Hypoxic ventilatory drive in normal man

John V. Weil, … , Giles F. Filley, Robert F. Grover

Research Article

A technique is described which permits the inscription of the ventilatory response to isocapnic hypoxia in man as a continuous curve relating alveolar oxygen tension and minute ventilation. The adjustment of ventilation to changes in alveolar oxygen tension is complete in 18-23 sec and this is sufficiently rapid to justify the use of a non-steady-state method. Changes in alveolar carbon dioxide tension are prevented by addition of carbon dioxide to the inspired gas. The resulting $[unk]V_E$-$P_{A_{O_2}}$ curves are hyperbolic such that falling $P_{A_{O_2}}$ produces only slight rises in $[unk]V_E$ until a critical $P_{A_{O_2}}$ range of 50-60 mm Hg is reached. With further fall in $P_{A_{O_2}}$, $[unk]V_E$ increases steeply and the slope of the curve approaches infinity at a tension of 30-40 mm Hg. For purposes of quantitation these curves are approximated by a simple hyperbolic function, the parameters of which are evaluated by a least squares fit of the data. The parameter A denotes curve shape such that the higher the value of A. the greater the increase in ventilation for a given decrease in $P_{A_{O_2}}$ and hence the greater the hypoxic drive. Curves are highly reproducible for each subject and curves from different subjects are similar. In 10 normal subjects at resting $P_{A_{CO_2}}$, A = 180.2 ±14.5 (SEM). When $P_{A_{CO_2}}$ is adjusted to levels 5 mm Hg above and […]

Find the latest version:

Hypoxic Ventilatory Drive in Normal Man

John V. Weil, Edward Byrne-Quinn, Ingvar E. Sodal, W. Otto Friesen,
Brian Underhill, Giles F. Filley, and Robert F. Grover

*From the Department of Medicine and Webb Waring Institute, University of
Colorado Medical Center, Denver, Colorado 80220*

A B S T R A C T A technique is described which permits
the inscription of the ventilatory response to isocapnic
hypoxia in man as a continuous curve relating alveolar
oxygen tension and minute ventilation. The adjustment
of ventilation to changes in alveolar oxygen tension is
complete in 18–23 sec and this is sufficiently rapid to
justify the use of a non–steady-state method. Changes
in alveolar carbon dioxide tension are prevented by ad-
dition of carbon dioxide to the inspired gas. The re-
sulting V_E–P_{AO_2} curves are hyperbolic such that falling
P_{AO_2} produces only slight rises in V_E until a critical
P_{AO_2} range of 50–60 mm Hg is reached. With further
fall in P_{AO_2}, V_E increases steeply and the slope of the
curve approaches infinity at a tension of 30–40 mm Hg.
For purposes of quantitation these curves are approxi-
mated by a simple hyperbolic function, the parameters
of which are evaluated by a least squares fit of the
data. The parameter A denotes curve shape such that
the higher the value of A, the greater the increase in
ventilation for a given decrease in P_{AO_2} and hence the
greater the hypoxic drive. Curves are highly repro-
ducible for each subject and curves from different sub-
jects are similar. In 10 normal subjects at resting P_{ACO_2},
A = 180.2 ±14.5 (SEM). When P_{ACO_2} is adjusted to
levels 5 mm Hg above and below control in six sub-
jects A = 453.4 ±103 and 30.2 ±6.8 respectively.
These latter values differed significantly from control
(P < 0.05). These changes in curve shape provide a
clear graphic description of interaction between hyper-
capnic and hypoxic ventilatory stimuli. At normal
P_{ACO_2} the V_E–P_{AO_2} curve has an inflection zone located
over the same P_{O_2} range as the inflection in the oxygen-
hemoglobin dissociation curve. This indicated that ven-
tilation might be a linear function of arterial oxygen
saturation or content. Studies in four subjects have

demonstrated that ventilation is indeed related to ar-
terial oxygen content in a linear fashion. These data
suggest, but do not prove, that oxygen tension in chem-
oreceptor tissue as in part determined by circulatory
oxygen delivery may be an important factor in con-
trolling the ventilatory response to hypoxia.

INTRODUCTION

Acute changes in pulmonary ventilation are predomi-
nantly under the control of the carbon dioxide–hydro-
gen ion system. However, chronic adjustments of ven-
tilation often appear to be dictated mainly by oxygen
requirements of the organism. Adaptation of animals
to high altitude, for example, is accompanied by in-
crease in ventilation and substantial reduction in
P_{ACO_2} (1). Similarly, evolution-related changes in ven-
tilation which occurred during the emergence of aquatic
animals from the water on to the land indicate that air
breathing which greatly increased the availability of
oxygen resulted in marked decreases in ventilation with
tenfold increases in carbon dioxide tension (2). In both
circumstances it would appear that chronic changes in
ventilation were dictated primarily by hypoxic ventila-
tory drive while renal mechanisms maintained normal
hydrogen ion concentration. There was little attempt
to hold carbon dioxide tension at any particular level.
In spite of its apparent importance in chronic adjustment
of ventilation hypoxic ventilatory drive has not been
commonly studied directly because it is technically diffi-
cult to measure. Hyperventilation induced by hypoxia
produces hypocapnia and alkalosis and both are potent
inhibitors of ventilation. Hence studies of the ventilatory
response to simple administration of low oxygen gases
describe a response which is a resultant of hypoxic
stimulation and hypocapnic-alkalotic inhibition. For
this reason ventilatory responses to hypoxia must be
measured under conditions in which the usual changes
in blood carbon dioxide tension and pH are prevented.
The studies of Loeschke and Gertz (3), Cormack, Cun-

ningham, and Gee (4), and Tenney, Remmers, and Mithoefer (5) utilized methods which permitted measurement of ventilatory responses to hypoxia at constant carbon dioxide tensions. Relatively few data points were obtained in each subject during these studies and there was little information concerning the precision with which carbon dioxide tension was controlled during hypoxia. More commonly, information concerning hypoxic respiratory drive is calculated from the change in slope of P_{CO_2}-ventilation lines done at different oxygen tensions (6, 7). However, this technique describes the ventilatory response to hypoxia as a single number, ΔV_{40}, and leaves the form of the ventilation-$P_{A_{O_2}}$ relationship undescribed. Ventilatory responses to single breath administration of nitrogen have also been used for this purpose but neither the intensity of the stimulus nor completeness of response is well documented with this method. As a result no studies have been reported in which a large volume of data has been collected in a given individual at a single sitting. Hence considerable variation exists in the literature regarding both the magnitude and the exact nature of the ventilatory response to hypoxia in normal man.

The present study is concerned with the description of the ventilatory response to isocapneic hypoxia as a continuous curve relating minute ventilation and alveolar oxygen tension. These curves are hyperbolic and closely resemble the oxygen-hemoglobin dissociation curve. In contrast, the relationship between arterial oxygen content and minute ventilation is essentially linear.

METHODS

Subjects participating in the study were normal males between the ages of 22 and 45 yr. None were actively involved in formal athletics or formal physical conditioning programs and none were born at altitudes greater than a few hundred feet above sea level. All were long-term residents (1–20 yr) of Denver, Colo. (1600 m). All studies were done in the laboratories of the Webb-Waring Institute and the University of Colorado Medical Center in Denver. Each subject was informed of the purpose and details of the study and consent was obtained from all participants.

