CONTRIBUTION OF POLYCYTHAEMIA TO PULMONARY HYPERTENSION IN SIMULATED HIGH ALTITUDE IN RATS

BY GWENDA R. BARER, DENISE BEE AND RICHARD A. WACH*

From the University Department of Medicine, Royal Hallamshire Hospital, Sheffield S10 2JF

SUMMARY

1. A rat model was used to assess the viscosity factor in pulmonary hypertension of high altitude.

2. Rats exposed to 10% O_2 for three weeks developed increased pulmonary vascular resistance (p.v.r.) and polycythaemia; the haematocrit (Hct) was 50–60%, values similar to those in normal men at high altitudes.

3. The contribution of high Hct to the increased p.v.r. was assessed in isolated perfused lungs of chronically hypoxic rats perfused with their own high Hct blood, or normal Hct blood from control rats. Pressure/flow relationships were measured over a wide range and the slope $(P/\dot{Q})$ of this relationship and its extrapolated intercept on the pressure axis were increased by high Hct blood. A return to low Hct blood did not restore initial conditions although a second perfusion with high Hct blood again increased p.v.r. and intercept. Lack of reversibility was attributed to changes with time in blood or lung.

4. In a second experiment designed to eliminate time changes, chronically hypoxic or litter-mate control rats were each perfused with only one blood, their own or each other's and $P/\dot{Q}$ relations were rapidly measured. The $P/\dot{Q}$ slope and pressure intercept increased progressively in the following groups: control rats perfused with their own blood (Hct 34%), control rats perfused with chronically hypoxic blood (Hct 56%), chronically hypoxic rats perfused with control blood (Hct 35%) and chronically hypoxic rats perfused with chronically hypoxic blood (Hct 53%).

5. To exclude factors in chronically hypoxic blood other than high Hct which might increase p.v.r., control rats were perfused with blood of different Hct obtained by centrifugation. High Hct again increased p.v.r.

6. There was a significant relationship in all rats between pulmonary artery pressure (P_{pa}), which takes into account both $P/\dot{Q}$ slope, intercept and Hct. There was substantial batch variation which may reflect sensitivity to hypoxia. In chronically hypoxic rats with high Hct blood, P_{pa} varied from 29–47 mmHg; with low Hct blood the range was 26–38 mmHg. Comparable values for control rats were 21–29 and 17–20 mmHg.

7. We conclude that the polycythaemic blood of chronic hypoxia contributes substantially to pulmonary hypertension. Where it is excessive, it may prejudice tissue blood flow.

* Authors' names are in alphabetical order.

INTRODUCTION

Changes in blood viscosity caused by alterations in the proportion of red cells to plasma have a substantial effect on both systemic and pulmonary vascular resistance. The packed cell volume, (haematocrit, Hct) is much increased in normal man living at high altitude and in patients with hypoxic lung disease. It is questionable whether the beneficial effect of the increased O_2 carrying capacity of the blood outweighs the deleterious effect of increased blood viscosity on tissue perfusion in all circumstances: chronic mountain sickness is probably one situation in which it does not. Moreover the contribution of polycythaemia to the pulmonary hypertension of high altitude has not been assessed. In normal animals changes in Hct have a substantial effect on pulmonary vascular resistance (Benis, Peslin, Mortara & Lockhart, 1967; Murray, Karp & Nadel, 1969), but the pulmonary circulation at high altitude differs from that at sea level. It resembles the fetal lesser circulation in that it is a high-pressure system with muscularized arterioles, whereas the precapillary vessels are normally thin-walled in the lung; the right ventricular wall is hypertrophied and the pulmonary arteries are less compliant (Emery, Bee & Barer, 1981). There have been many studies of the pulmonary circulation in simulated high altitude in animals but with the exception of studies on whole rats, where the viscosity factor is not assessed, (Kentera, Sušic, Cvetković & Djordjević, 1981) all have used blood of normal Hct.

