Regional Pulmonary Blood Flow in Sitting and Supine Man during and after Acute Hypoxia

ARTHUR DAWSON

From the Division of CardioPulmonary Diseases, Scripps Clinic and Research Foundation, La Jolla, California 92037

ABSTRACT Regional pulmonary blood flow was measured by external counting of intravenously injected ^{133}Xe during 20 min of breathing 14.2% oxygen and during 20 min of recovery from hypoxia. 16 normal human volunteers were studied, nine sitting and seven supine. During hypoxia there was a slight but significant increase in relative perfusion of the upper portions of the lungs in both the sitting and supine subjects. During recovery from hypoxia, blood flow distribution differed significantly from the control. The erect subjects showed increased relative perfusion of the lung bases and the supine subjects showed increased relative perfusion of the upper zones.

Comparison of the distribution of inhaled and intravenously injected isotope showed that in the sitting subjects the altered distribution during hypoxia tended to make alveolar oxygen tension more uniform. In the supine subjects, however, the shift in blood flow increased the perfusion of the regions with the lowest ventilation/perfusion, tending to accentuate uneven alveolar oxygen tension. Therefore it does not seem that the altered blood flow distribution during hypoxia was due to selective vasoconstriction in the regions of lowest alveolar oxygen tension, but rather that vasoconstriction was greatest in the lower lung zones because the vessels there are more responsive to hypoxia. During mild acute hypoxia, vasoconstrictor tone does not seem to effectively match ventilation and perfusion.

The altered distribution of pulmonary blood flow during recovery from hypoxia suggests the occurrence of posthypoxic vasodilation. Failure to consider this possibility may lead to erroneous interpretation of pulmonary hemodynamic measurements made after the inspired oxygen concentration has been changed.

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INTRODUCTION

In a wide variety of human and animal experiments inhaled oxygen concentration has been shown to influence pulmonary vascular resistance (1). von Euler and Liljestrand (2) suggested that pulmonary blood flow distribution is regulated by a local action of alveolar oxygen tension on the blood vessels which produces optimal matching of ventilation and perfusion. This hypothesis stimulated many studies of the effect of regional hypoxia on local pulmonary vascular resistance but it is still unknown whether alveolar oxygen tension significantly influences blood flow distribution under physiological conditions. Fishman, Himmelstein, Fritts, and Cournand (3) found no consistent reduction of blood flow to the hypoxic lung when 8–12% oxygen was breathed through a bronchospirometric catheter and Fishman, after reviewing the considerable literature on this subject, concluded that under normal conditions the effect of local gas composition on the distribution of blood flow was small when compared with gravitational and mechanical influences (1). However, Arborelius (4) claimed that a consistent reduction of blood flow to the hypoxic lung occurs during unilateral inhalation of 15% oxygen, a relatively mild hypoxic stimulus. He suggested that the variable results of other workers were due to the inaccuracy of oxygen uptake as a measure of flow to the hypoxic lung and that his observations based on the recovery of intravenously injected ^{85}Kr from each lung supported the hypothesis of von Euler and Liljestrand.

Since the introduction of radioactive gas methods for the study of regional ventilation and perfusion a great deal more has been learned about the factors influencing the distribution of blood and gas in the lungs. West, Dollery, and Naimark (5) showed that in isolated perfused lungs blood flow was highest in the dependent part of

the lung and its distribution could be explained by the interplay between arterial, venous, and alveolar pressures. Anthonisen and Milic-Emili (6) showed that blood flow was similarly distributed in intact human lungs. The radioactive gas studies have emphasized the importance of gravity and lung mechanics in determining blood flow distribution and Campbell recently observed that "other factors such as vasomotor tone have not yet been shown to play a significant part in determining the regional distribution of pulmonary blood flow in man" (7).

Apart from one study which showed no effect of breathing 100% oxygen (8) little use has been made of the radioactive gas methods to reexamine the effect of inspired gas composition on blood flow distribution in man though with these methods regional blood flow can be measured without the discomfort and unphysiological conditions which cannot be avoided during bronchospirometry.

This study was done to see how exposure of the whole lung to mild acute hypoxia affects blood flow distribution and to gain further information about the importance of inspired oxygen tension in the regulation of regional pulmonary blood flow.

METHODS

16 normal volunteers were studied (11 male, 5 female, age range 23–43), nine sitting erect and 7 supine. Regional pulmonary function was measured by a ^{133}xenon technique similar to that described by Ball, Stewart, Newsham, and Bates (9). The sitting studies were done with the subject in a special chair with a straight back of transparent plastic. Four scintillation detectors with crystals 2 inches in diameter and six inch cylindrical collimators having a 1 inch wide horizontal slit were mounted on a moveable rack so that count rate could be measured in two positions of the detectors. The detectors were positioned in relation to a standard upright posteroanterior radiograph of the chest taken at full inspiration. The seventh cervical spine was used as a landmark and the position of the subject was kept constant by lining up a wax pencil cross on his skin with a cross on the transparent back of the chair. The supine studies were done similarly with the subject lying on a table with a transparent window and the detectors were placed under the table so that they viewed the posterior chest.

The pulses from the detectors were directly recorded on multichannel magnetic tape with a voice commentary and were later replayed through a scaler-pulse height analyzer set to accept pulses corresponding to both 30 and 81 kev photons. The scaler was set to 1 sec counting time and its output was fed through a digital-analog converter to a direct writer recorder.

The subject was instructed in the breathing maneuvers and a 25 cm polyethylene catheter was placed in an antecubital vein. After a 15 min wait to reestablish resting conditions and to accustom the subject to the mouthpiece, blood flow distribution was measured by intravenous injections of the isotope. The subject inspired fully and was switched to a spirometer with a linear potentiometer and ammeter connected to its pulley. The ammeter had been calibrated by a second potentiometer to read per cent vital capacity and by observing the needle the subject could hold his breath at a desired lung volume. He exhaled to 40% of his vital capacity and then held his breath with the glottis open while 0.5–1.0 mc of ^{133}xenon dissolved in 5 ml of sterile saline was rapidly injected intravenously followed by a 15 ml saline flush. He continued to hold his breath at 40% vital capacity for approximately 10 sec until a stable count rate was reached over one of the chest counters whose output was continuously monitored and then rapidly inspired to total lung capacity where the count was recorded for 10–12 sec in each of the two positions of the detectors.

