Ventilation-perfusion inequality in normal humans during exercise at sea level and simulated altitude

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GALE, GWEN E., JOSÉ R. TORRE-BUENO, RICHARD E. MOON, HERBERT A. SALTZMAN, AND PETER D. WAGNER. *Ventilation-perfusion inequality in normal humans during exercise at sea level and simulated altitude.* J. Appl. Physiol. 58(3): 978–988, 1985.—To investigate the effects of both exercise and acute exposure to high altitude on ventilation-perfusion ($\dot{V}_A/\dot{Q}$) relationships in the lungs, nine young men were studied at rest and at up to three different levels of exercise on a bicycle ergometer. Altitude was simulated in a hypobaric chamber with measurements made at sea level (mean barometric pressure = 755 Torr) and at simulated altitudes of 5,000 (632 Torr), 10,000 (523 Torr), and 15,000 ft (429 Torr). $\dot{V}_A/\dot{Q}$ distributions were estimated using the multiple inert gas elimination technique. Dispersion of the distributions of blood flow and ventilation were evaluated by both $\log_e$ standard deviations (derived from the $\dot{V}_A/\dot{Q}$ 50-compartment lung model) and three new indices of dispersion that are derived directly from inert gas data. Both methods indicated a broadening of the distributions of blood flow and ventilation with increasing exercise at sea level, but the trend was of borderline statistical significance. There was no change in the resting distributions with altitude. However, with exercise at high altitude (10,000 and 15,000 ft) there was a significant increase in dispersion of blood flow ($P < 0.05$) which implies an increase in intraregional inhomogeneity that more than counteracts the more uniform topographical distribution that occurs. Since breathing 100% O_2 at 15,000 ft abolished the increased dispersion, the greater $\dot{V}_A/\dot{Q}$ mismatching seen during exercise at altitude may be related to pulmonary hypertension.

ventilation-perfusion dispersion; pulmonary gas exchange; inert gases; hypobaric chamber

THE RELATIVE CONTRIBUTION of each of the factors affecting the efficiency of gas exchange in humans during exercise in a hypoxic environment has not been clearly defined. The effects of exercise at sea level (4, 8, 27) and at high altitude (1, 12, 13, 16, 17, 25, 26) on gas exchange in the lungs have been studied with considerable interest. However, there has been limited quantitative analysis of all factors affecting gas exchange under these conditions [i.e., hyperventilation, ventilation-perfusion ($\dot{V}_A/\dot{Q}$) relationships including intrapulmonary shunt, O_2 diffusion limitation, extrapulmonary shunt, hemoglobin concentration and P_{50} (P_{O_2} at 50% saturation of hemoglobin), and hemodynamic variables]. The multiple inert gas elimination technique (6) allows some discrimination between these factors by providing an estimate of $\dot{V}_A/\dot{Q}$ distributions of blood flow and ventilation.

The purpose of our study was to investigate several of the factors affecting gas exchange in normal humans at rest and exercising at sea level and simulated altitude. One of the most important elements affecting the efficiency of gas exchange under extreme conditions, O_2 diffusion limitation (13) is analyzed in a companion article (18). This paper focuses on $\dot{V}_A/\dot{Q}$ relationships and addresses the questions: Is there a change in the degree of $\dot{V}_A/\dot{Q}$ maldistribution with increasing levels of exercise, or with exposure to high altitude, or with both together?

The overall topographical distributions of perfusion and ventilation in the lungs become more uniform with either exercise (2) or exposure to high altitude (3). Despite this contribution towards homogeneity, there is evidence suggesting that in humans functional $\dot{V}_A/\dot{Q}$ relationships actually worsen during exercise (8) and also at high altitude (9). This study explores these possibilities more extensively.

We used two different numerical approaches to quantitate the degree of $\dot{V}_A/\dot{Q}$ inequality. One approach uses the $\dot{V}_A/\dot{Q}$ 50-compartment lung model to generate distributions from which log standard deviations are calculated (6). A second approach has been developed herein to estimate $\dot{V}_A/\dot{Q}$ dispersion directly from the inert gas retention and excretion data.

METHODS

Subjects

Nine healthy male subjects, 19–35 yr old (mean = 26 yr), were studied. All lived near Durham, North Carolina (elevation 460 ft), were normal on physical examination, had no history of smoking or pulmonary disease, and had essentially normal pulmonary function (Table 1). The subjects covered a range of physical fitness levels, and no attempt was made to select on the basis of athletic abilities. Informed consent was obtained from all subjects.

Each individual came to the laboratory twice, once for preliminary testing and the second time for the full altitude and exercise study. The purpose of the prelimi-

TABLE 1. *Anthropometric and pulmonary function data*

Subj	Age, yr	Height, m	Weight, kg	TLC, %P	VC, %P	RV, %P	FEV_1/FVC, %P	FEF_{25-75}, %P	D_{LCO}, %P
CM	23	1.88	81.8	101	99	107	94	76	134
PW	29	1.76	76.8	79	81	76	110	121	104
*CBd**	19	1.75	71.4	75	88	68	119	160	88
LW	29	1.78	70.0	87	97	84	103	114	110
CBy	19	1.80	64.5	93	100	79	91	103	113
*EO**	30	1.73	77.3	110	98	137	105	113	129
PB	35	1.79	76.8	92	101	76	109	117	132
MS	22	1.70	66.4	103	96	110	90	66	110
MH	24	1.85	70.0	95		92	99	97	146
Means	26	1.78	72.8	93	93	92	102	107	118
± SD	± 6	± 0.06	± 5.7	± 11	± 9	± 22	± 10	± 27	± 18

TLC, total lung capacity VC, vital capacity; RV, residual volume; FEV_1/FVC, forced expired volume in 1 s as a fraction of forced expired volume; FEF_{25-75}, mean flow rate over middle 50% of a forced expiration; D_{Lco}, single breath CO diffusing capacity, %P, % predicted for each variable. * Black, but predicted values for caucasian.

nary visit was twofold: to familiarize each subject with the personnel, equipment, environmental chamber, and exercise protocol and to characterize each subject's work capacity. The exercise testing consisted of measuring the metabolic consumption of O_2 ($\dot{V}O_2$), metabolic production of CO_2 ($\dot{V}CO_2$), minute ventilation ($\dot{V}E$), and heart rate at separate progressively increased levels of steady-state exercise. The results were used to select the work loads for the main experiment to give heart rates close to 120 for light, 150 for moderate, and 180 beats/min for heavy exercise.

For the full altitude and exercise study, subject preparation included placement of chest electrocardiogram (ECG) electrodes and insertion of three catheters and a rectal temperature probe. The catheters included a central venous line (superior vena cava) for indocyanine green dye injection, a radial artery line for arterial blood samples, and a peripheral venous line for infusion of inert gases dissolved in saline. In the environmental chamber a net vest was used to secure the ECG electrodes, and a safety harness was fastened by straps to the ceiling of the chamber whenever the subject was on the bicycle.

General Protocol

Measurements were made on each subject in a series of sets starting at ambient barometric pressure (P_B) with the chamber door open (sea-level mean P_B = 755, range 751–761 Torr) first at rest and then at three levels of exercise on a bicycle ergometer. The hypobaric chamber was then decompressed over 2–4 min to a simulated standard altitude of 5,000 ft (1,524 m, P_B = 632 Torr), and rest and three exercise levels were repeated. Following this, equivalent elevations of 10,000 (3,048 m, P_B = 523 Torr) and 15,000 ft (4,572 m, P_B = 429 Torr) were successively attained. Rest measurements and up to three exercise sets, depending on the condition of the subject at the time, were made at each of these elevations. Before ascent from 10,000 to 15,000 ft, all people in the chamber breathed 100% O_2 for 15 min in accordance with chamber safety rules. Once the chamber was decompressed to an equivalent altitude of 15,000 ft, the subject breathed ambient air, but the investigators remained on O_2.