In chronic hypoxia, whether due to high altitude (Lockhart, Zelter, Mensch-Dechenne, Antezana, Paz-Zamora, Vargas & Condert, 1976), lung disease in man (Abraham, Cole & Bishop, 1968) or simulated high altitude in animals (Herget, Suggett, Leach & Barer, 1978), pulmonary hypertension is only partially relieved when arterial P_{O_2} is brought to normal values. The residual hypertension is thought to be due to encroachment of new muscle on the lumen of resistance vessels and to high blood viscosity. In this study we have assessed the contribution of the raised Hct of chronic hypoxia to pulmonary vascular resistance. We have perfused lungs from chronically hypoxic and litter-mate control rats with their own or each others blood. The experiments were designed to exclude the effects of storing the blood or deterioration of the lung. In both groups of rats the high Hct blood had a substantial effect on pulmonary vascular resistance. To exclude the possibility that it was some property of this blood other than high viscosity (such as a vasoactive substance) which increased resistance, we showed that centrifuged normal blood of high Hct had the same effect. A preliminary account has been published, (Bee & Wach, 1981).

METHODS

SPF Wistar rats (Tuck's) were used. Litters of six male rats were obtained at 21 days and allowed to adapt to the laboratory for one or two weeks. Half of each litter was then placed in a normobaric environmental chamber, previously described, for 21 days (Leach, Howard & Barer, 1977) while the other half were kept in the same room in air. A proportion of the rats were non litter-mates of the same strain. O_2 concentration in the chamber was regulated at 10 %; CO_2 was absorbed with soda-lime and water vapour with silica gel; the chamber gases were circulated through two freezer units for cooling. We had previously shown that in a hypobaric chamber the changes in the right heart, pulmonary arterioles, pulmonary vascular resistance and Hct were similar to those which developed in the normobaric chamber at an equivalent O_2 partial pressure (Hunter, Barer, Shaw & Clegg, 1974).

The isolated perfused lung

All studies were made on isolated lungs perfused *in situ* by a modification of Hauge's method (Hauge, 1968; Emery *et al.* 1981). They were ventilated with 5 % CO_2 in air at 60 strokes/min (tidal volume 3–4 ml.). Blood was pumped from a reservoir kept at 37 °C, with a Marlow roller pump, through an electromagnetic flowmeter (Barer, Barer & Robinson, 1972; a modification of Wyatt, 1961) into the main pulmonary artery; it emerged from a cannula tied into the left atrium and returned to the reservoir. The resistance of the cannulae was negligible at the flows used. Mean inflow pressure and pulmonary artery pressure (P_{pa}) were measured laterally close to the pulmonary artery cannula. There was a bubble trap on the inflow side and blood samples for the measurement of Hct were taken from the effluent side. Blood flow ($\dot{Q}$) was set at 18–20 ml./min, which is approximately 100 ml./kg for the average weight of rat used. The same flow was used for control and chronically hypoxic litter-mates; although growth of the latter is retarded, there is evidence that in hypoxia the lungs grow normally and the pulmonary vascular bed is not smaller (Emery *et al.* 1981). Pressure/flow lines were obtained by altering the output of the pump and measuring the resultant P_{pa}. Within the flow range studied, except where stated, the relationship between flow and pressure was linear. Regression lines are therefore shown.

The circuit was initially washed through with saline and then filled with dextran which was pumped through the lungs to clear them of blood. The lungs were then perfused with blood. Between sequential perfusions of blood of differing Hct, the lungs were washed through with dextran. There was minimal dilution of blood with dextran. The rats were anaesthetized with pentobarbitone I.P. (60 mg/kg) and 8–10 ml. blood was taken from the inferior vena cava into heparinized syringes. When required, extra blood was taken from another chronically hypoxic or control rat. Blood pH was measured with a Corning electrode and, if low, was adjusted with small quantities of $NaHCO_3$. The time from taking blood to establishing the circuit was *ca.* 15 min. The chest was opened rapidly under artificial ventilation and the heart continued to beat until the moment the cannula was pushed through the right ventricle into the pulmonary artery and was tied with a ligature which also occluded the aorta. From cardiac arrest to the beginning of perfusion took <5 min. P_{pa} (mean), referred to the level of the pulmonary artery, was measured with an Elema-Schönander pressure transducer and together with mean flow, was displayed on an SE Laboratories U.V. recorder. Left atrial pressure (P_{la}) was constant and determined by a short horizontal tube to the reservoir on a level with the left atrium. The reference point was above the level of the top of the lung in inflation; both P_{pa} and P_{la} were greater than alveolar pressure so that $P_{pa} - P_{la}$ determined blood flow. For clarity, the exact differences of detail between experiments and the reason for them is given with the results.