Duplicate control injections were made separated by 10–15 min. Injections were then repeated during the 7th, 14th, and 21st minutes of breathing 14.2% oxygen and during the 7th, 14th, and 21st minutes of breating air after the hypoxic period.

The distribution of ventilation was measured in duplicate during air breathing by having the subject take an inspiratory capacity breath of 0.5 mc/liter of ^{133}xenon in air from his resting end-expiratory position and counting for 10 sec in each of the two positions of the detectors. The count rate/concentration calibrating factor was determined for each of the eight detector positions by having the subject rebreathe 0.5 mc/liter of ^{133}xenon in air from a closed-circuit spirometer for 3–4 min after which the count rate was measured during two or three breath holds at full inspiration as before.

The total radiation dose resulting from intravenous injection of 8 mc of ^{133}Xe, from two breaths of 0.5 mc/liter held for 30 sec, and from rebreathing 0.5 mc/liter for 5 min would be approximately 400 mrad to the tracheal mucosa, 100 mrad to the lung and 5 mrad to the gonads (10).

Calculations. Relative perfusion ($\dot{Q}_R$) for each detector position was calculated as follows:

$$\dot{Q}_R = (c/\Sigma c)/(e/\Sigma e)$$

where c is the count rate at a given position after intravenous injection; Σc is the sum of the count rates at all eight positions; e is the count rate after rebreathing at the same position; and Σe is the sum of rebreathing count rates at all eight positions.

Since the measurement is made at total lung capacity where the volume of all the alveoli is approximately equal, the result gives relative perfusion "per alveolus" at 40% of the vital capacity (6). An analogous calculation of relative ventilation "per alveolus" ($\dot{V}_R$) was made from the distribution of inhaled isotope. As Anthonisen and Milic-Emili have shown (6), regional ventilation "per alveolus" is independent of the initial lung volume provided that the preinspiratory volume is greater than 20% of the vital capacity. All of the single breath ventilation measurements satisfied this condition. $\dot{V}_R/\dot{Q}_R$, the ratio of relative ventilation to relative perfusion "per alveolus" will be referred to as the "ventilation/perfusion quotient."

For individual subjects the data from each injection were compared by calculating the "perfusion gradient" (11) which is the slope of the line of best fit of relative perfusion ($\dot{Q}_R$) plotted against vertical distance from the apex of the lung (calculated by the method of least squares). The perfusion gradients were calculated separately for each injection. However, there was no evidence of a progressive alteration of perfusion distribution during either the hypoxic or the recovery periods and therefore the values of $\dot{Q}_R$ for each of the three periods (control, hypoxia, and recovery) were averaged and the perfusion gradient was calculated from the mean.

For a more detailed analysis of the results, the data from

the individual detector positions were pooled for all of the sitting and for all the supine subjects. The ratio of $\dot{Q}_R$ during hypoxia to the control $\dot{Q}_R(\dot{Q}_{14}/\dot{Q}_{21})$ was plotted against D, the distance from the lung apex and against $\dot{V}_R/\dot{Q}_R$, the ventilation-perfusion quotient. Similar calculations were made for $\dot{Q}_R$ during the posthypoxic period ($\dot{Q}_{PH}$).

RESULTS

Sitting subjects. Blood flow distribution in the sitting subjects is given in Table I. In all subjects the perfusion gradient had a positive value (i.e., perfusion increased from the apex to the base of the lung). An area of relatively reduced perfusion as described by Hughes, Glazier, Maloney, and West (12) could be identified in only two subjects but the number of detector positions was insufficient for detailed description of the pattern of blood flow distribution.

In two of the nine sitting subjects (H. D. and J. G.) there was a definite reduction of the perfusion gradient during hypoxia indicating reduction of relative blood

