Cerebrovascular Response to Acute Hypocapnic and Eucapnic Hypoxia in Normal Man

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ABSTRACT Alterations in human cerebral blood flow and related blood constituents were studied during exposure to acute hypoxia. Observations were made during serial inhalation of decreasing O_2 concentrations with and without maintenance of normocarbia, during 8 min inhalation of 10% O_2, and after hyperventilation at an arterial P_{O_2} of about 40 mm Hg. In the range of hypoxemia studied, from normal down to arterial P_{O_2} of about 40 mm Hg, the magnitude of the cerebral vasodilator response to hypoxia appeared to be largely dependent upon the coexisting arterial CO_2 tension. The mean slope of the increase in cerebral blood flow with decreasing arterial O_2 tension rose more quickly ($P < 0.05$) when eucapnia was maintained when compared with the slope derived under similar hypoxic conditions without maintenance of eucapnia. When 12 subjects inhaled 10% oxygen, cerebral blood flow rose to more than 135% of control in four whose mean decrease in arterial CO_2 tension was -2.0 mm Hg. The remaining eight had flows ranging from 97 to 120% of control, and their mean decrease in CO_2 tension was -5.1 mm Hg. When mean arterial P_{O_2} was 37 mm Hg, hyperventilation was carried out in 10 subjects. Arterial P_{O_2} increased insignificantly, arterial P_{CO_2} declined from 34 to 27 mm Hg ($P < 0.05$), and cerebral blood flow which had been 143% of control decreased to 109%, a figure not significantly different from control.

These data demonstrate the powerful counterbalancing constrictor effects of modest reductions in CO_2 tension on the vasodilator influence of hypoxia represented by arterial P_{O_2} reductions to about 40 mm Hg. Indeed, mild hyperventilation completely overcame the vasodilator effect provided by an arterial O_2 tension as low as 40 mm Hg. The effects of hypoxia on the control of the cerebral circulation must be analyzed in terms of the effects of any associated changes in CO_2 tension.

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INTRODUCTION

Lowering the arterial or cerebral tissue P_{O_2} in normal conscious subjects results in cerebral vasodilatation, increased cerebral blood flow (CBF) (1), and, in humans breathing at least 7% oxygen, no change in the cerebral rate of O_2 utilization (2). The magnitude of the increases in cerebral blood flow after moderately severe hypoxia appear to be less than the response to a comparable amount of hypercapnia (3). Simultaneously induced hypoxia and hypercapnia result in additive rather than synergistic effects on cerebral blood flow (4).

There is little information available concerning the separate and possibly antagonistic effects on the cerebral vasculature of the hypocapnia frequently associated with exposure to acute hypoxia. Although cerebral vasodilatation was reportedly enhanced during acute hypoxia with normocarbia, the reduction of arterial P_{O_2} was marked, and control observations without added CO_2 were omitted (2). Hyperventilation has been considered to attenuate the hypoxic response to high altitude, but cerebrovascular data before 6 hr exposure to altitude are unavailable (5).

The purpose of the present study was to provide a description of the alterations in cerebral blood flow and related blood constituents immediately following achievement of the steady state after induction of various de-

TABLE I

*Effects of Graded Hypoxia on Cerebral Blood Flow (CBF), Cerebrovascular Resistance (CVR), Mean Arterial Pressure (MABP), Arterial and Jugular Venous O_2 and CO_2 Tensions, and Cerebral O_2 Delivery**