Details of the method are outlined in Fig. 1. The subject breathes through a respiratory valve (Hans Rudolph) from
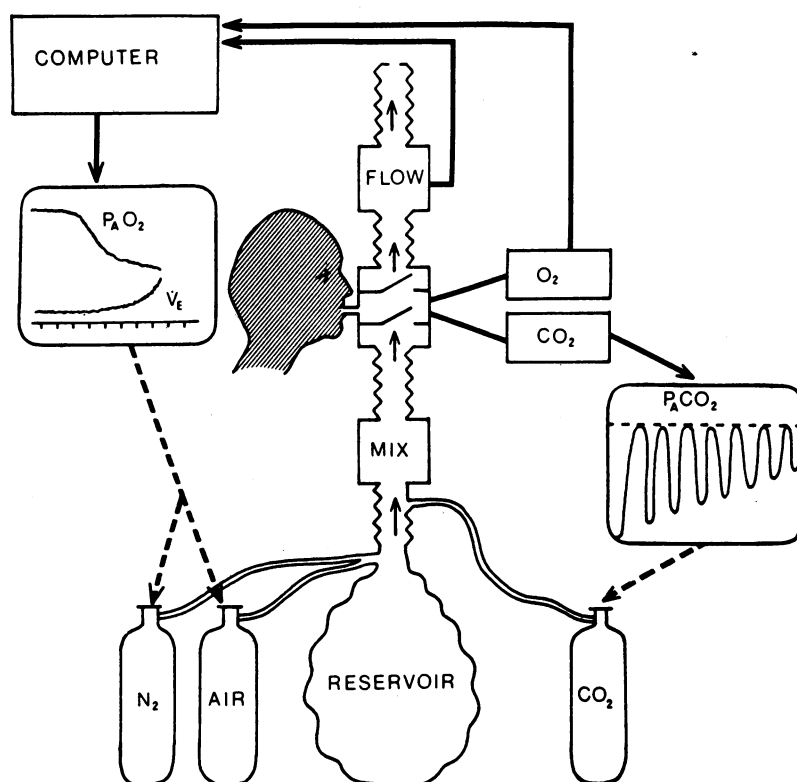

FIGURE 1 Outline of method used to induce progressive isocapnic hypoxia. Alveolar oxygen tension is computed from fuel cell oxygen analyzer signal and used to guide addition of nitrogen to inspired gas. Output of CO_2 analyzer provides a guide to the addition of CO_2 to inspired gas in amounts sufficient to prevent hypocapnia.
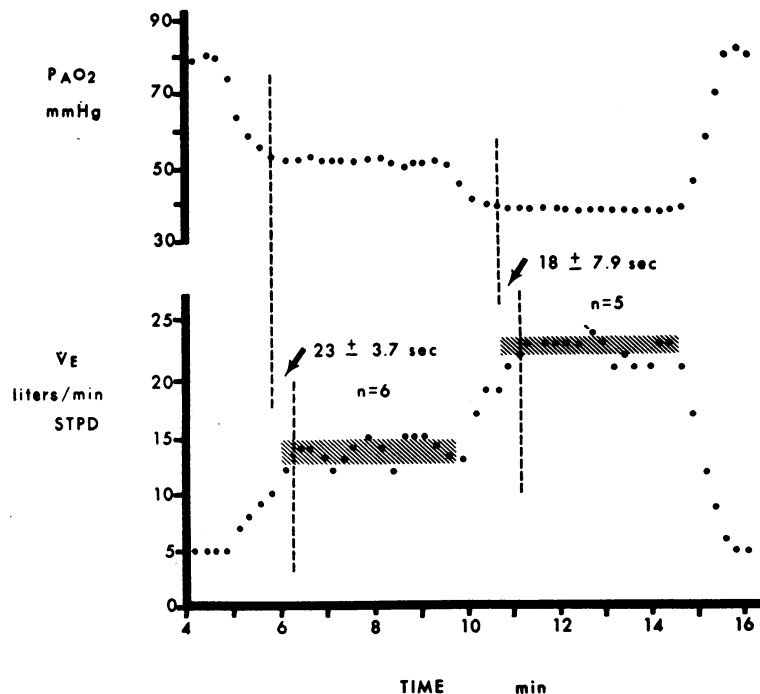
FIGURE 2 Kinetics of the ventilatory response to sudden introduction of two successive hypoxic gas mixtures. Alveolar P_{O_2} and $\dot{V}_E$ are from a representative study while the numbers shown for phase lag are mean of six and five studies.

which gases are sampled by an infrared carbon dioxide analyzer (Beckman LB-1) and by a fuel cell, rapid oxygen analyzer. Design and performance of the latter instrument have been described elsewhere (8, 9). Output from the fuel cell O_2 analyzer together with information from a pneumotachograph are fed into an on-line PDP-8 computer. These data emerge as nearly continuous, real time, oscilloscopic plots of end-tidal oxygen tension, carbon dioxide tension, and minute ventilation. The end-tidal oxygen plot is used as a guide to the manual addition of 100% nitrogen to the stream of inspiratory gas such as to produce a gradual fall in end-tidal tension from 120 to 40 mm Hg over 15–20 min. Output from the carbon dioxide analyzer is also displayed on an oscilloscope and this information is used during the study to guide the manual addition of 100% carbon dioxide to the inspired gas in amounts sufficient to prevent hypocapnia. This process is represented schematically in Fig. 1 by a rising inspired CO_2 tension with constant end-tidal tension. Resting or control P_{ACO_2} was determined by measurement of end-tidal P_{CO_2} during several brief periods of breathing room air through the circuit used in the study. On occasion P_{ACO_2} was low initially and tended to increase slightly over several minutes, eventually stabilizing at a higher value. A P_{ACO_2} which remained stable during successive 3- to 5-min breathing periods was accepted as the control value.

In order to determine whether data collected in such non-steady-state circumstances could be used in any meaningful fashion, a series of studies was conducted to examine the kinetics of ventilatory adjustment to square-wave hypoxic gas stimuli under isocapnic conditions. In each of six subjects breathing room air, an inspiratory gas mixture con-

taining 10.27% O_2 in N_2 was suddenly introduced for 5 min and constant end-tidal P_{CO_2} was maintained as described above. After this 5 min period, a second gas containing 8.51% O_2 in N_2 was introduced for another 5 min. At the end of this period the inspiratory gas was abruptly changed to room air (see Fig. 2). After the introduction of hypoxic gases rather long periods of up to 2 min were required to lower alveolar oxygen tension. However, the intervals between the time at which stabilization of alveolar P_{O_2} occurred and the time at which the ventilation curve entered its 95% tolerance band were very short. For the room air to 10.27% O_2 portion of the study, alveolar P_{O_2} fell from 85 ±2.3 (SEM) to 50.6 ±0.81 mm Hg and the interval between stabilization of P_{O_2} and stabilization of ventilation averaged 23 ±3.7 sec. The second phase of the study reduced P_{O_2} from 50.6 ±0.81 to 39.2 ±0.31. In this case ventilation stabilized within 18 ±7.9 sec of attainment of stable O_2 tension. In the non–steady-state studies described above the rate of change of oxygen tension below 60 mm Hg is 3.6 mm Hg/min. Thus a 20 sec delay interval represents a maximal effective P_{AO_2} phase error of 1.2 mm Hg higher than actually observed at that time. It should be emphasized that these data were computed during sudden changes in P_{AO_2} and hence represent more rigorous conditions than those actually pertaining during slowly progressive hypoxia. Thus the measured phase error represents the worst possible case and undoubtedly overestimates that encountered during the studies to be described.

