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Research Article

Pulmonary hemodynamics and gas exchange were studied in four physicians during 72 hr acclimatization to 12,470 ft. Pulmonary catheters were left in three subjects for 72 hr. Resting mean pulmonary arterial pressure ($P\bar{A}P$) rose progressively during the first 24 hr from 10.3 ±1.0 to 21.1 ±4.0 torr and remained at this level. During this same 24 hr period cardiac output increased from 7.1 ±1.4 to 8.4 ±2.0 liters/min and total pulmonary resistance rose from 122 ±16 to 209 ±40 dynes·sec/cm^{-5}. Excercise at 60 w after 24 hr of hypoxia increased $P\bar{A}P$ to 28.8 ±5.1 torr and decreased total pulmonary resistance to 155 ±25. Shunt fractions were 11 ±3.8% after 24 hr at altitude and fell to 7 ±0% after 72 hr. Alveolar to arterial O_2 difference ($P(A\text{-}a)_{O_2}$) breathing oxygen fell from 116 ±10.8 to 92 ±33.3 torr during the same period of acclimatization, whereas dead space to tidal volume ratio (V_D/V_T) rose from 33 ±4.0% to 40 ±5.3% and $P(A\text{-}a)_{O_2}$ breathing ambient air rose from 8 ±2.6 to 11 ±3.0 torr. Inspiratory static lung compliance decreased significantly from a control of 176 ±8 to 141 ±8 ml/cm H_2O after 72 hr of hypoxia.

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ABSTRACT Pulmonary hemodynamics and gas exchange were studied in four physicians during 72 hr acclimatization to 12,470 ft. Pulmonary catheters were left in three subjects for 72 hr. Resting mean pulmonary arterial pressure ($\overline{PAP}$) rose progressively during the first 24 hr from 10.3 ±1.0 to 21.1 ±4.0 torr and remained at this level. During this same 24 hr period cardiac output increased from 7.1 ±1.4 to 8.4 ±2.0 liters/min and total pulmonary resistance rose from 122 ±16 to 209 ±40 dynes·sec/cm^{-5}. Excercise at 60 w after 24 hr of hypoxia increased $\overline{PAP}$ to 28.8 ±5.1 torr and decreased total pulmonary resistance to 155 ±25. Shunt fractions were 11 ±3.8% after 24 hr at altitude and fell to 7 ±0% after 72 hr. Alveolar to arterial O_2 difference ($P(A\text{-}a)_{O_2}$) breathing oxygen fell from 116 ±10.8 to 92 ±33.3 torr during the same period of acclimatization, whereas dead space to tidal volume ratio (V_D/V_T) rose from 33 ±4.0% to 40 ±5.3% and $P(A\text{-}a)_{O_2}$ breathing ambient air rose from 8 ±2.6 to 11 ±3.0 torr. Inspiratory static lung compliance decreased significantly from a control of 176 ±8 to 141 ±8 ml/cm H_2O after 72 hr of hypoxia.

After 4–7 days at altitude, further deterioration in gas exchange was observed after a 5 mile, 1800 ft climb to the summit (14,255 ft) and return. $P(A\text{-}a)_{O_2}$ on air rose from 2.5 ±2.1 just before starting, to 16.3 ±2.8 at the summit (rested), and was still 9.0 ±2.2 several hours after returning. The O_2-breathing values paralleled these, whereas dead space appeared to fall. We speculate that the hypoxic pulmonary hypertension which develops over 24 hr in some way may be responsible for a reduction of compliance and deterioration in oxygen exchange efficiency, possibly representing a subclinical form of pulmonary edema of high altitude. The increased alveolar to arterial O_2 difference induced by hypoxic exercise persists for several hours of hypoxic rest.

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INTRODUCTION

An increase in pulmonary arterial pressure in man at high altitude was first demonstrated conclusively by Rotta, Canepa, Hurtado, Velasquez, and Chavez in 1956 (1) and has been confirmed many times since, both in acclimatized natives (2, 3) and in newcomers (4). The relationship of this pulmonary hypertension to the development of high altitude pulmonary edema (HAPE) is uncertain, but pulmonary artery pressure is higher during episodes of HAPE than during control observations in the same individuals (5), and persons who have had such episodes previously have higher pulmonary artery pressures when reexposed to altitude than nonsusceptible individuals under the same conditions (6). Although it is recognized that the peak incidence of HAPE occurs 1–3 days after entry to high altitude (7), it has not been established whether pulmonary arterial pressure rises in a progressive fashion over the same time course. A progressive rise in pulmonary arterial pressure during a 6 wk period at 12,700 ft has been reported in steers, apparently associated with the right heart failure termed "brisket disease" (8), but was not observed in lambs in a matched experiment (9). Therefore, we decided to investigate in ourselves the time course of the pulmonary arterial pressure both at rest and during exercise at 12,470 ft and to examine other aspects of cardiovascular function over the same time span. We also explored the possibility suggested by Haab, Held, Ernst, and Farhi (10) and Reeves, Halpin, Cohn, and Daoud (11) that hypoxia widens the alveolar to arterial O_2 difference.

METHODS

Subjects

The seven subjects whose physical characteristics are given in Table I were male physicians familiar with the equipment and techniques used in the study. The four subjects participating in the 72 hr acclimatization study were transported to the Barcroft Laboratory (12,470 ft) in an unpressurized aircraft. Except for a 1 hr stay at 4000 ft, they breathed air enriched with oxygen at flow rates of 2 liters/min while in transit and until catheterization and the control studies had been completed at the Barcroft Laboratory. This flow of oxygen was sufficient to maintain Pa_{O_2} over 150 torr. The three subjects who only participated in the summit climb study traveled to altitude by car. They spent 1 night at 10,500 ft and arrived at 12,470 ft about 30 hr before the other four subjects.