TABLE I
Sitting Studies

Subject, sex, age (yr)		Relative perfusion per alveolus ($\dot{Q}_R$)								Perfusion gradient
A. D., M, 34	Detector position	L6.5	L11.5	L18.0	L24.5	R6.0	R12.5	R17.5	R24.0	
	Air control ($\dot{Q}_{21}$)	0.59	0.89	1.07	1.02	0.65	1.00	1.20	1.27	+0.029
	Hypoxia ($\dot{Q}_{14}$)	0.68	0.96	1.06	1.16	0.65	0.93	1.11	1.19	+0.028
	Air recovery ($\dot{Q}_{PH}$)	0.66	0.95	1.03	1.17	0.52	0.84	1.12	1.37	+0.037
H. D., F, 31	Detector position	L3.0	L 9.5	L13.5	L20.0	R4.0	R10.5	R14.0	R20.5	
	Air control ($\dot{Q}_{21}$)	0.70	0.97	1.06	1.06	0.64	0.98	1.14	1.22	+0.028
	Hypoxia ($\dot{Q}_{14}$)	0.89	1.01	1.00	0.92	0.82	1.05	1.12	1.05	+0.008
	Air recovery ($\dot{Q}_{PH}$)	0.65	0.92	1.06	1.14	0.61	0.95	1.16	1.24	+0.034
J. V., M, 39	Detector position	L4.0	L10.0	L15.0	L21.5	R4.5	R10.5	R15.0	R21.0	
	Air control ($\dot{Q}_{21}$)	0.59	0.81	1.03	1.54	0.73	0.76	0.92	1.29	+0.044
	Hypoxia ($\dot{Q}_{14}$)	0.62	0.85	1.06	1.40	0.77	0.82	0.95	1.23	+0.037
	Air recovery ($\dot{Q}_{PH}$)	0.64	0.85	1.10	1.39	0.71	0.78	0.97	1.21	+0.038
E. S., M., 43	Detector position	L5.5	L12.0	L17.5	L24.0	R5.5	R12.0	R17.5	R23.5	
	Air control ($\dot{Q}_{21}$)	1.01	1.04	1.00	1.01	0.69	0.88	1.08	1.15	+0.013
	Hypoxia ($\dot{Q}_{14}$)	0.88	0.97	1.07	1.07	0.67	0.83	1.04	1.18	+0.020
	Air recovery ($\dot{Q}_{PH}$)	0.74	0.90	1.05	1.17	0.50	0.76	1.09	1.30	+0.034
D. M., M, 40	Detector position	L6.5	L13.0	L18.5	L25.0	R5.0	R11.5	R16.0	R22.5	
	Air control ($\dot{Q}_{21}$)	0.61	0.78	1.07	1.17	0.63	0.71	1.15	1.41	+0.038
	Hypoxia ($\dot{Q}_{14}$)	0.62	0.74	1.07	1.22	0.60	0.69	1.15	1.41	+0.040
	Air recovery ($\dot{Q}_{PH}$)	0.63	0.77	1.02	1.18	0.60	0.71	1.16	1.43	+0.039
J. O., F, 31	Detector position	L5.5	L12.0	L15.0	L21.5	R3.0	R 9.5	R13.0	R19.5	
	Air control ($\dot{Q}_{21}$)	0.97	0.99	0.97	0.92	0.84	0.97	1.09	1.16	+0.008
	Hypoxia ($\dot{Q}_{14}$)	0.94	0.99	0.99	1.01	0.79	0.93	1.04	1.14	+0.013
	Air recovery ($\dot{Q}_{PH}$)	0.83	1.00	1.01	1.06	0.68	0.89	1.06	1.17	+0.022
J. G., M, 42	Detector position	L6.0	L12.0	L16.0	L22.5	R5.5	R11.5	R16.0	R22.0	
	Air control ($\dot{Q}_{21}$)	0.77	1.03	1.07	1.05	0.68	0.90	1.07	1.10	+0.021
	Hypoxia ($\dot{Q}_{14}$)	0.88	1.07	0.91	0.94	0.82	1.01	1.04	1.12	+0.009
	Air recovery ($\dot{Q}_{PH}$)	0.74	0.98	1.10	1.17	0.65	0.82	1.02	1.13	+0.028
W. K., M, 39	Detector position	L5.0	L11.5	L18.5	L25.5	R5.5	R12.0	R16.5	R23.0	
	Air control ($\dot{Q}_{21}$)	0.62	0.83	1.05	1.13	0.65	0.98	1.09	1.24	+0.028
	Hypoxia ($\dot{Q}_{14}$)	0.69	0.88	1.01	1.09	0.67	0.97	1.15	1.19	+0.023
	Air recovery ($\dot{Q}_{PH}$)	0.52	0.77	1.08	1.19	0.58	0.88	1.15	1.30	+0.040
R. U., M, 31	Detector position	L6.0	L12.5	L19.0	L25.0	R6.0	R12.5	R18.5	R25.0	
	Air control ($\dot{Q}_{21}$)	0.67	0.96	1.05	1.16	0.68	1.01	1.12	1.18	+0.025
	Hypoxia ($\dot{Q}_{14}$)	0.69	0.95	0.95	1.10	0.79	1.00	1.14	1.23	+0.021
	Air recovery ($\dot{Q}_{PH}$)	0.52	0.86	1.07	1.24	0.53	0.88	1.24	1.39	+0.042

Detector positions are given as left (L) or right (R) in centimeters measured from the apex of the lung. The perfusion gradient is given as change in relative perfusion per centimeter distance.

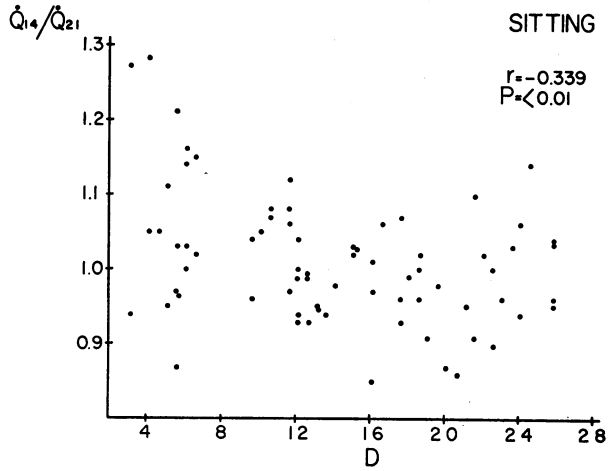

FIGURE 1 Relationship between distance from the lung apex and effect of acute hypoxia on regional blood flow in sitting subjects. $\dot{Q}_{14}/\dot{Q}_{21}$ is the blood flow per alveolus during hypoxia divided by the control blood flow per alveolus. D is the distance from the apex of the lung in centimeters. There are 72 points representing eight detector positions in each of nine sitting subjects. There is a significant negative correlation indicating a tendency to reduced relative perfusion during hypoxia in the lower zones of the lungs.

flow to the lung bases. In the remainder the changes were small and inconsistent. The decrease in the average perfusion gradient from + 0.026 to + 0.022 was not statistically significant.

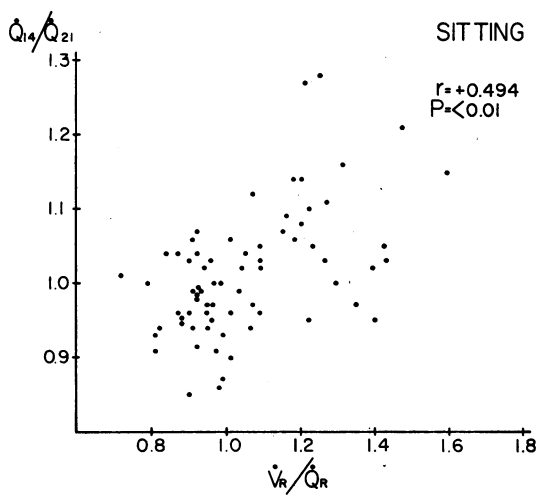

FIGURE 2. Relationship between ventilation/perfusion quotient and effect of acute hypoxia on regional blood flow in sitting subjects. $\dot{Q}_{14}/\dot{Q}_{21}$ is the blood flow per alveolus during hypoxia divided by the control blood flow per alveolus. $\dot{V}_R/\dot{Q}_R$ is the "ventilation/perfusion quotient" (see text). There are 72 points representing eight detector positions in each of nine sitting subjects. There is a significant positive correlation indicating a tendency for relative perfusion to decrease during hypoxia in the regions which are most poorly ventilated in relation to their perfusion.

