Components of alveolar-arterial O_2 gradient during rest and exercise at sea level and high altitude

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SYLVESTER, J. T., A. CYMERMAN, G. GURTNER, O. HOTTENSTEIN, M. COTE, AND D. WOLFE. *Components of alveolar-arterial O_2 gradient during rest and exercise at sea level and high altitude.* J. Appl. Physiol.: Respirat. Environ. Exercise Physiol. 50(6): 1129–1139, 1981.—To determine the effects of exercise and high altitude on the contributions of shunt, ventilation-perfusion ($\dot{V}/\dot{Q}$) nonhomogeneity, and diffusion limitation to the alveolar-arterial O_2 gradient ($AaDo_2$), we measured pulmonary exchange of O_2, CO_2, and six inert gases (SF_6, ethane, cyclopropane, halothane, diethyl ether, and acetone) during rest and exercise in unanesthetized dogs at sea level and after acute exposure to an altitude of 6,096 m in a hypobaric chamber. Shunt and dead-space fractions, calculated from inert gas measurements, did not change. High altitude decreased the inert gas partial pressure gradients between mixed alveolar gas and mixed end-capillary blood, indicating that $\dot{V}/\dot{Q}$ relationships became more homogeneous. Exercise had no effect on these gradients. At sea level, $AaDo_2$ was mainly due to $\dot{V}/\dot{Q}$ nonhomogeneity, with a small portion due to shunt. At high altitude, the contribution of shunt became negligible and that of $\dot{V}/\dot{Q}$ nonhomogeneity diminished. These improvements were partially offset, however, by a gradient due to diffusion limitation. Exercise had no effect on $AaDo_2$ or any of its components. At high altitude, estimated pulmonary O_2 diffusing capacity averaged 20.8 $ml \cdot min^{-1} \cdot Torr^{-1}$ at rest and 35.3 $ml \cdot min^{-1} \cdot Torr^{-1}$ during exercise.

inert gas exchange; dogs; shunt; dead space; ventilation-perfusion nonhomogeneity; oxygen diffusing capacity

IN MAN AT HIGH ALTITUDE, the gradient between the partial pressure of oxygen in the alveolar gas and that in the arterial blood ($AaDo_2$) is increased by exercise (1, 7, 24, 26, 34, 35), suggesting that the efficiency of O_2 exchange in the lung deteriorates under these conditions. The same may be true of dogs, as implied by the data of Banchero et al. (2). This increase in $AaDo_2$ could result from *1*) a pulmonary O_2 diffusing capacity insufficient to maintain arterial O_2 tension at resting levels; *2*) increased nonhomogeneity of the relationship between alveolar ventilation and perfusion; or *3*) an increased fraction of blood flowing through unventilated lung. Despite many previous investigations of gas exchange at high altitude, the relative importance of each of these factors remains unclear (27). This lack of clarity may be due in part to the lack of adequate methods.

Recently, Wagner and his associates (43–47) introduced a new method for evaluating gas exchange that allows the effects of shunt, ventilation-perfusion nonhomogeneity, and limitation of diffusion to be distinguished. This method is based on the principles of inert gas exchange elucidated by Farhi and Yokoyama (10, 11, 50) and utilizes numerical techniques and measurements of inert gas concentrations in mixed expired air and mixed venous and arterial blood to determine how pulmonary ventilation and blood flow are distributed with respect to ventilation-perfusion ratio. Although the principles are well accepted, the measurements are difficult and the techniques used to analyze the measurements have provoked considerable controversy (8, 21, 30, 42). Perhaps because of this controversy, alternative methods of analysis that do not depend on complex numerical techniques have been proposed (18, 29).

The purpose of the present study was twofold. First, because of the paucity of data available in the dog, we measured $AaDo_2$ and relevant ventilatory and circulatory variables in this species during rest and exercise at sea level and after acute exposure to an altitude of 6,096 m in a hypobaric chamber. Second, we used measurements of O_2 and inert gas exchange to determine the contributions of diffusion limitation, ventilation-perfusion nonhomogeneity, and shunt to the observed changes in $AaDo_2$. This determination was made possible by an analysis of inert gas data, similar to those of West et al. (49), Neufeld et al. (29), and Hlastala and Robertson (18), which allowed us to deal directly with the measurements.

THEORY

Inert gas exchange in a three-compartment model. Our analysis is limited to the steady-state exchange of gases, which exhibit a linear relationship between blood partial pressure and content and achieve diffusion equilibrium in the lung; i.e., the so-called "inert gases." It is based upon a three-compartment lung model (Fig. 1), similar to that used by Riley and Cournand (36), which consists of *a*) a shunt compartment, having blood flow ($\dot{Q}_S$) but no ventilation, *b*) a dead-space compartment, having ventilation ($\dot{V}_D$) but no blood flow, and *c*) an alveolar compartment, having both ventilation ($\dot{V}_A$) and blood flow ($\dot{Q}_A$). We will assume that the inspired ven-

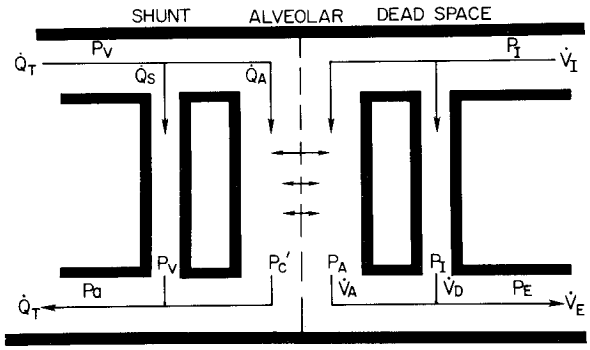

FIG. 1. Three-compartment model of lung. $\dot{Q}t$, $\dot{Q}s$, $\dot{Q}A$: total, shunt, and alveolar blood flows; $\dot{V}I$, $\dot{V}A$, $\dot{V}D$, $\dot{V}E$: inspired, alveolar, dead-space, and expired ventilations; Pv, Pc′, Pa, PI, PA, PE: partial pressures of inert gas in mixed venous, end-capillary, and arterial blood and in inspired, alveolar, and mixed expired air.

tilation of the alveolar compartment is equal to its expired ventilation and that the gas side of this compartment is well mixed.

Retention (R) is defined as $(Pa - PI)/(P\bar{v} - PI)$, where Pa, $P\bar{v}$, and PI are the partial pressures of the gas in the arterial and mixed venous blood and inspired air, respectively (10, 47). Since in the steady state the amount of gas entering the lung per unit time in the mixed venous blood and inspired air must equal that leaving in the arterial blood and mixed expired air, it can be shown that retention in the three-compartment lung is

$$R = \frac{\dot{Q}s}{\dot{Q}t} + \left(1 - \frac{\dot{Q}s}{\dot{Q}t}\right)\left(\frac{1}{1 + \dot{V}A/\dot{Q}A\lambda}\right) \qquad (1)$$

where $\dot{Q}t = \dot{Q}s + \dot{Q}A$ and λ is the Ostwald partition coefficient of the exchanging gas. Moreover

$$R = \frac{\dot{Q}s}{\dot{Q}t} + \left(1 - \frac{\dot{Q}s}{\dot{Q}t}\right)\left(\frac{Pc' - PI}{P\bar{v} - PI}\right) \qquad (2)$$

where Pc′ is the partial pressure of the gas in the end-capillary blood of the alveolar compartment.

Excretion (E) is defined as $(PE - PI)/(P\bar{v} - PI)$, where PE is the partial pressure of the gas in the mixed expired air (10, 47). Again, from considerations of mass balance, it can be shown that excretion in the three-compartment lung is

$$E = \left(1 - \frac{\dot{V}D}{\dot{V}E}\right)\left(\frac{1}{1 + \dot{V}A/\dot{Q}A\lambda}\right) \qquad (3)$$

or

$$E = \left(1 - \frac{\dot{V}D}{\dot{V}E}\right)\left(\frac{PA - PI}{P\bar{v} - PI}\right) \qquad (4)$$

where $\dot{V}E = \dot{V}A + \dot{V}D$ and PA is the partial pressure of the gas in the alveolar air.

