SAM-TDR-62-70

EFFECTS OF CHANGES IN BLOOD P_{CO_2} ON BRAIN OXYGENATION AT 147 MM. HG AMBIENT PRESSURE (39,000 FEET)

TECHNICAL DOCUMENTARY REPORT NO. SAM-TDR-62-70

June 1962

School of Aerospace Medicine
Aerospace Medical Division (AFSC)
United States Air Force
Brooks Air Force Base, Texas

Project No. 7756, Task No. 59692

(Prepared under contract No. AF 41 (657)-16 by the University of Pennsylvania Schools of Medicine, Philadelphia, Pennsylvania)

School of Aerospace Medicine, Brooks AF Base, Tex. SAM-TDR-62-70. EFFECTS OF CHANGES IN BLOOD P_{CO_2} ON BRAIN OXYGENATION AT 147 MM. HG AMBIENT PRESSURE (39,000 FEET). June 62, 17 pp. incl. illus.

Hyperventilation during the breathing of 100 percent oxygen elevates the P_{O_2} of alveolar gas by the same amount that it lowers its P_{CO_2}. Since the development of arterial hypocapnia causes cerebral vasoconstriction, brain oxygenation is drastically decreased even while arterial oxygenation is improved by the hyperventilation. Administration of 30 percent CO_2 with oxygen at an ambient pressure

1. Physiology
2. Hyperventilation
3. Cerebral circulation

I. AFSC Project 7756, Task 59692
II. Contract AF 41(657)-16
III. E. C. Pierce, Jr., C. J. Lambertsen, M. J. Strong, S. C. Alexander, D. Steele
IV. In ASTIA collection

School of Aerospace Medicine, Brooks AF Base, Tex. SAM-TDR-62-70. EFFECTS OF CHANGES IN BLOOD P_{CO_2} ON BRAIN OXYGENATION AT 147 MM. HG AMBIENT PRESSURE (39,000 FEET). June 62, 17 pp. incl. illus.

Hyperventilation during the breathing of 100 percent oxygen elevates the P_{O_2} of alveolar gas by the same amount that it lowers its P_{CO_2}. Since the development of arterial hypocapnia causes cerebral vasoconstriction, brain oxygenation is drastically decreased even while arterial oxygenation is improved by the hyperventilation. Administration of 30 percent CO_2 with oxygen at an ambient pressure

1. Physiology
2. Hyperventilation
3. Cerebral circulation

I. AFSC Project 7756, Task 59692
II. Contract AF 41(657)-16
III. E. C. Pierce, Jr., C. J. Lambertsen, M. J. Strong, S. C. Alexander, D. Steele
IV. In ASTIA collection

School of Aerospace Medicine, Brooks AF Base, Tex. SAM-TDR-62-70. EFFECTS OF CHANGES IN BLOOD P_{CO_2} ON BRAIN OXYGENATION AT 147 MM. HG AMBIENT PRESSURE (39,000 FEET). June 62, 17 pp. incl. illus.

Hyperventilation during the breathing of 100 percent oxygen elevates the P_{O_2} of alveolar gas by the same amount that it lowers its P_{CO_2}. Since the development of arterial hypocapnia causes cerebral vasoconstriction, brain oxygenation is drastically decreased even while arterial oxygenation is improved by the hyperventilation. Administration of 30 percent CO_2 with oxygen at an ambient pressure

1. Physiology
2. Hyperventilation
3. Cerebral circulation

I. AFSC Project 7756, Task 59692
II. Contract AF 41(657)-16
III. E. C. Pierce, Jr., C. J. Lambertsen, M. J. Strong, S. C. Alexander, D. Steele
IV. In ASTIA collection

School of Aerospace Medicine, Brooks AF Base, Tex. SAM-TDR-62-70. EFFECTS OF CHANGES IN BLOOD P_{CO_2} ON BRAIN OXYGENATION AT 147 MM. HG AMBIENT PRESSURE (39,000 FEET). June 62, 17 pp. incl. illus.