However, Fig. 1 shows the effect of hypoxia on relative flow to the individual detector positions (expressed as $\dot{Q}_{14}/\dot{Q}_{21}$, the ratio of flow during breathing 14% oxygen to flow during air breathing) plotted against D, the distance from the apex of the lung when the data from the nine sitting subjects were pooled. $\dot{Q}_{14}/\dot{Q}_{21}$ shows a significant negative correlation with D ($r = -0.339$, $P = < 0.01$) indicating a tendency to reduced basal perfusion and increased apical perfusion during hypoxia.

Fig. 2 shows that when the effect of hypoxia on relative regional blood flow ($\dot{Q}_{14}/\dot{Q}_{21}$) was plotted against the relative ventilation/perfusion quotient, $\dot{V}_R/\dot{Q}_R$, a significant positive correlation was found ($r = +0.494$, $P = < 0.01$). Therefore hypoxia tended to increase the relative perfusion of those regions which were best ventilated in relation to their perfusion. Though $\dot{V}_R/\dot{Q}_R$ showed a significant negative correlation with D ($r = -0.613$, $P = < 0.01$), the value of r for $\dot{Q}_{14}/\dot{Q}_{21}$ vs. $\dot{V}_R/\dot{Q}_R$ was higher than r for $\dot{Q}_{14}/\dot{Q}_{21}$ vs. D suggesting that the positive correlation between $\dot{Q}_{14}/\dot{Q}_{21}$ and $\dot{V}_R/\dot{Q}_R$ cannot be entirely explained by their mutual correlation with D.

On resumption of air breathing, the perfusion gradient increased to higher than its control value in seven of the nine subjects. The average perfusion gradient of + 0.035 was significantly greater than the control value

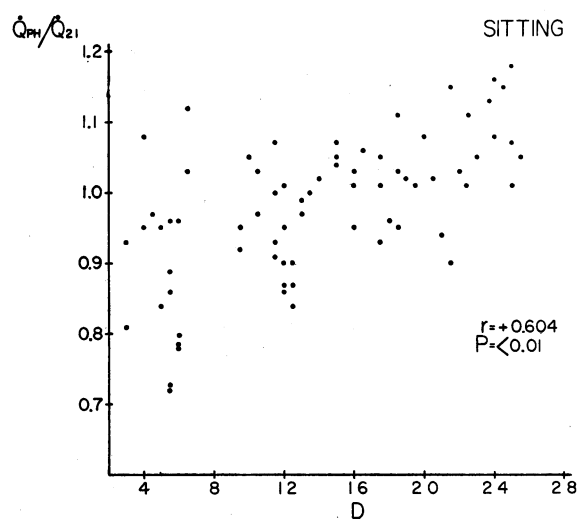

FIGURE 3 Relationship between distance from the lung apex and effect of recovery from hypoxia on regional blood flow in sitting subjects. $\dot{Q}_{PH}/\dot{Q}_{21}$ is the blood flow per alveolus during posthypoxia divided by the control blood flow per alveolus. D is the distance from the apex of the lung in centimeters. There are 72 points representing eight detector positions in each of nine sitting subjects. There is a significant positive correlation indicating a tendency to increased relative perfusion during posthypoxia in the lower zones of the lungs.

($P = < 0.02$). There was no evidence of a progressive change in the gradient when the results from the 7th, 14th, and 21st minutes were compared (7 min + 0.037, $P = < 0.01$; 14 min, + 0.032, P not significant; 21 min, + 0.035, $P = < 0.02$).

When the data for all of the individual detector positions were pooled, $\dot{Q}_{PH}/\dot{Q}_{21}$ (the ratio of relative perfusion during posthypoxia to relative perfusion during air breathing) showed a significant positive correlation with D, the distance from the lung apex (Fig. 3) but no correlation with $\dot{V}_R/\dot{Q}_R$, the relative ventilation/perfusion quotient ($r = -0.028$).

Supine subjects. The blood flow distribution in the supine subjects is given in Table II. Perfusion was more uniform in the supine than in the sitting position, as indicated by the smaller values (disregarding sign) of the perfusion gradient. In six of the seven subjects the perfusion gradient had a negative value indicating a tendency to higher perfusion per alveolus in the apical than in the basal portions of the lung.

During hypoxia, the perfusion gradient decreased moderately in three subjects and changed little in the other four. The change in the average perfusion gradient from − 0.006 to − 0.010 was not significant.

However, when the data were pooled for the individual detector positions in all seven subjects, $\dot{Q}_{14}/\dot{Q}_{21}$ showed a significant correlation with D (Fig. 4). There was no significant correlation between $\dot{Q}_{14}/\dot{Q}_{21}$ and $\dot{V}_R/\dot{Q}_R$ ($r = -0.174$). Therefore during hypoxia in the supine subjects, relative perfusion of the lung bases decreased. The change was not significantly correlated with the relative ventilation/perfusion quotient and the negative value of r indicates that, if anything, ventilation/perfusion inequality tended to increase during hypoxia.