In six subjects ventilation-P_{AO_2} curves were measured following acutely sustained alterations in alveolar P_{ACO_2}. These curves were done at control P_{ACO_2}, at P_{ACO_2} 5 mm Hg above control and at P_{ACO_2} 5 mm Hg below control. Hypo-

capnia was produced by voluntary hyperventilation suffi-
cient to reduce the P_{ACO_2} to a level 5 mm Hg below control.
After this had been achieved voluntary hyperventilation was
discontinued and induction of progressive hypoxia was
begun. Hypercapnia was produced by progressive addition
of carbon dioxide to the inspired gas until a P_{ACO_2} 5 mm
Hg greater than control was achieved. This level was main-
tained throughout the hypoxic study.

Arterial blood studies. In four subjects the ventilatory
response to progressive isocapnic hypoxia was measured
in conjunction with arterial blood gases and pH. After two
complete P_{AO_2}–V_E curves had been inscribed a Cournand
needle was placed in either a radial or brachial artery.
Progressive isocapnic hypoxia was induced as described
above and 8-ml arterial blood samples were taken over the
first 20 sec of each minute of the 15–20 min study. Samples
were collected anaerobically in oiled, heparinized syringes
and placed in ice. Within a few minutes P_{AO_2}, and P_{ACO_2} and
pH were measured with appropriate electrodes (Radiometer
Co., Copenhagen). Oxygen content and capacity were mea-
sured with a Van Slyke apparatus on each sample within
120 min.

Accuracy of transducers. Our experience with analysis
of oxygen using the fuel cell oxygen analyzer has been
previously described (8). Currently, results with this
device differ from Scholander data by 0.008 volume % with
a standard deviation of 0.015 volume % over a range of
5–21% O_2. Ventilation is measured using a pneumotacho-
graph. Because of the inherent alinearity of this instrument
a calibration curve with two linear phases is employed: one
for gas flows below, and one for flows in excess of 640
liters/min. The computer program is designed to apply two
separate respective calibrations for flows in these two
ranges. This corrects for turbulence errors and produces
agreement to better than 5% with simultaneous volumes
measured with a Tissot spirometer over the entire range
encountered in these studies.

Computer program. The sampling rate of the on-line
computer (PDP-8) is 50 samples per sec for all incom-
ing analog signals. During the sampling interval (20 msec)
calculation of values for P_{AO_2}, P_{ACO_2}, and ventilation is
completed. These data are displayed as real time output
and are stored on magnetic disc for later transmission to
a larger time-shared computer system (GE-400) for non-
linear least squares curve fitting.

RESULTS

Results of a typical study are shown in Fig. 3. This
plot relating alveolar oxygen tension and ventilation is
composed of points which represent the mean value
for P_{AO_2} and ventilation computed from three successive
breaths..

In order to compare individual curves more conveni-
ently we have employed a simple empirical equation
relating ventilation and alveolar P_{O_2} which constitutes a
reasonably close description of these curves. Those
values for the parameters of such an equation which
produce an optimum least squares fit for a given curve
provide quantitative information regarding the shape
and position of that curve. We have tested several ex-
pressions and have found that an equation similar to
one originally suggested by Lloyd, Jukes, and Cunning-
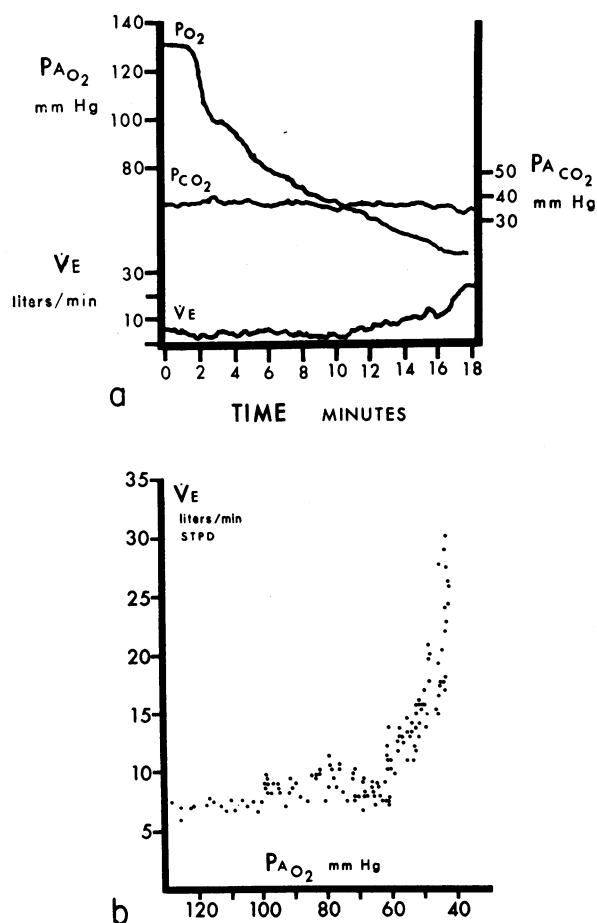ham (7) works as well as any for this purpose. The

FIGURE 3 Ventilatory response to progressive isocapnic
hypoxia in a typical normal subject. (*a*) Time course of
ventilation, alveolar oxygen tension, and carbon dioxide
tension. (*b*) Relationship between minute ventilation and
alveolar oxygen tension in this same subject. Each point
represents the mean value for oxygen tension and ventilation
for three successive breaths.

equation relates ventilation and alveolar P_{O_2} as follows:
$V_E = V_E^0 + A/(P_{AO_2} - 32)$, where V_E and P_{AO_2} are
minute ventilation in liters per minute STPD and alveo-
lar P_{O_2} in millimeters of mercury respectively. Parameter
V_E^0 is the asymptote for ventilation obtained by extra-
polation and parameter A determines the shape of the
curve such that the higher the value for A the greater
the hypoxic ventilatory drive. (see Fig. 4). The con-
stant 32 represents the P_{AO_2} at which the slope of the
V_E–P_{AO_2} curve approaches infinity and was obtained by
extrapolation in 18 studies in six normal subjects. In
practice the curve fitting procedure including evalua-
tion of parameters is accomplished using a GE-400 com-
puter programmed for a least squares fit using Mar-
quardt's method (10). This equation yields curves which
fit the observed data very closely over a wide range of
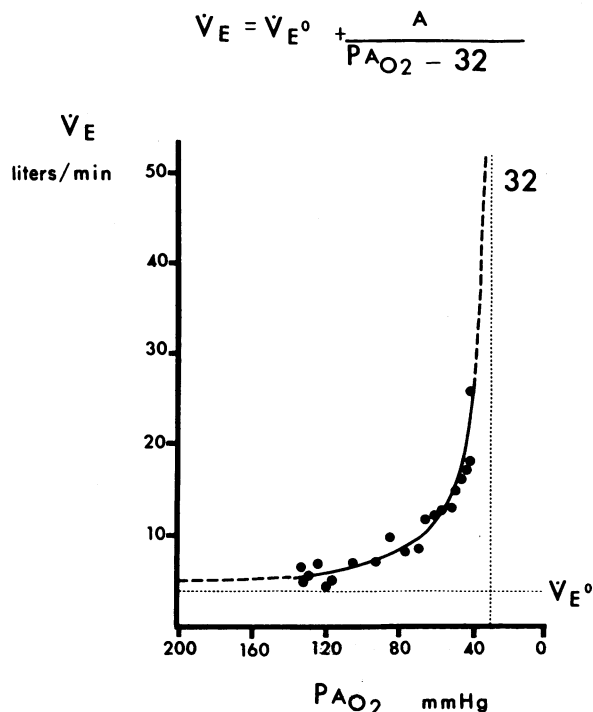
$$\dot{V}_E = \dot{V}_E^0 + \frac{A}{P_{A_{O_2}} - 32}$$