From *Eqs. 2* and *4*, the difference between the end-capillary and alveolar partial pressures, normalized by $P\bar{v} - PI$, can be expressed by

$$\frac{Pc' - PA}{P\bar{v} - PI} = \frac{R - \dot{Q}s/\dot{Q}t}{1 - \dot{Q}s/\dot{Q}t} - \frac{E}{1 - \dot{V}D/\dot{V}E} \qquad (5)$$

In the three-compartment lung, this gradient equals zero; however, in the lung with more than one gas-exchanging compartment, it will have a finite value, as discussed below.

Shunt and dead space. From *Eq. 1* it is apparent that R approaches $\dot{Q}s/\dot{Q}t$ as λ approaches zero. Thus, $\dot{Q}s/\dot{Q}t$ can be estimated by measuring the retention of a highly insoluble gas. In the present study, the fraction of blood flow perfusing unventilated areas of lung was estimated by the measured retention of SF_6, the least soluble gas we used. We will refer to this estimate as "SF_6 shunt."

From *Eq. 3* it is seen that E approaches $(1 - \dot{V}D/\dot{V}E)$ as λ approaches infinity; i.e., $\dot{V}D/\dot{V}E$ can be estimated by subtracting the measured excretion of a highly soluble gas from one. Thus, we calculated the fraction of ventilation going to unperfused areas of lung as one minus the excretion of acetone, the most soluble gas we used. We will refer to this estimate as "acetone dead space."

It should be emphasized that SF_6 retention will be significantly influenced by lung units with $\dot{V}/\dot{Q}$ below about 0.1 and acetone excretion, by lung units with $\dot{V}/\dot{Q}$ above about 30. Thus, SF_6 shunt and acetone dead space may overestimate true shunt and true dead space, respectively.

Ventilation-perfusion nonhomogeneity. The real lung, of course, has more than one alveolar compartment. If these compartments are arranged in parallel, the difference between the partial pressures in the mixed end-capillary blood ($\bar{P}c'$) and mixed alveolar gas ($\bar{P}A$), can be expressed by

$$\frac{\bar{P}c' - \bar{P}A}{P\bar{v} - PI} = \sum_{i=1}^{n} \frac{\dot{Q}_i}{\dot{Q}A}\left(\frac{1}{1 + \dot{V}_i/\dot{Q}_i\lambda}\right) - \sum_{i=1}^{n} \frac{\dot{V}_i}{\dot{V}A}\left(\frac{1}{1 + \dot{V}_i/\dot{Q}_i\lambda}\right) \qquad (6)$$

where $\dot{V}_i$ and $\dot{Q}_i$ are the ventilation and blood flow of the ith alveolar compartment, $\dot{V}A$ and $\dot{Q}A$ are the total alveolar ventilation and blood flow, and n is the number of compartments (49). Since $\bar{P}c'$ is the flow-weighted average of the individual end-capillary partial pressures, whereas $\bar{P}A$ is the ventilation-weighted average of the individual alveolar gas partial pressures, $\bar{P}c'$ must be different from $\bar{P}A$ whenever the lung consists of more than one alveolar compartment and the ventilation-perfusion ratios of these compartments are different. Furthermore, the magnitude of the difference between these pressures will be proportional to the degree of ventilation-perfusion nonhomogeneity (18, 29, 49). Thus, in the present study, we used the difference between $\bar{P}c'$ and $\bar{P}A$ as an index of the degree of ventilation-perfusion nonhomogeneity. By applying *Eq. 5* to the real lung, this difference is

$$\frac{\bar{P}c' - \bar{P}A}{P\bar{v} - PI} = \frac{R - \dot{Q}s/\dot{Q}t}{1 - \dot{Q}s/\dot{Q}t} - \frac{E}{1 - \dot{V}D/\dot{V}E} \qquad (7)$$

where $\dot{Q}s/\dot{Q}t$ and $\dot{V}D/\dot{V}E$ are, respectively, the measured values of SF_6 shunt and acetone dead space and R and E are, respectively, the measured excretion and retention of an inert gas more soluble than SF_6 but less soluble than acetone.

Since in the steady state the amount of gas leaving the lung per unit time in the arterial blood is equal to the sum of that leaving in mixed end-capillary and shunted

blood, it can be shown that the partial pressure gradient due to shunt ($Pa - \bar{P}c'$), normalized by ($P\bar{v} - PI$), is

$$\frac{Pa - \bar{P}c'}{P\bar{v} - PI} = \frac{(1 - R)\dot{Q}s/\dot{Q}t}{1 - \dot{Q}s/\dot{Q}t} \quad (8)$$

Oxygen diffusion. Oxygen differs from the inert gases in that its blood solubility coefficient is not constant over the normal range of P_{O_2}, as is easily appreciated from an oxyhemoglobin dissociation curve. If, however, the range of P_{O_2} is limited to tensions on the steep, nearly linear portion of the dissociation curve, the solubility of O_2 can be assumed to be constant and we can derive an equation for the difference between mixed alveolar oxygen tension ($\bar{P}A_{O_2}$) and mixed end-capillary blood oxygen tension ($\bar{P}c'_{O_2}$) from *Eq. 7* by multiplying both sides of the equation by $-(P\bar{v} - PI)$; thus

$$\bar{P}A_{O_2} - \bar{P}c'_{O_2} = \frac{PE_{O_2} - PI_{O_2}}{1 - \dot{V}D/\dot{V}E} - \frac{(Pa_{O_2} - PI_{O_2}) - (P\bar{v}_{O_2} - PI_{O_2})\dot{Q}s/\dot{Q}t}{1 - \dot{Q}s/\dot{Q}t} \quad (9)$$

where PE_{O_2}, PI_{O_2}, Pa_{O_2}, and $P\bar{v}_{O_2}$ are the partial pressures of O_2 in the mixed expired and inspired gas and in the arterial and mixed venous blood, respectively. The sign change is necessary because O_2, unlike the inert gases in our experiments, diffuses from gas to blood rather than from blood to gas.

There is another difference between oxygen and the inert gases. Under certain circumstances (e.g., exercise at high altitude) the lung may provide a significant barrier to oxygen diffusion, so that the O_2 tension in the end-capillary blood of an alveolar compartment could be different from that in its expired gas. If O_2 solubility is constant (i.e., if the range of O_2 tension is limited to the nearly linear portion of the dissociation curve), the presence of diffusion limitation of O_2 exchange can be detected, and its degree quantified, by measuring the alveolar end-capillary gradient for O_2 (*Eq. 9*) and, from this value, subtracting the gradient measured for an equally soluble gas whose exchange is not limited by diffusion. In the absence of diffusion limitation, there should be no difference between these gradients. In its presence, a positive difference should exist, the magnitude of which will be proportional to the degree of diffusion limitation (27).

The solubility of O_2 in blood at high altitude was expressed by its "effective" Ostwald partition coefficient (λ_{O_2}), calculated as

$$\lambda_{O_2} = \frac{Ca_{O_2} - C\bar{v}_{O_2}}{Pa_{O_2} - P\bar{v}_{O_2}}(PB - Pw) \quad (10)$$

where Ca_{O_2} and $C\bar{v}_{O_2}$ are the oxygen contents of arterial and mixed venous blood, expressed in milliliters of O_2 (BTPS) per milliliter of blood, PB is barometric pressure, and Pw is the vapor pressure of water at body temperature. The term "effective" is used to indicate that this expression for solubility is determined by the slope of the oxyhemoglobin dissociation curve and not by the relatively insignificant physical solubility of O_2 in plasma. Calculated in this manner, λ_{O_2} averaged 3.28 ± 0.58. This was not significantly different from λ measured for halothane (3.16 ± 0.22), a gas that is not diffusion limited (47).