Hyperventiiation during the breathing of 100 percent oxygen elevates the P_{O_2} of alveolar gas by the same amount that it lowers its P_{CO_2}. Since the development of arterial hypocapnia causes cerebral vasoconstriction, brain oxygenation is drastically decreased even while arterial oxygenation is improved by the hyperventilation. Administration of 30 percent CO_2 with oxygen at an ambient pressure

1. Physiology
2. Hyperventilation
3. Cerebral circulation

I. AFSC Project 7756, Task 59692
II. Contract AF 41(657)-16
III. E. C. Pierce, Jr., C. J. Lambertsen, M. J. Strong, S. C. Alexander, D. Steele
IV. In ASTIA collection

equivalent to that at 39,000 feet altitude prevented alkalemia and, in spite of hyperventilation, restored central oxygenation to a level at least equivalent to that found when pure oxygen was breathed at rest at the same altitude. The respiratory minute volume during administration of CO_2 with O_2 was greater than when O_2 alone was breathed at the reduced ambient pressure. Since neither arterial P_{O_2} nor central P_{CO_2} values differed in these two experimental situations, the respiratory stimulation may represent the quantitative demonstration in man of a respiratory effect of carbon dioxide which is mediated solely by the chemoreceptors exposed to arterial blood and which acts in the absence of a change in direct central stimulation by CO_2.

equivalent to that at 39,000 feet altitude prevented alkalemia and, in spite of hyperventilation, restored central oxygenation to a level at least equivalent to that found when pure oxygen was breathed at rest at the same altitude. The respiratory minute volume during administration of CO_2 with O_2 was greater than when O_2 alone was breathed at the reduced ambient pressure. Since neither arterial P_{O_2} nor central P_{CO_2} values differed in these two experimental situations, the respiratory stimulation may represent the quantitative demonstration in man of a respiratory effect of carbon dioxide which is mediated solely by the chemoreceptors exposed to arterial blood and which acts in the absence of a change in direct central stimulation by CO_2.

equivalent to that at 39,000 feet altitude prevented alkalemia and, in spite of hyperventilation, restored central oxygenation to a level at least equivalent to that found when pure oxygen was breathed at rest at the same altitude. The respiratory minute volume during administration of CO_2 with O_2 was greater than when O_2 alone was breathed at the reduced ambient pressure. Since neither arterial P_{O_2} nor central P_{CO_2} values differed in these two experimental situations, the respiratory stimulation may represent the quantitative demonstration in man of a respiratory effect of carbon dioxide which is mediated solely by the chemoreceptors exposed to arterial blood and which acts in the absence of a change in direct central stimulation by CO_2.

equivalent to that at 39,000 feet altitude prevented alkalemia and, in spite of hyperventilation, restored central oxygenation to a level at least equivalent to that found when pure oxygen was breathed at rest at the same altitude. The respiratory minute volume during administration of CO_2 with O_2 was greater than when O_2 alone was breathed at the reduced ambient pressure. Since neither arterial P_{O_2} nor central P_{CO_2} values differed in these two experimental situations, the respiratory stimulation may represent the quantitative demonstration in man of a respiratory effect of carbon dioxide which is mediated solely by the chemoreceptors exposed to arterial blood and which acts in the absence of a change in direct central stimulation by CO_2.

FOREWORD

This report was prepared by the following personnel in the Laboratories of Pharmacology at the University of Pennsylvania, Schools of Medicine, Philadelphia:

E. C. PIERCE, Jr.
C. J. LAMBERTSEN
M. J. STRONG
S. C. ALEXANDER
D. STEELE

The authors acknowledge the excellent technical assistance provided by B. Hanley and E. Jones.