FIGURE 4 The curve resulting from a least squares fit to the equation shown above. The parameter $\dot{V}_E^0$ is the value for ventilation extrapolated to an infinitely great $P_{A_{O_2}}$ while the parameter A describes curve shape. The data points shown were obtained by reduction of the original 150 points (Fig. 3 b) to 20 points by taking serial means.

curve shapes (see Fig. 6). Analysis of variance of the regression revealed a very low error or residual contribution such that in all cases $P < 0.005$ for regression and in most cases $P < 0.0005$. The goodness of
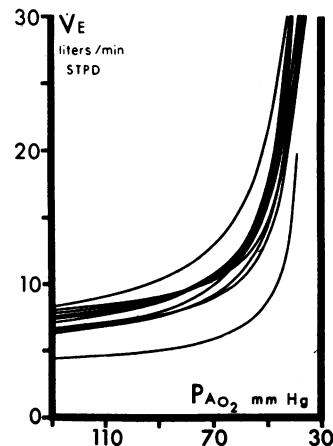
FIGURE 5 Alveolar oxygen tension–minute ventilation curves in 10 normal subjects. Curves are the result of nonlinear least squares fit as described in the text.

fit of the computed curves to the actual data may also be gauged by examination of residuals, that is the difference between the ventilation measured at a given $P_{A_{O_2}}$ and that calculated from the fitted curve. In 20 studies for $P_{A_{O_2}} = 40$–45 mm Hg this residual difference for ventilation averaged -0.49 ± 0.37 (sem) liter/min. For this $P_{A_{O_2}}$ range ventilation averages about 25 liter/min so the observed residual error is about 2%.

Curves in 10 normal subjects are shown in Fig. 5 and values for A and $\dot{V}_E^0$ in Table I. The mean value for A at control $P_{A_{CO_2}}$ was 180.2 ± 14.5 (sem) and $\dot{V}_E^0$ averaged 4.8 ± 0.5 l/min. In order to estimate the precision with which changes in $P_{A_{CO_2}}$ were prevented mean values for $P_{A_{CO_2}}$ during the "normoxic" phase of the study ($P_{O_2} > 85$ mm Hg) were compared with mean $P_{A_{CO_2}}$

TABLE I
Hypoxic Ventilatory Drive in 10 Normal Subjects

| Subject	Age	Ht	Wt	BSA	$P_{A_{CO_2}}$ Normoxia	$P_{A_{CO_2}}$ Hypoxia	A	$\dot{V}_E^0$	No. of studies
	yr	cm	kg	m²	mm Hg				
1. E. B.-Q.	33	175	74.1	1.90	36.1	35.0	159.7	5.3	7
2. V. C.	22	181	68.6	1.87	41.9	41.0	99.5	4.4	3
3. R. F. G.	45	180	71.0	1.91	39.0	38.7	194.8	4.9	4
4. M. J.	22	180	88.6	2.09	32.2	31.9	169.6	5.0	2
5. R. McG.	26	185	93.9	2.19	39.1	37.8	170.1	6.2	3
6. M. R.	23	180	105.5	2.25	33.1	33.8	176.9	4.8	2
7. I. E. S.	35	182	67.7	1.88	32.9	32.7	142.5	5.8	5
8. B. U.	30	182	67.7	1.88	38.2	38.2	272.2	4.3	4
9. J. V. W.	34	175	75.5	1.91	36.8	35.6	217.2	2.6	7
10. R. Y.	22	179	88.6	2.08	36.1	34.8	199.8	5.0	2
Mean					36.5	36.0	180.2	4.8	
sem					1.0	0.9	14.5	0.3	
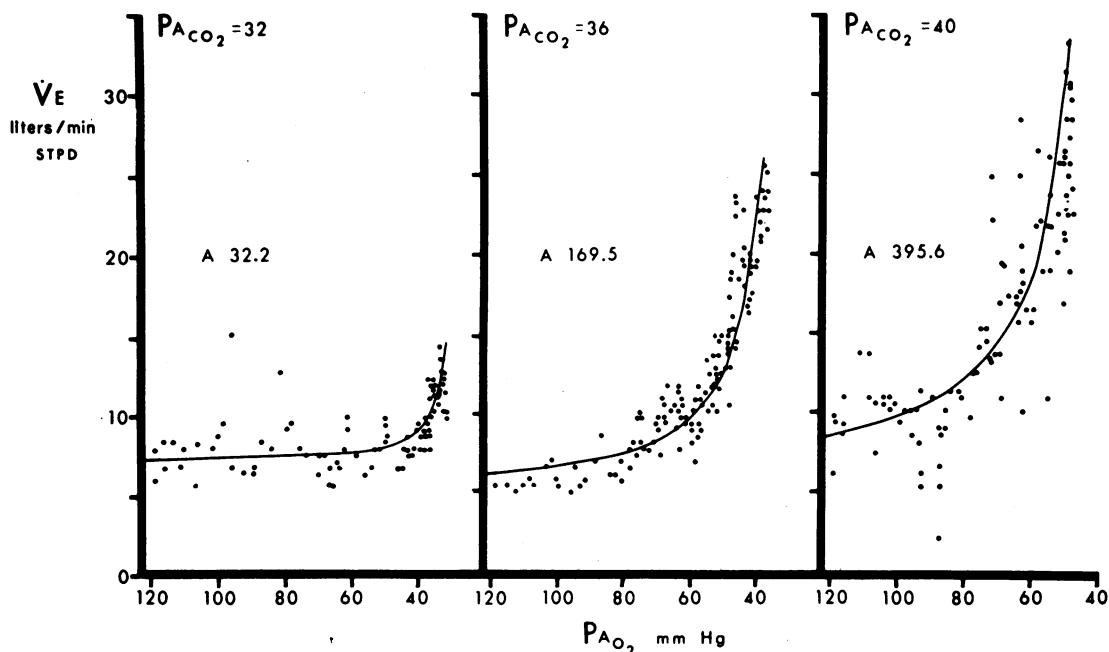
FIGURE 6 Influence of acute sustained alteration in alveolar carbon dioxide tension on ventilatory response to hypoxia in a typical subject (E. B.-Q.). Observed data points are shown in relation to the computed curve for each study.

during the "hypoxic" phase ($P_{A_{O_2}} < 85$ mm Hg). The difference between these two values for 10 studies averaged $- 0.89$ mm Hg with a standard deviation of 1.09 mm Hg.