72 hr acclimatization study

Catheterization. Upon arrival at the Barcroft Laboratory, a 36 inch Portex epidural catheter (Portex Ltd., Hythe-Kent, England) with a square cut tip orifice was inserted percutaneously into the left basilic vein and advanced, while monitoring pressure, to the pulmonary artery. A second catheter was placed in the left brachial artery using the Seldinger technique. We intended that these catheters remain in place for 72 hr. Between studies they were filled with heparin and the skin entry sites covered with antibiotic ointment and sterile gauze.

Experiments. Daily complete studies consisted of measurements of pulmonary and systemic arterial pressures, heart rate, cardiac output, arterial and mixed venous blood samples for pH, P_{O_2}, P_{CO_2}, O_2 content, saturation, hemoglobin, osmolarity, oxygen consumption (V_{O_2}), static lung compliance (C_L), maximum expiratory flow rate (MEFR), functional residual capacity (FRC), and vital capacity (VC). The subjects were studied at rest and during exercise at 60 w with a bicycle ergometer, during 3–5 min at an alveolar P_{O_2} (end tidal) maintained at 40 torr and during 5 min of 100% oxygen breathing. Mixed expired gas was collected to permit calculation of dead space to tidal volume ratio (V_D/V_T), shunt fractions ($Q_S/\dot{Q}t$), and alveolar to arterial difference for oxygen ($P(A\text{-}a)_{O_2}$). The latter was measured while subjects breathed both ambient air and 100% O_2. In addition to these daily studies, we measured pulmonary arterial pressure and arterial and mixed venous blood gas tensions after 6, 12, 30, 36, and 54 hr of hypoxia. All measurements except for lung compliance were made with subjects supine. F. W.'s pulmonary artery catheter was removed during the 48 hr complete study because it had slipped into the right ventricle. The same problem occurred in subject W. N. during the 72 hr complete study. Subject R. K. asked to have his brachial artery catheter withdrawn after 54 hr. His arterial blood was obtained thereafter by single needle punctures. Except for subject R. H.'s brachial artery catheter, all remaining catheters were removed after the 72 hr complete study.

TABLE I

Physical Characteristics of Subjects

Subject*	Age	Ht.	Wt.	Body surface area
	yr	*cm*	*kg*	m^2
R. H.	37	178	68	1.84
F. W.	39	195	91	2.19
R. K.	31	183	73	1.92
W. N.	31	183	70	1.91
J.S.	47	183	77	1.98
P. S.	45	180	68	1.86
E. N.	27	175	83	1.98

* Subjects R. H., F. W., R. K., and W. N. participated in the 72 hr acclimatization study; J. S., P. S., and E. N. together with R. H. participated in the summit climb study.

Analytical techniques. Systemic and pulmonary arterial pressures were recorded with Statham P23G transducers attached to a Model 5 Polygraph (Grass Instrument Co., Quincy, Mass.). The zero reference point for the pressure measurements was 5 cm dorsal to the angle of Louis. Mean pressures were obtained electrically or in a few cases by adding one-third of the pulse pressure to the diastolic pressure. Cardiac output was computed from Cardio-Green (indocyanine green) dilution curves, after injection into the pulmonary artery, and also by the direct Fick method from the measured O_2 consumption and pulmonary arterial oxygen content.

The ventilatory apparatus used to control end tidal P_{O_2} consisted of a Wedge spirometer (Med-Science Electronics, Inc., St. Louis, Mo.) with integrating electrical recording, a CO_2 absorber, flow meters for controlling O_2, N_2, and suction, an infrared CO_2 analyzer and a new automatic sampling end tidal oxygen electrode (12) maintained at 37°C and covered with 6 μ Teflon. The operator monitored the Grass recording of P_{O_2} and adjusted the flow meters accordingly.

Blood and expired gas tensions were determined with O_2 and CO_2 electrodes at 37°C and the blood values were corrected to body temperature. One oxygen electrode was used for measurements at high P_{O_2}, another at low P_{O_2} (i.e., venous blood), to minimize the errors and delays resulting from electrode hysteresis. The high P_{O_2} was also used for analyses of blood O_2 content by the method of Klingenmaier, Behar, and Smith (13), in which P_{O_2} is determined after 50-fold anaerobic dilution of blood with CO-saturated water. Hemoglobin and oxygen saturation were measured with an Instrumentation Laboratories Model 182 CO-Oximeter. Samples were analyzed immediately except for those obtained on the summit which were packed in snow and analyzed 6 hr later at the Barcroft Laboratory. Saturation calculated from P_{O_2} and pH (14) averaged 0.04 $\pm$2.3% higher than the Instrumentation Laboratories Oximeter reading, while saturation calculated from measured oxygen content and computed capacity (1.34 $\times$ Hgb) averaged 2.1 $\pm$3.5% lower than the oximeter readings ($P < 0.001$). Frozen serum was transported to San Francisco where osmolarity was determined using a Fiske osmometer (Fiske Associates, Inc., Uxbridge, Mass.).

While breathing air through a Lloyd valve, expired gas was collected for 3 min in a 120 liter Tissot spirometer and its O_2 and CO_2 concentrations determined by electrodes. Oxygen consumption was determined after at least 3 min of preoxygenation using a closed system with CO_2 absorber, a Wedge spirometer filled with 100% O_2, and a Grass recorder. Methods were altered slightly for the summit climb study in that end tidal samples were collected manually during inspiration from just beyond the expiratory port of the Lloyd nonrebreathing valve and mixed expired gas was collected in a meteorological balloon.

Maximum expiratory flow rate and vital capacity were determined with a wedge spirometer and Grass recorder. FRC was measured by having the subjects rebreathe for 15 sec from a 3.0 liter bag filled with O_2 using the technique described by Lundsgaard and Van Slyke (15), as modified by Severinghaus, Bainton, and Carcelen (16). Static lung compliance was mea-

sured with the subjects seated breathing from a Wedge spirometer. A Statham PM131TC strain gage transduced the differential pressure between mouth pressure and a 10 cm long air-filled esophageal balloon positioned just above the cardia. The balloon was passed via the nose into the stomach (positive deflection with inspiration), withdrawn until a negative deflection on inspiration appeared, and then withdrawn an additional 10 cm. The final balloon volume was adjusted to 0.2 ml. The operator occluded the airway with a solenoid valve for 3 sec at incremental inspired steps of approximately 500 ml until 70–80% of total lung capacity was reached. Similar recordings were then obtained during expiration. Four to six inspiratory and expiratory pressure volume curves were obtained during each compliance determination. Each curve was plotted separately and the values given represent the mean slopes.