ABSTRACT

Hyperventilation during the breathing of 100 percent oxygen elevates the P_{O_2} of alveolar gas by the same amount that it lowers its P_{CO_2}. Since the development of arterial hypocapnia causes cerebral vasoconstriction, brain oxygenation is drastically decreased even while arterial oxygenation is improved by the hyperventilation. Administration of 30 percent CO_2 with oxygen at an ambient pressure equivalent to that at 39,000 feet altitude prevented alkalemia and, in spite of hyperventilation, restored central oxygenation to a level at least equivalent to that found when pure oxygen was breathed at rest at the same altitude. The respiratory minute volume during administration of CO_2 with O_2 was greater than when O_2 alone was breathed at the reduced ambient pressure.. Since neither arterial P_{O_2} nor central P_{CO_2} values differed in these two experimental situations, the respiratory stimulation may represent the quantitative demonstration in man of a respiratory effect of carbon dioxide which is mediated solely by the chemoreceptors exposed to arterial blood and which acts in the absence of a change in direct central stimulation by CO_2.

This technical documentary report has been reviewed and is approved.

Robert B. Payne

ROBERT B. PAYNE
Colonel, USAF, MSC
Chief, Operations Division

EFFECTS OF CHANGES IN BLOOD P_{CO_2} ON BRAIN OXYGENATION AT 147 MM. HG AMBIENT PRESSURE (39,000 FEET)

1. INTRODUCTION

Forty years ago, early in the history of aviation, the addition of carbon dioxide to inspired oxygen was suggested to improve the tolerance of aviators to altitude (1). Whether an increase in inspired P_{CO_2} at altitude does in fact offer physiologic advantages and improved performance has been extensively studied, especially during World War II. There is no doubt that, during the breathing of air at moderately high altitudes (2-5) and when inhaling low-oxygen mixtures at 1 atmosphere (6, 7, 8), the addition of carbon dioxide to the inspired gas reduces anoxia and improves altitude tolerance. This improvement is largely related to the increase in alveolar and arterial oxygen tension associated with CO_2-induced respiratory stimulation (2-8) although greater unloading of oxygen (7, 8) has been offered as an additional mechanism.

The situation is less clearly defined when pure oxygen is breathed at altitude (5, 9, 10, 11). An increase in alveolar P_{CO_2} during oxygen breathing at any ambient pressure must result in a displacement of oxygen and a lowering of alveolar and arterial P_{O_2}. This effect has been demonstrated and has formed the basis for the view that induced hypercapnia during oxygen breathing at high altitude will lead to exaggeration of anoxia.

In the present study emphasis has been given to the possibility that administration of carbon dioxide with oxygen at altitude may lead to (a) improvement in oxygenation of the brain in spite of exaggeration of arterial anoxemia, and (b) prevention of anoxia of the central nervous system resulting from reduction of brain blood flow by hyperventilation hypocapnia (12). The first possibility, suggested by the now well-established cerebral vasodilator effect of hypercapnia, has been studied previously (10). The second, which may be related to the development of unconsciousness in pilots of high-performance aircraft, has also been studied at 1 atmosphere (13), but has not yet been experimentally evaluated in man at reduced ambient pressure.

Received for publication on 19 February 1962.

2. METHODS

This study was conducted in a large decompression chamber. Control measurements were made at the prevailing barometric pressure (table I) and experimental measurements at an ambient pressure of 147 mm. Hg. This pressure (equivalent to an altitude of about 39,000 feet) was selected to provide an alveolar P_{O_2} lower than normal but not so low as to interfere with the conduct of the experiments.

Subjects

The ages, body measurements, and rectal temperatures of the five normal men studied are shown in table I. In a separate series of pilot experiments without vascular punctures, the subjects were familiarized with carbon dioxide inhalation, active hyperventilation, the respiratory apparatus, and the sensations of changes in ambient pressure. On the days of actual study, the subjects reported to the chamber at 8 a.m. after a light carbohydrate breakfast, and lay supine on a padded hospital litter throughout the experiment. After receiving vascular punctures, the subjects were allowed to rest for at least thirty minutes before the first measuring period began.