Resistance

The resistance of the pulmonary vascular bed (p.v.r.) was defined as the slope of the regression line relating P_{pa} to $\dot{Q}$ ($P/\dot{Q}$).

Statistics

Means and standard errors of the mean (S.E. of mean) were calculated. Significance of differences was assessed by the Student two-tailed *t* test. Regression lines were calculated by the method of least squares.

RESULTS

Chronically hypoxic rat lungs perfused with high and low Hct blood

Experiment 1. In two series of experiments ($n = 6$, $n = 7$) the lungs of chronically hypoxic rats were perfused alternately with blood drawn from chronically hypoxic or control rats and placed in two plastic reservoirs at 37 °C; the unused reservoir was kept stirred. The low Hct blood was used first except in two experiments but the order did not affect results. Fig. 1 shows the results from a typical experiment; the continuous line indicates the first pair of results measured when the blood was fresh (the first two lines only are used in subsequent statistics). The slope of the line (p.v.r.)

increased when the blood was changed from lower to higher Hct. When repeated (dashed lines), a return to a near initial Hct did not restore initial resistance although it was raised again with higher Hct blood.

The two series of experiments differed in that the P_{pa} at the same flow and the pulmonary vascular resistance were consistently higher in one group of rats than the other and this was the group with the lower haematocrit. No difference in technique was detected. Table 1 lists the mean slope related to the haematocrit in the two series
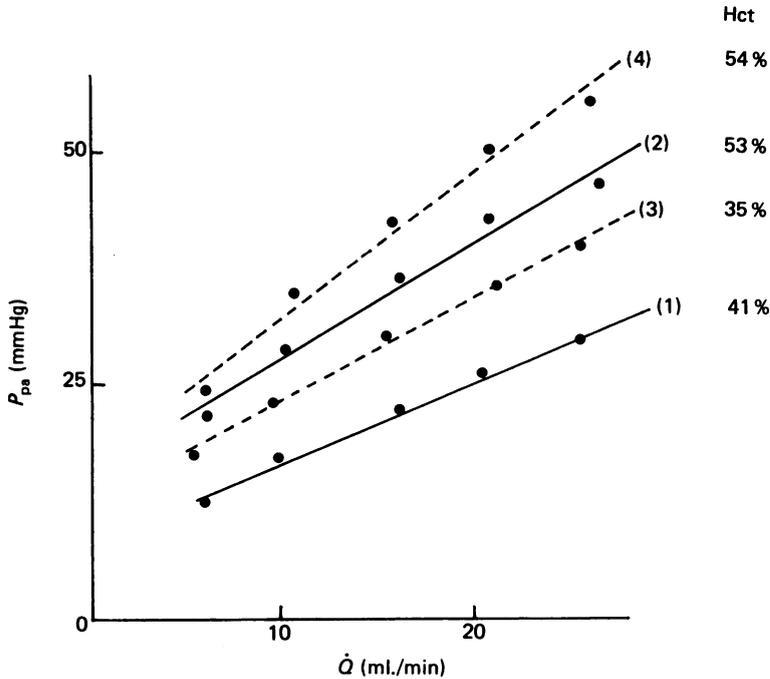

Fig. 1. Four sets of pressure flow data obtained from one chronically hypoxic rat lung measured in the sequence shown in brackets. Blood was perfused from low and high Hct reservoirs. Hct values are given beside the calculated regression lines. Note the increased slope with increased Hct but that the second pair of tests (●– – –●) does not reproduce the conditions of the first pair (●———●).

of experiments (1 *A* and *B*). The pulmonary artery pressure (P_{pa}) at a flow rate of 20 ml./min. (read from the lines) is also listed for comparison with other groups, since this takes into account both slope and extrapolated intercept and is the mean load born by the right ventricle. There was a statistically significant relationship between P_{pa} and Hct for both experiments; the relationship for the group with the lower Hct was much steeper; P_{pa} rose 3 mmHg for each 10 % rise in Hct in group A and 10 mmHg in group B.