Calculations. Alveolar oxygen tension for the determination of $P(A\text{-}a)_{O_2}$ and $\dot{Q}s/\dot{Q}t$ was calculated from arterial P_{CO_2} and mixed expired gas. When R was not measured it was assumed to be 0.8. Since the measured values for R during the major studies were always greater than 0.8, we probably have underestimated the $P(A\text{-}a)_{O_2}$. It was discovered near the end of the study that the O_2 demand regulator used for 100% O_2 breathing permitted inward leak of enough air to lower $P_{I_{O_2}}$ by 14 torr. $P_{A_{O_2}}$ on 100% O_2 was thus (P_B-47-P_{ACO_2}-14). On the summit climb, end tidal P_{O_2} was directly measured. Left atrial pressure was assumed to be zero for the calculation of total pulmonary resistance. The V_D/V_T calculation includes 46 ml of dead space in the nonrebreathing valve.

TABLE II

*72 hr Acclimatization Study: P_{50} Data Obtained on Four Subjects at Barcroft Laboratory (12,470 ft)**

Subject	Duration of hypoxia			
	0 (Control)‡	24 hr	48 hr	72 hr
R. H.	25.8	26.8	26.6	25.9
F. W.	27.5	27.7	—	—
R. K.	26.8	26.5	25.8	28.6
W. N.	24.2	25.6	27.4	24.8
Mean ±SD	26.1 ±1.4	26.7 ±0.9	26.6 ±0.8	26.4 ±1.9

* P_{50} is the P_{O_2} (torr) at 50% saturation, pH 7.4, and temperature 37°C. The data reported were calculated from saturations measured directly in mixed venous blood obtained while subjects were breathing ambient air at rest.
‡ Subjects breathing supplemental oxygen.

TABLE III

*72 hr Acclimatization Study: Hemodynamic Data Obtained on Four Subjects at Barcroft Laboratory (12,470 ft)**

Variable	Duration of hypoxia							
	0 (Control)‡		24 hr		48 hr		72 hr	
	Rest	Exercise	Rest	Exercise	Rest	Exercise	Rest	Exercise
Mean PAP, *torr*	10.3 ±1.0	20.1 ±5.0	21.0 ±1.4	28.8 ±5.1	21.0 ±4.0 (3)	28.5 ±3.1 (3)	20.0 ±3.6 (3)	30.0 (2)
Cardiac output, *liters/min*	7.1 ±1.4	14.2 ±1.4	8.4 ±2.0	15.0 ±0.4	8.5 ±0.8	14.0 ±3.5	6.9 (2)	12.8 (2)
Heart rate, *beats per min*	72 ±17.1	110 ±8.5	95 ±18.1	132 ±10.4	81 ±20.5 (3)	133 ±9.9 (3)	69 (2)	132 (1)
Mean BAP, *torr*	91 ±7.5	115 ±17.0 (3)	93 ±6.5	111 ±3.5	92 ±6.4	102 ±2.8	83 (2)	97 (1)
Stroke volume, *ml*	96 ±9.8	132 ±19.8 (3)	83 ±6.4	114 ±6.7	110 ±38.2 (3)	116 ±34.6 (3)	102 (2)	97 (1)
TPR, *dynes·sec/cm⁵*	122 ±16	120 ±24 (3)	209 ±40	155 ±25	216 ±41 (3)	178 ±16 (3)	225 (2)	

Abbreviations: PAP, pulmonary arterial pressure; BAP, brachial arterial pressure; TPR, total pulmonary resistance.
* Values are mean ±SD. Numbers in parenthesis indicate number of subjects when less than 4.
‡ Control measurements were done while subjects were breathing supplementary oxygen; all other measurements were made while the subjects were breathing ambient air.

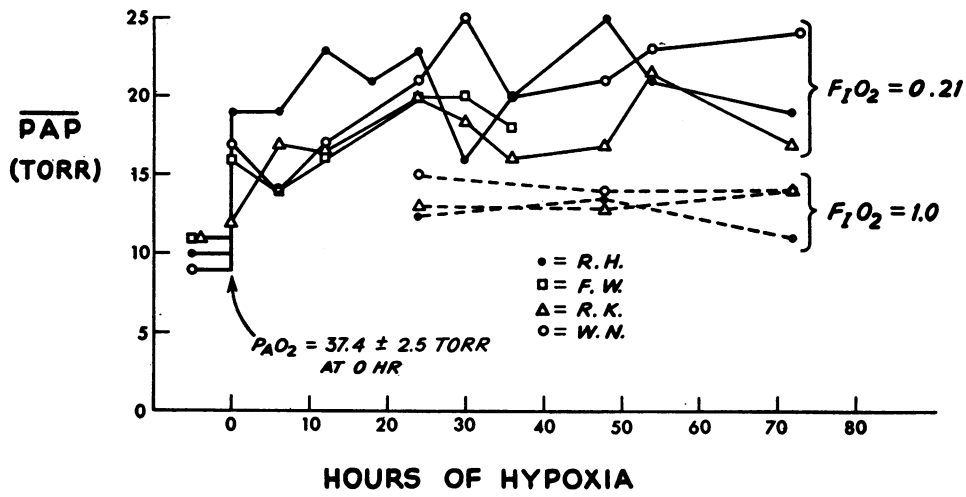

FIGURE 1 Mean pulmonary artery pressure ($\overline{PAP}$) breathing both room air (solid lines) and 100% O_2 (broken lines) in each of the four subjects at 12,470 ft. Inspired O_2 was adjusted at 0 hr to produce an alveolar P_{O_2} of about 37 torr for 5 min before mask rem oval. Unless otherwise noted in this and all subsequent figures, measurements were made while the subjects were supine and breathing supplemental oxygen by mask during the control study. Mask removal occurred at 0 hr.