At 15,000 ft a final run was made with the subject breathing 100% O_2 at the maximum work level previously reached breathing ambient air at 15,000 ft. The purpose of this was to investigate the possibility of a postpulmonary shunt significant enough to contribute to alveolar-arterial O_2 differences (18). Fortuitously, the 100% O_2 data were also a valuable addition to the analysis of $\dot{V}_A/\dot{Q}$ relationships, as will be shown.

Each exercise period lasted ~7–9 min with sample collection starting ~6 min into the set when a steady state had been reached. Steady-state conditions were assessed by continuously monitoring mixed expired and end-tidal fractional O_2 (FO_2) and CO_2 (FCO_2), heart rate, and $\dot{V}E$ minute by minute. A longer time was allowed before obtaining control measurements at rest to ensure steady state, with sampling at 9–11 min. After each exercise set the subjects were rested to allow recovery and return to close to resting heart rate. These rest periods lasted ~15, 20, and 25 min after light, moderate, and heavy exercise, respectively.

Experimental details

The primary concern at all times during the experiment was the safety of the subject. A physician was always present inside the chamber. Medical evaluation of the subject included retinal and chest exams at each elevation. Outside the chamber, a Medical Safety Officer (MD) monitored the subjects' ECG, arterial blood pressure, and expired gases and received feedback on arterial blood gases. The Safety Officer and chamber operators were in communication with the investigators in the chamber via headsets and TV monitors.

The Monarch bicycle ergometer was calibrated to give set work loads by an adjustable mechanical friction belt. To achieve constant work rates the subject pedaled in time to a metronome at 60 rpm. A fan was placed in front of the bicycle to help cool the subject during heavy exercise.

The inert gas mixture in saline was continuously infused throughout the experiment by a roller pump. Using sterile technique the mixture was made from SF_6, ethane, and cyclopropane gas and enflurane, diethyl ether, and acetone liquids (20). This solution was infused through

a 0.22-μm high-pressure Millipore filter to ensure sterility. The infusion was started 40 min prior to any testing. With higher levels of exercise, the infusion rate was increased (in proportion to steady-state $\dot{V}E$ as determined by the preliminary exercise runs) to maintain arterial concentrations of the six gases at measurable levels.

The experimental setup is shown in Fig. 1. The subject wore a noseclip and breathed through a mouthpiece on a two-way valve connected to both inspired ad expired lines. Inspired air came from collapsible Douglas bags filled with air from outside the chamber. In this way the subject's inspired gas was maintained at chamber pressure but was not affected by fluctuations in chamber gas concentrations. Expired gas was directed through heated wide-bore tubing to a heated metal mixing box and then into a Tissot spirometer for VE measurement. A fuel cell O_2 analyzer and an infrared CO_2 analyzer were used to continuously measure either mixed expired or end-tidal F_{O_2} and F_{CO_2}. They were recalibrated at each simulated elevation.

Cardiac output was measured by the indicator-dilution method using indocyanine green dye. Of the 126 cardiac output measurements made, 18 were lost for technical reasons. These were estimated using a multiple linear regression of the remaining measured cardiac output values on $\dot{V}O_2$, heart rate, and altitude. Heart rate was determined from the ECG tracing. Respiratory frequency was recorded from a thermistor in the mouthpiece.

Two arterial and two mixed expired samples were collected for each rest or exercise set. Of the two arterial samples, one was for arterial P_{O_2} (Pa_{O_2}), arterial P_{CO_2} (Pa_{CO_2}), and pH and the other for inert gas measurements. Including the cardiac output measurements, the total blood volume withdrawn in each period was ~17 ml, making a total blood donation of $\leq$ 300 ml. One of the mixed expired samples was collected in a 100-ml lactated glass syringe for mixed expired F_{O_2} and F_{CO_2} determination by gas chromatography, and the other was for inert gas analysis. All four syringes were locked out of the chamber after each run for immediate analysis in the laboratory.

Calculations and Statistics

$\dot{V}O_2$ and $\dot{V}CO_2$ were calculated from the mixed expired F_{O_2} and F_{CO_2} and $\dot{V}E$ measured over the period of expired gas sampling, using the principle of N_2 conservation. The

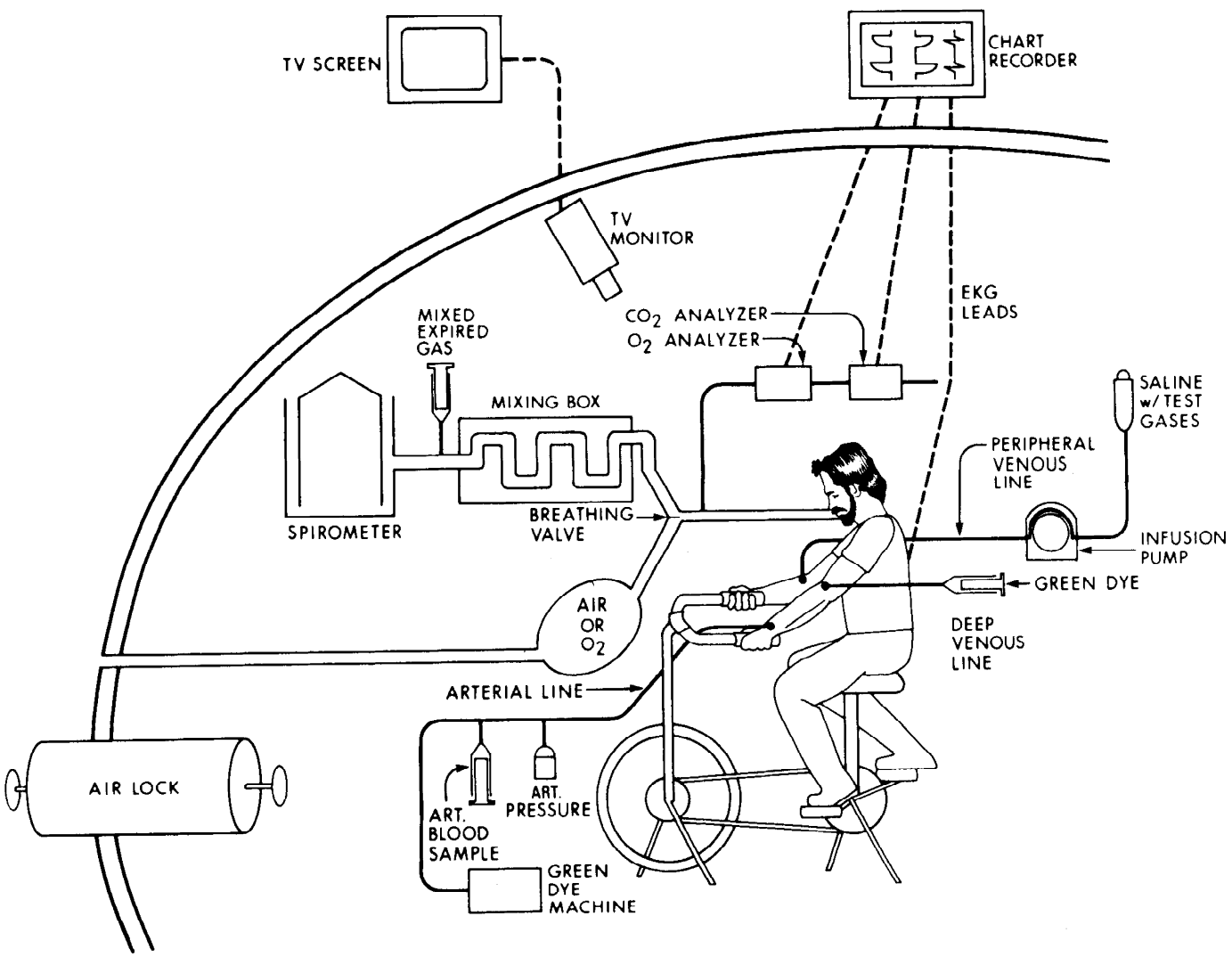


FIG. 1. Schematic of setup in hypobaric chamber.

inert gases were analyzed by techniques previously described (21) using a Varian 3700 gas chromatograph. Corrections were made (according to Boyle's law) for the compression of the expired gas samples outside of the hypobaric chamber: measured expired peaks for the six gases were multiplied by the ratio of volumes of the dry gas sample at sea level and altitude. Since just arterial and expired samples were collected and the cardiac output was measured, the mixed venous concentrations for the six inert gases were calculated using the Fick principle. The $\dot{V}_A/\dot{Q}$ distributions of blood flow and ventilation for the 50-compartment lung model were estimated using enforced smoothing ($Z = 40$) (6).