TABLE I

Experimental conditions, ages, and body measurements of subjects

Experiment	Subject	Prevailing barometric pressure (mm. Hg)	Age	Height (in.)	Weight (lb.)	BSA ($m.^2$)	Body temperature (°C.)			
							Phase			
							I	II	III	IV
1	JK	765.6	21	72	175	2.02	37.2	37.2	37.2	37.2
2	SH	764.4	22	73	172	2.02	37.0	37.0	37.0	37.0
3	BC	761.1	21	70	145	1.82	37.1	37.0	37.0	37.0
4	JC	765.5	21	74	212	2.29	36.5	36.5	36.5	36.5
5	DZ	762.0	21	69	170	1.92	37.0	37.0	37.0	37.0
Mean		763.72	21.2	71.6	174.8	2.01	36.96	36.94	36.94	36.94

Phase I = Natural ventilation, air breathing, sea level (prevailing barometric pressure).
Phase II = Natural ventilation, 100% O_2 breathing, 39,000 ft. (147 mm. Hg).
Phase III = Active hyperventilation, 100% O_2 breathing, 39,000 ft. (147 mm. Hg).
Phase IV = Natural ventilation, 30% CO_2 in 70% O_2 breathing, 39,000 ft. (147 mm. Hg).

General procedure

Each of the five experiments was divided into four phases with conditions as described in table I. Phase I consisted of the conventional control, with the subjects breathing air at atmospheric pressure. After the control measurements of phase I and before "ascent" to simulated altitude, the subject and the investigators denitrogenated by breathing 100 percent oxygen for one hour to lessen the likelihood of subsequent dysbarism. The ascent to 39,000 feet proceeded at a rate of approximately 3,000 feet per minute; at this simulated altitude, the measurements for the remaining phases were performed. In phase II the subjects breathed 100 percent oxygen at rest. During phase III they actively hyperventilated while still breathing 100 percent oxygen. In phase IV the subjects inhaled 30 percent carbon dioxide in oxygen at rest. The order of phases III and IV was reversed for experiments 2 and 3, making the sequence I, II, IV, and III. Measurements were not begun until at least six minutes after the administration of a new gas and until the alveolar P_{CO_2} was stable except in phase III when the measuring period began approximately three minutes after initiation of active hyperventilation, at which time the alveolar P_{CO_2} was below 24 mm. Hg and nearly stable.

Maintenance of environmental conditions

An absolute ambient pressure of 147 mm. Hg was obtained in each experiment and was measured directly with a mercury manometer. Variations in chamber pressure were kept to less than ± 0.5 mm. Hg by the use of an auxiliary water manometer, activated by the mercury manometer at 162 mm. Hg (37,000 feet). The ability of this system to maintain a stable altitude was tested by using an infrared CO_2 analyzer, containing a fixed concentration of carbon dioxide in the cuvet, as a pressure gage. Chamber temperature was maintained at approximately 21° C. ± 1° C. by the chamber thermostatic control system.

Gas administraton and respiratory measurements

The subjects inhaled the various gases through a respiratory system consisting of mouthpiece, nose clip, low dead-space breathing valves (14), 2-inch internal diameter corrugated tubing, and a sensitive demand valve[1] supplied at 50 p.s.i. from cylinders of compressed, water-pumped gas. Expired gases passed through 2-inch internal diameter, smooth-walled, rubber tubing to a wet-test, rotary gasometer with a rated capacity of 141.5 liters

[1]Low pressure demand regulator, CH-47878, from the Mine Safety Appliances Co., Pittsburgh, Pa.

per minute. Resistance to the maximal inhalations and exhalations did not exceed 1.0 cm. H_2O.

End-tidal gas was automatically sampled (15), analyzed with a calibrated Beckman Model LB-1 infrared CO_2 analyzer, and the percent of carbon dioxide in the gas was recorded on an Esterline-Angus recorder. At reduced barometric pressure, calibration was complicated by pressure effects from slight variations in flow rates of the calibration gas. This difficulty was eliminated by withdrawing the calibration gas from an anesthesia bag, the subject activating the end-tidal gas sampler to provide the same flow rate for calibration as during actual end-tidal gas sampling.