Inspired gas	CBF	CVR	MABP	Pa_{O_2}	Pv_{O_2}	Pa_{CO_2}	Pv_{CO_2}	O_2 delivery
	% control	*% control*	*mm Hg*	*mm Hg*	*mm Hg*	*mm Hg*	*mm Hg*	*% control*
Air	100	100	98 ±4.3	91 ±3.1	36 ±1.4	38 ±1.7	46 ±2.3	100
18% Oxygen	99 ±4.7	99 ±5.3	97 ±2.1	74 ±1.7	33 ±1.2	37 ±2.0	46 ±2.3	98 ±4.7
16% Oxygen	105 ±2.8	92 ±3.0‡	96 ±4.3	64 ±1.9	32 ±1.1	36 ±1.9	45 ±2.1	101 ±2.5
14% Oxygen	105 ±3.5	92 ±1.4§	96 ±5.1	55 ±1.5	30 ±1.1	36 ±1.9	44 ±2.0	98 ±2.7
12% Oxygen	115 ±4.5‖	87 ±3.4‖	98 ±5.3	47 ±0.9	29 ±1.2	35 ±1.8	43 ±2.1	100 ±3.3
10% Oxygen	135 ±9.7‖	72 ±4.3§	94 ±4.8	40 ±1.3	27 ±2.0	33 ±1.8	40 ±2.2	107 ±5.7
10% Oxygen $+CO_2$	143 ±8.4§	68 ±3.0§	95 ±5.0	41 ±2.4	29 ±2.0	36 ±2.0	43 ±2.5	115 ±5.1§

* Values are mean ± standard error of the mean for six subjects. Symbols represent results of paired *t* test analysis.
‡ $0.05 > P > 0.02$.
§ $P < 0.01$.
‖ $0.02 > P > 0.01$.

TABLE IA

Relationship of Statistical Similarities and Differences between the Data in Table I according to Duncan's Multiple Range Test (11)

Mean values represented by and connected by the lines are not significantly dissimilar. Mean values on separated lines are different at the 5% level. Overlapping lines are caused by means which represent intermediate values not statistically different from other means which are separated by $P < 0.05$.*

% Oxygen	21	18	16	14	12	10	10 + CO_2
CBF and CVR		———	———————			———	
Pa_{O_2}	———	———	———	———	———	———	
Pv_{O_2}	———	———————	———————	———————	———————	———————	———
Pa_{CO_2}	———————	———	———————	———	———		———
Pv_{CO_2}	———————	———————			———	———	
O_2 delivery		———————	———————	———————	———	———————	———

* Example: The values for O_2 delivery obtained at the 18, 16, 14, 12, and 10% levels were not significantly different. The value at 10% was sufficiently greater than the others so that it was not significantly different from the 10% + CO_2 value. This latter mean value, however, was $P < 0.05$ greater than the 18, 16, 14, and 12% values.

TABLE II

*Effects of Controlled and Uncontrolled Arterial CO_2 Tension and Hyperventilation during Hypoxia on Cerebral Blood Flow, Cerebrovascular Resistance, Mean Arterial Pressure, and Arterial and Jugular Venous O_2 and CO_2 Tensions**

Inspired gas	CBF	CVR	MABP	Pa_{O_2}	Pv_{O_2}	Pa_{CO_2}	Pv_{CO_2}
	% control	*% control*	*mm Hg*	*mm Hg*	*mm Hg*	*mm Hg*	*mm Hg*
Air	100	100	97 ±2.4	95 ±1.8	37 ±1.2	38 ±0.7	47 ±0.7
18% Oxygen $+CO_2$	105 ±1.8‡	95 ±1.6§	96 ±2.1	82 ±1.7	36 ±1.2	38 ±0.8	48 ±0.8
14% Oxygen $+CO_2$	107 ±1.3‖	94 ±1.4‖	98 ±2.7	68 ±2.3	35 ±1.2	39 ±0.8	37 ±0.8
9.5% Oxygen $+CO_2$	128 ±4.8‖	81 ±4.0‖	99 ±3.0	49 ±1.5	32 ±1.5	39 ±0.8	47 ±1.2
10.4% Oxygen, no CO_2	143 ±11.4‖	71 ±6.4‖	92 ±3.4	37 ±1.0	26 ±1.3	34 ±0.7	40 ±0.8
9.5% Oxygen hypervent.	109 ±7.5	93 ±5.9	95 ±2.9	42 ±2.2	25 ±1.5	27 ±1.4	35 ±1.1