Chronically hypoxic and control rats perfused with their own or each others blood

Experiment 2. The above experiments showed that pulmonary vascular resistance always increased with Hct in chronically hypoxic rats and that this effect was reversible but not completely. Thus in Experiment 2, in order to avoid the possible effects due to the passage of time and storage of blood, each rat was perfused with one kind of blood only. Pressure/flow relationships were measured as soon as the pH was adjusted so that the duration of the test was brief and blood was not stored. The

TABLE 1. Pulmonary vascular resistance and pulmonary artery pressure (P_{pa}) related to haematocrit (Hct) in chronically hypoxic and control rats

Experiment (n)		Hct (%)	†Slope of $P/\dot{Q}$ line	P_{pa} at 20 ml./min (mmHg)
(1) Chronically hypoxic (CH) rats, groups A and B
(6)	A	42±2·0	0·79±0·05	20·0
	A	61±2·0**	1·15±0·07*	28·8
(7)	B	39±0·9	0·9±0·07	27·2
	B	52±0·6**	1·53±0·11**	40·8
(2) Chronically hypoxic (CH) and control (C) rats
(7)	CH	35±0·6	1·43±0·11	37·8
(5)	CH	53±3·8**	1·70±0·09	46·8
(8)	C	34±0·3	0·68±0·03	17·6
(9)	C	56±2·4**	1·08±0·06**	26·4
(3) Control rats (C), centrifuged blood A and B
(6)	A	40±0·8	0·81±0·05	19·7
	A	58±2·3**	1·38±0·13**	28·7
(7)	B	51±0·8	0·88±0·04	21·1
	B	42±0·9**	0·69±0·04*	18·1
	B	32±0·7**	0·61±0·04	17·0

Values are means ± S.E. of mean. Experiment 1: Two reservoirs; Experiment 2: one rat–one type of blood; Experiment 3: A, centrifuged blood two reservoirs, B, centrifuged blood, twice diluted. Body weights (g): Experiment 1A, 264±6; 1B, 285±6; 2CH, 196±5; 2C, 261±7; 3A, 323±13; 3B, 407–20. For slope of regression line, correlation coefficient > 0·91 except once (0·85).
* Significantly different from value in line above, $P < 0.01$; ** $P < 0.001$.
† mmHg/ml./min.
P_{pa} read from $P/\dot{Q}$ lines.

pressure/flow regression lines from the four groups showed increasing slopes and extrapolated intercepts in the following order: control rats perfused with control blood, control rats perfused with chronically hypoxic blood, chronically hypoxic rats perfused with control blood and chronically hypoxic rats perfused with their own blood. There was very little overlap between the pressure flow lines of these groups. Thus in Fig. 2, lines for the four groups calculated from the mean slopes and intercepts of each of them are shown. This statistical estimation assumes that there is only random within-group variation which is probably correct; the lines show the clear separation of the four groups. Details of slopes, P_{pa} and Hct are shown in Table 1. (Experiment 2). In order to explore a wider flow range four further chronically hypoxic and four control rats were perfused with their own blood and P_{pa} was

measured at flow rates ranging from 5–50 ml./min. Differences similar to those shown in Fig. 2 were seen but the $P/\dot{Q}$ line curved slightly towards the flow axis at high flow rates.