During the posthypoxic period the perfusion gradient

TABLE II
Supine Studies

Subject, sex, age (yr)		Relative perfusion per alveolus ($\dot{Q}_R$)								Perfusion gradient
N. F., M, 28	Detector position	L5.5	L11.0	L18.0	L23.5	R5.5	R10.5	R16.0	R21.5	
	Air control ($\dot{Q}_{21}$)	1.14	1.12	0.97	0.94	1.05	1.05	0.98	0.94	−0.010
	Hypoxia ($\dot{Q}_{14}$)	1.15	1.10	0.96	0.85	1.05	1.09	0.97	0.98	−0.012
	Air recovery ($\dot{Q}_{PH}$)	1.14	1.06	1.02	0.86	1.02	1.08	1.01	0.95	−0.010
R. R., M, 39	Detector position	L7.0	L13.5	L17.0	L23.5	R4.5	R11.0	R15.5	R22.0	
	Air control ($\dot{Q}_{21}$)	1.42	1.08	0.96	0.83	1.09	1.17	1.04	0.85	−0.023
	Hypoxia ($\dot{Q}_{14}$)	1.30	1.08	0.90	0.84	1.08	1.25	1.05	0.86	−0.021
	Air recovery ($\dot{Q}_{PH}$)	1.41	1.06	0.94	0.85	1.36	1.22	0.97	0.81	−0.033
S. W., F, 23	Detector position	L6.0	L11.0	L17.0	L23.0	R4.0	R 9.0	R15.5	R21.0	
	Air control ($\dot{Q}_{21}$)	1.06	1.09	0.96	0.92	0.99	1.07	1.00	0.89	−0.008
	Hypoxia ($\dot{Q}_{14}$)	1.18	1.09	0.94	0.86	1.11	1.06	0.94	0.82	−0.018
	Air recovery ($\dot{Q}_{PH}$)	1.12	1.14	0.95	0.87	0.99	1.02	1.00	0.87	−0.011
B. M., F, 39	Detector position	L5.0	L10.5	L16.5	L22.0	R3.5	R 9.0	R14.0	R19.0	
	Air control ($\dot{Q}_{21}$)	0.94	0.92	0.93	1.11	1.20	1.04	0.94	1.05	−0.001
	Hypoxia ($\dot{Q}_{14}$)	0.96	0.96	0.92	1.01	1.33	1.07	0.91	0.98	−0.011
	Air recovery ($\dot{Q}_{PH}$)	1.02	0.96	0.91	0.88	1.32	1.03	0.98	1.01	−0.015
G. V., F, 36	Detector position	L7.0	L14.0	L17.5	L24.0	R5.0	R11.5	R16.0	R22.5	
	Air control ($\dot{Q}_{21}$)	0.98	1.06	0.96	1.18	0.85	0.99	0.95	1.11	+0.012
	Hypoxia ($\dot{Q}_{14}$)	0.99	1.05	0.94	1.19	0.83	0.92	0.95	1.21	+0.017
	Air recovery ($\dot{Q}_{PH}$)	0.98	1 05	0.93	1.11	0.88	0.96	0.99	1.15	+0 011
R. F. R., M, 25	Detector position	L5.5	L11.0	L16.0	L21.0	R4.5	R 9.0	R15.0	R20.5	
	Air control ($\dot{Q}_{21}$)	1.10	1.05	0.95	0.96	0.98	1.06	1.03	0.94	−0.006
	Hypoxia ($\dot{Q}_{14}$)	1.08	1.01	0.90	0.92	1.05	1.10	1.05	0.95	−0.009
	Air recovery ($\dot{Q}_{PH}$)	1.09	1.04	1.02	0.92	1.07	1.07	1.04	0.94	−0.009
J. M., M, 42	Detector position	L5.0	L10.5	L18.5	L24.0	R3.5	R 8.5	R16.5	R22.0	
	Air control ($\dot{Q}_{21}$)	0.99	1.09	1.02	0.85	1.11	1.06	1.07	0.89	−0.009
	Hypoxia ($\dot{Q}_{14}$)	1.11	1.11	0.95	0.84	1.25	1.10	0.97	0.81	−0.019
	Air recovery ($\dot{Q}_{PH}$)	1.06	1.07	0.98	0.84	1.12	1.07	1.03	0.89	−0.012

Detector positions are given as left (L) or (R) in centimeters measured from the apex of the lung. The perfusion gradient is given as change in relative perfusion per centimeter distance.

showed no consistent change from its value during hypoxia (three subjects showed an increase, three a decrease, and one no change). However, in six out of seven subjects the absolute value of the gradient was less during recovery from hypoxia than it was during the control period. The seventh subject showed no change. The average perfusion gradient during recovery of -0.014 was significantly less than the average control ($P = < 0.05$).

$\dot{Q}_{PH}/\dot{Q}_{21}$ showed a significant negative correlation with distance from the apex (D) in the supine subjects (Fig. 5) but was not significantly correlated with $\dot{V}_R/\dot{Q}_R$, the ventilation/perfusion quotient ($r = -0.200$). Therefore during recovery from hypoxia, relative perfusion increased in the upper zones of the lungs, but the alteration in blood flow distribution did not show any significant relationship with regional ventilation/perfusion.

Ventilation distribution. Table III summarizes the ventilation distribution in the experimental subjects. All of the sitting subjects showed a small positive value of ventilation gradient indicating that a larger proportion "per alveolus" of an inspiratory capacity breath was distributed to the lung bases. The supine subjects also had positive but smaller values of ventilation gradient indicating more even ventilation in the supine position.

Ventilation/perfusion. In the sitting subjects ventilation/perfusion decreased from the apical to the basal regions of the lung. The correlation coefficient for $\dot{V}_R/\dot{Q}_R$ vs. distance from the apex of the lung was

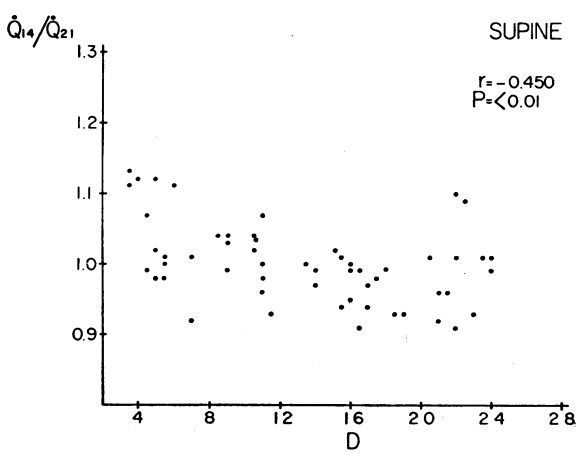

FIGURE 4 Relationship between distance from the lung apex and effect of acute hypoxia on regional blood flow in supine subjects. $\dot{Q}_{14}/\dot{Q}_{21}$ is the blood flow per alveolus during hypoxia divided by the control blood flow per alveolus. D is the distance from the apex of the lung in centimeters. There are 56 points representing eight detectors in each of seven supine subjects. There is a significant negative correlation indicating a tendency to reduced relative perfusion during hypoxia in the lower zones of the lung.