In each of the experimental phases simultaneous measurements of total respirations, total expired volume, and end-tidal P_{CO_2} were made over four-minute periods.

Blood sampling and analysis

Blood sampling needles (19-gage) were inserted into a femoral artery and the right internal jugular bulb after local infiltration of each site with 2 to 3 ml. of 1 or 2 percent procaine solution and were connected with a heparin-filled sampling manifold (16). Simultaneous arterial and cerebral venous blood samples were obtained in heparinized syringes at a uniform rate over the middle two minutes of the four-minute period of respiratory measurement. During the last minute of the period a separate sample of arterial blood was drawn for determination of O_2 capacity. The blood samples were immediately placed in crushed ice. In sampling, the previously described (17) flushing of syringe dead space was employed to minimize error because of dilution of blood by heparin solution. It is also noteworthy that, at the low ambient pressure, the sampling of internal jugular venous blood was extremely difficult because of the tendency of water vapor to form and fill the syringe as the plunger was withdrawn. This large "gas phase" disappeared spontaneously as sampling was completed.

Blood pH measurements were determined anaerobically in duplicate at sea level within one hour, using a McInnes-Belcher glass electrode and an Electronics Industries Ltd. electrometer. All components of the glass electrode assembly including the calomel half-cell, KCl reservoir, and silver-silver chloride junction were enclosed in an electrically shielded, temperature controlled, Lucite chamber maintained at a temperature averaging 37.19 ± .025° C. The output of the electrometer was recorded on a Texas Instrument Company Rectiriter such that resolution was ± 0.001 pH units. The iced blood samples were rewarmed in a 37° C. water bath for approximately two minutes before pH measurement; the temperature of solutions in the glass electrode was measured at the time of each determination by means of a thermistor bridge with the thermistor located within the glass electrode. The electrometer was calibrated before and after each pH measurement by means of standard buffers. Blood pH was corrected to the measured body temperature using the temperature coefficient 0.0147 per degree centigrade (18), for glycolysis, and for effects of whole blood on the glass electrode (19). In the 40 paired pH determinations obtained in the present study the mean difference between duplicate samples was 0.004 ± 0.0006 unit (standard error of difference).

Determination of blood gas composition was performed manometrically (20) in duplicate on 1 ml. aliquots within three hours of sampling. Percentage oxygen saturation of hemoglobin was determined from the manometrically measured values after the usual correction for physically dissolved oxygen and for hemoconcentration in the determination of oxygen capacity (21, 22, 23). Blood oxygen tension was estimated from values for percentage hemoglobin saturation, pH, and body temperature, using the nomogram of Severinghaus (24). Plasma CO_2 content was estimated from whole blood CO_2 content, pH, and O_2 capacity by means of the nomogram of Van Slyke and Sendroy (25). CO_2 tension was calculated from plasma CO_2 content and whole blood pH