Effects of acute alterations in alveolar carbon dioxide tension. Acute reduction of alveolar P_{CO_2} by voluntary hyperventilation resulted in an attenuation of the ventilatory response to hypoxia in all six subjects. This was reflected in a consistently decreased value for A, the shape-determining parameter, in these subjects. Con-

versely acute hypercapnia accentuated the response of ventilation to hypoxia and increased the value for A in all subjects (Table II). A representative series of studies at three $P_{A_{CO_2}}$ levels in a single subject is shown (Fig. 6). These changes were found to be statistically significant by analysis of variance ($P < 0.05$).

Arterial blood studies. In four subjects arterial blood samples were collected at 1 min intervals during progressive hypoxia (Table III). Results of a representative study are plotted against time in Fig. 7. Mean ventila-

TABLE II
The Effect of Changes in $P_{A_{CO_2}}$ on Hypoxic Ventilatory Drive in Normal Man

Subject n = 6	Hypocapnia			Normocapnia			Hypercapnia		
	$P_{A_{CO_2}}$	A	V_E^0	$P_{A_{CO_2}}$	A	V_E^0	$P_{A_{CO_2}}$	A	V_E^0
E. B.-Q.	32.3	32.2	7.4	36.1	159.5	5.3	40.2	395.6	4.2
V. C.	37.8	19.7	4.1	41.9	99.5	4.4	44.3	160.4	12.2
R. F. G.	28.2	5.2	9.3	39.0	194.8	4.9	43.4	331.7	5.7
I. E. S.	30.2	46.7	7.2	32.9	142.5	5.8	38.6	379.4	5.9
B. U.	33.7	49.7	8.1	38.2	272.2	4.3	46.3	898.7	1.1
J. V. W.	30.3	27.7	6.9	36.8	217.2	2.6	41.2	554.8	2.2
Mean	32.1	30.2	7.2	37.5	181.0	4.6	42.3	453.4	5.2
SEM	1.4	6.8	0.7	1.2	24.8	0.5	1.2	103.0	1.6
P^*	<0.01	<0.01	<0.05	—	—	—	<0.01	<0.05	NS

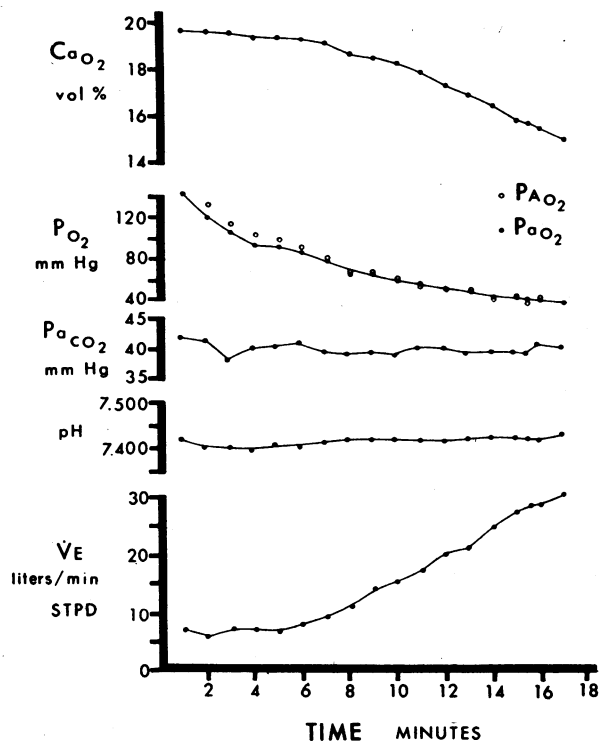* Values refer to difference from normocapnia.

FIGURE 7 Serial values for CaO₂, PₐO₂, PaCO₂ pHₐ and Vᴇ collected over 17 min in a typical subject (R. McG.) during progressive, isocapnic hypoxia (see Table III).

FIGURE 9 Minute ventilation-alveolar oxygen tension curve plotted in relation to an inverted oxygen-hemoglobin dissociation curve on common Po₂ axis. Similarity between these curves in terms of similarity of oxygen tension range over which the respective inflection zones occur is evident.

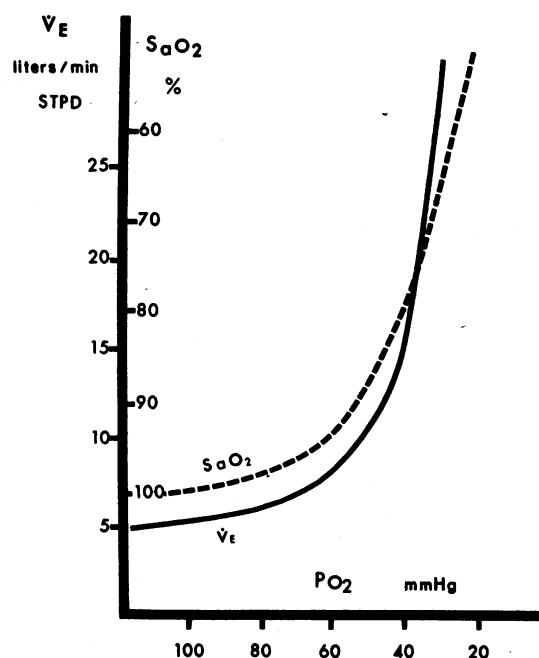tion values for each minute were viewed in relation to the oxygen content of simultaneous arterial blood samples in each subject. In contrast to the curvilinear relationship between oxygen tension and ventilation, oxygen content was related to ventilation in an essentially linear fashion (see Fig. 8). Regression lines were determined by least squares method.
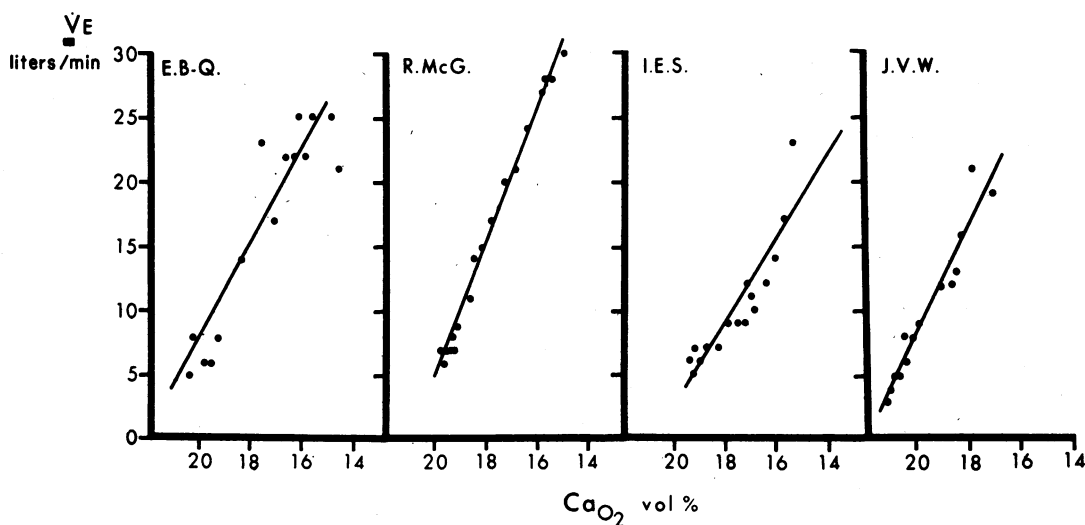

FIGURE 8 Linear relationship between minute ventilation and arterial oxygen content during progressive isocapnic hypoxia in four normal subjects.