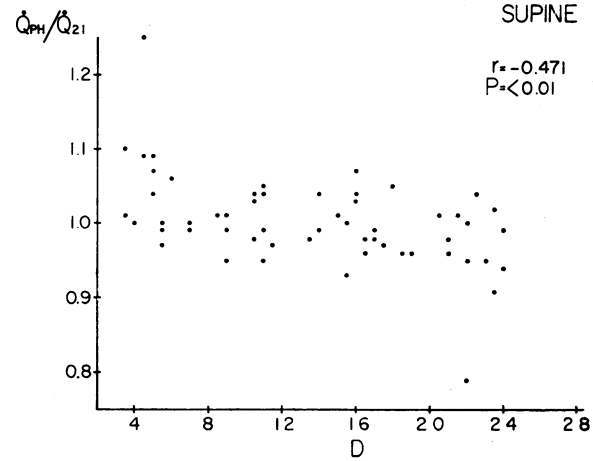

FIGURE 5 Relationship between distance from the lung apex and effect of recovery from hypoxia on regional blood flow in supine subjects. $\dot{Q}_{PH}/\dot{Q}_{21}$ is the blood flow per alveolus during posthypoxia divided by the control blood flow per alveolus. D is the distance from the apex of the lung in centimeters. There are 56 points representing eight detector positions in each of seven supine subjects. There is a significant negative correlation indicating a tendency to increased relative perfusion during posthypoxia in the upper zones of the lungs.

-0.613. In the supine subjects the ventilation gradient remained positive while the perfusion gradient was generally negative and ventilation/perfusion increased from the apex to the base. The correlation coefficient for $\dot{V}_R/\dot{Q}_R$ vs. distance from the apex of the lung in the supine subjects was $+0.712$.

DISCUSSION

These results show that during mild acute hypoxia, relative perfusion of the lung bases decreases, both in the erect and in the supine positions. The only comparable human study of the effect of hypoxia of both lungs on regional pulmonary blood flow was done by Fowler and Read (13) who developed an ingenious but indirect method of measuring the ratio of upper to lower zone flow based on "cardiogenic oscillations" of the expired gas composition. They reported that during breathing of 13.5% oxygen there was a large increase in upper zone perfusion in three of six sitting normal subjects with little change in the other three. Relative upper zone perfusion also increased during supine hypoxia though the change was less than it was in the erect position. Dugard and Naimark (11) described reduction of relative perfusion of the lung bases during inhalation of 9–11% oxygen in erect anesthetized dogs studied by intravenous injections of ^{133}xenon.

A shift of relative perfusion from the lower to the upper portions of the erect lung could be explained by increased cardiac output (15), by elevated pulmonary

TABLE III

Ventilation Distribution during Air Breathing

Subject		Sitting studies								Ventilation gradient
A. D.	Detector position	L6.5	L11.5	L18.0	L24.5	R6.0	R12.5	R17.5	R24.0	
	$\dot{V}_R$	0.94	1.02	1.00	1.22	0.84	0.92	0.97	1.04	+0.011
H. D.	Detector position	L3.0	L 9.5	L13.5	L20.0	R4.0	R10.5	R14.0	R20.5	
	$\dot{V}_R$	0.85	0.89	1.01	1.22	0.80	0.90	1.04	1.20	+0.023
J. V.	Detector position	L4.0	L10.0	L15.0	L21.5	R4.5	R10.5	R15.0	R21.0	
	$\dot{V}_R$	0.84	0.88	0.99	1.25	0.90	0.91	1.00	1.13	+0.019
E. S.	Detector position	L5.5	L12.0	L17.5	L24.0	R5.5	R12.0	R17.5	R23.5	
	$\dot{V}_R$	1.00	1.03	1.15	1.19	0.74	0.80	0.94	1.04	+0.014
D. M.	Detector position	L6.5	L13.0	L18.5	L25.0	R5.0	R11.5	R16.0	R22.5	
	$\dot{V}_R$	0.85	0.95	1.04	1.23	0.88	0.96	0.83	1.11	+0.016
J. O.	Detector position	L5.5	L12.0	L15.0	L21.5	R3.0	R 9.5	R13.0	R19.5	
	$\dot{V}_R$	0.93	0.97	1.06	1.12	0.89	0.92	0.96	1.07	+0.012
J. G.	Detector position	L6.0	L12.0	L16.0	L22.5	R5.5	R11.5	R16.0	R22.0	
	$\dot{V}_R$	0.91	0.87	0.96	1.06	1.00	0.96	1.02	1.14	+0.009
W. K.	Detector position	L5.0	L11.5	L18.5	L25.5	R5.5	R12.0	R16.5	R23.0	
	$\dot{V}_R$	0.79	0.84	1.06	1.23	0.82	0.89	0.99	1.12	+0.021
R. U.	Detector position	L6.0	L12.5	L19.0	L25.0	R6.0	R12.5	R18.5	R25.0	
	$\dot{V}_R$	0.96	0.99	1.02	1.11	0.89	0.94	1.05	1.03	+0.008
		Supine Studies								
N. F.	Detector position	L5.5	L11.0	L18.0	L23.5	R5.5	R10.5	R16.0	R21.5	
	$\dot{V}_R$	1.00	1.02	1.04	1.08	0.87	0.98	0.97	1.00	+0.006
R. R.	Detector position	L7.0	L13.5	L17.0	L23.5	R4.5	R11.0	R15.5	R22.0	
	$\dot{V}_R$	0.93	1.02	1.01	1.05	0.89	0.99	1.01	1.00	+0.007
S. W.	Detector position	L6.0	L11.0	L17.0	L23.0	R4.0	R 9.0	R15.5	R21.0	
	$\dot{V}_R$	1.00	1.09	1.11	0.95	0.92	0.98	0.97	0.96	+0.001
B. M.	Detector position	L5.0	L10.5	L16.5	L22.0	R3.5	R 9.0	R14.0	R19.0	
	$\dot{V}_R$	0.92	0.98	1.01	1.17	1.16	0.96	0.91	0.99	+0.003
G. V.	Detector position	L7.0	L14.0	L17.5	L24.0	R5.0	R11.5	R16.0	R22.5	
	$\dot{V}_R$	0.89	1.02	1.04	1.18	0.81	0.96	1.00	1.16	+0.018
R. F. R.	Detector position	L5.5	L11.0	L16.0	L21.0	R4.5	R 9.0	R15.0	R20.5	
	$\dot{V}_R$	0.99	1.03	1.00	1.09	0.91	0.97	0.98	1.01	+0.006
J. M.	Detector position	L5.0	L10.5	L18.5	L24.0	R3.5	R 8.5	R16.5	R22.0	
	$\dot{V}_R$	1.01	1.07	1.10	1.09	0.87	0.94	0.93	0.97	+0.005