The upper part of Fig. 3 shows the relationship between P_{pa} and Hct for the four groups shown in Fig. 2. For a 10% rise in Hct P_{pa} rose 3 mmHg in controls and 5 mmHg in chronically hypoxic rats. P_{pa} was higher at all Hct values in the latter.
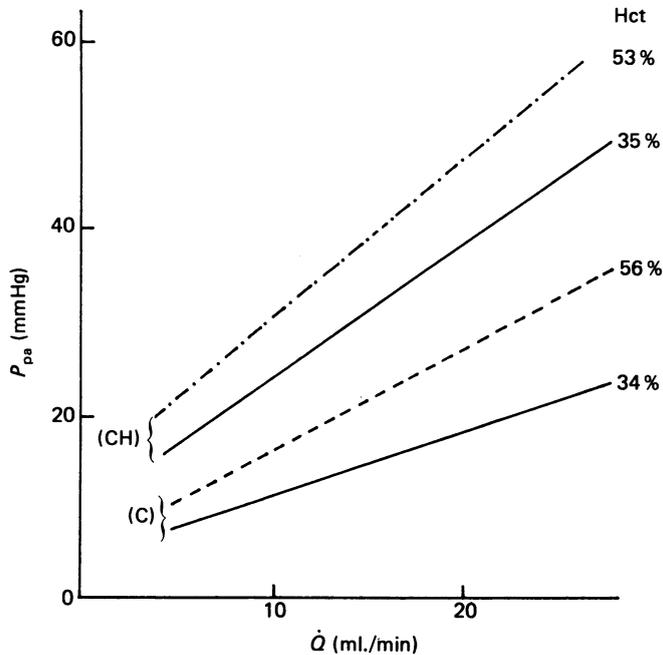

Fig. 2. Summary of $P/\dot{Q}$ lines from Experiment 2. Chronically hypoxic (CH) and control (C) rats were perfused with their own or each other's blood. Mean regression lines for C rats perfused with control blood ($n = 8$, ——), C rats perfused with CH rat blood ($n = 9$, – – –), CH rats perfused with C rat blood ($n = 7$, ——), and CH rats perfused with CH rat blood ($n = 5$, –·–). There was virtually no overlap between the individual $P/\dot{Q}$ lines of the four groups from which these mean lines were calculated. Note increasing slope in the four groups in order described above. Mean Hct values are shown.

When perfusion of control and chronically hypoxic lungs with high Hct blood was prolonged, the P_{pa} began to increase; the increase was much more pronounced in chronically hypoxic lungs. This suggested that some property other than viscosity might be the cause of the high resistance and P_{pa} in the chronically hypoxic group. No obvious mal-distribution of perfusion was present as dye injected into the inflow line was uniformly distributed macroscopically. There was an element of vasoconstriction because at the end of the experiments large doses of isoprenaline (1 μg) reduced P_{pa} but not to initial levels. Thus it was necessary to see if control blood of different Hct caused similar effects.
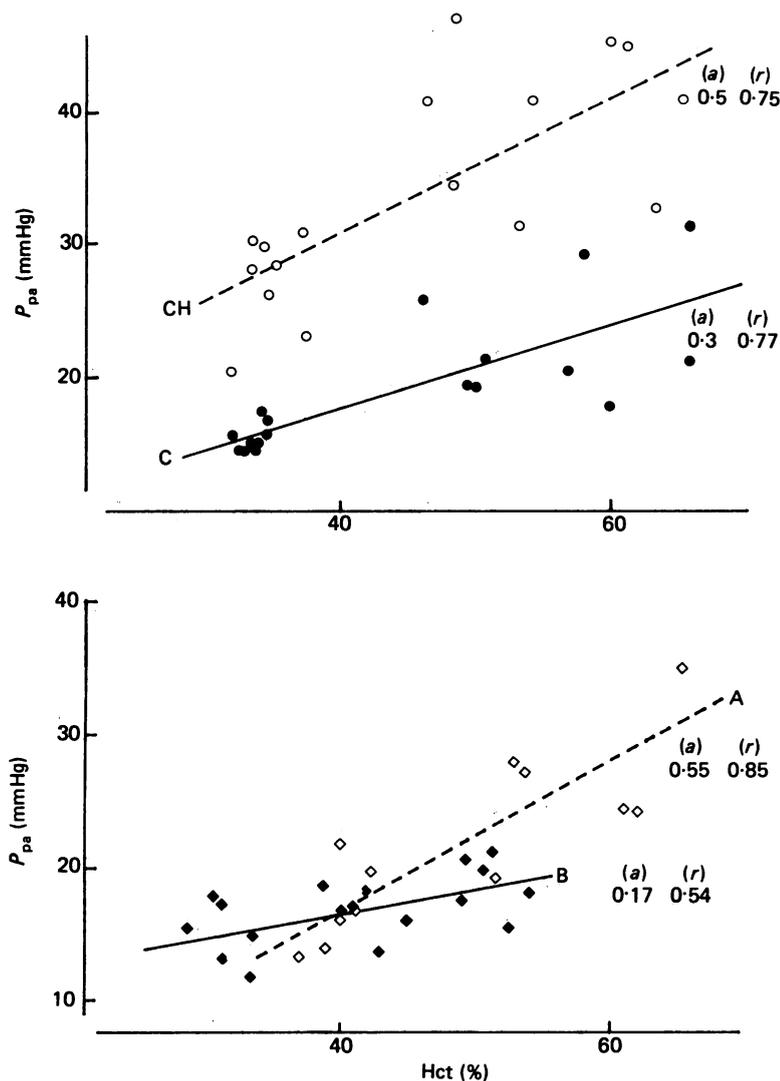
Fig. 3. Relationship between pulmonary artery pressure (P_{pa}) and Hct for chronically hypoxic and control rat lungs. Above, P_{pa} is plotted against Hct for all the chronically hypoxic (CH, $\bigcirc$, ---) and control rat lungs (C, $\bullet$, ——) in Experiment 2 (each lung was perfused with high or low Hct blood only), P_{pa} was measured from the pressure/flow relationships at a flow rate of 20 ml./min. Below, the similar relationship for control rats in Experiment 3. The relationship for the rats shown in line A ($\Diamond$---$\Diamond$) was obtained by perfusing their lungs from two reservoirs, first with low and then high Hct blood obtained by centrifugation. The relationship for rats shown in line B ($\blacklozenge$---$\blacklozenge$) was obtained by perfusing their lungs with centrifuged blood of high Hct which was then diluted twice with plasma. All points obtained at a constant flow rate in both A and B (18 ml./min). Slopes (a) and correlation coefficients (r) are given beside each regression line. All regression lines were significantly different from zero by the null hypothesis.