TABLE II

Mean and individual values obtained in the four

Subject	Respiration			Blood compositi							
				Arterial							Mean b capill
	Respiratory min. vol. (liter/min.)	Tidal volume (liter)	Respiratory rate per min.	P_{CO_2} (mm. Hg)	pH units	CO_2 content (vol. %)	P_{O_2} (mm. Hg)	Hb saturation (%)	O_2 content (vol. %)	O_2 capillary (vol. %)	Po (mm.
Phase I — Natural respiration, breathing air at 1.0 a											
JK	6.32	0.645	9.8	41.3	7.350	44.3	95.4	96.2	20.6	21.1	51.
SH	6.06	0.438	13.8	43.0	7.348	47.2	116.6	97.8	17.9	17.9	53.
BC	4.81	0.474	10.1	45.4	7.357	50.1	90.9	95.8	18.7	19.2	52.
JC	5.26	0.502	10.5	43.6	7.373	51.1	109.0	97.7	17.5	17.6	53.
DZ	5.70	0.400	14.3	44.4	7.355	48.9	101.9	96.9	19.1	19.4	56.
Mean	5.63	0.492	11.7	43.5	7.357	48.3	102.8	96.9	18.8	19.0	53.
Phase II — Natural respiration, breathing O_2 at 147											
JK	6.26	0.564	11.1	40.1	7.346	42.4	56.5	85.7	19.3	22.3 *	40.
SH	7.32	0.541	13.5	40.8	7.403	50.3	52.3	85.4	16.0	18.5	37.
BC	4.90	0.436	11.3	41.0	7.398	49.4	54.4	86.5	17.5	20.0	38.
JC	7.63	0.709	10.8	39.9	7.409	50.4	54.9	87.8	16.1	18.1	38.
DZ	6.55	0.430	15.3	39.9	7.394	47.3	62.6	90.1	18.5	20.3	42.
Mean	6.53	0.536	12.4	40.3	7.390	48.0	56.1	87.1	17.5	19.8	39.
Phase III — Voluntary hyperventilation, breathing O											
JK	33.95	1.101	30.8	22.1	7.503	32.0	84.3	96.5	22.1	22.7	37.
SH	29.79	0.896	33.2	26.8	7.532	43.1	85.5	96.9	18.7	19.1	37.
BC	20.93	0.611	34.3	24.6	7.547	40.6	84.4	97.0	19.8	20.2	36.
JC	60.63	1.779	34.1	17.7	7.661	38.1	67.2	96.3	18.4	18.9	30.
DZ	53.01	1.441	36.8	17.5	7.637	34.7	83.2	97.6	20.4	20.6	34.
Mean	39.66	1.166	33.8	21.7	7.576	37.7	80.9	96.9	19.9	20.3	35.
Phase IV — Natural respiration, breathing CO_2 in O_2											
JK	12.29	0.672	18.3	40.7	7.345	42.7	56.5	85.7	19.4	22.4	40.
SH	19.65	1.188	16.5	45.5	7.368	52.1	53.5	85.0	16.1	18.7	40.
BC	13.30	0.709	18.8	44.4	7.371	50.6	54.2	85.4	17.2	19.9	40.
JC	16.80	0.975	17.3	40.8	7.403	50.6	54.4	87.2	16.5	18.7	40.
DZ	16.65	0.812	20.5	43.8	7.351	47.3	61.3	88.5	18.6	20.8	45.
Mean	15.74	0.871	18.3	43.0	7.368	48.7	56.0	86.4	17.6	20.1	41.

Values for mean brain capillary Po_2 were calculated as described in text. Brain blood flow index represents the ratio of the A-V O_2 difference observed