Thus, the alveolar end-capillary O_2 diffusion gradient ($\Delta P_{O_2\,diff}$) was estimated, first, by multiplying the measured halothane gradient (*Eq. 7*) by ($PI_{O_2} - P\bar{v}_{O_2}$), to convert it to the units of measurement for O_2, and then subtracting the product from $\bar{P}A_{O_2} - \bar{P}c'_{O_2}$, calculated from *Eq. 9*. To the extent that end-capillary oxygen tensions in the lung at high altitude fell on the alinear portion of the dissociation curve, this estimate will be in error. The magnitude and direction of this error is examined in the APPENDIX.

Estimating the alveolar end-capillary O_2 diffusion gradient enables estimation of the lung's O_2 diffusing capacity. Assuming that λ_{O_2} is constant and that all O_2 exchange occurs in a single compartment having ventilation, $\dot{V}A$, and blood flow, $\dot{Q}A$, an estimate of O_2 diffusing capacity ($D^*L_{O_2}$) can be derived (32, 33)

$$D^*L_{O_2} = \ln\left(\frac{\bar{P}A_{O_2} - P\bar{v}_{O_2}}{\Delta P_{O_2\,diff}}\right)\frac{\dot{Q}A\lambda_{O_2}}{K} \quad (11)$$

where K relates the volume and pressure units used in $D^*L_{O_2}$ (STPD, mmHg) to those used in λ (BTPS, atm), and where, from considerations of mass balance, $\bar{P}A_{O_2}$ is calculated by

$$\bar{P}A_{O_2} = \frac{PE_{O_2} - PI_{O_2}(\dot{V}D/\dot{V}E)}{1 - \dot{V}D/\dot{V}E} \quad (12)$$

Fractionation of the alveolar-arterial P_{O_2} gradient. With both our high altitude and sea-level studies, the total alveolar-arterial P_{O_2} gradient may be calculated by subtracting measured arterial P_{O_2} from the mixed alveolar gas P_{O_2}, determined from *Eq. 12*. The method by which this total gradient is apportioned to shunt, ventilation-perfusion nonhomogeneity and diffusion limitation, however, will be different under these two conditions.

The assumption of near linearity of the oxyhemoglobin dissociation curve over the range of P_{O_2} encountered during the high altitude studies permitted the diffusion component of the alveolar-arterial gradient ($\Delta P_{O_2\,diff}$) to be calculated as described above. When $\Delta P_{O_2\,diff}$ is subtracted from the total gradient, a finite remainder will exist due to shunt and/or ventilation-perfusion nonhomogeneity. From *Eqs. 7* and *8* the percentage contributions of ventilation-perfusion nonhomogeneity and shunt to the alveolar-arterial gradient measured for halothane can be determined. These percentages may then be used to apportion the remaining O_2 gradient.

A different approach was necessary to fractionate gradients measured at sea level, when λ_{O_2} was clearly not constant. In this case, we assumed that no alveolar end-capillary diffusion gradient existed, an assumption which seems reasonable on the basis of both theory (16, 22, 40, 41) and experiment (5). That portion of the total gradient due to shunt was calculated by first determining the saturation of the mixed end-capillary blood from the shunt equation and measured values of arterial and mixed venous O_2 saturation and SF_6 shunt. Knowing

mixed end-capillary and arterial O_2 saturation and Pa_{O_2}, $\bar{P}c'_{O_2}$ could then be determined from the oxyhemoglobin dissociation curve and the gradient due to shunt calculated as $\bar{P}c'_{O_2} - Pa_{O_2}$. Subtracting this gradient from the total gradient yielded the gradient due to ventilation-perfusion nonhomogeneity.

METHODS

Preparation and protocol. Experiments were performed on eight adult mongrel dogs (17.7–24.6 kg) trained to run on a treadmill. Each animal had a chronic tracheostomy and a unilateral carotid loop. Two days before an experiment, the dogs were anesthetized with intravenous thiamylal sodium (18 mg/kg initially, 20–40 mg subsequently as necessary), a double-lumen Swan-Ganz catheter (5 or 7 French) was positioned in a pulmonary artery via an external jugular vein, and an 18-gauge, 2-in. plastic catheter was introduced into the contralateral external jugular vein. After recovery, feeding and watering were continued until 12 h before the beginning of the experiment. At the time of the experiment, the carotid loop was cannulated percutaneously with an 18-gauge, 1.25-in. plastic catheter, a stainless steel tracheostomy tube (0.5 in. ID) with a latex balloon cuff was introduced into the trachea, and a temperature probe (Yellow Springs Instrument) was inserted into the rectum.

Each animal was studied twice, first at high altitude (6,096 m, BP, 349 mmHg) and, approximately 1 wk later, at sea level. All studies took place in a hypobaric chamber (9 x 12 ft) the temperature of which was controlled at 16°C. The rate of ascent was 300–450 m/min. One hour after ascent, the animal was placed on the treadmill and the tracheostomy tube was connected to a J valve, the expiratory side of which was connected to a mixing chamber, constructed as described by Wagner et al. (45). A normal saline solution of SF_6, ethane, cyclopropane, halothane, diethyl ether, and acetone, prepared as described by Wagner et al. (45), was infused into the external jugular vein at 3.8 ml/min. After 20–25 min, ventilatory and circulatory measurements were made and samples of mixed venous and arterial blood and mixed expired air were obtained over a period of 2–3 min. During this time, the expired gas was also collected in a meteorological balloon. With the infusion continuing, the dog began treadmill exercise at a speed of 8.0 km/h. Grade was adjusted from 0 to 3–5% over a period of 2 min. The grade used was chosen on the basis of our subjective impression of the dog's willingness to run under these severely hypoxic conditions. After 12.8–19.8 min of exercise (mean 17.8 min), all measurements were repeated. Approximately 1 wk later, each dog was studied at sea level in the same manner. The speed and grade of the treadmill at sea level were the same as at high altitude.

Measurements. Minute ventilation ($\dot{V}_E$) was measured by electrical integration of the expiratory flow signal recorded from a differential pressure transducer (Hewlett-Packard model 270) connected to a no. 5 Fleisch pneumotachograph (Instrumentation Associates) calibrated at the altitude of the experiment. The fractional concentration of O_2 and CO_2 in the dried mixed-expired gas ($F_{E_{O_2}}$, $F_{E_{CO_2}}$) was measured with Beckman E2 and LB2 analyzers, respectively. Oxygen consumption ($\dot{V}_{O_2}$), carbon dioxide production ($\dot{V}_{CO_2}$), and the respiratory exchange ratio were calculated in the standard manner (31). Arterial and mixed venous pH and O_2 and CO_2 tensions were measured with a blood gas analyzer (Radiometer model BMS3-MK2). Oxygen saturations and hemoglobin concentrations were measured spectrophotometrically (Instrumentation Laboratories model 180 CO-oximeter), enabling calculation of arterial (Ca_{O_2}) and mixed venous ($C\bar{v}_{O_2}$) oxygen contents. Ideal alveolar P_{O_2} was calculated from the alveolar air equation (31). Lactate concentrations in arterial blood samples obtained 3 min after cessation of exercise were measured enzymatically (28) in one animal at sea level and at high altitude. Mean carotid, pulmonary arterial, and pulmonary capillary wedge pressures ($\bar{P}a$, $\bar{P}pa$, $\bar{P}pcw$) were measured with pressure transducers (Statham P23) with the midchest level taken as zero pressure. Cardiac output ($\dot{Q}$) was calculated by dividing $\dot{V}_{O_2}$ by the difference between Ca_{O_2} and $C\bar{v}_{O_2}$. Systemic vascular resistance (SVR) was calculated as $\bar{P}a/\dot{Q}$ and pulmonary vascular resistance (PVR) as $(\bar{P}pa - \bar{P}pcw)/\dot{Q}$.