Lenfant, Torrance, English, Finch, Reynafarje, Ramos, and Faura (17) have observed a shift to the right of the oxygen-hemoglobin dissociation curve with chronic hypoxia. They showed P_{50} (P_{O_2} at 50% saturation, pH 7.4, temperature 37°C) rose from the normal value of 27 to about 31 torr. We calculated P_{50} in mixed venous blood in the four subjects with pulmonary artery catheters, using the directly measured saturation, and P_{O_2}, correcting to pH 7.4. No change in P_{50} with increasing time at altitude was seen in any of the four subjects (Table II). We therefore used the normal O_2 dissociation curve for calculating mixed venous O_2 content when neither saturation nor content was directly measured.

Summit climb study

On the fourth day at altitude we investigated the effect of climbing in subject R. H. and three additional subjects who had been at altitude for 5¼ days (Table I). $P(A\text{-}a)_{O_2}$ and V_D/V_T were measured while subjects sat at the Barcroft Laboratory (12,470 ft) at 10:00 a.m. They then climbed steadily to the summit laboratory (14,255 ft), a horizontal distance of 5 miles, reaching it at 2:00 p.m. The $P(A\text{-}a)_{O_2}$ and V_D/V_T measurements were repeated on the summit after 1–2 hr rest and again (except in R. H.) after descent to Barcroft and 2 hr rest.

RESULTS

72 hr acclimatization study. The hemodynamic data obtained during the 72 hr study are given in Table III and Figs. 1 and 2. During the initial control study, mean pulmonary arterial pressure increased promptly from 10.3 ±1.0 torr to 16.1 ±3.6 torr (mean ±SD) after 3–5 min exposure to $P_{A_{O_2}} = 40$. After mask removal there was a continuous rise in the mean pulmonary arterial pressure during the first 24 hr to an average pressure of 21.0 ±1.4 torr. In three of the four subjects the pressure continued to increase between 12 and 24 hr. The fourth subject (R. H.) had reached a near maximum level by 12 hr. After 24 hr there were variations in mean pulmonary artery pressure between 15 and 25 torr without discernible trends. Reduction of $P_{A_{O_2}}$ to 40 (from a mean of about 50 torr) raised pulmonary arterial pressure an average of 2 torr. 100% oxygen breathing for 5 min reduced mean pulmonary arterial pressure almost but not completely to control levels (Fig. 1). Both resting and exercising heart rates increased during the first 24 hr. The exercising heart rates remained at this higher level while the resting heart rates returned to control levels. Mean brachial arterial blood pressure did not change. Compared to control, resting cardiac output was increased in three of four subjects at 24 hr, and increased in two of three subjects at 48 hr (Fig. 2). Both cardiac output and stroke volume, measured during 60 w of exercise, showed a tendency to fall after 24 hr of hypoxia, the one exception being subject R. H.'s resting and exercising stroke volumes between 24 and 48 hr. Total pulmonary resistance at rest and during exercise increased with hypoxia but did not change with time. The increase in resting resistance between normoxia and hypoxia was significant (P ˊ 0.01). Exercise reduced total pulmonary resistance during hypoxia but not normoxia.

Acclimatization to altitude occurred in every subject as evidenced by a progressively falling arterial P_{CO_2} and pH and a rising alveolar P_{O_2}. Mean values for P_{CO_2} and pH are illustrated in Fig. 3, and mean alveolar and arterial P_{O_2} are shown in Fig. 4. Although alveolar P_{O_2} rose during the course of the study, arterial P_{O_2} remained relatively constant, indicating a progressively increasing alveolar to arterial difference for O_2. Individual values of $P(A\text{-}a)_{O_2}$ during air breathing are shown in Fig. 5. The mean values (±SD) in all four subjects

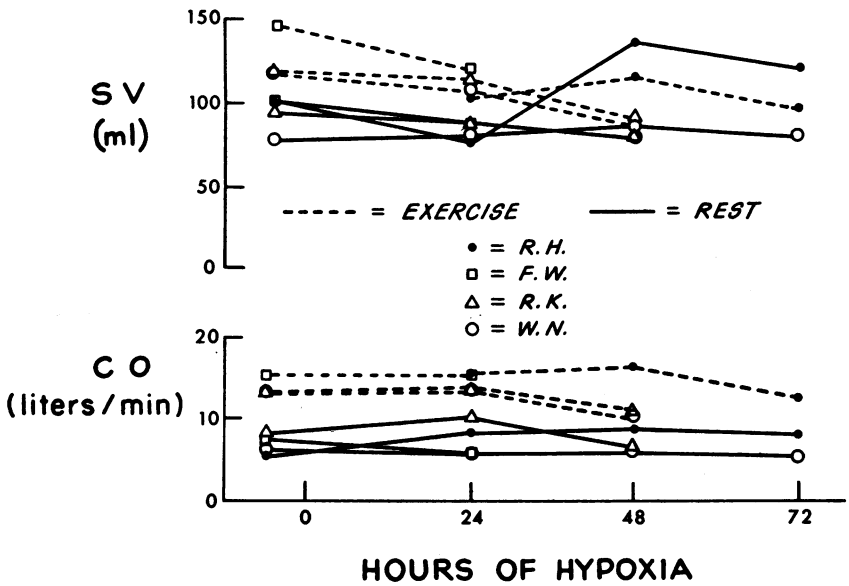

FIGURE 2 Stroke volume (SV) and cardiac output (CO) during rest and 60 w of exercise (both supine) in each of four subjects at 12,470 ft.

rose from 8 ±2.6 to 11 ±3.0 torr between 24 and 72 hr. In three of the four subjects V_D/V_T increased during the same time (Fig. 6). Mean values (±SD) for V_D/V_T were 33 ±4.7% at 24 hr and 40 ±5.3% at 72 hr. In contrast, the shunt fraction fell from 11 ±4% at 24 hr to 7 ±0% at 72 hr. $P(A\text{-}a)_{O_2}$ breathing oxygen averaged 116 ±10.8, 114 ±16.4, and 92 ±33.3 (torr ±SD) at 24, 48, and 72 hr of acclimatization. Since supplemental rather than 100% oxygen was used during the control study, we have not reported control shunt fractions or $P(A\text{-}a)_{O_2}$. Alveolar to arterial oxygen gradients breathing both 100% and 13% oxygen were measured in the four subjects at sea level 2 months after their return from altitude. These were 15.7 ±3.9 on 100% oxygen and 3.1 ±2.2 on 13% oxygen.