* Values are mean ± standard error of the mean for 10 subjects.
‡ $0.05 > P > 0.02$. Results of paired t test analysis.
§ $0.02 > P > 0.01$. Results of paired t test analysis.
‖ $P < 0.01$. Results of paired t test analysis.

grees of acute hypoxia. By this means, attempts were made to define the threshold of the cerebrovascular response to hypoxia and to expose the magnitude of the potentially counterbalancing effects of the hypocapnia often associated with significant hypoxia.

METHODS

The subjects of 28 studies were 13 healthy males, aged 25–40 yr (average age 32) in the postabsorptive resting state. The planned procedures were discussed fully, and all gave their informed consent. After local procaine infiltration, cannulae were placed in the brachial artery and in the internal jugular bulb. Oxygen saturations were determined by the Nahas spectrophotometric method (6), and blood O_2 and CO_2 tensions and pH were determined with an electrode system (7).[1] Methods for expired CO_2 monitoring,

[1] Epsco Blood Parameter Analyzer, Epsco, Inc., Westwood, Mass.

TABLE IIA

Relationship of Statistical Similarities and Differences between the Data in Table II According to Duncan's Multiple Range Test

Mean values represented by and connected by the lines are not statistically dissimilar. Mean values on separated lines are different at the 5% level. Overlapping lines are caused by means which represent intermediate values not statistically different from other means which are separated by $P < 0.05$.*

% Oxygen	21	18 + CO_2	14 + CO_2	9.5 + CO_2	10.4	9.5+ Hypervent.
CBF and CVR		———	———	———		———
Pa_{O_2}	———	———	———	———	———	———
Pv_{O_2}	———	———	———	———	———	———
Pa_{CO_2} and Pv_{CO_2}	———	———	———	———	———	———

* See footnote on Table IA.

delivery of gas mixtures, and recording have been described in detail (8–10).

Graded hypoxemia. In six studies arterial and jugular venous blood samples were obtained after serial 5-min inhalations of air, 18, 16, 14, 12, and 10% O_2, and 10% O_2 with CO_2 added to the inspired gas line to restore the end-tidal CO_2 concentration as close as possible to the control level.

8 min of 10% oxygen inhalation. In 12 studies, arterial and internal jugular venous blood samples were obtained during the control state and at 1 min intervals during an 8 min period of 10% inhalation.

Eucapnic hypoxia. In 10 studies, arterial and jugular venous blood was obtained after the subjects breathed the following for serial 10-min periods: air 18, 14, 9.5, 10.4, and 9.5% O_2. End-tidal CO_2 content was maintained at the control level by adding CO_2 to the inspired gas line during the inhalation of 18, 14, and the first 9.5% O_2 periods. No CO_2 was added while breathing 10.4% O_2, and the subjects hyperventilated during the second period of 9.5% O_2 inhalation.

Since inspired O_2 concentrations as low as 7% do not effect the rate of cerebral oxygen consumption (2), it was valid to apply the $1/(A\text{-}V)O_2$ method for estimation of cerebral blood flow. The validity of this method and the necessary calculations have been discussed in detail (5, 8–10).

The data (Tables I and II) were subjected to an analysis of variance, and where significant differences ($P < 0.05$) were found, Duncan's multiple range test was applied to discover which treatments differed by $P < 0.05$ (Tables I A and II A) (11). Since one of the critical assumptions for analysis of variance is the equality of variances within treatments, and since there was by definition no variability in the control values for cerebral blood flow, cerebrovascular resistance, and cerebral oxygen delivery, paired t tests were also applied to these data.

The technics for regression analysis and for testing the two regression lines derived for CBF vs. Pa_{O_2} followed the methods of Ostle (11), and the multiple regression analyses followed the methods of Draper and Smith (12).