Hypoxic Ventilatory Drive in Normal Man 1067

TABLE III
Results of Arterial Blood Studies during Progressive Isocapnic Hypoxia in Four Subjects

	Time	C_{aO_2}	P_{AO_2}	P_{aO_2}	P_{ACO_2}	P_{aCO_2}	pH_a	$\dot{V}_E$
	min	*vols %*	*mm Hg*	*mm Hg*	*mm Hg*	*mm Hg*		*liters/min*
E. B.-Q.	1	19.81	124.0	120	35.0	36.0	7.415	6
	2	—	116.0	112	35.6	36.5	7.410	4
	3	20.46	97.5	73.5	35.6	35.5	7.405	5
	4	20.33	91.9	89	34.4	35.5	7.400	7
	5	19.61	83.1	80.5	33.8	35.0	7.415	6
	6	—	76.9	78	34.4	34.5	7.410	9
	7	19.32	68.8	69	34.4	35.5	7.415	11
	8	—	60.6	63	34.4	35.0	7.395	11
	9	18.38	53.8	54	32.5	32.0	7.415	16
	10	17.10	48.1	49	33.1	31.5	7.430	17
	11	17.61	44.4	47.5	33.1	33.0	7.430	23
	12	16.62	41.9	42	34.4	33.0	7.430	23
	13	15.89	41.9	42	34.4	32.5	7.425	23
	14	16.11	40.0	41	33.8	36.0	7.425	25
	15	14.93	40.6	40	34.4	32.0	7.420	23
	16	16.38	40.0	40	33.1	35.0	7.425	23
	17	15.64	37.5	38.5	35.6	34.0	7.430	25
	17.5	14.58	38.8	36	34.4	32.5	7.430	23
R. McG.	1	19.82		131.0	38.4	42.0	7.420	7
	2	19.70	120.3	111.0	38.4	41.5	7.405	6
	3	19.60	105.2	100.0	37.8	38.0	7.405	7
	4	19.44	97.0	88.0	37.8	40.0	7.400	7
	5	19.42	94.5	87.0	36.5	40.0	7.410	7
	6	19.36	86.3	83.0	37.8	41.0	7.410	8
	7	19.18	76.9	75.5	37.2	39.0	7.415	9
	8	18.65	66.8	64.0	37.8	39.0	7.420	11
	9	18.53	63.0	62.5	38.4	39.0	7.420	14
	10	18.25	57.3	58.5	37.8	38.5	7.420	15
	11	17.85	52.9	54.5	37.8	40.0	7.420	17
	12	17.29	49.8	50.0	38.4	39.5	7.420	20
	13	16.90	46.6	47.5	37.2	38.5	7.425	21
	14	16.38	43.5	44.5	37.2	39.0	7.430	24
	15	15.78	42.2	42.0	37.2	39.0	7.430	27
	15.5	15.68	41.6	41.5	36.5	38.5	7.430	28
	16	15.38	39.7	40.5	37.8	40.5	7.425	28
	17	14.97	37.8	38.5	37.2	40.0	7.435	30
J. V. W.	1	21.10	131.3	127.0	—	39.0	7.420	4
	2	20.81	125.6	115.0	—	39.0	7.420	3
	3	20.80	114.3	101.5	—	36.0	7.420	5
	4	20.73	99.2	89.0	—	38.5	7.425	5
	5	20.38	92.3	92.0	—	34.5	7.450	8
	6	20.29	86.0	90.0	—	37.0	7.430	6
	7	20.12	80.4	85.0	—	37.0	7.420	8
	8	19.91	68.5	75.5	—	38.0	7.420	9
	9	18.99	60.3	68.0	—	38.0	7.415	12
	10	18.62	54.6	63.0	—	36.5	7.420	12
	11	18.40	49.0	57.0	—	36.5	7.425	13
	12	18.19	47.1	53.0	—	36.5	7.420	16
	13	17.80	44.6	51.0	—	38.0	7.410	21
	14	16.99	42.1	48.0	—	32.0	7.455	19

TABLE III (continued)

	Time	CaO2	PAO2	Pao2	PACO2	Paco2	pHa	VE
	min	vols %	mm Hg	mm Hg	mm Hg	mm Hg		liters/min
I. E. S.	1	19.45	—	141.0	31.6	29.5	7.395	6
	2	19.24	124.0	135.0	32.4	33.0	7.400	5
	3	19.21	103.0	103.0	31.0	33.0	7.410	7
	4	19.00	87.4	90.0	31.0	31.5	7.420	6
	5	18.70	80.6	77.0	31.6	32.5	7.420	7
	6	18.30	73.8	74.0	31.0	32.0	7.420	7
	7	17.91	65.7	65.5	31.0	32.0	7.430	9
	8	17.50	62.6	61.5	31.6	30.0	7.430	9
	9	17.25	62.0	60.5	32.9	32.0	7.430	9
	10	17.12	58.3	59.5	32.4	33.0	7.420	12
	11	17.03	52.7	54.5	31.6	32.0	7.435	11
	12	16.87	49.6	51.5	31.6	32.0	7.440	10
	13	16.45	46.5	48.5	32.4	31.0	7.445	12
	14	16.12	42.8	45.5	31.0	31.0	7.450	14
	15	15.68	40.3	42.0	31.0	30.0	7.445	17
	16	15.40	39.4	39.0	30.1	30.5	7.445	23

DISCUSSION

Measurement of the ventilatory response to isocapnic hypoxia in man was first described by Loeschke and Gertz (3). Subsequently, Cormack et al. (4) and Tenney et al. (5) both reported similar studies. All of these studies were prolonged, often required more than one sitting, and provided limited numbers of data points. The present study provides abundant data, but suffers from the potential disadvantage of being a non–steady-state method. For this reason the kinetics of ventilatory adjustment to hypoxia were carefully considered. It is certainly well established that ventilation responds rapidly to hypoxemia and the commonly employed single breath test of chemoreceptor function is based upon this knowledge (11). However, the lack of a continuous, rapid-responding oxygen analyzer capable of a high level of precision hampered attempts to define rigorously the time course of changes in ventilation in relation to alveolar oxygen tension. Availability of a fuel cell oxygen analyzer (8, 9) has solved this problem and studies using this instrument reveal that ventilation stabilizes at a steady-state value within approximately 18–23 sec after attainment of a stable alveolar Po_2 under isocapnic conditions. These figures were obtained using abrupt changes in inspired oxygen concentration and hence probably overestimate the extent of delay in ventilatory adjustment to gradual changes in inspired oxygen concentration. The prolonged periods often described for adjustment of ventilation to hypoxia are due mainly to the long period (1–2 min) required to lower alveolar Po_2 following introduction of a hypoxic gas mixture. The true phase difference between changes in alveolar Po_2 and changes in ventilation appears to be sufficiently

small to justify the use of slowly progressive hypoxia as a test of ventilatory responsiveness. As already described the potential error introduced by this time delay is very small.