Detector positions are given as left (L) or right (R) in centimeters measured from the apex of the lung. V_R is relative ventilation per alveolus measured by a single inspiratory capacity breath of ^{133}Xe in air. Ventilation gradient is given as change in relative ventilation per centimeter distance.

artery pressure due to generalized vasoconstriction (5) or by selective constriction of vessels at the lung bases. One might add the possibility of upper zone vasodilation but this will not be considered further because hypoxia is a known stimulus to pulmonary vasoconstriction. Fowler and Read (13) thought that the alteration in distribution which they observed was too large to be explained by changes in cardiac output and pulmonary artery pressure and believed that there must be some selective vasoconstriction at the lung bases. Dugard and Naimark (11) believed that the redistribution during hypoxia in their dogs could have been entirely

due to changes in pulmonary artery pressure and cardiac output. The alterations in the present study were quite small and are compatible with any of these explanations.

In the supine position the gravitational gradient is small and changes in cardiac output and pulmonary artery pressure should have little effect on the ratio of apical to basal perfusion. Fowler and Read (13) attributed the increased upper zone perfusion during supine hypoxia to selective vasoconstriction in the lower zones. Evidence of selective vasoconstriction at the bases was also found by Arborelius, Lindell, and Malmborg (16) who reported that during unilateral inhalation of 100% nitrogen, not only was relative perfusion of the hypoxic lung reduced, but there was an increase in the ratio of apical to basal perfusion on the hypoxic side.

In the present study the distribution of ventilation was measured only during air breathing. Arborelius (4) reported small changes in ventilation distribution during regional hypoxia, but other workers have found the distribution of inhaled gas unaffected by hypoxia (11, 17). If it is assumed that there was no change during the hypoxic period, it is possible to calculate the regional alveolar oxygen tensions from the values of $\dot{V}_R/\dot{Q}_R$. A ventilation/perfusion diagram for 14.2% oxygen at sea level was constructed assuming an overall ventilation/perfusion ratio of 0.83, normal values during air breathing (respiratory quotient of 0.8, mixed venous oxygen tension of 39.5 and CO_2 tension of 43) and no change in metabolism, alveolar ventilation, and cardiac output during hypoxia. Fig. 6 shows regional alveolar oxygen tension plotted against distance from

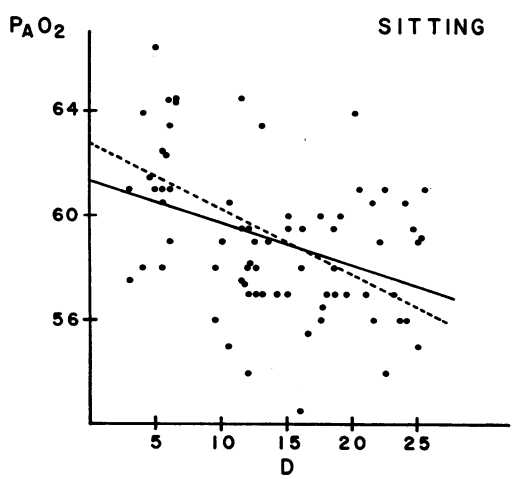

FIGURE 6 Calculated regional alveolar oxygen tension (P_{AO_2}) as a function of distance (D) from the apex of the lung in the sitting subjects. The regression line is solid ($Y = -0.163X + 61.4$). The dashed line represents the regression line of calculated alveolar P_{O_2} versus distance if perfusion distribution were unchanged during hypoxia ($Y = -0.253X + 62.8$).

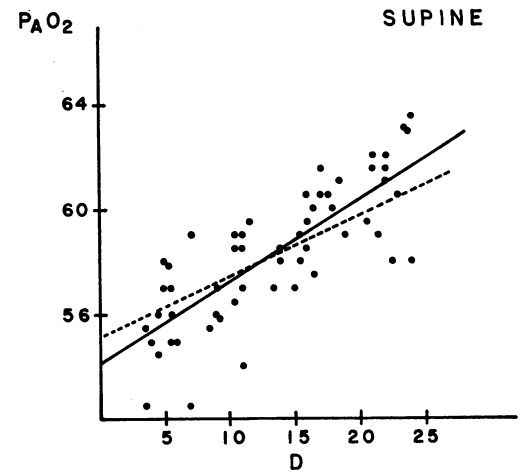

FIGURE 7 Calculated regional alveolar oxygen tension (P_{AO_2}) as a function of distance (D) from the apex of the lung in the supine subjects. The regression line is solid ($Y = 0.311X + 54.1$). The dashed line represents the regression line of calculated alveolar P_{O_2} versus distance if perfusion distribution were unchanged during hypoxia ($Y = 0.230X + 55.1$).

the lung apex for the sitting subjects with the regression line. The dashed line represents the regression line calculated from the $\dot{V}_R/\dot{Q}_R$ values which would have existed if perfusion distribution did not change during hypoxia. The change in perfusion distribution during hypoxia decreased the arithmetic value of the slope in the sitting subjects indicating that alveolar oxygen tension became more even. The reduced relative perfusion of the lung bases raised the oxygen tension where it tended to be lowest, thereby tending to minimize arterial hypoxemia.