Inert gas concentrations in the mixed venous and arterial blood and mixed expired gas were measured chromatographically within 1 h of sampling using the approach of Wagner et al. (46). Our technique differed from that of Wagner et al. in two ways. First, the inert gases dissolved in the blood samples were extracted into nitrogen, which was the carrier gas used by our gas chromatograph (Perkin-Elmer model 900). Second, rather than measuring the peak heights of the chromatogram, we measured the area under each peak with an appropriately programmed digital integrator (Spectra-Physics Autolab system 1). The reproducibility of these measurements, measured as described by Wagner et al. (46) and expressed as coefficients of variation, were (%): SF_6, 9.8; ethane, 4.2; cyclopropane, 3.8; halothane, 2.9; diethyl ether, 5.2; and acetone, 3.8. These values are 1.1–2.9 times greater than those reported by Wagner et al. (46). Measurement of the peak heights of the chromatogram, rather than areas under the peaks, did not improve reproducibility. From the measurements of areas, the ratios of arterial to mixed venous and mixed expired to mixed venous concentrations were calculated, and minimum variance estimates of excretion and retention determined in the manner described by Evans and Wagner (9).

Statistical analysis. Statistical analysis of the data was performed using either a two-factor, repeated measures analysis of variance or t test, as appropriate. Differences were considered significant when P was less than or equal to 0.05. Of the eight animals prepared, two were unable to exercise at high altitude and were excluded from analysis. A third animal had to be excluded because ventilation during exercise was greater than could be measured with our system and because a mixed expired gas sample was lost. The data presented, therefore, are the means of measurements obtained from the remaining five animals.

Methodological limitations. The right-to-left shunt caused by Thebesian venous drainage into the left ventricle is not measured by SF_6 retention and in our analysis

its contribution to $AaDo_2$ would be ascribed to diffusion limitation at high altitude and $\dot{V}/\dot{Q}$ nonhomogeneity at sea level. To assess this possible source of error, we measured O_2 tensions in blood samples drawn simultaneously from the left atrium, left ventricle, and carotid artery in two additional dogs anesthetized with pentobarbital (30 mg/kg iv) and ventilated at a constant frequency and tidal volume. In the first dog, O_2 tensions at these sites during ventilation with 22.4% O_2 were 109, 107, and 106 mmHg, respectively. After 25 min of hypoxia (inspired O_2 concentration = 12.1%), P_{O_2} at all three sites was 47 mmHg. The second animal gave similar results. In addition, this animal was given a 10-min intravenous infusion of norepinephrine during hypoxia to raise arterial pressure and increase myocardial O_2 consumption. Under these conditions, O_2 tensions in the left atrium, left ventricle, and carotid artery were 51, 51, and 50 Torr, respectively. These data suggest that Thebesian drainage was not a source of significant artifact in our high-altitude experiments. The small difference between left atrial and carotid O_2 tensions seen during normoxia, however, suggests that Thebesian drainage may have caused the contribution of $\dot{V}/\dot{Q}$ nonhomogeneity to $AaDo_2$ at sea level to be overestimated by 2–3 Torr. As will be seen, this error is too small to alter the qualitative conclusions of our study. We were unable to assess similar artifacts that may have been caused by bronchial venous drainage into the pulmonary veins.

It is unlikely, but possible, that in these tracheostomized dogs the inspired air was not fully humidified by the time it reached the alveoli. If this occurred, the assumption of complete humidification in our analysis would lead to underestimation of $\bar{P}_{A_{O_2}}$ and, therefore, of $AaDo_2$, its $\dot{V}/\dot{Q}$ component at sea level, and its diffusion component at high altitude. These errors, if present, would tend to offset those possibly caused by Thebesian or bronchial venous drainage.

RESULTS

As shown in Table 1, the ideal alveolar-arterial P_{O_2} difference, was significantly reduced at high altitude. Exercise had no effect on this measurement. For the same absolute intensity of exercise, $\dot{V}_{O_2}$ increased less at high altitude than at sea level. Although $\bar{P}pa$ increased at high altitude and increased further with exercise at high altitude, no significant changes in pulmonary vascular resistance were observed. Arterial O_2 saturation increased with exercise at high altitude in association with a significant increase in Pa_{O_2} and pH and a significant decrease in Pa_{CO_2}.

The mean retention and excretion values for each of the six inert gases under the four experimental conditions are shown in Fig. 2. The results of the analysis of this inert gas data are shown in Fig. 3. Shunt fraction, determined from the retention of SF_6, was very low and not significantly altered during the experiments. Acetone dead space was high, presumably because of panting and, like shunt, did not exhibit a significant change. Mean $\dot{V}_A/\dot{Q}_A$ was increased by high altitude and by exercise. The increase with exercise was greater at high altitude than at sea level. In absolute terms, $\dot{V}_A$ and $\dot{Q}_A$ both increased significantly during exercise, but no significant effects of altitude were observed. Exercise had no effect on the relationship between $(\bar{P}c' - \bar{P}_A)/(P\bar{v} - P_I)$ and λ. High altitude, however, caused significant decreases in

TABLE 1. *Means and variance ratios of ventilatory, circulatory, and gas exchange measurements*

	Sea Level		High Altitude		Variance Ratios		
	Rest	Exercise	Rest	Exercise	Rest vs. exercise	Sea level vs. high altitude	Interaction
Ideal $AaDo_2$, Torr	19.2	18.7	6.0	6.7	0	72.5*	0.02
$\dot{V}_E$, l BTPS/min	11.9	36.3	12.7	39.7	93.0*	0.18	0.26
$\dot{V}_{O_2}$, ml STPD/min	188	568	162	346	29.9*	4.12	17.1*
$\dot{V}_{CO_2}$, ml STPD/min	138	425	151	354	24.8*	0.43	3.38
R	0.760	0.733	0.946	1.03	2.33	13.54*	2.30
$\dot{Q}t$, l/min	4.88	8.85	4.25	5.48	11.6*	5.40	5.16
$\bar{P}a$, Torr	120	125	118	125	0.97	0.02	0.19
$\bar{P}pa$, Torr	11.7	13.8	17.8	20.2	11.7*	8.15*	0.01
$\bar{P}pcw$, Torr	1.2	1.5	3.4	8.2	8.48*	5.62	2.48
PVR, Torr·l^{-1}·min	3.03	1.56	3.16	3.08	0.76	0.55	0.71
SVR, Torr·l^{-1}·min	29.8	15.0	29.1	24.3	4.42	0.35	1.14
$[HbO_2]_a$, %	97.2	97.8	70.2	77.0	9.55*	175*	9.73*
Pa_{O_2}, Torr	88.4	92.7	35.0	40.4	7.29*	605*	0.05
Pa_{CO_2}, Torr	31.0	27.4	21.2	16.4	13.1*	55.6*	2.23
pH_a	7.394	7.430	7.494	7.572	55.0*	14.7*	2.98
$[HbO_2]_{\bar{v}}$, %	70.6	54.6	42.7	36.5	225*	138*	23.9*
$P\bar{v}_{O_2}$, Torr	41.0	35.0	25.0	23.3	22.5*	21.7*	6.47
$P\bar{v}_{CO_2}$, Torr	33.6	34.9	23.7	20.5	7.24*	89.1*	6.44
$pH_{\bar{v}}$	7.368	7.401	7.503	7.542	8.93*	126*	0.20
Ca_{O_2}-$C\bar{v}_{O_2}$, vol%	3.86	6.49	3.87	6.26	76.6*	0.08	0.29
Hb, g/100 ml	10.6	10.8	11.6	11.7	1.38	2.81	0.36

For explanation of abbreviations see text. * $P < 0.05$.