For statistical evaluation, t tests were used instead of two-way analysis of variance for repeated measures. Even though two factors were tested (exercise and altitude), analysis of variance could not be used because not every subject completed all levels of exercise at altitude. In fact, one subject did not go above 5,000 ft. To test for trends, we used paired t tests comparing the slopes of the regression lines of each variable in question vs. $\dot{V}_{O_2}$ with a slope of zero. $P < 0.05$ determines statistical significance.

Assessment of $\dot{V}_A/\dot{Q}$ Mismatch

A quantitative index of dispersion is necessary to evaluate the degree of $\dot{V}_A/\dot{Q}$ mismatching in the lungs. Here we used two types of indices of dispersion; one type is calculated from the distributions of the 50 $\dot{V}_A/\dot{Q}$ compartment lung model analysis, and the other is derived directly from retention and excretion data.

The log standard deviations of blood flow and ventilation ($\log SD_Q$ and $\log SD_V$), derived from the 50-compartment lung model, are well-established as indices of dispersion (23). The $\log SD_Q$ is calculated as the square root of the second moment about the mean on a natural log scale for compartmental blood flow in the 48 $\dot{V}_A/\dot{Q}$ compartments other than shunt and dead space. The $\log SD_V$ is calculated from the ventilation distribution in an analogous manner. The $\log SD_Q$ and $\log SD_V$ explicitly exclude shunt and dead space, respectively, because of the problem of taking the log of $\dot{V}_A/\dot{Q} = 0$ or ∞ and because they are often thought of separately from $\dot{V}_A/\dot{Q}$ maldistribution.

Because $\log SD_Q$ and $\log SD_V$ may not be normally distributed, thus posing a statistical analysis problem and because these variables are derived from the 50-compartment model, we felt it important to also estimate dispersion directly from retention and excretion data.

We define three parameters of dispersion as root mean square differences between *1*) measured retentions and excretions ($DISP_{R\text{-}E}$, *Eq. 1*), *2*) measured retentions (R) and those of the homogeneous lung (RH) of the same alveolar ventilation and blood flow as the lung under study ($DISP_R$, *Eq. 2*), and *3*) measured excretions (E) and those of the homogeneous lung (EH) ($DISP_E$, *Eq. 3*). For $DISP_{R\text{-}E}$ and $DISP_E$, excretions are first corrected for dead space (E*). This is done because without a dead-space correction these indices would vary with percent dead space even when the degree of $\dot{V}_A/\dot{Q}$ mismatch remains constant. The method of Evans and Helton (6) is used to estimate maximum possible dead-space ventilation directly from retention data (see APPENDIX).

$$DISP_{R\text{-}E} = 100 \times \sqrt{\frac{\sum_{i=1}^{n} (R_i - E_i^*)^2}{n}} \quad (1)$$

$$DISP_R = 100 \times \sqrt{\frac{\sum_{i=1}^{n} (R_i - RH_i)^2}{n}} \quad (2)$$

$$DISP_E = 100 \times \sqrt{\frac{\sum_{i=1}^{n} (EH_i - E_i^*)^2}{n}} \quad (3)$$

where

$$EH_i = RH_i = \frac{\lambda_i}{\lambda_i + \dot{V}_A/\dot{Q}_T}$$

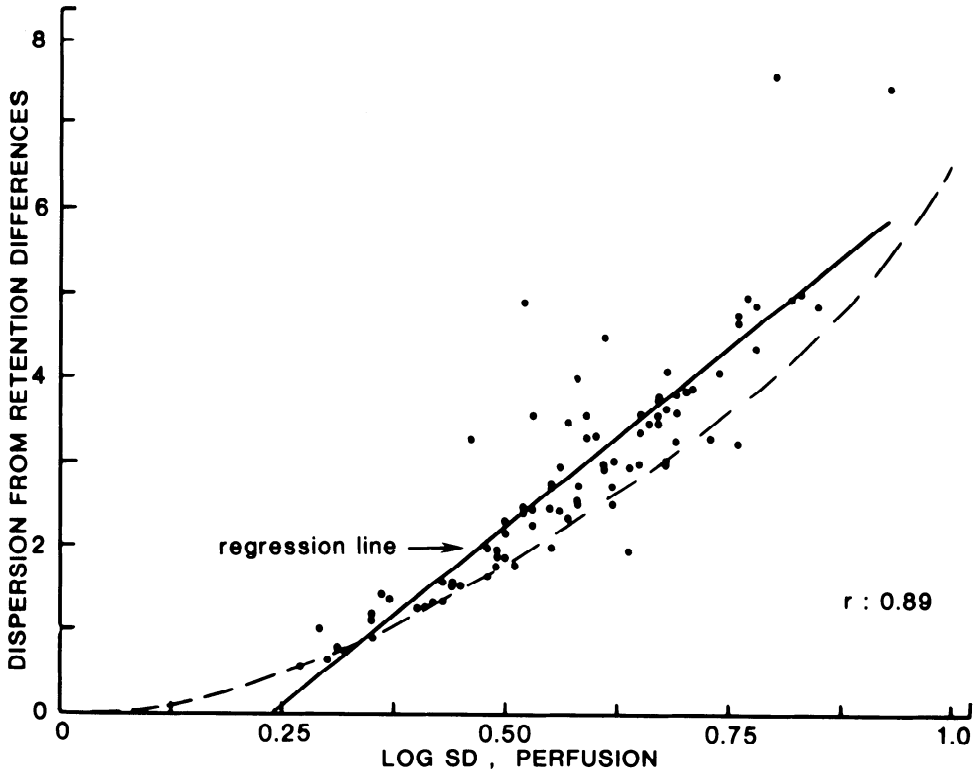
and

$$\dot{V}_A = \dot{V}_E\,(1 - V_D/V_T)$$

Both $\dot{V}_E$ and $\dot{Q}_T$ are measured values of minute ventilation and cardiac output, respectively, in liters per minute; λ_i ($1 \le i \le n$) is the blood gas partition coefficient for the $n = 6$ gases. $E_i^* = E_i/(1 - V_D/V_T)$ where V_D/V_T is the fractional dead space (APPENDIX). Retentions (R_i) and excretions (E_i) are essentially the measured values but after correction for experimental error. This correction is essential so that the derived indices are estimates of $\dot{V}_A/\dot{Q}$ mismatch, not error. The best way to correct for random error would be to use a Monte Carlo simulation to determine feasible retentions from the actual measured retentions (6). We used ridge regression as a more practical approximation to this technique (19). This algorithm is the same as that used to fit the inert gas retention data. However, the important difference is that only the feasible retentions are used and not the calculated blood flows and ventilations of the 50-compartment lung model.