Control rat lungs perfused with low and high Hct blood contained by centrifugation

Experiment 3. (A). Lungs from six control rats were perfused first with blood of low and then high Hct from two reservoirs; this procedure was repeated. The protocol was similar to that used on chronically hypoxic lungs in the first experiment except that blood of high Hct was obtained by re-suspending the red blood cells in plasma after centrifugation. Four pressure/flow lines were determined; control blood was perfused first. In every rat the slope of the $P/\dot{Q}$ line increased with Hct. When the low Hct perfusion was repeated the original value of p.v.r. was not restored, although it was raised again with high Hct blood (Table 1).
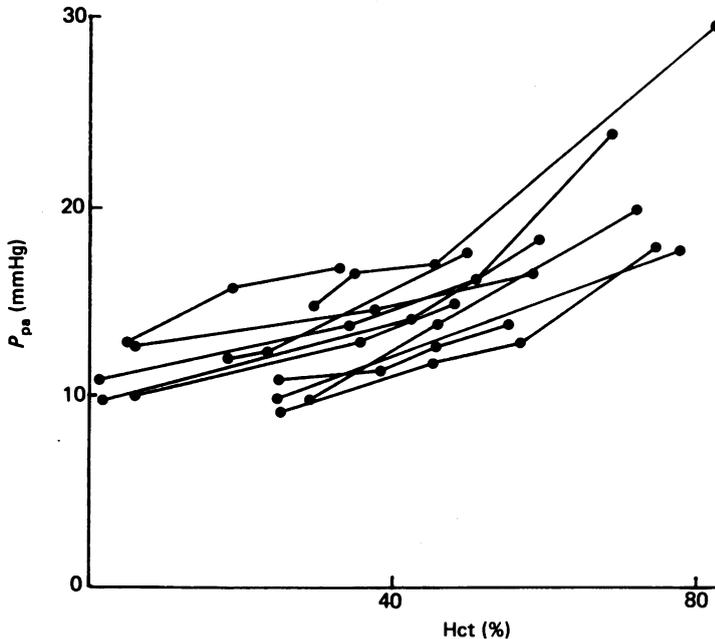

Fig. 4. Relationship between P_{pa} and Hct and for individual control rats in Experiment 3 (C). Rat lungs were perfused in pairs, one with high, one with low Hct blood (centrifuged). Reservoirs were changed several times so that P_{pa} at constant flow (18 ml./min) could be obtained at several Hct values. Note similarity of relationship in different rats.