TABLE II

Individual values obtained in the four indicated study conditions

Blood composition												Brain blood flow index
			Mean brain capillary	Venous						A-V differences		
Hb saturation (%)	O_2 content (vol. %)	O_2 capillary (vol. %)	P_{O_2} (mm. Hg)	P_{CO_2} (mm. Hg)	pH units	CO_2 content (vol. %)	P_{O_2} (mm. Hg)	Hb saturation (%)	O_2 content (vol. %)	P_{O_2} (mm. Hg)	O_2 content (vol. %)	
Natural respiration, breathing air at 1.0 atm.												
96.2	20.6	21.1	51.8	55.6	7.280	51.9	36.4	61.1	13.0	59.0	7.6	1.00
97.8	17.9	17.9	53.5	53.6	7.293	53.0	36.1	62.0	11.2	80.5	6.7	1.00
95.8	18.7	19.2	52.5	56.3	7.309	56.8	36.9	65.1	12.6	54.0	6.1	1.00
97.7	17.5	17.6	53.8	52.4	7.329	56.5	35.5	64.8	11.5	73.5	6.0	1.00
96.9	19.1	19.4	56.9	54.0	7.313	54.7	40.7	70.1	13.7	61.2	5.4	1.00
96.9	18.8	19.0	53.7	54.4	7.305	54.6	37.1	64.6	12.4	65.6	6.4	1.00
Natural respiration, breathing O_2 at 147 mm. Hg ambient pressure												
85.7	19.3	22.3	40.2	51.5	7.300	49.9	30.6	52.0	11.7	25.9	7.6	1.00
85.4	16.0	18.5	37.6	49.8	7.356	56.1	28.4	51.4	9.6	23.9	6.4	1.05
86.5	17.5	20.0	38.6	51.2	7.348	56.3	28.7	52.0	10.5	25.7	7.0	0.87
87.8	16.1	18.1	38.6	48.7	7.364	56.6	27.9	51.9	9.5	27.0	6.6	0.91
90.1	18.5	20.3	42.4	49.5	7.344	53.6	31.6	57.1	11.7	31.0	6.8	0.79
87.1	17.5	19.8	39.5	50.1	7.342	54.5	29.4	52.9	10.6	26.7	6.9	0.92
Voluntary hyperventilation, breathing O_2 at 147 mm. Hg ambient pressure												
96.5	22.1	22.7	37.7	43.5	7.360	48.0	21.8	37.0	8.5	62.5	13.6	0.56
96.9	18.7	19.1	37.1	42.1	7.418	54.5	21.6	39.8	7.7	63.9	11.0	0.61
97.0	19.8	20.2	36.0	41.1	7.428	53.6	20.8	38.6	7.9	63.6	11.9	0.51
96.3	18.4	18.9	30.5	34.3	7.494	52.6	17.3	33.9	6.5	49.9	11.9	0.50
97.6	20.4	20.6	34.1	35.4	7.468	50.1	20.4	39.3	8.2	62.8	12.2	0.44
96.9	19.9	20.3	35.1	39.3	7.434	51.8	20.4	37.7	7.8	60.5	12.1	0.52
Natural respiration, breathing CO_2 in O_2 at 147 mm. Hg ambient pressure												
85.7	19.4	22.4	40.8	47.9	7.314	47.7	31.0	54.0	12.2	25.5	7.2	1.06
85.0	16.1	18.7	40.5	52.6	7.333	56.5	32.2	57.8	10.9	21.3	5.2	1.29
85.4	17.2	19.9	40.9	54.7	7.319	56.4	32.4	57.8	11.6	21.8	5.6	1.09
87.2	16.5	18.7	40.3	48.6	7.358	55.3	30.4	57.2	10.8	24.0	5.7	1.05
88.5	18.6	20.8	45.0	50.3	7.319	51.3	35.0	62.5	13.1	26.3	5.5	0.98
86.4	17.6	20.1	41.5	50.8	7.329	53.4	32.2	57.9	11.7	23.8	5.8	1.09

the ratio of the A-V O_2 difference observed during natural respiration of air at 1.0 atmosphere to the A-V O_2 difference observed during a study condition.

by means of the Henderson-Hasselbalch equation, using the solubility factor and pK′ of CO_2 in plasma (19,26).

Calculation of mean brain capillary P_{O_2} and cerebral blood flow index

Mean tissue capillary P_{O_2} represents a mathematical, nonmeasurable value of blood oxygen tension compatible with the rate of oxygen uptake by the tissue, the tissue diffusion coefficient for oxygen, and the mean tissue oxygen tension (27-30). For the brain it can be considered the average P_{O_2} in the average brain capillary.

Mean capillary P_{O_2} has been estimated by several different procedures. The graphic integration method for determining mean capillary P_{O_2} initially devised by Bohr was concerned with the pulmonary capillary (27). Barcroft's algebraic expression for the peripheral tissues:

$$\text{Mean capillary } P_{O_2} = \text{Venous } P_{O_2} + \frac{\text{Arterial } P_{O_2} - \text{Venous } P_{O_2}}{3}$$

provides a close approximation only when arterial P_{O_2} is low (28). Houston and Riley calculated the mean peripheral tissue capillary P_{O_2} more reliably by using a modification of the Bohr graphic integration method (29).