The mean control values for the following variables

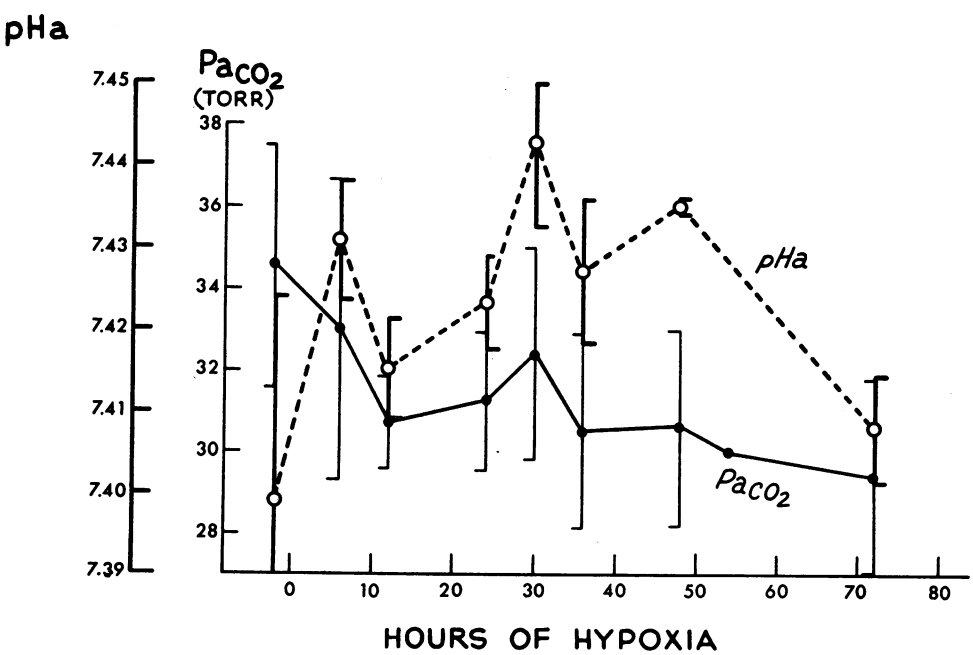

FIGURE 3 Arterial P_{CO_2} (solid line) and pH (broken line) in the four subjects at 12,470 ft (mean ±SD).

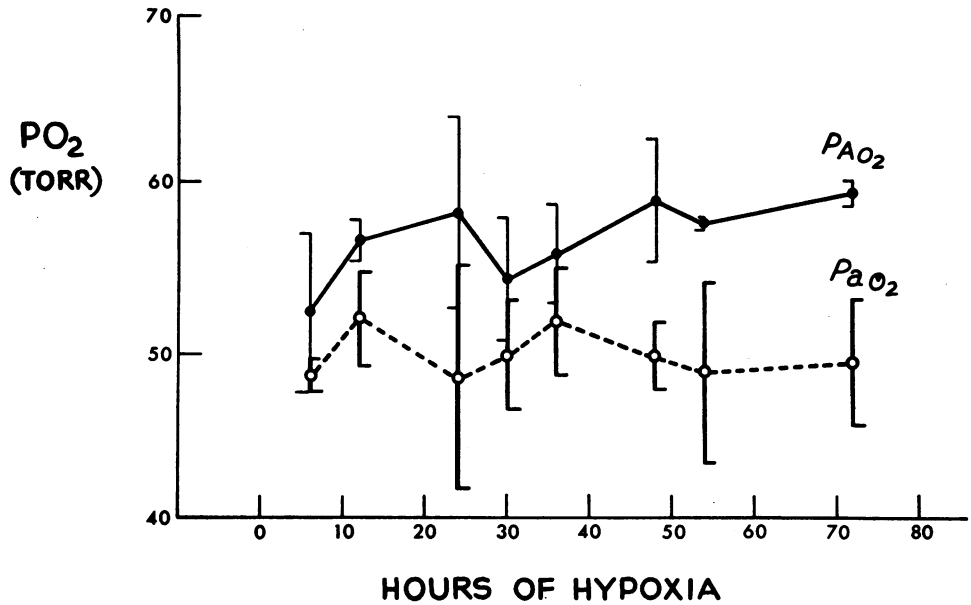

FIGURE 4 Alveolar (solid line) and arterial (broken line) P_{O_2} in the four subjects at 12,470 ft (mean ±SD).

were: $\dot{V}_{O_2}$, 316 ml/min STPD; vital capacity, 5.1 liters; FRC, 2.9 liters; MEFR, 515 liters/min; static expiratory lung compliance, 216 ml/cm H_2O; and serum osmolarity, 292 mOsmoles. None of these variables changed significantly from their control values during the study. Minute ventilation increased slightly during the study from a control mean of 9.8 liters/min to 11.4 liters/min after 72 hr.

Only one compliance measurement was made during the 48 hr major study. The mean values (±SEM) for inspiratory lung compliance at 0 (control), 24, and 72 hr of hypoxia were: 176 ±7.9, 169 ±15.7, and 141 ±8.2 ml/cm H_2O. The decrease in inspiratory compliance between 24 and 72 hr was significant ($P < 0.025$).