The variable $DISP_R$ is comparable with $\log SD_Q$ in that both are parameters of the perfusion distribution. Similarly, $DISP_E$ and $\log SD_V$ relate to the ventilation distribution. $DISP_{R\text{-}E}$ is an overall index of dispersion that has no counterpart in the moment analysis using the 50-compartment model. The upper panel in Fig. 2 shows how $DISP_R$ and $\log SD_Q$ values from subjects in the present study correlate, and the lower panel shows how $DISP_E$ and $\log SD_V$ correlate. In both cases, these indices do correlate well, and the correlations follow the pattern of theoretical log normal distributions. Unlike $\log SD_Q$, $DISP_R$ includes shunt ($\dot{V}_A/\dot{Q} = 0$) wherever this is present. In constructing Fig. 2, only data sets with <1% shunt were used, so these two variables could be directly compared.

We conclude from this analysis that both $\log SD_Q$ and $\log SD_V$ are variables that can be used with confidence. However, some investigators may prefer the more direct approach defined here. As we will show, the conclusions



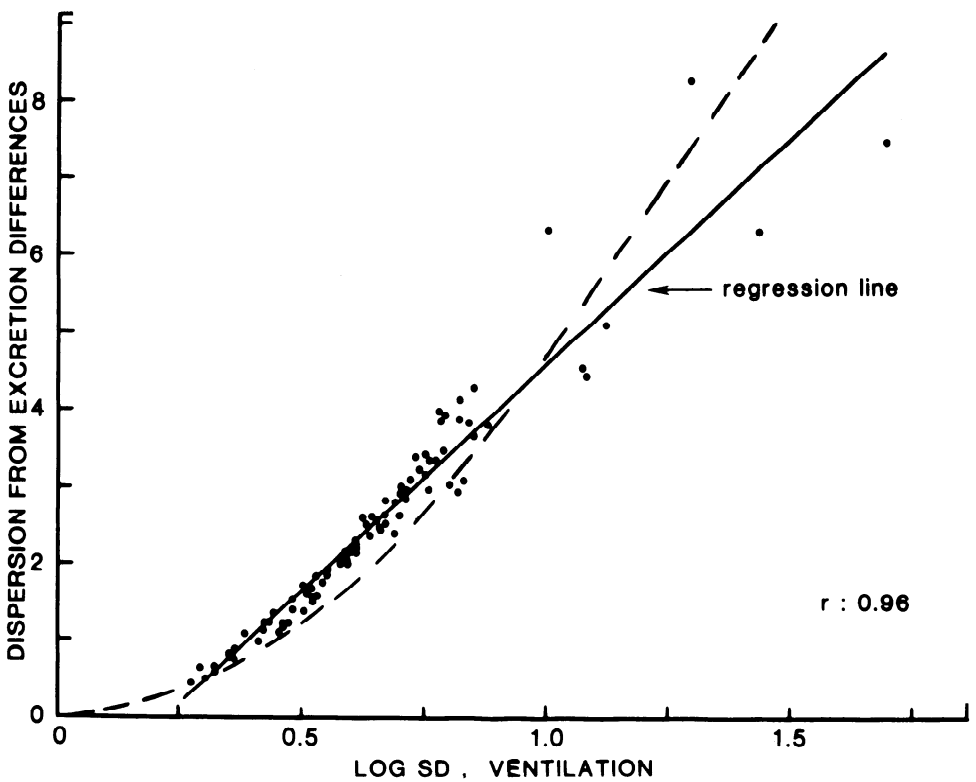


FIG. 2. *Top:* dispersion calculated directly from retention data compared with log standard deviation of blood flow calculated from 50-compartment model. *Regression line* is least-squares best fit to data (r = 0.89). *Dashed line* is for purposes of orientation only and represents expected relationship for logarithmically normal $\dot{V}_A/\dot{Q}$ distributions. *Bottom:* corresponding relationship between dispersion calculated from excretion and log standard deviation of ventilation (r = 0.96). *Dashed line* again represents relationship expected for a log normal distribution.

reached in this paper do not depend on which method is used to quantitate dispersion.

RESULTS

General Measurements

The mean $\dot{V}_{O_2}$, $\dot{Q}_T$, heart rate, $\dot{V}_E$, respiratory frequency, $\dot{V}_E/\dot{Q}_T$, $\dot{V}_{CO_2}$, and respiratory exchange ratio for each level of exercise and altitude are shown in Table 2. Resting $\dot{V}_{O_2}$ increased with altitude. Exercise $\dot{V}_{O_2}$ for the same work load also increased slightly with altitude (5,000 ft vs. sea level). At a given $\dot{V}_{O_2}$, heart rate increased with altitude and was responsible for the increase in $\dot{Q}_T$. $\dot{V}_E$ likewise increased with altitude, and as a result, mean $\dot{V}_A/\dot{Q}$ increased with exercise but not with altitude.

TABLE 2. *Mean pulmonary and cardiovascular data*

	Rest	Light Exercise	Moderate Exercise	Heavy Exercise
	Sea level, P_B = 755 Torr			
$\dot{V}_{O_2}$, l·min^{-1}	0.35 ±0.04	1.29 ±0.16	2.03 ±0.26	2.71 ±0.53
work, kp	0.0	1.2 ±0.4	2.4 ±0.4	3.4 ±0.6
$\dot{Q}_T$, l·min^{-1}	6.5 ±1.3	13.8 ±2.8	18.4 ±2.3	21.7 ±3.4
HR, min^{-1}	78 ±15	114 ±14	140 ±13	166 ±13
$\dot{V}_E$, l·min^{-1}	11.6 ±3.3	32.2 ±4.9	50.0 ±6.0	80.4 ±27.1
f, min^{-1}	13.6 ±5.4	23.3 ±7.5	27.7 ±8.0	41.1 ±18.1
$\dot{V}_E/\dot{Q}_T$	1.9 ±0.7	2.4 ±0.6	2.7 ±0.4	3.7 ±1.0
$\dot{V}_{CO_2}$, l·min^{-1}	0.32 ±0.06	1.20 ±0.19	1.96 ±0.26	2.75 ±0.51
R	0.93 ±0.11	0.93 ±0.06	0.96 ±0.04	1.05 ±0.09
n	9	8	8	9
	5,000 ft, P_B = 632 Torr			
$\dot{V}_{O_2}$, l·min^{-1}	0.41 ±0.07	1.36 ±0.23	2.01 ±0.29	2.72 ±0.34
work, kp	0.0	1.2 ±0.3	2.3 ±0.4	3.2 ±0.5
$\dot{Q}_T$, l·min^{-1}	7.6 ±1.3	14.1 ±2.3	18.6 ±2.6	23.2 ±1.8
HR, min^{-1}	92 ±16	127 ±15	148 ±12	168 ±11
$\dot{V}_E$, l·min^{-1}	12.3 ±2.1	33.8 ±5.7	50.8 ±5.8	80.9 ±16.3
f, min^{-1}	13.8 ±6.1	25.7 ±7.8	30.0 ±7.8	35.9 ±7.0
$\dot{V}_E/\dot{Q}_T$	1.6 ±0.4	2.4 ±0.3	2.8 ±0.4	3.5 ±0.7
$\dot{V}_{CO_2}$, l·min^{-1}	0.34 ±0.06	1.21 ±0.22	1.91 ±0.30	2.84 ±0.40
R	0.85 ±0.09	0.89 ±0.04	0.95 ±0.05	1.04 ±0.07
n	9	9	9	9
	10,000 ft, P_B = 523 Torr			
$\dot{V}_{O_2}$, l·min^{-1}	0.44 ±0.12	1.40 ±0.37	1.97 ±0.41	2.43 ±0.26
work, kp	0.0	1.1 ±0.4	2.0 ±0.5	2.8 ±0.4
$\dot{Q}_T$, l·min^{-1}	8.2 ±2.2	14.4 ±3.1	17.9 ±2.4	21.0 ±2.5
HR, min^{-1}	98 ±16	133 ±19	153 ±17	163 ±18
$\dot{V}_E$, l·min^{-1}	12.5 ±2.9	35.4 ±8.7	56.1 ±14.8	79.0 ±18.1
f, min^{-1}	13.9 ±6.1	24.6 ±5.0	30.9 ±5.4	37.3 ±6.1
$\dot{V}_E/\dot{Q}_T$	1.6 ±0.6	2.5 ±0.5	3.2 ±0.8	3.7 ±0.5
$\dot{V}_{CO_2}$, l·min^{-1}	0.37 ±0.10	1.24 ±0.37	1.89 ±0.45	2.47 ±0.30
R	0.86 ±0.11	0.88 ±0.05	0.96 ±0.07	1.02 ±0.05
n	8	8	8	5
	15,000 ft, P_B = 429 Torr			
$\dot{V}_{O_2}$, l·min^{-1}	0.48 ±0.17	1.28 ±0.32	1.60 ±0.17	
work, kp	0.0	1.0 ±0.5	1.8 ±0.3	
$\dot{Q}_T$, l·min^{-1}	9.0 ±1.8	14.6 ±2.7	19.2 ±2.9	
HR, min^{-1}	107 ±17	147 ±10	159 ±4	
$\dot{V}_E$, l·min^{-1}	14.7 ±3.1	40.9 ±11.9	63.1 ±15.9	
f, min^{-1}	15.5 ±7.6	25.6 ±4.9	32.9 ±8.0	
$\dot{V}_E/\dot{Q}_T$	1.7 ±0.7	2.8 ±0.7	3.4 ±1.4	
$\dot{V}_{CO_2}$, l·min^{-1}	0.42 ±0.14	1.15 ±0.36	1.55 ±0.21	
R	0.88 ±0.08	0.89 ±0.05	0.97 ±0.03	
n	8	6	3	