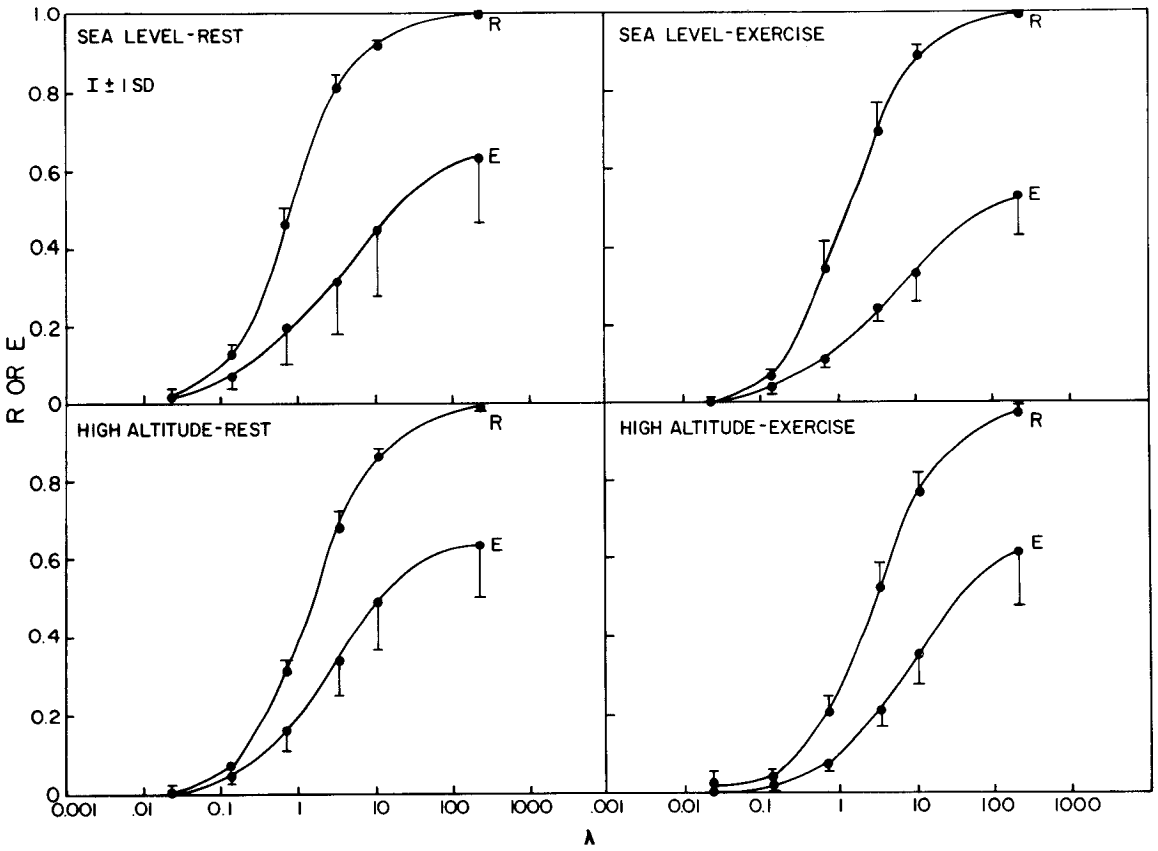

FIG. 2. Mean retentions and excretions of inert gases as a function of solubility (λ). From least to most soluble, they are SF_6, ethane, cyclopropane, halothane, diethyl ether, and acetone.

$(\bar{P}c' - \bar{P}A)/(P\bar{v} - PI)$ at all λ. As discussed below, a flattening of this relationship toward the abscissa implies an improvement in ventilation-perfusion relationships.

As shown in Fig. 3, the $AaDo_2$ calculated from inert gas data (*Eq. 12*, Fig. 3), like the ideal $AaDo_2$ (Table 1), was reduced by high altitude, but unaltered by exercise. As expected, the inert gas $AaDo_2$ was larger than the ideal $AaDo_2$. This is because the acetone dead space, used in the calculation of the former, is smaller than the CO_2 dead space (18). At sea level, approximately 88% of the gradient was due to $\dot{V}/\dot{Q}$ nonhomogeneity and 22% due to shunt. Diffusion limitation was assumed to play no role. These contributions did not change during exercise. At high altitude, the total gradient decreased significantly because of significant reductions in the contributions of $\dot{V}/\dot{Q}$ nonhomogeneity and shunt. The gradient was not as low as it might have been, however, because diffusion limitation now contributed, accounting for approximately 50% of the total gradient. Ventilation-perfusion nonhomogeneity accounted for the remaining 50%, the contribution of shunt being negligible. As at sea level, exercise had no effect.

Exercise at high altitude caused $D^*_{L_{O_2}}$ to increase significantly from 20.8 to 35.3 ± 10.2 $ml \cdot min^{-1} \cdot Torr^{-1}$ ($P < 0.025$).

In the one animal in which it was measured, arterial lactate concentration measured 3 min after exercise was higher at altitude than at sea level (6.41 vs. 1.42 meq/l).

DISCUSSION

As shown in Table 1 and Fig. 3, acute exposure of the dog to high altitude caused the resting $AaDo_2$ to decrease. This is consistent with previous results in both dogs (2, 23) and humans (1, 20). With exercise at high altitude, we observed no further change in $AaDo_2$. Results of studies in dogs by Banchero et al. (2) suggested that $AaDo_2$ would increase with exercise, but in that study the increase was slight and may not have been statistically significant. In humans, most investigators have observed an increase in the gradient under these conditions (1, 7, 24, 26, 34, 35).

A change in $AaDo_2$ must be explained by a change in shunt fraction, the degree of ventilation-perfusion nonhomogeneity, or the degree to which exchange of O_2 is diffusion limited in the lung. In THEORY we describe an analysis of inert gas data, which allows evaluation of the effects of these three factors on pulmonary O_2 exchange. We discuss the application of this analysis to our experimental data, treating the roles of diffusion limitation, $\dot{V}/\dot{Q}$ nonhomogeneity, and shunt in turn.

Diffusion limitation. In our measurements of O_2 diffusion gradients at high altitude, we assumed that the solubility of O_2 was constant; i.e., that the O_2 tensions of all the gas-exchanging compartments in the lung fell on the "linear" portion of the oxyhemoglobin dissociation curve. The same assumption has been made in most

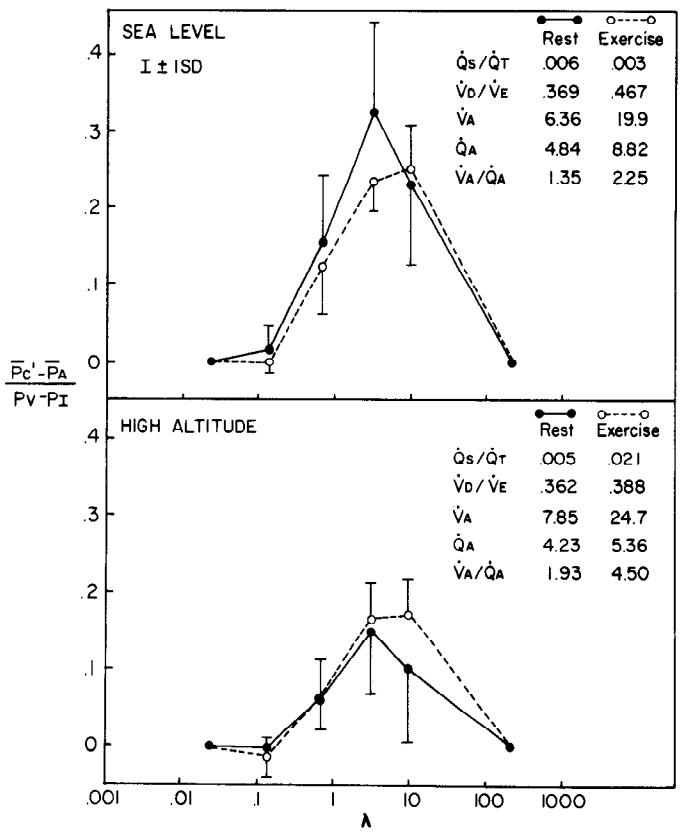

FIG. 3. Mean values of inert gas partial pressure gradients between mixed end-capillary blood ($\bar{P}c'$) and mixed alveolar air ($\bar{P}A$) normalized by difference between mixed venous ($P\bar{v}$) and inspired (PI) partial pressures, shunt ($\dot{Q}s/\dot{Q}t$) and dead-space ($\dot{V}D/\dot{V}E$) fractions, alveolar ventilation ($\dot{V}A$), alveolar perfusion ($\dot{Q}A$), and overall $\dot{V}A/\dot{Q}A$.