Summit climb study. The analytical and gas exchange data for the summit climb study are given in Table IV. The four subjects in this study, one of whom (R. H.) also took part in the 72 hr study, all had normal air and oxygen breathing $P(A\text{-}a)_{O_2}$ values before the climb. They were studied in the sitting position. There

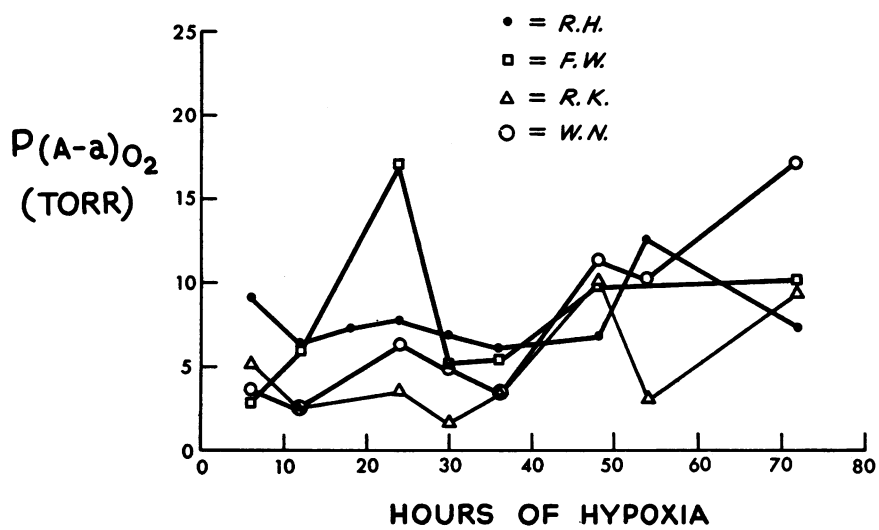

FIGURE 5 Air breathing alveolar to arterial differences for oxygen in each of the four subjects at 12,470 ft. Alveolar P_{O_2} was calculated assuming a respiratory exchange ratio of 0.8.

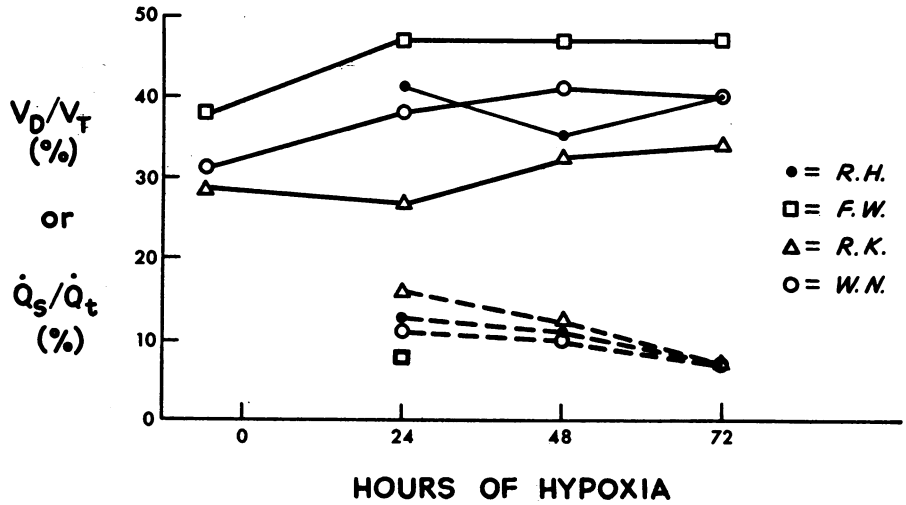

FIGURE 6 Dead space to tidal volume ratios (V_D/V_T) and shunt fractions ($\dot{Q}s/\dot{Q}t$) in each of the four subjects at 12,470 ft. V_D/V_T measured breathing ambient air. $\dot{Q}s/\dot{Q}t$ measured breathing 100% O_2.

was an increase in $P(A\text{-}a)_{O_2}$ during both air and oxygen breathing after the ascent to the summit with a partial return towards preclimb values after descent. V_D/V_T did not show this pattern but decreased progressively in three of the four subjects during the course of the day.

Preliminary tests of ventilatory response. Before going to altitude, we assessed each subject's ventilatory response to hypoxia both by progressively decreasing alveolar P_{O_2} from 100 to 40 over 3–4 min at a constantly maintained $P_{A_{CO_2}}$, and also with single vital capacity breaths of 5% CO_2 in O_2, 5% CO_2 in N_2, 15% CO_2 in O_2, and 15% CO_2 in N_2. The latter test was used to assess the contribution of the peripheral chemoreceptors to the ventilatory response to hypoxia without the medullary effects of hypoxia (direct depression, increased blood flow, and thus lowered P_{CO_2}) (18). As shown in Table V, all the subjects had a definite peripheral chemoreceptor response as evidenced by an increase in ventilation on the second and third breaths after a vital capacity inspiration of 15% CO_2 in 85% N_2. Subject F. W. consistently had the lowest ventilatory response to hypoxia by both the progressive hypoxia and single breath methods, and subject R. H. the highest. Subject F. W. also had the lowest arterial oxygen tensions at altitude and was the only one of the four subjects to develop altitude sickness with headache and vomiting the first night at altitude. He did not exhibit more rise of pulmonary artery pressure than the others.

DISCUSSION

The pulmonary arterial pressure rise seen in this study is similar to that seen by Hultgren, Kelly, and Miller (4) in normal acclimatized adults at 12,300 ft in Peru and by Vogel, Goss, Mori, and Brammell in four subjects 24–48 hr after arrival at 14,260 ft (19). The increase was due primarily to an increase in total pulmonary resistance (Table II). These data are consistent with the generally accepted hypothesis that pulmonary hypertension at altitude is due to an increase in pulmonary arteriolar resistance. Pulmonary capillary wedge and left atrial pressure have been found to be normal at altitude (3), even during HAPE (5).