Values shown are means ± SD where $\dot{V}_{O_2}$ is O_2 consumption; work (1 kilopond is 60 watts); $\dot{Q}_T$, cardiac output; HR, heart rate; $\dot{V}_E$, minute ventilation; f, respiratory frequency; $\dot{V}_{CO_2}$, CO_2 production; R, respiratory exchange ratio; *n*, no. of subjects.

$\dot{V}_A/\dot{Q}$ Mismatching

Exercise at sea level. There was an increase in both $\log SD_Q$ and $DISP_R$ with increasing levels of exercise at sea level (Fig. 3). Figure 4 shows the slope of the regression lines of each dispersion index against $\dot{V}_{O_2}$ (at any given altitude) plotted individually for each subject. Probabilities are given in each panel that the mean regression slope is no different from zero. Individual variability was considerable, and therefore the trend was not statistically significant for $\log SD_Q$ ($P = 0.09$); however, it was for $DISP_R$ ($P = 0.04$). $\log SD_V$ and $DISP_E$ also showed an upward trend with exercise that was not statistically significant ($P = 0.08$ for both). As expected from the increase in both $DISP_R$ and $DISP_E$, $DISP_{R\text{-}E}$ also increased with exercise ($P = 0.06$). Overall, these results indicate a trend in worsening of $\dot{V}_A/\dot{Q}$ relationships during sea-level exercise that is of borderline statistical significance.

Rest at altitude. The degree of $\dot{V}_A/\dot{Q}$ inequality in the lungs at rest did not significantly change with altitude, as shown consistently by all five dispersion variables, $\log SD_Q$, $DISP_R$, $\log SD_V$, $DISP_E$, and $DISP_{R\text{-}E}$ ($P = 0.30$–0.47).

Exercise at altitude. The three levels of exercise at 5,000 ft produced no trends in any of the five dispersion variables (Figs. 3 and 4). However, at both 10,000 and 15,000 ft there was a statistically significant increase in $\log SD_Q$ ($P = 0.01$ and 0.003, respectively) and $DISP_R$ ($P = 0.04$ and 0.05, respectively) with increasing levels of exercise. In contrast, $\log SD_V$, $DISP_E$, and $DISP_{R\text{-}E}$ did not increase with exercise at these elevations. These results indicate that with altitude and exercise there is a broadening of the blood flow distribution with respect to $\dot{V}_A/\dot{Q}$ in the lungs. However, the distribution of ventilation does not significantly worsen.

Hyperoxia at 15,000 ft. Breathing 100% O_2 at 15,000 ft resulted in an improvement of $\dot{V}_A/\dot{Q}$ relationships in the lungs compared with breathing room air whether at rest or exercise (Fig. 5). Both $\log SD_Q$ and $DISP_R$ were significantly smaller for O_2 measurements ($P = 0.003$ and 0.01), indicating a reversal of the observed broadening of

