe, tracing of blood flow and PAP record: bronchus was occluded at arrow and flow fell in two phases. Samples 1–4 (slight artifact just before sample 2).

Sample values:	P_{O_2} (torr)	P_{CO_2} (torr)	pH
Control (before trace)	510	28·5	7·390
(1) 1st phase	405	66	7·100
(2)	38	65	7·125
(3) 2nd phase	36	47	7·190
(4)	34	52	7·190

Initial blood flow 193 ml./min, PVP fell 1·3 torr.

B. Stimulus–response curve for hypoxia (●).

Sample values:	P_{O_2} (torr)	P_{CO_2} (torr)	pH
100 % O_2	470	33·5	7·310
30 % O_2 in N_2	152	30	7·346
Air	63	28·8	7·400
10 % O_2 in N_2	48	29	7·380
	43	31	7·460
approx. 7 % O_2 in N_2	29	22·5	7·470

Initial blood flow 222 ml./min, PAP fell 1·0, PVP 0·6 torr.

(×) Control point and point measured near equilibrium (sample 4) in the second phase fall in flow after bronchial occlusion.

(▲) Hypoventilation:

Sample values:	P_{O_2} (torr)	P_{CO_2} (torr)	pH
Air	92	27	7·350
Stroke of ventilating pump	78	32·5	7·290
reduced twice	49	53	7·200

No control sample on 100 % O_2 and this point not shown. Initial blood flow 145 ml./min, PAP rose 1·0, PVP fell 0·3 torr.

C. Stimulus–response curve for hypercapnia (●).

Sample values:	P_{O_2} (torr)	P_{CO_2} (torr)	pH
100 % O_2	475	30	7·330
5 % CO_2 in O_2	495	46	7·245
10 % CO_2 in O_2	420	65	7·120
15 % CO_2 in O_2	485	76	7·080

Initial blood flow 237 ml./min, PAP fell 1·0, PVP fell 1·5 torr.

(×) Control point and point measured during the first phase fall in flow after bronchial occlusion (sample 1).

effect of hypercapnia on local flow adjustments is much less than that of hypoxia. However, there is evidence (Enson, Giuntini, Lewis, Morris, Ferrer & Harvey, 1964; Rudolph & Yuan, 1966; G. R. Barer, J. R. McCurrie & J. W. Shaw, unpublished) that the acidifying effect of hypercapnia may enhance the effect of hypoxia. This has not been studied in this work.

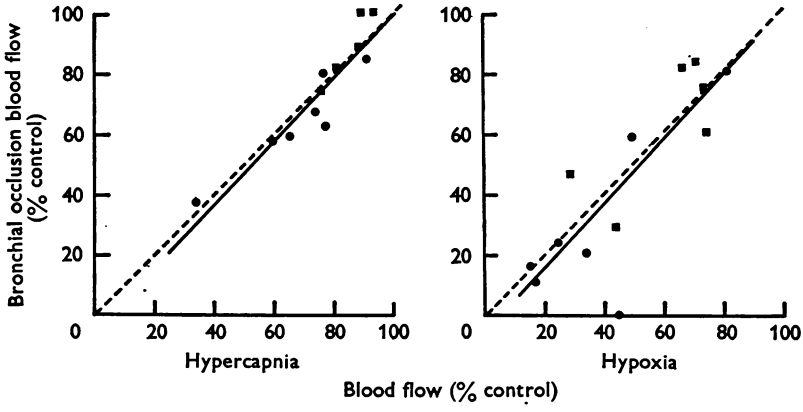

Fig. 8. Left: plot of % fall in blood flow in the first phase after bronchial occlusion against % fall during hypercapnia in the same animal (read from the stimulus–response curve at the same P_{CO_2}). $r = 0{\cdot}926$, $P < 0{\cdot}001$. Right: plot of % fall in blood flow in the second phase after bronchial occlusion against percentage fall during hypoxia in the same animal (read from the stimulus–response curve at the same P_{O_2}). $r = 0{\cdot}829, P = < 0{\cdot}001$. Data from nine cats (●) and five dogs (■). —— = regression line; ------ = line of 100 % agreement.