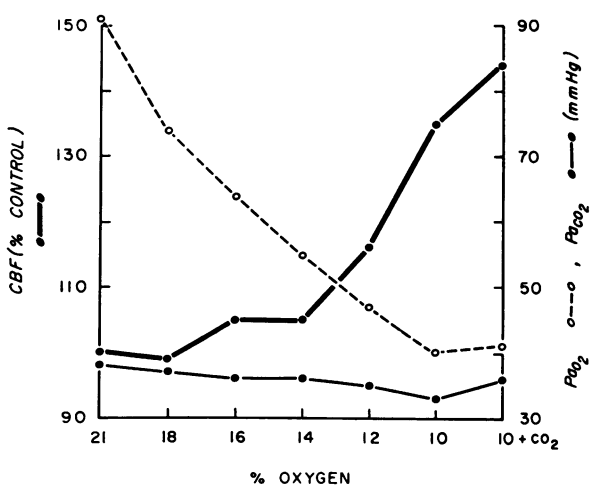

FIGURE 1 The mean alterations of cerebral blood flow (CBF), arterial O_2 and CO_2 tensions during serial reductions in inspired oxygen concentration. See text for discussion.

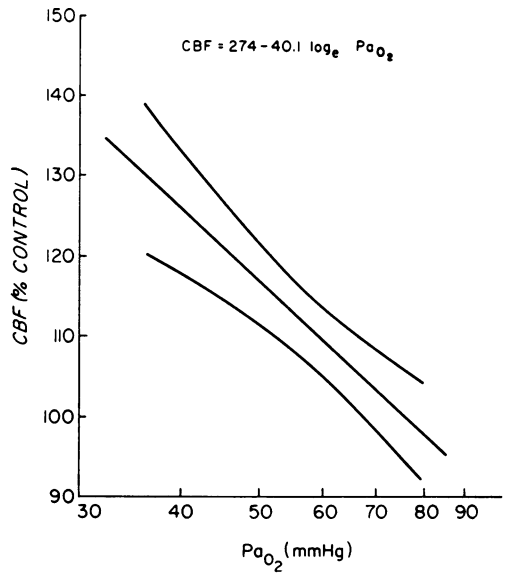

FIGURE 2 Mean slope and 95% confidence limits of cerebral blood flow response during serial reductions in arterial O_2 tension without maintenance of arterial CO_2 tension at control level.

RESULTS

Graded hypoxemia. Table I and Fig. 1 present the data obtained following 5-min serial inhalations of decreasing concentrations of inspired O_2 without added CO_2. Significant increases in cerebral blood flow followed 12 and 10% O_2 inhalation, although cerebrovascular resistance was reduced after less marked reductions in inspired O_2. Addition of CO_2 when 10% O_2 was inspired resulted in a further rise in flow and reduction in vascular resistance. Table I A demonstrates the significant changes wrought by the entire series of interventions. It was apparent that estimated total O_2 delivery to the brain was significantly increased during inhalations of 10% O_2 and 10% O_2 + added CO_2.

The decreases in arterial O_2 and CO_2 tensions are seen in Tables I and I A and in Fig. 1. The jugular venous O_2 tensions decreased less than did the arterial Po_2. Changes in pH of the arterial and venous blood paralleled the changes in CO_2 tension and are not tabulated.

Fig. 2 shows the relationship between cerebral blood flow and arterial O_2 tension when hypocapnia was not corrected as derived from the regression equation, CBF (as per cent of control) $= 274 - 40.1 \log_e Pa_{O_2}$. The mean curve and the 95% confidence limits are shown.

8 min of 10% oxygen inhalation. The individual results are shown in Table III in order of decreasing maximum change in cerebral blood flow. The time to maximum cerebral blood flow was estimated to be approximately 6–7 min.