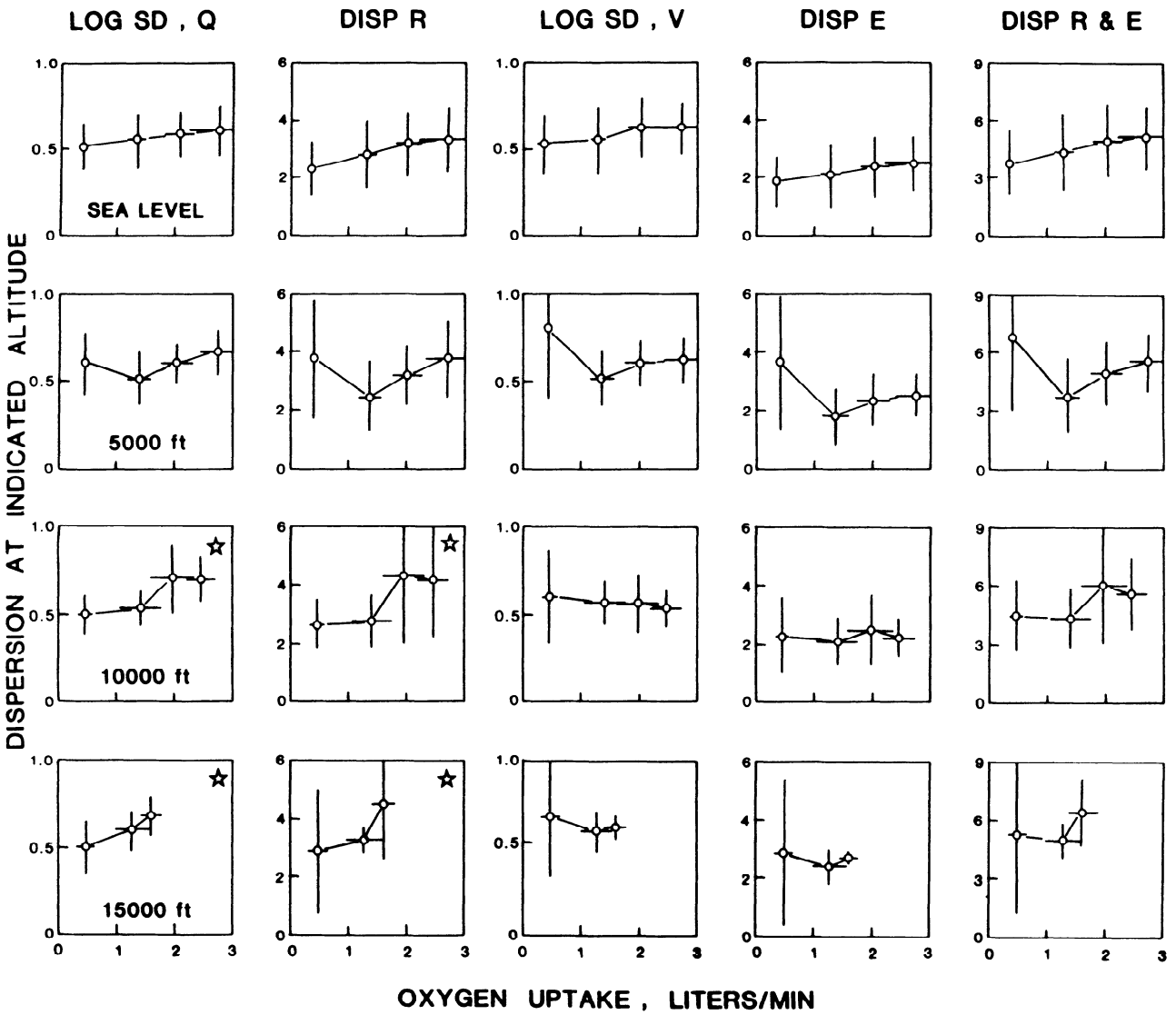


FIG. 3. Mean values of 5 indicated parameters of dispersion at each of 4 indicated altitudes. *Error bars* represent 1 SD. Data are plotted as a function of O_2 uptake. All variables tend to increase with exercise at sea level, but changes are of borderline statistical significance. At 10 and 15,000 ft, however, parameters of the perfusion distribution ($logSD_Q$ and $DISP_R$) significantly increased with exercise as indicated by *stars* in each panel. ($P < 0.05$ by paired t test comparing slopes of each relationship to 0.) See text for abbreviations.

the distribution of perfusion with exercise. Mean $logSD_V$, $DISP_E$, and $DISP_{R-E}$ also decreased with hyperoxia; this was significant for $DISP_E$ and $DISP_{R-E}$ ($P = 0.01$ and 0.01) but not for $logSD_V$ ($P = 0.12$). As also shown in Fig. 5, the values of $logSD_Q$ and $DISP_R$ obtained while breathing O_2 at 15,000 ft were not different from the base-line values observed breathing air at sea level.

DISCUSSION

Summary of Results

At sea level all indices of dispersion tended to increase with exercise, but the results were of borderline statistical significance ($0.04 < P < 0.09$). The scatter in the data requires that this work be extended, using more subjects and even higher levels of exercise. At 5,000 ft there was an initial decrease in mean $\dot{V}A/\dot{Q}$ dispersion comparing rest and light exercise with a subsequent increase in dispersion with heavy exercise (Fig. 3). This is consistent with the sea level data of Whipp and Wasserman (27), although we have to conclude that there is no systematic effect of exercise at this altitude. In contrast, at 10,000 and 15,000 ft, dispersion of the perfusion distribution clearly increased with exercise but dispersion of ventilation did not. Finally, on breathing 100% O_2 at 15,000 ft at the highest work load, $\dot{V}A/\dot{Q}$ relationships were restored to their sea-level resting control values (Fig. 5).

Applicability of Multiple Inert Gas Elimination Technique to This Study

Most previous work in humans with this technique has been done at rest. The few applications to exercise have generally involved $\dot{V}O_2$ levels of <2 l/min at sea level (4, 8). On the other hand, Sylvester et al. (17) performed studies in dogs during mild exercise in a hypobaric chamber. In all of these experiments there is evidence that adequate steady-state conditions were reached. However, we were especially concerned about this in our study because a true long-term steady state is unlikely to be reached during severe (anaerobic) exercise

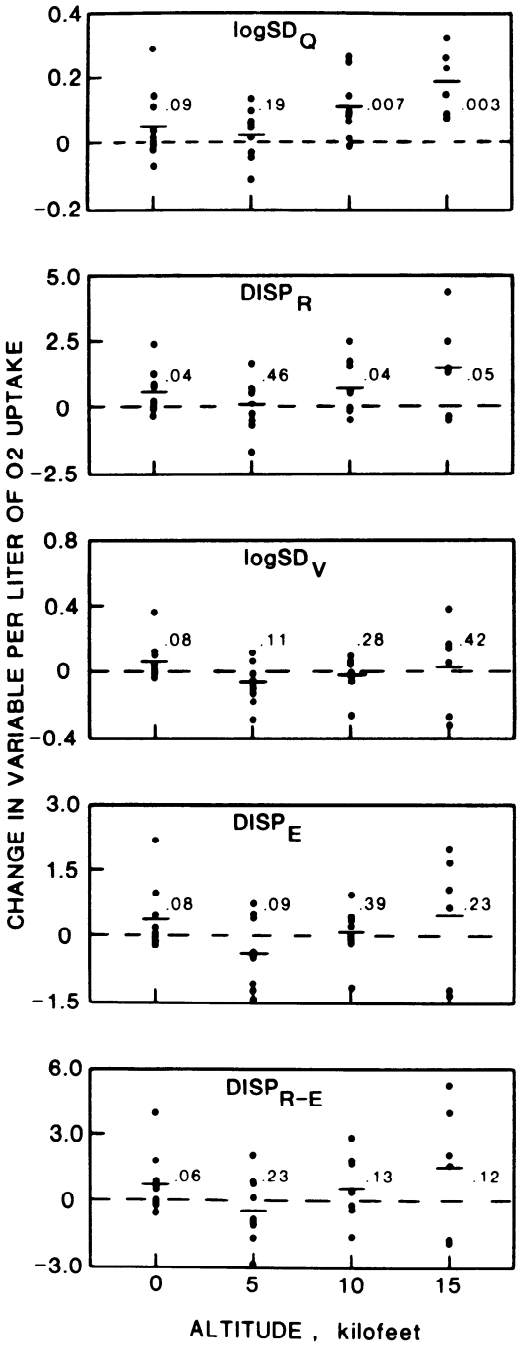


FIG. 4. Slope of regression line between dispersion index indicated at top of each panel and O_2 consumption. Data are shown for sea level and 5, 10, and 15,000 ft. Each *point* represents slope of this regression for an individual subject. *Nos.* within each panel are probabilities that mean values indicated by *horizontal bars* are no different from 0, which is indicated by *dashed line*. See text for abbreviations.

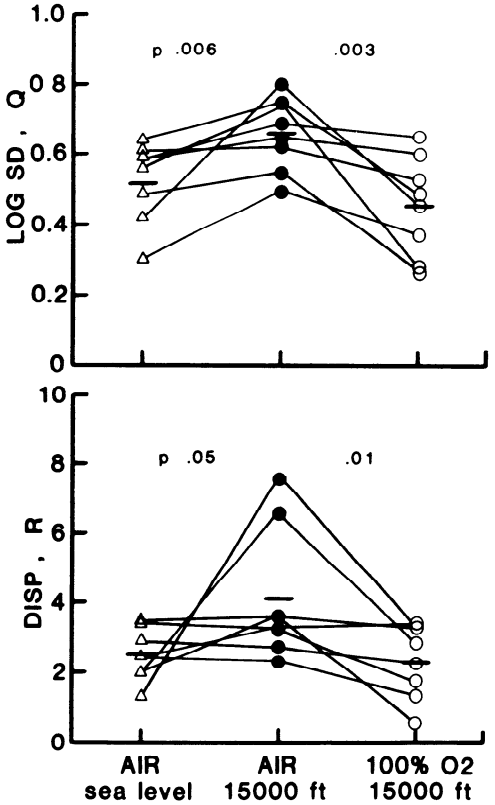


FIG. 5. Dispersion of perfusion distribution under 3 conditions. At *left* are data for all subjects at rest breathing air at sea level. *Points* in middle represent values obtained breathing ambient air at 15,000 ft. These data were obtained at highest exercise level attainable by each subject, and *points* on right represent measurements made under same conditions at 15,000 ft except that 100% O_2 was substituted for air. Mean values are indicated by *horizontal bars*, and probabilities for no difference between conditions are indicated. For both dispersion indices there was a statistically significant increase at 15,000 ft breathing room air compared with base-line data at sea level. Values subsequently decreased significantly when 100% O_2 was used. There was no statistical difference between values obtained breathing 100% O_2 at 15,000 ft during exercise and those obtained at rest breathing air at sea level. See text for abbreviations.

such as at our heaviest exercise levels ($\dot{V}O_2$ up to 3.5 l/min). By the criteria listed in METHODS, adequate steady-state conditions were reached before and maintained during all sampling periods. The ability to fit the inert gas data obtained during exercise confirms this.