The rather steady rise of the pulmonary arterial pressure during the first 24 hr of hypoxia is of interest. The level of pulmonary arterial pressure reached after 24 hr was greater in every case than that caused by a 5 min exposure to a $P_{A_{O_2}}$ of 40 torr during the control study, even though the degree of hypoxia during the brief exposure was greater. This finding is consistent with the observation by Grover, Reeves, Will, and Blount (8) in calves that pulmonary artery pressure increases during several weeks at altitude. 5 min of oxygen breathing at various times during the 72 hr study lowered the pulmonary arterial pressure considerably, but in no case was the prehypoxic control pressure achieved. Hultgren, Kelly, and Miller (20) noted that oxygen breathing lowered the pulmonary arterial pressure of acclimatized normal Peruvian natives only about 5 torr. Our study suggests that, as early as 24 hr after altitude exposure, some changes may occur in the pulmonary vascular bed which are not immediately reversible with oxygen.

All the subjects had a similar degree of pulmonary arterial pressure rise (Fig. 5), but F. W., who had the least ventilatory response to hypoxia, was the only subject with a fall in cardiac output between the control and 24-hr measurements. His total pulmonary resist-

TABLE IV

Summit Climb Study: Blood Gas Tensions

Subject‡	Before climb at Barcroft (P_B = 490 torr)					After climb at Summit (P_B = 455 torr)§	
	Pa_{O_2}	Pa_{CO_2}	pHa	$P(A\text{-}a)_{O_2}$	V_D/V_T‖	Pa_{O_2}	Pa_{CO_2}
				torr	%		
Breathing air							
R. H.	53	30	7.42	3	38	42	28
P. S.	57	29	7.41	2	35	46	25
J. S.	59	30	7.44	5	24	47	26
E. N.	54	31	7.39	0	42	38	31
Mean ±SD	55.8 ±2.8	29.9 ±0.9	7.41 ±0.02	2.5 ±2.1	34.8 ±7.7	43.1 ±4.0	27.5 ±2.6
Breathing oxygen							
R. H.	292	31	7.40	74		241	26
P. S.	318	28	7.42	52		278	30
J. S.	322	29	7.42	47		288	33
E. N.	307	30	7.38	60		236	36
Mean ±SD	310 ±13.4	29.4 ±1.5	7.41 ±0.02	58.1 ±11.6		260.5 ±26.1	31.0 ±4.1

Abbreviations: P_B, barometric pressure; $P(A\text{-}a)_{O_2}$, alveolar to arterial O_2 difference; V_D/V_T, dead space to tidal volume ratio.

* All measurements made with patients seated and at rest.

‡ At the time of the study, R. H. had been at Barcroft Laboratory (12,470 ft) for 4 days and the other subjects for $5\frac{1}{4}$ days.

§ After 2 hr rest.

‖ Includes valve dead space of 46 ml.

ance increased 113% during this period, approximately twice the increase of the other three subjects. We conclude that the ventilatory response to hypoxia may predict the degree of hypoxia and the subsequent effects of that hypoxia on altitude sickness and cardiac output in a subject at altitude, but cannot be used to predict the severity of his pulmonary hypertension.

As expected, hypoxia caused an elevation in the resting heart rate in all four subjects. Resting cardiac outputs changed little throughout the study whereas the exercising outputs decreased between 24 and 72 hr at altitude. The time course and direction of the changes in heart rate, stroke volume, and cardiac output are similar to those reported in two young subjects studied at the same altitude by Klausen (21).

Kreuzer, Tenney, Mithoefer, and Remmers (22) found an increased alveolar to arterial O_2 difference ($P(A\text{-}a)_{O_2}$) in Andean natives. Haab et al. measured alveolar to arterial differences for N_2 and CO_2 in nine subjects at 2000 ft and for 5 days after ascent to 11,500 ft (10). On the basis of calculated predicted values for these variables, they suggested that ventilation/perfusion abnormalities persisted throughout the 5 days of altitude exposure. Reeves et al., by use of more direct measurements, reported an increase in $P(A\text{-}a)_{O_2}$ in seven subjects during 4 hr of acute exposure to a simulated altitude of 15,000 ft (11). Conflicting data has also been reported. Kreuzer et al. (23) reported a decrease in $P(A\text{-}a)_{O_2}$ and in shunt fractions in dogs after 5 days exposure to 14,300 ft. Kreuzer and van Lookeren observed no differences in steady-state diffusing capacities for carbon monoxide and oxygen or in $P(A\text{-}a)_{O_2}$ in five men studied at seal level and 4560 m (24). The $P(A\text{-}a)_{O_2}$ differences breathing ambient air in our subjects were quantitatively about the same as those observed by Reeves et al. during short exposures to a P_B = 425 torr (11). In addition to the air-breathing gradients, we also observed large gradients breathing oxygen. These confirm the presence of a significant shunt during the first 72 hr at altitude.

The $P(A\text{-}a)_{O_2}$ breathing air remained relatively constant or rose slightly with time while the shunt fractions and the gradients breathing O_2 decreased. This would imply a gradual increase in the relative role of ventilation/perfusion ($\dot{V}/\dot{Q}$) abnormalities or diffusion limitation. To illustrate this, we used the individual shunt fractions measured while breathing 100% O_2 to solve the shunt equation for arterial P_{O_2}. In making this calculation we assumed a hemoglobin concentration of 13.4 g/100 ml, an arterial pH of 7.40, a mixed venous pH of 7.35, alveolar oxygen tensions varying from 50 to 70 torr, and mixed venous saturations ranging from 20

*and Gas Exchange Data on Four Subjects**

After climb at Summit (P_B = 455 torr)§			After descent at Barcroft§				
pHa	$P_{(A-a)O_2}$	V_D/V_T‖	P_{aO_2}	P_{aCO_2}	pHa	$P_{(A-a)O_2}$	V_D/V_T‖
	torr	%				*torr*	%
7.42	15	27	46	29	7.44	12	
7.42	19	21	53	24	7.38	9	24
7.44	13	19	50	26	7.42	8	16
7.40	18	35	48	26	7.42	7	25
7.42 ±0.02	16.3 ±2.8	25.5 ±7.2	49.3 ±3.0	26.3 ±2.1	7.41 ±0.03	9.0 ±2.2	21.7 ±4.9
7.40	131						
7.40	92		365	26	7.37	45	
7.40	78		320	31	7.38	84	
7.37	45		299	30	7.39	97	
7.39 ±0.01	86.5 ±35.6		328 ±33.7	29.0 ±2.6	7.38 ±0.01	75.3 ±27.1	

to 60% at each alveolar P_{O_2}. We then constructed a plot enabling us to predict the amount of alveolar to arterial O_2 difference accounted for by shunting while breathing ambient air. The results shown in Fig. 7 indicate that the amount of this difference attributable to causes other than shunting increases during acclimatization. The increase in V_D/V_T with time also suggests some maldistribution of ventilation and/or perfusion. The