The pulmonary vasoconstrictor effect of CO_2 may be due to the fall in blood pH which it causes (Barer *et al.* 1967; Bergofsky, Lehr & Fishman, 1962). In this work the pH/blood flow curves were similar to the P_{CO_2}/ blood flow curves. Earlier work from this laboratory has shown that for a given change in blood pH, the vasoconstrictor effect of CO_2 is less than that of fixed acids. Viles & Shepherd (1968) also observed, in isolated cat lungs, that CO_2 at a given pH had a much smaller constrictor action than lactic acid. They suggested that the CO_2 molecule can cause vasodilatation. Recently Shaw (1970) has found direct evidence for a dilator action of CO_2 in the isolated perfused rat lung. The present work provides no direct evidence for vasodilatation but the curvilinear stimulus–response relationship and the 'adaptation' at high P_{CO_2} levels could be explained by a balance between constrictor and dilator mechanisms.

Hypoxia is probably the most important cause of a reduction in pulmonary blood flow during hypoventilation and after bronchial occlusion.

The fall in blood flow during hypoventilation was similar to that found during ventilation with different O_2 mixtures. Occasional displacement to the right of the stimulus–response curve may indicate another factor, such as CO_2, in operation. After bronchial occlusion of an O_2-filled lobe, blood flow falls in two phases (Barer *et al.* 1969). Flow measured in the first phase fits the hypercapnia curve well and flow during the second phase fits the hypoxia stimulus–response curve. This strongly suggests that hypercapnia is responsible for the first phase fall and hypoxia for the second phase fall in blood flow. Thus hypoxia is the main cause of the reduction in flow through a collapsed lung but hypercapnia may play a small additional part. Also mechanical factors could not have been important in reducing flow in these experiments, as indicated in the previous study.

Some workers believe mechanical factors wholly explain the distribution of gas and blood in the lung under normal conditions. Hypoxic vasoconstriction is considered to be a relic of a foetal mechanism which only operates in the adult under abnormal conditions. The stimulus–response curves found in our experiments do not support this contention. West & Dollery (1960) have shown by a radioactive gas technique that there is a gradient of $\dot{V}/\dot{Q}$ ratios increasing from the base to the apex of the upright human lung, which can be explained entirely on mechanical grounds. Yet West's calculations based on these measurements (1962) predict that there would be large differences in gas tensions in blood leaving different vertical levels of the lung, (P_{O_2} 132 torr and P_{CO_2} 28 torr at the apex; P_{O_2} 89 torr and P_{CO_2} 43 torr at the base). Reference to our stimulus–response curves, if applicable to man, show that these differences would affect blood flow. But West also calculated that $\dot{V}/\dot{Q}$ inequalities of this magnitude would only cause a fall in arterial P_{O_2} of 4–5 torr, a disability so negligible as to render adjustment of blood flow to ventilation unnecessary. However, these calculations stem from measurements in awake upright man often after a deep breath, which would minimize local variations in gas tensions. During quiet respiration it is likely that parts of the lung are poorly ventilated and local regulation of blood flow of greater consequence.

An interesting comparison can be drawn between the shape of our stimulus–response curves and those for the carotid body. The relation between P_{O_2} in the fluid perfusing the carotid body to the rate of discharge of the carotid nerve fibres (Hornbein, 1968) is similar in shape to our hypoxia curve. Both have high thresholds and a steep increase in response in the physiological range. The high threshold to changes in oxygen tension is of particular interest and may indicate an unusual biochemical mechanism (Coxon, 1968). Alternatively the distance and barriers through which oxygen must diffuse before reaching the receptor could be such that the receptor is subject to an O_2 tension much lower than that in the alveolus.

Forster (1968) has discussed this problem in relation to the carotid body. The parallelism between the lung and carotid body is of special interest in the light of Torrance's view (1969) that studies on the lung vessels may 'reveal the intimate mechanism of a very elementary excitatory response to hypoxia'. There is no evidence that a nervous mechanism is involved in the lung but the first steps in the chain of events initiated by hypoxia might be similar in the two organs. The parallelism between the carotid body and lung extends to the action of CO_2. In both, the action of CO_2/pH is less than that of hypoxia and in both the two interact. In the carotid body the action of hypoxia can be modified independently of that of pH (Krylov & Anichkov, 1968). In the lung the action of hypoxia was abolished by pharmacological agents which left the response to CO_2 relatively intact (Barer, 1966*b*; Barer & McCurrie, 1969).

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