(B). Lungs from seven control rats were perfused with blood of high Hct obtained by removing plasma from centrifuged blood. After $P/\dot{Q}$ lines had been measured, the blood was diluted with plasma in two stages. Following each dilution there was a fall in p.v.r. and P_{pa}.

The details of the slopes of the $P/\dot{Q}$ lines and the P_{pa} are given in Table 1. In these experiments the slope always increased with raised Hct. The lower half of Fig. 3 shows the relationship between P_{pa} and Hct for groups A and B. In group A where Hct was raised, the rate of the rise of P_{pa} with Hct was greater than in the group where blood was diluted. It is apparent that storage of blood was again a problem in these

experiments. Therefore the following experiments were designed both to avoid this factor and obtain measurements at several Hct values.

(C). Pairs of isolated lungs of control rats were set up. They were each perfused from a reservoir with either high or low Hct blood obtained by pooling and centrifuging blood from several rats. When P_{pa} had stabilized the perfusion was momentarily stopped and the reservoirs were exchanged. A little blood remained in the lung and circuit so that Hct increased in one reservoir and decreased in the other. In this way P_{pa} at constant flow (18 ml./min) was obtained over a range of Hct values in each animal until the reservoirs became similar. Fig. 4 shows the relationship between Hct and P_{pa} for eight lungs. There was a close similarity in the lines obtained. A few lungs perfused at very low Hct were lost because they became oedematous.

Viscosity measurements

In vivo measurements of blood viscosity by a torque method gave values for blood from six chronically hypoxic and seven control rats of, respectively, $8 \cdot 4 \pm 0 \cdot 3$ centipoise (Hct $62 \cdot 2 \pm 2 \cdot 2 \%$) and $4 \cdot 4 \pm 0 \cdot 3$ (Hct $43 \cdot 4 \pm 1 \cdot 6 \%$) at 230 c/s and $13 \cdot 9 \pm 0 \cdot 8$ and $7 \cdot 8 \pm 0 \cdot 6$ centipoise respectively at 23 c/s ($P < 0 \cdot 001$).

DISCUSSION

Polycythaemic blood from chronically hypoxic rats increased vascular resistance in both chronically hypoxic and control rat lungs. In chronically hypoxic rats the haematocrit was raised to 50–60 %; this compares with a mean value of 60 % for man at 15,000 ft. (Monge & Whittenbury, 1976). The slope of the pressure/flow line was increased. The changes were such that at a flow rate of 20 ml./min, chronically hypoxic rats with a haematocrit of 53 % would have a P_{pa} of 47 mmHg compared with 38 mmHg for blood of Hct 35 %. One cannot assume that the high Hct was the sole cause of this effect. Other factors which affect blood viscosity in chronic hypoxia that have not yet been studied such as red-cell aggregation and deformability, tendency to platelet aggregation and the presence of vasoactive substances might be involved. The similar results obtained in control rats with centrifuged blood suggest that high red cell concentration is the most likely cause. When the experiments on chronically hypoxic rats and, to a lesser extent, control rats were prolonged, basic pressure rose. This suggests that some vasopressor agent accumulated. Potassium is a possibility as some haemolysis is always observed after a time when a roller pump is used. The greater increase in pressure in the chronically hypoxic rats could be due to their abnormally muscular arterioles. The results obtained quickly in the one rat – one blood experiments probably represent the true effect of the blood, unaffected by changes in its composition or in the isolated lung preparation.

We have previously observed in many experiments that there is 'batch' variation in response to hypoxia. There have been differences in the degree of polycythaemia, pulmonary hypertension, muscularization of pulmonary arterioles, right heart hypertrophy and carotid-body enlargement, without any detectable differences in conditions (Leach, 1978). Similarly it has been shown that individual humans vary in their pulmonary vascular response to hypoxia (Abraham, Cumming, Horsfield & Prowse, 1970) as well as their ventilatory response to hypoxia. The differences in sensitivity

may be genetic, as has been demonstrated in cattle (Will, Hicks, Card & Alexander, 1975). The increased vascular resistance in chronically hypoxic rats compared with control rats when perfused with normal blood was demonstrated previously and attributed to narrowing of the arterioles by new muscle (Emery *et al.* 1981).