TABLE III

Maximum Alterations in Cerebral Blood Flow and Associated Arterial O_2 and CO_2 Tensions in 12 Subjects Breathing 10% O_2 for 8 Min without Added CO_2

Maximum CBF	Δ P_{aCO_2} at maximum CBF	P_{aO_2} at maximum CBF	Time to maximum CBF
% control	*mm Hg*	*mm Hg*	*min*
158	−4.3	39	8+*
147	−1.8	37	7
140	+0.3	46	7
135	−2.2	40	5
120	−7.4	50	5
120	−4.2	38	6
118	−4.9	45	7
108	−4.7	42	8+*
100	−1.9	52	7
98	−9.1	44	8+*
97	−3.7	50	5
97	−4.7	40	6

* Plateau in response of cerebral blood flow not achieved during observation period.

Multiple regression analysis revealed that time and the arterial CO_2 tension were statistically significant correlates of cerebral blood flow during this period of 10% O_2 inhalation, CBF = 51.8 + 1.9 × time (min) + 1.56 P_{aCO_2} − 0.19 P_{aO_2}.

Fig. 3 presents mean values for the four studies with the largest rises in cerebral blood flow (135% or more of the control). An increase in cerebral blood flow was evident after 2–3 min of 10% O_2 inhalation, and CBF

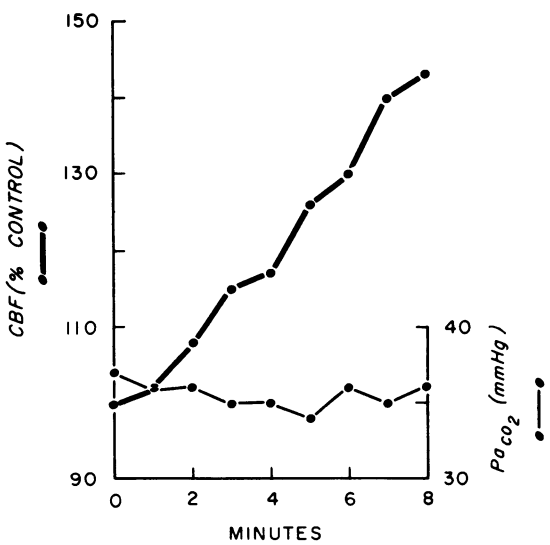

FIGURE 3 Mean cerebral blood flow and arterial CO_2 tensions during 8 min of 10% O_2 inhalation in four subjects with largest increases in blood flow.

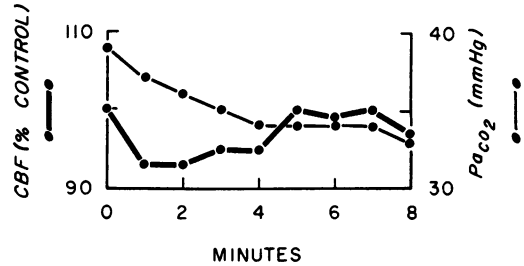

FIGURE 4 Mean cerebral blood flow and arterial CO_2 tensions during 8 min of 10% O_2 inhalation in eight subjects with maximal flow increases of 120% or less of control.

increased further thereafter. The mean decrease in arterial P_{CO_2} was 2.0 mm Hg. In the remaining eight subjects, the mean maximum cerebral blood flow was 7% above control, and the mean decrease in arterial P_{CO_2} at the time of peak cerebral blood flow was 5.1 mm Hg (Fig. 4). The differences between the arterial O_2 tensions for these groups at the times of peak cerebral blood flow (40 vs. 45 mm Hg) as well as their lowest arterial O_2 tensions (40 vs. 43 mm Hg) were not significant, but the difference between the mean decreases in CO_2 tensions was significant (Δ − 2.0 vs. Δ − 5.1 mm Hg, $P < 0.05$). Alterations in mean arterial blood pressure were insignificant in both groups.