other previous attempts to measure DL_{O_2} (14, 19, 33). If the lungs of our dogs contained a significant number of compartments with O_2 tensions on the alinear portion of the dissociation curve, our analysis would yield a diffusion gradient even if diffusion equilibrium were achieved in every compartment. As described in the APPENDIX, we attempted to quantify this source of error and found that at high altitude the artifactual end-capillary O_2 diffusion gradient was unlikely to have been greater than 2 Torr at rest or 3 Torr during exercise. This degree of error is not large enough to alter qualitatively the conclusions we will make.

The presence of an alveolar-end-capillary O_2 diffusion gradient at rest means that, faced with a required amount of O_2 consumption and a low alveolar P_{O_2} (at altitude $\bar{P}A_{O_2}$ averaged 49.3 mmHg), the diffusing capacity of the lung was insufficient to allow equilibration of O_2 between alveolar gas and end-capillary blood. The average estimated DL_{O_2} under resting conditions in our dogs, which weighed an average of 21.5 kg, was 20.8 ± 5.3 ml·min^{-1}·Torr^{-1}. In anesthetized dogs weighing an average of 22.5 kg and breathing 7% O_2 spontaneously, Scheid et al. (38) measured a DL_{O_2} of 18.8 ml·min^{-1}·Torr^{-1} with a rebreathing method and 25.8 ml·min^{-1}·Torr^{-1} with a steady-state method. The consistency among these values lends credence to the various methods of estimation. Measurements of DL_{O_2} in humans at rest under hypoxic conditions have generally been on the order of 30 ml·min^{-1}·Torr^{-1} (4, 14, 19, 33). Thus, it appears that DL_{O_2} per unit body weight is less in humans than in dog. If true, this means that the end-capillary diffusion gradient, measured under similar conditions in humans could have been even larger than we measured in the dog.

The alveolar-end-capillary O_2 diffusion gradient did not increase with exercise at high altitude (Fig. 3). There are two explanations for this finding. First, $DL^*_{O_2}$ was doubled by exercise. Approximately the same percentage change has been observed in man during exercise (4, 6). The mechanisms for the increase in $DL^*_{O_2}$ are unknown, but the increased ventilation, cardiac output, and pulmonary arterial pressure observed under these conditions (Table 1) may have caused either the recruitment of additional surface area for O_2 exchange or improved the relationship between diffusing capacity and perfusion in the lung (12). Second, exercise $\dot{V}O_2$ at high altitude was only twice the resting level. Had higher $\dot{V}O_2$ been achieved, an increase in the diffusion gradient, and therefore, $AaDo_2$, would probably have occurred. The small increase in $\dot{V}O_2$ with exercise at high altitude in our dogs probably explains the discrepancy with man, where increases in $AaDo_2$ have been measured during three- to fivefold increases in resting $\dot{V}O_2$ (7, 34, 35).

We cannot explain why the same amount of exercise increased $\dot{V}O_2$ less at high altitude than at sea level (Table 1). Similar findings however, have been previously reported in dogs (2). One possibility is that work of breathing, which can constitute a considerable proportion of total $\dot{V}O_2$ in spontaneously breathing awake dogs (37), was reduced at high altitude because of the decrease in air density. Another is that $\dot{V}O_2$ did not achieve a steady state during exercise at high altitude. Against this possibility are the low intensity and long duration of the exercise and previous studies of $\dot{V}O_2$ kinetics in man that demonstrate the time course of $\dot{V}O_2$ after the onset of exercise to be unaltered by acute exposure to an altitude of 3,810 m (3). On the other hand, in one animal postexercise lactate concentration was higher at high altitude than at sea level, suggesting that a steady-state $\dot{V}O_2$ may not have been achieved. Further investigation will be required to determine if any of these explanations is correct.

$\dot{V}/\dot{Q}$ nonhomogeneity. Ventilation-perfusion nonhomogeneity was assessed by measuring the end-capillary-alveolar gradients for the inert gases, shown in Fig. 3. At sea level, the maximum value of these gradients was between 0.2 and 0.3. This is larger than that reported previously for normal, anesthetized, mechanically ventilated dogs (20). Possibly, this discrepancy is related to a difference in the distribution of ventilation caused by the irregular, low-volume, high-frequency ventilatory pattern characteristic of awake spontaneously breathing dogs.

High altitude decreased the end-capillary-alveolar inert gas gradients. Neufeld et al. (29) and Hlastala and Robertson (18) have shown that this type of change is caused by decrease in the dispersion of the distribution of blood flow with respect to $\dot{V}/\dot{Q}$ in the lung. That this should be so is intuitively evident when one realizes that a "perfect" lung (i.e., a lung with only one gas exchange

compartment and, therefore, no possibility of dispersion of $\dot{Q}$ with respect to $\dot{V}/\dot{Q}$) can have no gradient between $\bar{P}c'$ and $\bar{P}A$ in the absence of diffusion limitation of the exchanging gas. Thus, we conclude that the relationship between $\dot{V}$ and $\dot{Q}$ became more uniform at high altitude. Exercise, however, had no effect on $\dot{V}/\dot{Q}$ nonhomogeneity either at sea level or at high altitude.

These results appear to differ from two previous studies in man. Haab et al. (15) found that the resting alveolar-arterial partial pressure gradient for N_2 did not change during 5 days of exposure to altitude of 3,505 m. Because inspired P_{N_2} fell, a decrease in this gradient would have been predicted in the absence of a change in $\dot{V}/\dot{Q}$ relationships. Their observations were therefore taken as evidence that $\dot{V}/\dot{Q}$ relationships deteriorated at high altitude. Gledhill et al. (13) used Wagner's approach (43–47) to determine the effects of exercise on the distribution of perfusion with respect to $\dot{V}/\dot{Q}$. A fourfold increase in resting $\dot{V}_{O_2}$ during exercise increased the dispersion of the distribution. In the former investigation, the hypoxia was milder and in the latter the intensity of exercise was greater than in our experiments. These differences, in addition to the species differences, may explain the discrepancies in results.

Our study was not designed to determine the mechanism by which ventilation-perfusion relationships became more uniform at high altitude; however, a significant increase in Ppa was observed (Table 1) and may have promoted homogeneity.

Mean $\dot{V}_A/\dot{Q}_A$ increased at high altitude (Fig. 3). This and the improvement in $\dot{V}/\dot{Q}$ nonhomogeneity had additive beneficial effects on $P_{a_{O_2}}$. The improvement in $P_{a_{O_2}}$ seen in the transition from rest to exercise at high altitude (Table 1), however, was due entirely to the increase in mean $\dot{V}_A/\dot{Q}_A$ and the attendant improvement in $\bar{P}_{A_{O_2}}$, since AaD_{O_2} did not change (Fig. 4). This improvement in $P_{a_{O_2}}$ and the leftward shift of the oxyhemoglobin dissociation curve that must have accompanied the respiratory alkalosis also induced by exercise undoubtedly explain the remarkable 7% increment in arterial O_2 saturation (Table 1).