Throughout these studies much emphasis has been placed on values derived from continuous analysis of gas tensions of end-tidal air and questions could be raised concerning the extent to which these values truly reflect the chemistry of arterial blood. For this reason only normal subjects have been studied. It is generally assumed that end-tidal and arterial carbon dioxide tensions are identical in normal man and this was essentially true in the present study. In addition fuel cell values for end-tidal oxygen tension closely approximated arterial values especially at lower oxygen tensions. Because the end-tidal oxygen tensions reflect the absolute minimum tension registered with each breath these values are lower than those recorded with other end-tidal sampling techniques or calculated from the alveolar air equation. In fact these values may be slightly lower than mixed arterial blood and a slightly negative alveolar-arterial difference can on occasion be measured.

The subjects participating in this study were all long-term residents of moderate altitude (1600 m) and the question arises as to whether this influenced hypoxic ventilatory drive. Depression of the ventilatory response to hypoxia has been observed in persons native to high altitude (12–15), but none of the subjects in the present study was born at altitudes appreciably above sea level. Although Forster et al. (16) described accentuation of ventilatory response to hypoxia in lowlanders residing at high altitude for 45 days, the re-

sponse in long-term residents was not very different from sea level residents. Similarly Sorenson and Severinghaus (17) found no difference in hypoxic ventilatory drive in sea level natives residing at high altitude and sea level natives living at sea level.

Differences in methods of calculation and expression of data made a direct comparison of hypoxic ventilatory responses between studies difficult. Some authors record a twofold increase in ventilation over control when alveolar P_{O_2} is reduced from 150 to 40 mm Hg (4, 7), whereas we find the increase to be approximately fourfold. Other workers express hypoxic sensitivity as the absolute difference in minute ventilation when alveolar P_{O_2} is lowered from 150 to 40 mm Hg expressed as liters per minute per square meter BSA (ΔV_{40}). Values for ΔV_{40} in normal man at sea level have been reported as 9.6 ± 2.4 (SEM) liters/min per m^2 (15), 10.4 ± 1.5 (16), and 33 ± 8.0 (18). From our data we have calculated the mean value of 17.0 ± 1.5 for this measurement which would appear to fall between the above values. Loeschke and Gertz (3) give no tabulated data but their figures relating ventilation to $P_{A_{O_2}}$ appear similar to ours.

The equation employed for curve fitting represents a standard expression for a hyperbolic function and was originally used for this purpose by Lloyd et al. (7). It must be emphasized that we do not regard this equation as a model of ventilatory control but employ it simply as a means of reducing a continuous curve to a few parameters which can be more conveniently handled by traditional statistical methods. It is especially important to indicate that the extrapolated portions of these curves are artificial constructions and should not be regarded as predictive of physiological responses. Hence the fact that the ventilatory asymptote V_E^o is not shifted by changes in $P_{A_{CO_2}}$ does not necessarily mean that alterations of $P_{A_{CO_2}}$ have no effect on ventilation at high $P_{A_{O_2}}$ levels. The data of the present study give a clear picture of the interaction between hypoxic and hypercapnic stimuli and indicate that ventilatory responsiveness to hypoxia is greatly altered by acute changes in carbon dioxide tension. These findings are in close agreement with those of Loeschke and Gertz (3), Cormack et al. (4), and Tenney et al. (5). While we have not attempted in these studies to separate the effects of alterations of carbon dioxide tension per se from the effects of altered hydrogen ion concentration, the studies of Tenney et al. (5) suggest that hydrogen ion concentration is of primary importance in this regard.

It seems possible that the shape of the ventilation-$P_{A_{O_2}}$ curve is of some inherent significance. We have been impressed by the resemblance of these curves to the oxygen-hemoglobin dissociation curve in that both curves show an inflection over the same P_{O_2} range (Fig. 9). This implies that only oxygen tensions which are low enough to lower oxygen saturation stimulate ventilation. This in turn suggests that ventilation might be a linear function of arterial oxygen saturation or oxygen content. The results of the arterial blood studies indicate that this is in fact the case. Other attempts to linearize these data, including the use of semilogarithmic plots, have been to no avail. In our experience the oxygen-hemoglobin dissociation relationship has shown unique capability in this regard. A similar relationship has been found between discharge frequency of the carotid body and arterial oxygenation. Von Euler, Liljestrand, and Zotterman (19) showed that the rate of carotid body discharge is a linear function of arterial oxygen saturation while Hornbein, Griffo, and Roos (20) demonstrated that discharge frequency and arterial oxygen tension were related in a curvilinear fashion which resembles the form of our ventilation-oxygen tension curves. Indeed Comroe, Forster, Dubois, Briscoe, and Carlsen (21) have suggested that the oxygen tension threshold for ventilation is very near the P_{O_2} which marks the beginning of the steep slope portion of the oxygen-hemoglobin dissociation curve.

We have previously reported studies in which a relationship was found between arterial oxygen tension and red cell mass in chronically hypoxic normal man which also resembled the oxygen-hemoglobin dissociation curve (22). In these subjects red cell mass was related in curvilinear fashion to $P_{a_{O_2}}$ such that increases in red cell mass were found only in those subjects in whom $P_{a_{O_2}}$ was low enough to depress oxygen saturation. The relationship between red cell mass and oxygen saturation was linear. It was concluded that blood oxygen content, a major determinant of circulatory oxygen delivery and thus of tissue oxygen tension, played a major role in regulation of erythropoiesis. The notion that erythropoiesis is controlled by the level of tissue oxygenation is generally accepted (23–25). It would appear that the ventilatory response to hypoxia might be controlled in similar fashion, but there are several potential objections to this concept. First, it is thought that blood flow to the carotid body is immense relative to tissue mass and that the oxygen requirements of the chemoreceptor can virtually be met by dissolved oxygen alone (26). If this is true it would seem unlikely that the carotid body could sense changes in total oxygen delivered. However, the true effective tissue blood flow in the carotid body has not to our knowledge ever been determined. In addition activation of the sympathetic nervous system which occurs during hypoxia may greatly reduce carotid body flow during hypoxia (26). Secondly, there is general agreement that administration of carbon monoxide which preserves normal arterial oxygen tension but lowers oxygen content fails to stimulate ventilation (27–29). This has been strong evidence in support of the notion that the carotid body senses arterial oxygen tension rather than content. On the other hand,

Mills and Edwards (30) have recently shown that although perfusion of the carotid body with blood containing various concentrations of carboxyhemoglobin does not stimulate ventilation, a marked rise in carotid body efferent impulses results. These findings stand in striking contrast to those of Duke and Neil (31) who found no evidence of carotid body stimulation under similar circumstances. It is possible that the failure of carbon monoxide to stimulate ventilation may in fact be the result of interference with central integrative mechanisms. Contrary to an often quoted statement that this is unlikely (32) there is considerable evidence that carbon monoxide can substantially disrupt central nervous system function at relatively small concentrations (33–35). For these reasons there must be some reservation regarding the ultimate significance of the effects of carbon monoxide on ventilation. Recent studies from our laboratory indicate that in awake cattle augmentation of oxygen transport produced by transfusion-induced increases in hematocrit decreased the ventilatory response to hypoxia (36). Yet studies by Eisele, Pegg, and Severinghaus (37) in anesthetized dogs showed no diminution in hypoxic drive following production of polycythemia. Hence we believe the nature of ventilatory control during hypoxia is not yet clear and should remain the object of further investigation.