Eucapnic hypoxemia. Tables II and IIA and Fig. 5 show that when eucapnia was maintained, significant increases in cerebral blood flow occurred after slight reductions in inspired O_2 concentration. During inhalation of 10.4% O_2 without added CO_2 the average arterial P_{O_2} was less than that during the preceding period when 9.5% O_2 with added CO_2 was inspired (37 vs. 49 mm Hg, respectively), and arterial P_{CO_2} declined. These simultaneous decreases in both arterial P_{O_2} and P_{CO_2}, were associated with rises in cerebral blood flow in six subjects and decreases in four subjects. Mean cerebral blood flow did not change materially despite more intense hypoxia in the presence of this degree of acute hypocapnia. After this intervention each subject hyperventilated while breathing 9.5% oxygen. This resulted in significant decrease in arterial P_{CO_2} and no material changes in P_{O_2} when both were compared with the preceding intervention (10.4% O_2 without added CO_2). Hyperventilation under these circumstances was associated with profound reductions in mean cerebral blood flow which became insignificantly different from control.

Fig. 6 shows the relationship of cerebral blood flow and arterial oxygen tension during eucapnic hypoxemia as derived from the regression equation, CBF = 274 − 38.6 $\log_e P_{aO_2}$. The mean curve and 95% confidence limits are shown. The CBF vs. P_aO_2 curves during graded hypoxemia (Fig. 2) and during eucapnic hypoxemia (Fig. 6) were significantly different from one

another, ($P < 0.05$), the latter showing a steeper response of the cerebral blood flow with decreasing arterial O_2 tension.

DISCUSSION

The important studies of Gibbs, Gibbs, Lennox, and Nims (13) demonstrated that during inhalation of 2 and 4% oxygen, additions of CO_2 to the inspired gas line increased the resulting cerebral blood flow and improved mental function as measured by the electroencephalogram, simple arithmetic tests, and time to unconsciousness. The potential importance of the level of the CO_2 tension in modulating the effects of any level of hypoxia was suggested in studies of cerebral blood flow in man at high altitude but studied only after prolonged exposure to high altitude (5). Acute exposure to hypoxia and the effects of correction of the associated hypocapnia were discussed but were not studied by these authors. Steady-state studies of cerebral blood flow at an even more severe level of hypoxia in the presence of normocarbia (9) appeared to show greater rises in flow with normocarbia than those previously reported when CO_2 tension was uncontrolled (2). The level of hypoxia was not precisely comparable to previous studies, and observations during uncontrolled respiration at the level of hypoxia studied were not made.

The present data showed that during reduction in inspired P_{O_2} without correction of hypocapnia, the level of the cerebral blood flow was largely dependent upon the response of the respiratory center as reflected by the arterial CO_2 tension level. Those subjects who had the least reduction in arterial CO_2 tension during inhalation of 10% O_2 exhibited the largest increases in cerebral blood flow (Fig. 3). Subjects with greater respiratory sensitivity showed little or no increase in cerebral blood flow despite reductions in arterial O_2 tension to 45–50 mm Hg (Fig. 4). Also, restoration of the slightly reduced arterial CO_2 tension to the normal range resulted in increases in cerebral blood flow and decreases in cerebrovascular resistance (Fig. 1). The data uncovered a sensitive cerebrovascular vasodilator response to very mild hypoxemia when eucapnia was maintained (compare Figs. 2 and 6).

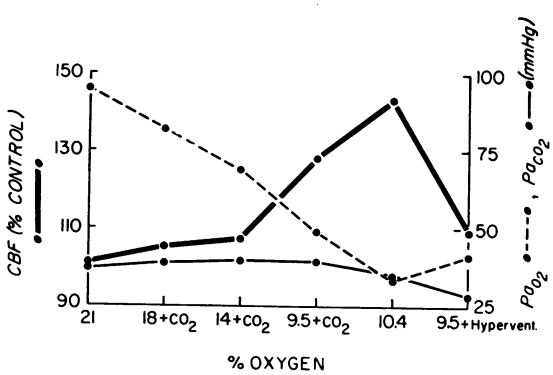

FIGURE 5 The mean effects of eucapnic and hypocapnic hypoxia and of hyperventilation on mean cerebral blood flow and arterial O_2 and CO_2 tensions in 10 subjects. See text for discussion.