Shunt. During rest at sea level, SF_6 shunt averaged 0.6%. This low value, which was not significantly altered by exercise or altitude, is consistent with other measurements of shunt fraction in normal dogs by inert gas methods (17, 44).

Previous studies of the effects of altitude and exercise on shunt fraction have employed inspiration of 100% O_2 (7, 23, 24). In general, values measured at sea level have been much higher than those shown in Fig. 3. Furthermore, after exposure to high altitude, resting shunt fraction decreased with time, whereas during exercise at high altitude it apparently increased. Comparison of these results with our data is difficult, however, because it is now recognized that breathing 100% O_2 in and of itself will increase shunt fraction, presumably because lung units with low $\dot{V}/\dot{Q}$ are converted to units with $\dot{V}/\dot{Q}$ of zero (45).

As shown in Fig. 4, the contribution of shunt to AaD_{O_2} at sea level was small and became negligible at high altitude. This is to be expected. A small shunt at high $P_{I_{O_2}}$ can contribute significantly to AaD_{O_2} because the oxyhemoglobin dissociation curve in this range is flat: small decreases in O_2 content lead to large decreases in P_{O_2}. The same shunt fraction at low inspired $P_{I_{O_2}}$ contributes much less because the dissociation curve in this range is steep: small decreases in content lead to small decreases in tension.

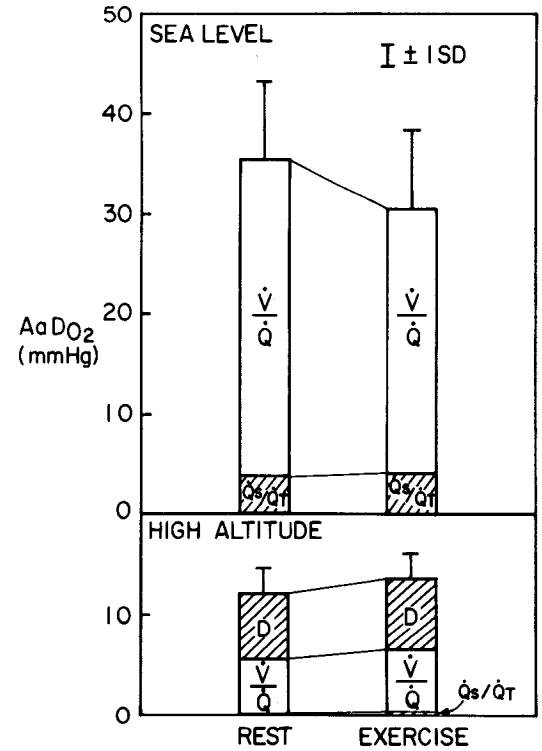

FIG. 4. Alveolar-arterial partial pressure gradient for O_2 (AaD_{O_2}) and its components derived from inert gas data during rest and exercise at sea level and high altitude. $\dot{V}/\dot{Q}$ denotes component due to $\dot{V}/\dot{Q}$ nonhomogeneity; $\dot{Q}s/\dot{Q}t$, component due to shunt; and D, component due to diffusion limitation.

To summarize, within the limitations of our analysis, our results suggest that in the awake resting dog at sea level, the AaD_{O_2} was due mainly to $\dot{V}/\dot{Q}$ nonhomogeneity. Only a small portion was due to shunt. After acute exposure to an altitude of 6,096 m, the contribution of shunt virtually disappeared and that of $\dot{V}/\dot{Q}$ nonhomogeneity diminished. These improvements were partially offset, however, by the appearance of a gradient due to diffusion limitation. Mild exercise had no significant effect on AaD_{O_2} or any of its components, either at sea level or at high altitude. Shunt and dead-space fractions were not affected by either exercise or exposure to high altitude.

APPENDIX

In calculating the end-capillary O_2 diffusion gradient at high altitude (see THEORY), we assumed that the solubility of O_2 in blood (i.e., the slope of the oxyhemoglobin dissociation curve) was constant over the range of P_{O_2} values likely to be encountered in this situation. Inspired P_{O_2} however, was 62 Torr, a value that lies on the alinear portion of the dissociation curve. We could not rule out the existence of significant numbers of lung compartments with high $\dot{V}/\dot{Q}$ which, because of their high $\dot{V}/\dot{Q}$, had P_{O_2} values approaching this value. If this were the case, our assumptions and the analysis based upon it, would be in error. Thus, we tested the validity of the assumption in two ways.

Our first test employed a two-compartment lung model. Both compartments exchanged gas and achieved diffusion equilibrium for O_2.

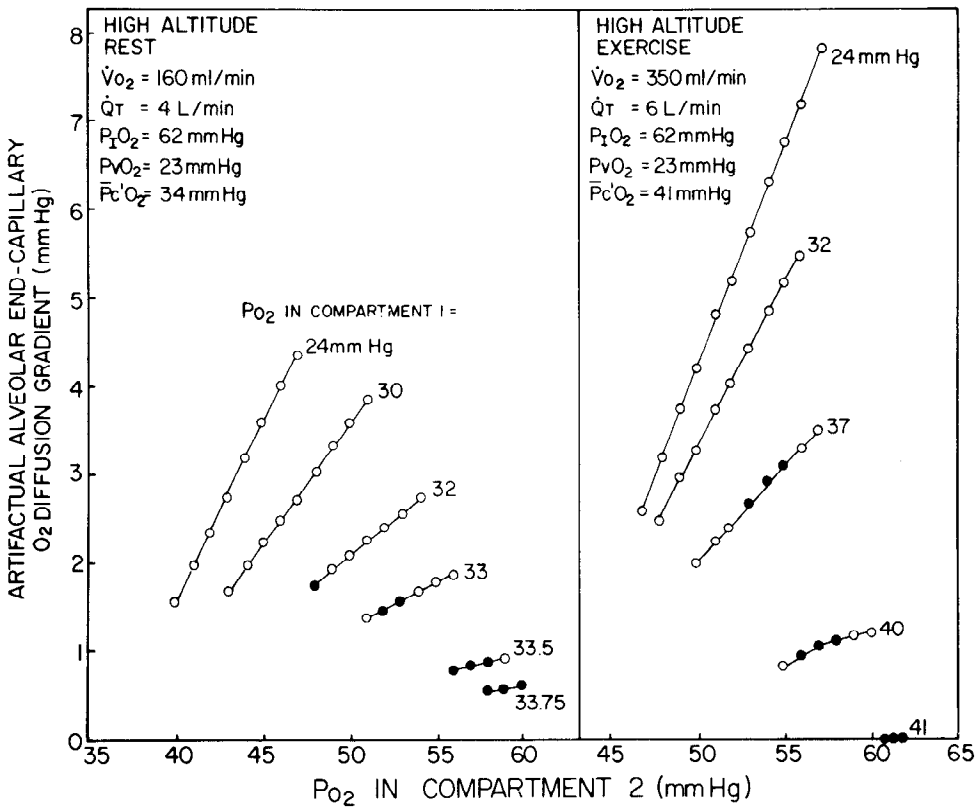

FIG. 5. Artifactual alveolar-end-capillary O_2 diffusion gradient in a 2-compartment lung model with diffusion equilibrium. Gradient is plotted as a function of P_{O_2} in compartment 2 in isopleths of P_{O_2} in compartment 1. Values used to calculate these relationships are shown in upper left of each panel. See APPENDIX for details. *Open symbols* indicate points that also yielded $(\bar{P}c' - \bar{P}A)/(P\bar{v} - PI)$ values for halothane that fell within 95% confidence interval actually observed. *Closed symbols* indicate points that, in addition, satisfied this requirement for diethyl ether and cyclopropane.