In Experiment 1 B, the chronically hypoxic rats with the lower mean haematocrit, there was a much steeper rise in P_{pa} with haematocrit than in 1 A whose polycythaemia was greater. Group B also had a higher P_{pa} and vascular resistance than A when perfused with normal blood, which suggests that they may have had more new muscle encroaching on the lumen of resistance vessels. There seems to have been a dissociation of different responses to chronic hypoxia. The rate of rise in P_{pa} with haematocrit was, with the exception of group 1 B, not large. However in the low resistance pulmonary circulation, where the mean normal pressure difference between the pulmonary artery and left atrium is of the order of 5 mmHg, the changes are substantial.

The viscosity of chronically hypoxic blood measured *in vitro* was about twice that of control blood which was much greater than the increase in resistance *in vivo*. Although many devices have been used in an attempt to mimic *in vivo* conditions, none have achieved this. The measured apparent viscosity *in vivo* is a sum of the viscosity in a series of tubes of different dimensions in which blood is subject to different shear stresses. Its viscous properties will differ along the vascular tree for both these reasons. It is non-Newtonian in that its viscosity is less at high shear stresses and its apparent viscosity is reduced in tubes of small diameter (Fahraeus–Lindquist effect). It has also been observed that the haematocrit value itself varies in vessels of different size due possibly to differential velocities of red cells and plasma; in the smallest vessels the red cells must be deformed. It can be expected however that the viscosity factor will be relatively high in the low pressure pulmonary vascular bed, which lacks the muscular arterioles which account for a large part of the resistance in the systemic vascular system. The 'tone' in chronic hypoxia may however be greater because of the muscularization already mentioned and hypoxic vasoconstriction.

Extrapolation of the $P/\dot{Q}$ lines to the pressure axis usually gave a larger intercept in chronically hypoxic lungs perfused with polycythaemic blood compared with those perfused with control blood; a similar difference was seen in control lungs (Fig. 2). Blood flow could not be measured at very low flow rates. We do not know whether there is a true intercept due to a high critical opening pressure or a very slow rise in flow at low pressures. The reason may be muscular tension or it might be due to 'plugging' by red cell aggregates, which would be released at slightly higher pressures.

Former work in controlled situations with polycythaemic blood has been done on the normal pulmonary vascular bed. Benis *et al.* (1967) showed that dog lungs perfused with different proportions of red cells and dextran showed similar changes to those seen here in chronically hypoxic rats. Murray *et al.* (1969) showed changes in resistance in isolated dog lungs when the viscosity of blood was raised either by increasing the proportion of red cells, or the molecular weight of the dextran in which they were suspended.

In conclusion, the high haematocrit of chronic hypoxia is a factor which substantially increases the pulmonary artery pressure, already raised by narrowed muscular-

arterioles and hypoxic vasoconstriction. It is probable that when Hct exceeds 60 % this factor becomes more important. Although healthy, high-altitude residents have a normal cardiac output this may be reduced in chronic mountain sickness in association with a very high haematocrit. Cardiac output was reduced in dogs by artificial elevation of Hct (McGrath & Weil, 1978). We do not know if the increased load on the right heart at high altitude has a deleterious effect. The normal, high-altitude dweller is capable of heavy exertion and there is no evidence of a high incidence of heart failure. Nevertheless there are certainly circumstances where oxygen delivery to the tissue is diminished rather than increased by polycythaemia. Cerebral flow was increased and oxygen delivery to the brain not significantly altered, when Hct was lowered in polycythaemic patients with hypoxic lung disease (Wade, Pearson, Russell & Wetherley-Mein, 1981). Alertness was increased by venesection in another study (Willison, du Boulay, Paul, Russell, Thomas, Marshall, Pearson, Symon & Wetherley-Mein, 1980) while Hoffman, Surjadhana, Boerboom & Rouleau (1977) showed poor sub-endocardial perfusion in dogs with an artificially raised Hct. We have also seen individual rats with paresis in the hypoxic chamber associated with a very high Hct. Transient paresis is common both in adapted lowlanders and highlanders (Heath & Williams, 1977). Problems of tissue perfusion may be less in life-long highlanders who may develop a higher capillary density.

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