Consequences of Experimental Sequence and Rapid Decompression

For practical reasons the experimental sequence in this study was always one of monotonically increasing altitude and exercise level at each altitude. Even though a randomized approach to both altitude and exercise would have been preferable, the return of dispersion indices at rest at each altitude to resting sea-level values suggests that systematic time effects were not occurring. More recent studies of a similar nature employed randomization of the altitude or the exercise sequences, and in both cases the results obtained were not affected by the experimental sequence (P. D. Wagner and M. D. Hammond, unpublished observations).

The fact that $\dot{V}_A/\dot{Q}$ distributions at rest did not change with altitude also suggests that there was no significant effect of rapid decompression on gas exchange. The rates of decompression never exceeded 5,000 ft changes over 2–4 min. In addition, before ascending from 10,000 to 15,000 ft, everyone in the chamber breathed 100% O_2 for 15 min and then during the ascent. The probability that significant venous gas microemboli developed is thus low. To the extent that they occurred, we should have seen the development of high $\dot{V}_A/\dot{Q}$ regions as did Hlastala et al. (11), using the same technique after introducing venous gas emboli. This would specifically become evident by changes in the dispersion of the ventilation distribution, which were not seen (Fig. 3).

Indices of Dispersion

For many years the second moment (on a logarithmic $\dot{V}_A/\dot{Q}$ scale) of the distribution has been used as an index of dispersion which is from the work of Farhi and Rahn (17) and West (23). Although we have considerable confidence in logSD, there has been concern that because the recovered $\dot{V}_A/\dot{Q}$ distribution is only one of a family of distributions compatible with the data (5, 15) it may be difficult to interpret. Accordingly, we have introduced here indices of dispersion that can be obtained directly from the inert gas data.

Other investigators have used measures of the difference between retention and excretion as indicators of $\dot{V}_A/\dot{Q}$ mismatch. Neufeld et al. (14) used a theoretical lung model with 64 gases of different solubility and calculated the R-E difference (expressed as the area under the fractional arterial-alveolar difference vs. λ curve)) for unimodal and bimodal log normal and skewed blood flow distributions. The area under this curve can be accurately calculated because there are 64 points on the curve. Hlastala and Robertson (10) looked at R-E data from normal, low $\dot{V}_A/\dot{Q}$, high $\dot{V}_A/\dot{Q}$, and shunt dog models using six inert gases. They plotted R-E vs. λ for the six gases and interpolated points for intermediate λ. By correcting for dead space and shunt, they derived an arterial-alveolar difference curve from this. This gives a qualitative assessment of $\dot{V}_A/\dot{Q}$ mismatch.

Our calculations of dispersion differ from both of the above approaches. The method of Neufeld et al. (14) is not applicable to real data for the following reason: *1*) there is an assumption of no shunt or dead space, *2*) it is based on R and E data for 64 gases, although only six are used experimentally, and *3*) the method is not formulated to cope with error-containing data. The approach of Hlastala and Robertson (10) is applicable to real data but is not useful for a quantitative estimate of dispersion. Their method correlates the shape of the R-E curves with distributions containing different types of $\dot{V}_A/\dot{Q}$ units but does not provide a quantitation of dispersion unless a four-compartment model is assumed which has the same (or more) limitations as the 50-compartment model. We interpret Fig. 2 as demonstrating not only a generally good-to-excellent relationship between dispersion indices obtained directly from retention and excretion data and those from the 50-compartment model but also a reinforcement of the values obtained in the 50-compartment model and general robustness of the calculation of dispersion overall.

Comparison of Results With Topographical Measurements of $\dot{V}_A/\dot{Q}$ Inequality

Topographical changes in the distribution of ventilation and in particular blood flow have been studied during exercise (2) and also at altitude (3). In both circumstances it has been found that the distribution of perfusion becomes topographically more uniform as a result of greater perfusion of the apices of the lung with increased pulmonary arterial pressure. From current understanding of topographical $\dot{V}_A/\dot{Q}$ relationships (24), this should cause a more even distribution of $\dot{V}_A/\dot{Q}$ and hence lessen the dispersion. However, it should be pointed out that the dispersion at rest in normal young subjects is very small, and lessening it would be difficult to observe. The results of this study show no improvement in $\dot{V}_A/\dot{Q}$ relationships with exercise or altitude and show worse $\dot{V}_A/\dot{Q}$ relationships during exercise at altitude. We do not feel that there is any fundamental incompatibility between the results of radioactive gas measurements and our functional measurements made using inert gas elimination. This is because radioactive techniques have limited spatial resolution and do not sample the entire lung. On the other hand, functional techniques, such as the inert gas approach, do sample the entire lung. Consequently, it is entirely possible that intraregional $\dot{V}_A/\dot{Q}$ mismatch worsens, whereas topographical relationships improve.

Comparison of Results With Other Functional Measurements of Gas Exchange

There have been many previous studies of gas exchange during exercise, both at sea level and altitude. Most of these have involved use of the respiratory gases O_2 and CO_2, and as made clear by Wasserman and Whipp in their review (22), it is not possible simply by measuring alveolar-arterial P_{O_2} differences to determine whether $\dot{V}_A/\dot{Q}$ relationships are deteriorating or not with exercise. Thus they state that the widening alveolar-arterial P_{O_2} differences observed by them during moderate to heavy exercise could be due to one or more of several phenomena. These include an increased effect of shunting due to the reduction in mixed venous P_{O_2}, worsening $\dot{V}_A/\dot{Q}$ relationships, or alveolar–end-capillary diffusion disequilibrium. The current study goes a long way towards resolving the question of the mechanism of the increased alveolar-arterial P_{O_2} differences with exercise. We found that $P_{a_{O_2}}$ measured in our subjects at sea level was predicted by the amount of $\dot{V}_A/\dot{Q}$ inequality observed at all exercise levels up to a $\dot{V}_{O_2}$ of 3 l/min. Consequently, all of the alveolar-arterial P_{O_2} difference, within the limits of error, is attributable to $\dot{V}_A/\dot{Q}$ mismatching, and the tendency towards an increase in dispersion is compatible with the increased alveolar-arterial P_{O_2} difference observed by many investigators (8, 13, 18, 19).

Our data are also compatible with those of Gledhill et al. (8) who found a trend towards increasing dispersion of $\dot{V}_A/\dot{Q}$ in subjects exercising up to 2 l/min $\dot{V}_{O_2}$. Derks (4) also studied normal subjects during light exercise at sea level and found no change in dispersion. Over the narrow range of exercise, this result is also compatible with our data.