TABLE V

Respiratory Sensitivity to Hypoxia in Four Subjects at Sea Level before 72 hr Acclimatization Study of 12,470 ft

Subject	Ventilatory response: To single breath of:* 5% CO_2 in O_2	5% CO_2 in N_2	15% CO_2 in O_2	15% CO_2 in N_2	To progressive hypoxia‡ $\Delta\dot{V}_{40}$
	liters/min per m² body surface area				
R. H.	3.3 ±0.8	10.7 ±4.1	15.2 ±3.5	26.4 ±3.3	26.5
F. W.	2.6 ±0.6	4.4 ±1.5	6.5 ±1.3	14.0 ±2.3	1.9
R. K.	2.5 ±0.3	6.9 ±1.3	11.8 ±2.3	19.4 ±2.7	10.0
W. N.	1.9 ±1.0	12.3 ±0.6	9.0 ±1.1	22.6 ±2.6	19.4
Mean ±SEM	2.5 ±0.2	8.4 ±1.1	10.6 ±1.0	20.6 ±1.3	14.3 ±5.5

* Ventilatory response in single breath test is defined as the average ventilation during the second and third breaths after a single vital capacity of the indicated gas. Individual values are mean ±SD of four tests with each gas.

‡ Progressive hypoxia is accomplished by lowering alveolar P_{O_2} from 100 to 40 torr at a constant alveolar P_{CO_2} of 37 torr. $\Delta\dot{V}_{40}$ is defined as the ventilation in liters/min per m² body surface area at a P_{AO_2} of 40 and a P_{ACO_2} of 37 minus 4 liters/min per m² body surface area.

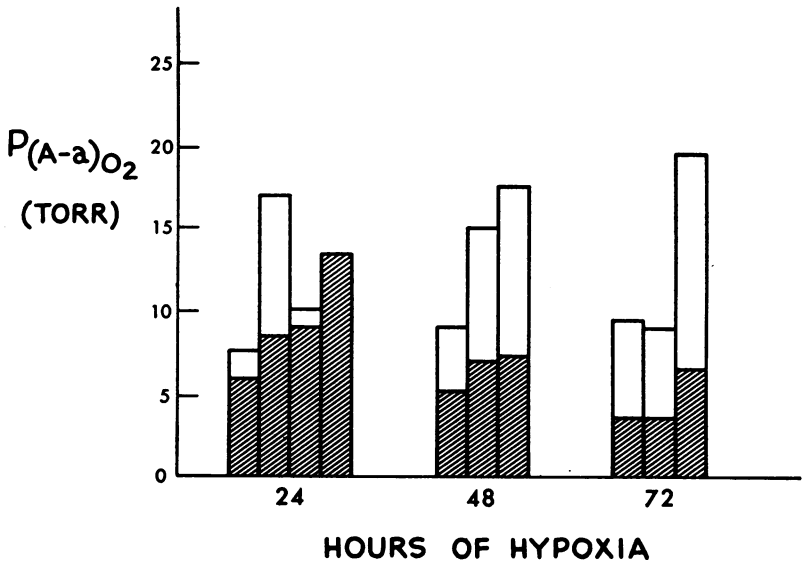

FIGURE 7 Alveolar to arterial difference for oxygen $P(A\text{-}a)_{O_2}$ in the four subjects at 12,470 ft. Hatched area indicates $P(A\text{-}a)_{O_2}$ calculated from the shunt measured during O_2 breathing. The remainder is attributable to either ventilation/perfusion abnormality or to diffusion limitation. Subject F. W. is missing from the 48 and 72 hr data.

supine position of our subjects may have accentuated these $\dot{V}/\dot{Q}$ abnormalities. Dawson has demonstrated that the supine posture aggrevates $\dot{V}/\dot{Q}$ changes in man during acute hypoxia (25).

After 5–7 days at altitude, but before climbing to the summit, the four climbers had normal $P(A\text{-}a)_{O_2}$ values, measured while breathing air and oxygen in the sitting position. Climbing to the 14,255 ft summit created abnormally high gradients which returned only part way to normal after descent. Reeves et al. also observed a correlation between increasing exercise and widening $P(A\text{-}a)_{O_2}$ in their acute study (11). In our summit climb study the V_D/V_T ratio fell progressively even during periods when $P(A\text{-}a)_{O_2}$ was rising. This suggests that exercise caused an exacerbation of the $\dot{V}/\dot{Q}$ abnormalities seen during the 72 hr study.

None of the subjects developed overt signs of pulmonary edema, although two of the four climbers noted some dyspnea and tachycardia for several hours after the exertion. There was a progressive decrease in the slope of the inspiratory limb of the static pressure volume curve with increasing time at altitude. This is the type of change in lung compliance that has been reported in cases of pulmonary edema; however, our compliances were still 4–5 times greater than those reported for patients in pulmonary edema (26).

The pathologic source of the widened oxygen gradient cannot be identified. Embolization from the pulmonary artery catheter could have occurred; however, the stability of the pulmonary arterial pressures both on air and 100% O_2 after 24 hr are against continued embolization. Another possibility is the presence of subclinical pulmonary edema, both at rest in the catheterized subjects and particularly after exercise in the four climbers. The combined contribution of diffusion limitation and ventilation/perfusion abnormalities to the $P(A\text{-}a)_{O_2}$ measured while breathing air, increased during acclimatization. It is not possible to determine whether the increased $P(A\text{-}a)_{O_2}$ was due to uneven pulmonary arteriolar constriction, ventilatory maldistribution, or both.

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