Oxygen consumption ($\dot{V}o_2$), total blood flow ($\dot{Q}t$), inspired O_2 tension (PI_{O_2}), and mixed venous O_2 content ($C\bar{v}_{O_2}$) were set (Fig. 5), using values approximating the mean values observed during the high-altitude experiments. From the Fick relationship, mixed end-capillary O_2 content ($\bar{C}c'_{O_2}$) was

$$\bar{C}c'_{O_2} = \frac{\dot{V}o_2}{10\ \dot{Q}t} + C\bar{v}_{O_2}$$

where 10 is a correction factor enabling expression of content in vol% when $\dot{V}o_2$ is expressed in ml·min^{-1} and $\dot{Q}t$ in l·min^{-1}. Mixed end-capillary and mixed venous O_2 tensions ($\bar{P}c'_{O_2}$, $P\bar{v}_{O_2}$) were determined from these contents using a computer-generated, "physiological" oxyhemoglobin dissociation curve (48). Oxygen tension in compartment 1 (P_1) was selected arbitrarily, but had to be higher than $P\bar{v}_{O_2}$ and lower than $\bar{P}c'_{O_2}$. Analogously, P_{O_2} in compartment 2 (P_2) was selected arbitrarily, but had to be higher than $\bar{P}c'_{O_2}$ and lower than PI_{O_2}. The corresponding O_2 contents in the blood leaving the two compartments (C_1, C_2) were determined from the dissociation curve.

Once this was done, the first step was to calculate the difference between $\bar{P}A_{O_2}$ and $\bar{P}c'_{O_2}$. Blood flow to compartment 1 ($\dot{Q}_1$) was

$$\dot{Q}_1 = \frac{\dot{V}o_2/10 - \dot{Q}t(C_2 - C\bar{v}_{O_2})}{C_1 - C_2}$$

Blood flow to compartment 2 ($\dot{Q}_2$) was

$$\dot{Q}_2 = \dot{Q}t - \dot{Q}_1$$

Ventilation to compartment 1 ($\dot{V}_1$) was

$$\dot{V}_1 = \frac{8.69\ \dot{Q}_1(C_1 - Cv_{O_2})}{PI_{O_2} - P_1}$$

and that to compartment 2 ($\dot{V}_2$) was

$$\dot{V}_2 = \frac{8.69\ \dot{Q}_2(C_2 - C\dot{v}_{O_2})}{PI_{O_2} - P_2}$$

where 8.69 is a correction factor allowing expression of $\dot{V}$ in BTPS units. It was now possible to solve for the P_{O_2} of the mixed alveolar gas ($\bar{P}A_{O_2}$) by mass balance; thus

$$\bar{P}A_{O_2} = \frac{\dot{V}_1}{\dot{V}_A} P_1 + \frac{\dot{V}_2}{\dot{V}_A} P_2$$

where $\dot{V}_A = \dot{V}_1 + \dot{V}_2$. The alveolar-end-capillary gradient was then calculated as $(\bar{P}A_{O_2} - \bar{P}c'_{O_2})$. This gradient was due only to $\dot{V}/\dot{Q}$ nonhomogeneity, since diffusion equilibrium was achieved in each compartment.

The next step was to predict what the alveolar-end-capillary gradient should be from inert gas data. The partition coefficient (λ) of the inert gas having the same solubility as O_2 was calculated from *Eq. 10*. Retention of the inert gas by compartment 1 (R_1) was

$$R_1 = (1 + \dot{V}_1/\dot{Q}_1\lambda)^{-1}$$

while that for compartment 2 (R_2) was

$$R_2 = (1 + \dot{V}_2/\dot{Q}_2\lambda)^{-1}$$

Retention (R) and excretion (E) for the entire two-compartment lung were, respectively

$$R = \frac{\dot{Q}_1}{\dot{Q}t} R_1 + \frac{\dot{Q}_2}{\dot{Q}t} R_2$$

and

$$E = \frac{\dot{V}_1}{\dot{V}_A} R_1 + \frac{\dot{V}_2}{\dot{V}_A} R_2$$

since retention and excretion were equal for an individual compartment. The inert gas partial pressure gradient between mixed alveolar air and mixed end-capillary blood, normalized by $(P\bar{v} - PI)$, was R − E. The alveolar-end-capillary O_2 gradient predicted on the basis of the inert gas gradient was (R − E) $(PI_{O_2} - P\bar{v}_{O_2})$. The difference between the actual and predicted gradients was the artifactual alveolar-end-capillary diffusion gradient.

Using the above model, the artifactual gradient was calculated by setting P_1 and varying P_2 systematically over a wide range. A new P_1 was then selected and the artifactual gradient was again calculated for different values of P_2. This procedure was repeated until the whole range of P_1 and P_2 had been covered. These calculations enabled us to plot the artifactual end-capillary diffusion gradient as a function of P_2 in isopleths of P_1, as shown in Fig. 5. Here, the points we plotted were

TABLE 2. *Artifactual alveolar-end-capillary O_2 diffusion gradients obtained from Wagner's 50-compartment model*

Condition at High Altitude	Dog No.	$\bar{P}_{A_{O_2}}$-$\bar{P}c'_{O_2}$		Artifactual Diffusion Gradient
		"Actual"	Predicted	
Rest	9020	1.33	1.14	0.19
	9068	6.60	5.68	0.92
	9069	6.26	5.46	0.80
	9733	2.83	1.74	1.09
	9740	0.71	0.50	0.21
Mean		3.54	2.90	0.64
±SD		±2.75	±2.47	±0.42
Exercise	9020	2.82	2.19	0.63
	9068	8.81	6.86	1.95
	9069	12.67	9.34	3.32
	9733	3.00	2.65	0.35
	9740	1.16	0.87	0.29
Mean		5.69	4.38	1.31
±SD		±4.86	±3.57	±1.31

Units of measurement, Torr.

limited to those which yielded $(\bar{P}c' - \bar{P}A)/(P\bar{v} - PI)$ values for halothane which fell within the 95% confidence interval of the values actually observed (open symbols). The range of possibility was further limited to those points that yielded $(\bar{P}c' - \bar{P}A)/(P\bar{v} - PI)$ values for diethyl ether and cyclopropane, which fell within the 95% confidence limits of the actual observations (closed symbols). These limitations are equivalent to limiting the degree of $\dot{V}/\dot{Q}$ nonhomogeneity to the range that actually existed. Using this approach, we determined that the maximum artifactual gradient at high altitude was about 2 Torr during rest and 3 Torr during exercise.

Our second approach employed the actual measurements of inert gas retentions and excretions during rest and exercise at high altitude and Wagner's analysis (43, 47). This analysis fits the inert gas data with a distribution of $\dot{Q}$ with respect to $\dot{V}/\dot{Q}$ and then uses this distribution to calculate end-capillary O_2 tensions and contents and alveolar O_2 tensions of each of the 48 gas-exchanging compartments used in the model. Thus, the difference between the P_{O_2} in mixed alveolar gas and mixed end-capillary blood (the "actual" $\bar{P}_{A_{O_2}} - \bar{P}c'_{O_2}$) can be calculated. The next step was to predict an alveolar-end-capillary O_2 gradient on the basis of the retention and excretion of an inert gas having the same solubility as O_2. This was done in the same manner as with the two-compartment model. The retention and excretion values of the inert gas were calculated from the distribution of $\dot{Q}$ with respect to $\dot{V}/\dot{Q}$ derived from Wagner's analysis. Again, the difference between the actual and predicted gradients was the artifactual diffusion gradient. The results of this analysis are shown in Table 2. It is seen that the artifactual gradient averaged 0.64 ± 0.42 Torr during rest and 1.31 ± 1.31 Torr during exercise.

On the basis of these model experiments, we conclude that our calculated alveolar-end-capillary diffusion gradients may have overestimated the real gradients, but only by a small amount; therefore, for purposes of detecting qualitative trends, we consider the assumption for constant O_2 solubility at high altitude to be reasonable under the conditions of our experiments.

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The views, opinions, and/or findings contained in this report are those of the authors(s) and should not be construed as an official Department of the Army position, policy, or decision, unless so designated by other official documentation.

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