Haab et al. (9) measured the alveolar-arterial N_2 difference in nine subjects at 2,000 and 11,500 ft. They found no reduction in the alveolar-arterial N_2 gradient as would have been predicted from the decrease in ambient pressure with constant $\dot{V}_A/\dot{Q}$ relationships. They thus infer a worsening of $\dot{V}_A/\dot{Q}$ relationships at the higher altitude. However, the predicted difference was small (3–4 Torr) in a technique known to be fairly noisy. They were unable to discern a mechanism for the increased inequality but suggested it was related to changes in the distribution of ventilation rather than blood flow.

As will be discussed later, the current study suggests the converse on the basis of the reversal of inequality with the administration of pure O_2.

West et al. (25, 26) also found gas exchange to be more inefficient during exercise at altitude on Mt. Everest. They found an increasing $P_{A_{O_2}}$ in the face of a fall in arterial saturation and attributed this to failure of alveolar–end-capillary diffusion equilibrium. This was at substantially higher altitudes than those attained in the acute exposure of our experiment. Although diffusion disequilibrium is highly probable as an important factor limiting arterial oxygenation at these altitudes, their data cannot truly separate between effects of $\dot{V}_A/\dot{Q}$ mismatch and those of diffusion impairment. Finally, Sylvester et al. (17) used the inert gas elimination technique in dogs exercising in a hypobaric chamber. They did not find worsening of $\dot{V}_A/\dot{Q}$ relationships, but their data are difficult to compare with those obtained in human subjects because of species differences.

Effects of Observed $\dot{V}_A/\dot{Q}$ Inequality on Arterial Oxygenation

An important question raised by our data concerns the potential deleterious effects of increasing $\dot{V}_A/\dot{Q}$ mismatch on Pa_{O_2} and arterial O_2 content. A companion article discusses this in detail (18). In summary, we found that during exercise at 15,000 ft about one-third of the alveolar-arterial P_{O_2} difference could be attributed to $\dot{V}_A/\dot{Q}$ inequality and the remainder to alveolar–end-capillary diffusion disequilibrium. The traditional argument that on the steep part of the dissociation curve $\dot{V}_A/\dot{Q}$ mismatch in normal exercising subjects contributes negligibly to alveolar-arterial P_{O_2} differences appears not to be supported.

Mechanism of Increase of $\dot{V}_A/\dot{Q}$ Mismatch With Exercise and Altitude

We suggest that the degree of $\dot{V}_A/\dot{Q}$ mismatch during exercise at altitude may be related to the degree of pulmonary hypertension. One possible mechanism for this is nonuniform hypoxic pulmonary vasoconstriction. This is certainly consistent with the reversal of inequality by breathing O_2, which would have been expected to reduce pulmonary arterial pressure significantly. Although we do not have direct measurements of pulmonary arterial pressure, mean cardiac output fell from 19.2 to 13.9 l/min in changing from air to pure O_2 at 15,000 ft at the same work rates, and there would have been release of hypoxic vasoconstriction due to increased alveolar P_{O_2}. Both of these events contribute considerably to a reduction in pulmonary arterial pressure (12).

Overall, we interpret our data as not supporting the hypothesis of Haab et al. (9) that the worsening $\dot{V}_A/\dot{Q}$ relationships result from a change of distribution of ventilation. If worsening $\dot{V}_A/\dot{Q}$ mismatch were the result of an increase in ventilation (perhaps on the basis of accentuated time constant inequalities), then we argue it should have been even more apparent at sea level when much higher exercise levels were attained and $\dot{V}_E$ and frequency were greater. Mean $\dot{V}_E$ during heavy exercise at sea level was 80.4 l/min, whereas at 15,000 ft mean maximum $\dot{V}_E$ was 63.1 l/min. The above arguments taken together with the reversibility of $\dot{V}_A/\dot{Q}$ mismatch by 100% O_2 breathing strongly suggests to us that the mechanism lies within the circulation rather than the airways.

In summary, we have shown an increase in $\dot{V}_A/\dot{Q}$ mismatching of borderline statistical significance with exercise at sea level. No such relationship was observed at 5,000 ft, but at 10,000 and 15,000 ft significant increases in $\dot{V}_A/\dot{Q}$ mismatch were observed, sufficient to account for significant alveolar-arterial P_{O_2} differences. These increases in $\dot{V}_A/\dot{Q}$ mismatching at altitude were completely reversed by breathing of 100% O_2 and suggest that the mechanism of worsening $\dot{V}_A/\dot{Q}$ relationships may be related to the development of pulmonary hypertension as a combined effect of exercise and hypoxia. Mechanisms by which an increase in pulmonary arterial pressure would result in $\dot{V}_A/\dot{Q}$ mismatch remain to be determined, but one possibility is nonuniform hypoxic vasoconstriction.

APPENDIX

Calculation of Maximum Possible Dead-Space Ventilation Directly From Retention Data, Total Ventilation, and Cardiac Output

Maximum possible dead-space ventilation ($\dot{V}_D$) can be determined directly from the six inert gas retentions (R), their partition coefficients, $\dot{Q}_T$, and $\dot{V}_E$. The purpose of these calculations is to obtain $\dot{V}_D$ independently of estimated blood flow and ventilation distributions. The reason we used maximum possible $\dot{V}_D$ is because it provides the best estimate of dead space that can be derived directly from the data. This results in a conservative estimate of dispersion by $DISP_E$ and $DISP_{R\text{-}E}$ because of the maximal dead-space correction of excretion. Furthermore, we have found that the fractional dead space from the 50-compartment model is not significantly different from the maximum possible dead space.

To determine $\dot{V}_D$, we use the recursion method of Evans and Helton (5) and include the pertinent calculations here. In our case the intent of this algorithm is to derive the maximum $\dot{V}_D$ from $\dot{V}_E$ and the minimum possible $\dot{V}_A$ compatible with the six inert gas retentions and the $\dot{Q}_T$. For details refer to (5). The recursion method requires using retentions corrected for error to calculate $\dot{V}_D$. (Infeasible retentions will produce negative values in the recursive calculations.)

Definition of terms: $d_q^6 = \dot{Q}_T$, $d_v^6 = \dot{V}_E$, and $d_i^6 = \dot{Q}_T \times R_i$, where R_i = retention of ith gas, $1 \le i \le 6$.

Recursive calculations

$$d_q^{k-1} = \frac{d_q^k}{d_k^k} - 1 \tag{4}$$

$$d_v^{k-1} = \frac{d_v^k}{d_k^k} - \lambda_k \times \frac{d_q^k}{d_k^k} \times \left(\frac{d_q^k}{d_k^k} - 1\right) \tag{5}$$

$$d_i^{k-1} = \frac{\lambda_i\,(d_i^k - d_k^k)}{\lambda_i d_k^k - \lambda_k d_i^k} \text{ for } 1 \le i \le k-1 \tag{6}$$

The eight data points: d_q^k, d_v^k, and six values of d_i^k are defined for $k = 6$. From this, we calculate d_q^5 from *Eq. 4*, d_v^5 from *Eq. 5*, and five values of d_i^5 from *Eq. 6*. Note that we have gone from eight to seven data points. If we continue to use *Eqs. 4, 5,* and *6* recursively, dropping one data point each time, we calculate d_q^0 and d_v^0 for $K = 0$. To obtain $\dot{V}_D$ and then fractional dead space, we use *Eqs. 7* and *8*.

$$\dot{V}_D = d_v^0 \times d_1^1 \times d_2^2 \times d_3^3 \times d_4^4 \times d_5^5 \times d_6^6 \tag{7}$$

$$\frac{V_D}{V_T} = \frac{\dot{V}_D}{\dot{V}_E} \tag{8}$$

In this way, we have determined dead space directly from the retention data without any estimation of compartmental distributions.

This is used as the dead-space correction for excretions in calculating $DISP_E$ and $DISP_{R-E}$.

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