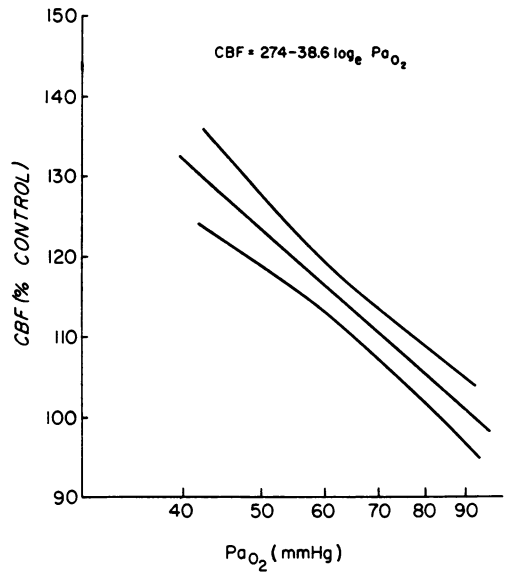

FIGURE 6 Mean slope and 95% confidence limits of cerebral blood flow response to eucapnic hypoxia. This slope was steeper ($P < 0.05$) than that derived during hypocapnic hypoxia (Fig. 2).

Thus, hypocapnia of mild to moderate degree may blunt or abolish the vasodilator stimulus of rather severe hypoxia. We are not aware of a previous demonstration of this phenomenon. Although hypoxia is commonly considered the most important stimulus to vasodilatation (5), it was apparent that, at the levels studied, moderate hypocapnia can overcome the vasodilatation of the hypoxic stimulus. Through the levels of hypoxia and arterial P_{CO_2} alteration studied, alterations in P_{CO_2} exert greater effects on the cerebral circulation than comparable alterations of arterial P_{O_2} (3, 4, 8, 9, 14). Additional evidence of more sensitivity to CO_2 than O_2 tension may be seen in the observed approximate mean time to peak flow response. During CO_2 inhalations the increase in cerebral blood flow achieved a plateau in about 2½ min (9), whereas the time to peak flow during 10% O_2 inhalation in the present series was approximately 6 min. These observations suggest that respiratory center sensitivity to any induced change in blood gas tension is crucial in determining the rapidity and extent of cerebrovascular response. In studies of the effects of simultaneously applied hypoxia and hypercapnia (10% O_2 + 5% CO_2 inhalation) (4), the respiratory response was marked with rapid changes in

blood gases, and the maximal level of cerebral blood flow occurred sooner than when either stimulus was applied separately.

While not exactly comparable because of the conditions of each study, the present data may be considered to complement certain aspects of the altitude studies of Severinghaus, Chiodi, Eger, Brandstater, and Hornbein (5). Their attempted prediction of the early response to hypoxia may now be modified and amplified with the data provided herein. In the main, their predictions underestimated the likely degree of hyperventilation present and its power to blunt the early vasodilator response to hypoxia.

The mechanism of the vascular changes in acute studies such as those described herein must be mediated through the effects of the acute changes in gas tensions on the respiratory center and the cerebral vasculature rather than by alterations in slowly diffusing substances as has been shown during acclimatization to the chronic hypocapnia and hypoxia at high altitude (5). Whether arterial or cerebral venous gas tensions are best correlated with changes in the cerebrovascular resistance has been the subject of conflicting data (9, 10, 15), but most investigators agree that the sites of ultimate regulatory importance are likely to be found in or near the cerebral vascular cells themselves (5). Any explanation of the effects of acute hypoxia must consider the counterbalancing effects on cerebral blood flow secondary to the associated rapid reductions of arterial P_{CO_2} as well as other factors which might be pertinent to specific clinical situations.

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