In the supine subjects, by contrast, the positive ventilation gradients with negative perfusion gradients resulted in increasing $\dot{V}_R/\dot{Q}_R$ from apex to base. Fig. 7 shows the calculated regional alveolar oxygen tension vs. distance from the apex with the regression line. The dashed line shows the regression line calculated from the values of $\dot{V}_R/\dot{Q}_R$ which would have existed if perfusion distribution had been unchanged. The increase in relative upper zone perfusion during hypoxia increased the already higher regional oxygen tensions as reflected by the increased slope of the regression line. Fowler and Read (13) also found that alveolar oxygen tension was higher in the lower than in the upper zones of some of their supine subjects who showed reduced basal perfusion during hypoxia.

Therefore the alteration of blood flow distribution during hypoxia cannot be explained by selective vasoconstriction in the regions of lowest alveolar oxygen tension. Lower zone perfusion decreases during hypoxia even when the bases are relatively well ventilated and Fowler and Read (13) have suggested that the lower

zone vessels are more responsive to hypoxia, possibly an adaptation to the erect posture in which ventilation/perfusion is most uneven (18). In the erect subjects the change in regional perfusion during hypoxia correlated better with the ventilation/perfusion quotient than it did with distance from the apex, suggesting that selective vasoconstriction in the most hypoxic regions may have contributed to the redistribution, but the influence of regional oxygen tension must be slight because it was overwhelmed by differences in regional reactivity in the supine position.

Even in the most responsive of the erect subjects, regional differences in ventilation/perfusion were not abolished during hypoxia and in most the redistribution had little effect on alveolar gas composition. A slight increase in ventilation would have more effectively increased arterial oxygen tension. Therefore it does not seem that hypoxic vasoconstriction provides a 'fine adjustment' for the regulation of local ventilation/perfusion ratios under normal conditions. However, it is possible that during chronic hypoxia (altitude adpatation or lung disease) or during more severe acute hypoxia, pulmonary vasoconstriction results in closer matching of ventilation and perfusion.

Fowler and Read (13) reported that reduced relative perfusion of the lung bases occurred reproducibly in those subjects who were "responsive" to hypoxia. 2 months after the first experiment subject H. D. who showed the largest change during hypoxia was restudied. A much smaller change in the perfusion gradient was observed on this occasion (control + 0.055, hypoxia + 0.048).

After acute hypoxia pulmonary blood flow distribution does not promptly return to normal. In the erect subjects relative perfusion of the bases increased over its control value and the change persisted for at least 20 min. A suggestion of the same phenomenon can be found in the data of other workers. In four of the six erect subjects of Fowler and Read (13) the ratio of apical to basal perfusion was lower during recovery from hypoxia than during the control period and in two subjects the difference persisted for 30 min or more. Dugard and Naimark (11) found that the posthypoxic perfusion gradients of erect anaesthetized dogs were slightly greater than the prehypoxia control gradients on the average, though the difference was not statistically significant. Supine subjects in the present study showed a significant increase in relative apical perfusion over the control value. Only two of the six supine subjects of Fowler and Read (13) showed such a trend during recovery from hypoxia, but in all three supine subjects of Arborelius et al. (16) there was an increase in the ratio of apical to basal flow over the control value in the hypoxic lung.

If the cardiac output of the erect subjects was high because of anxiety during the control measurement, relative apical perfusion would have been elevated (15). During posthypoxia the subjects may have been more relaxed and relative perfusion of the lung bases would then be higher. It is not likely that this explains the difference between the control and the posthypoxic distribution because there was no significant difference between the distribution of the two control injections, though 10–15 min elapsed between them. It is also conceivable that during recovery from hypoxia the cardiac output falls to a subnormal value but it is unlikely that cardiac output changed enough to alter the blood flow distribution of the supine subjects. Therefore, it is suggested that active vasodilation occurs in the pulmonary vascular bed during recovery from hypoxia. While posthypoxic vasodilation has not previously been reported in the pulmonary circulation, Bergofsky has described (but not commented upon) a decrease in tension exerted by stretched guinea pig pulmonary artery strips after exposure to hypoxia as compared with control values (14). In the erect subjects, vasodilation would increase relative perfusion of the bases whether it was generalized or confined to the lower zones. The alteration of posthypoxic distribution showed no correlation with ventilation/perfusion quotient suggesting that vasodilation was not more pronounced in the regions of lowest alveolar oxygen tension. In most of the supine subjects, the perfusion gradients were initially negative, indicating a tendency to greater perfusion of the apices. Bryan and associates (15) also observed reversal of the perfusion gradient in the supine position and suggested that when the subject lies on a table the buttocks tilt the lung apices slightly downward. In the present study all of the detectors were placed below the chest and the upper zone detectors probably viewed a greater proportion of dependent lung which would tend to accentuate the tendency to high apical blood flow. The effect of generalized vasodilation during recovery from hypoxia would therefore be to increase the relative perfusion of the upper zones.

In both erect and supine subjects, pulmonary blood flow changed in a manner consistent with the occurrence of "posthypoxic vasodilation." It is not clear what could be the function of posthypoxic vasodilation in the lung. Such a mild degree of hypoxia would not have produced any significant oxygen lack in the lung tissues and there is no evidence that the posthypoxic change in distribution had any beneficial effect on ventilation/perfusion. Reeves and Leathers (19) have made the interesting suggestion that hypoxic vasoconstriction is a residual mechanism from fetal life having no useful function in the adult. Posthypoxic vasodilation may also represent persistence of a fetal mechanism which contributes to inflation and perfusion of the lung when

the first breath abruptly raises the alveolar oxygen tension.

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