ACKNOWLEDGMENTS

REFERENCES

1. Altman, P. L., and D. S. Dittmer. 1966. Environmental Biology. Fed. Amer. Soc. Exp. Biol. Bethesda. 368.
2. Rahn, H. 1966. Development of gas exchange. Proc. Roy. Soc. Med. 59: 493.
3. Loeschcke, H. H., and K. H. Gertz. 1958. Einfluss des O₂—Druckes in Der Einatmungsluft auf die Atemtätigkeit des Menschen, geprüft unter Konstanthaltung des alveolaren CO₂—Druckes. Pfluegers Arch. Gesamte Physiol. Menshen Tiere. 267: 460.
4. Cormack, R. S., D. J. C. Cunningham, and J. B. L. Gee. 1957. The effect of carbon dioxide on the respiratory response to want of oxygen in man. Quart. J. Exp. Physiol. 42: 303.
5. Tenney, S. M., J. E. Remmers, and J. C. Mithoefer. 1963. Interaction of CO₂ and hypoxic stimuli on ventilation at high altitude. Quart. J. Exp. Physiol. 48: 192.
6. Nielsen, M., and H. Smith. 1952. Studies on the regulation of respiration in acute hypoxia. Acta Physiol. Scand. 24: 293.
7. Lloyd, B. B., M. G. M. Jukes, and D. J. C. Cunningham. 1958. The relation between alveolar oxygen pressure and the respiratory response to carbon dioxide in man. Quart. J. Exp. Physiol. 43: 214.
8. Weil, J. V., I. E. Sodal, and R. P. Speck. 1967. A modified fuel cell for the analysis of oxygen concentration of gases. J. Appl. Physiol. 23: 419.
9. Sodal, I. E., R. R. Bowman, and G. F. Filley. 1968. A fast response oxygen analyzer with high accuracy for respiratory gas measurement. J. Appl. Physiol. 25: 181.
10. Burnette, W. A., and C. S. Roberts. 1967. NLLSQ—A Fortran IV Nonlinear least squares Fitting Program. Memorandum. Bell Telephone Laboratories.
11. Dejours, P. 1962. Chemoreflexes in breathing. Physiol. Rev. 42: 335.
12. Chiodi, H. 1957. Respiratory adaptation to chronic high altitude hypoxia. J. Appl. Physiol. 10: 81.
13. Severinghaus, J. W., C. R. Bainton, and A. Carcelen. 1966. Respiratory insensitivity to hypoxia in chronically hypoxic man. Resp. Physiol. 1: 308.
14. Milledge, J. S., and S. Lahiri. 1967. Respiratory control in lowlanders and Sherpa highlanders at altitude. Resp. Physiol. 2: 310.
15. Sorensen, S. C., and J. W. Severinghaus. 1968. Irreversible respiratory insensitivity to acute hypoxia in man born at high altitude. J. Appl. Physiol. 25: 217.
16. Forster, H. V., J. A. Dempsey, M. L. Birnbaum, W. G. Reddan, J. S. Thoden, R. F. Grover, and J. Rankin. 1969. Comparison of ventilatory responses to hypoxic and hypercapnic stimuli in altitude-sojourning lowlanders, lowlanders residing at altitude and native altitude residents. Fed. Proc. 28: 1274.
17. Sorensen, S. C., and J. W. Severinghaus. 1968. Respiratory sensitivity to acute hypoxia in man born at sea level residing at high altitude. J. Appl. Physiol. 25: 211.
18. Kronenberg, R., F. N. Hamilton, R. Gabel, R. Hickey, D. J. C. Read, and J. Severinghaus. 1969. Quantitation of respiratory response to hypoxia in man. Clin. Res. 17: 416.
19. von Euler, U. S., G. Liljestrand, and Y. Zotterman. 1939. The excitation mechanism of the chemoreceptors of the carotid body. Scand. Arch. Physiol. 83: 132.
20. Hornbein, T. F., Z. J. Griffo, and A. Roos. 1961. Quantitation of chemoreceptor activity: interrelation of hypoxia and hypercapnia. J. Neurophysiol. 24: 561.
21. Comroe, J. H., Jr., R. E. Forster II, A. B. Dubois, W. A. Briscoe, and E. Carlsen. 1962. The Lung. Year Book Medical Publishers. Chicago. 2nd edition.
22. Weil, J. V., G. Jamieson, D. W. Brown, and R. F. Grover. 1968. The red cell mass-arterial oxygen relationship in normal man. J. Clin. Invest. 47: 1627.
23. Fried, W. L., L. F. Plzak, L. O. Jacobson, and E. Goldwasser. 1957. Studies on erythropoiesis. III. Factors controlling erythropoietin production. Proc. Soc. Exp. Biol. Med. 94: 237.
24. Stohlman, F., Jr. 1962. Erythropoiesis. N. Engl. J. Med. 267: 342.
25. Charache, S., D. J. Weatherall, and J. B. Clegg. 1966. Polycythemia associated with a hemoglobinopathy. J. Clin. Invest. 45: 813.
26. Daly, M. De B., C. J. Lambertsen, and A. Schweitzer. 1954. Observations on the volume of blood flow and oxygen utilization of the carotid body in the cat. J. Physiol. 125: 67.

27. Comroe, J. H., Jr., and C. F. Schmidt. 1938. The part played by reflexes from the carotid body in the chemical regulation of respiration in the dog. *Amer. J. Physiol.* **121**: 75.

28. Chiodi, H., D. B. Dill, F. Consolazio, and S. M. Horvath. 1941. Respiratory and circulatory responses to acute carbon monoxide poisoning. *Amer. J. Physiol.* **134**: 683.

29. Klausen, K., B. Rasmussen, H. Gjellerod, H. Madsen, and E. Petersen. 1968. Circulation, metabolism and ventilation during prolonged exposure to carbon monoxide and to high altitude. *Scand. J. Clin. Lab. Med.* **22** (Suppl. 103): 26.

30. Mills, E., and M. W. Edwards, Jr. 1968. Stimulation of aortic and carotid chemoreceptors during carbon monoxide inhalation. *J. Appl. Physiol.* **25**: 494.

31. Duke, H. N., J. A. Green, and E. Neil. 1952. Carotid chemoreceptor impulse activity during inhalation of carbon monoxide mixtures. *J. Physiol.* **118**: 520.

32. Root, W. S. 1965. Carbon monoxide. *In* Handbook of Physiology. W. O. Fenn and H. Rahn, editors. The American Physiology Society, Washington. **2**: 1087.

33. Lilienthal, J. L., Jr., and C. H. Fugitt. 1946. The effect of low concentrations of carboxyhemoglobin on the "altitude tolerance" of man. *Amer. J. Physiol.* **145**: 359.

34. Schulte, J. H. 1963. Effects of mild carbon monoxide intoxication. *Arch. Environ. Health* **7**: 524.

35. Beard, R. R., and G. A. Wertheim. 1967. Behavioral impairment associated with small doses of carbon monoxide. *Amer. J. Public Health Nat. Health.* **57**: 2012.

36. Bisgard, G. E., H. G. Alvarez, and R. F. Grover. 1969. Decreased ventilatory response to hypoxia during acute polycythemia in the calf. *Resp. Physiol.* **7**: 369.

37. Eisele, J. H., J. Pegg, and J. W. Severinghaus. 1969. Ventilatory response to hypoxia in acutely polycythemic dogs. *J. Appl. Physiol.* **26**: 757.