In the present study, mean brain capillary P_{O_2} was calculated by an integration procedure which used the experimentally determined values for hemoglobin oxygen capacity and for arterial and cerebral venous oxygen content, oxygen tension, and pH. In carrying out this procedure, it was assumed that the decreases in both blood oxygen content and pH were linear as blood was changed from the arterial to the venous state in the brain. Considering the alteration in pH across the average brain capillary to be linear is very likely in error (31); however, owing to the very small magnitude of the pH change from artery to vein, this assumption introduces no gross error in estimating mean brain capillary P_{O_2}. While adequate for present purposes, assuming a linear rate of fall in blood oxygen content across the brain capillary will eventually be justified only by showing that (a) mean linear velocity of brain capillary blood flow is uniform and (b) the rate of oxygen consumption of cells supplied by successive segments of each brain capillary is either constant or it varies in a random manner.

A useful indication of alterations in the rate of cerebral blood flow is provided by the *cerebral blood flow index*, i.e., the ratio of the arteriovenous O_2 difference breathing air at 1.0 atmosphere to the arteriovenous O_2 difference measured during an experimental situation (32).

A change in the cerebral blood flow index can be produced by separate or simultaneous changes in brain blood flow and oxygen consumption. However, in situations where a detectable alteration in the rate of cerebral oxygen consumption does not occur, this index provides an accurate, quantitative measure of percentage change in brain blood flow.

3. RESULTS

Individual data obtained in the four phases of this study are shown in table II. The mean difference, standard error of mean difference, and probabilities that the changes are significant, with statistical evaluation, are shown in table III. The data of phase I, obtained during air breathing at 1.0 atmosphere, represent normal values at rest in the subjects studied. For convenience, the results will be presented, first, by comparing the effects on brain oxygenation of changes in blood values among the various phases, and then by noting the effects on respiration. All changes cited in the text are statistically significant unless otherwise indicated.

Changes in brain oxygenation

Figures 1 and 2 illustrate the alterations in blood oxygenation associated with the alterations effected in P_{CO_2}. Figure 3 shows the corresponding changes in the brain blood flow

TABLE III

Changes observed between the various experimental conditions

	Phases					
	I-II Mean Δ ± S.E.	I-III Mean Δ ± S.E.	I-IV Mean Δ ± S.E.	II-III Mean Δ ± S.E.	II-IV Mean Δ ± S.E.	III-IV Mean Δ ± S.E.
Respiration						
Respiration min. vol. (liters/min.)	+ 0.90 ±0.44†	+34.03 ±7.41*	+10.11 ±1.32	+33.13 ±7.10	+ 9.21 ±1.03	−23.92 ±7.11*
Tidal volume (liter)	+ 0.044 ±0.051†	+ 0.674 ±0.210*	+ 0.379 ±0.121*	+ 0.630 ±0.178*	+ 0.335 ±0.089*	− 0.294 ±0.211†
Respiration rate (per min.)	+ 0.7 ±0.3†	+22.1 ±0.9	+ 6.6 ±1.1	+21.4 ±0.8	+ 5.9 ±0.8	−15.6 ±0.8
Arterial blood						
P_{CO_2} (mm. Hg)	− 3.2 ±0.7	−21.8 ±2.0	− 0.5 ±0.9†	−18.6 ±1.6	+ 2.7 ±0.8*	+21.3 ±1.5
pH	+ 0.033 ±0.010*	+ 0.219 ±0.028	+ 0.011 ±0.007†	+ 0.186 ±0.026	− 0.022 ±0.008†	− 0.208 ±0.027
P_{O_2} (mm. Hg)	−46.6 ±5.4	−21.8 ±6.5*	−46.8 ±5.1	+24.8 ±3.7	− 0.2 ±0.4†	−24.9 ±3.5
Hb saturation %	− 9.8 ±0.9	0 ±0.5†	−10.5 ±0.7	+ 9.8 ±0.8	− 0.7 ±0.3†	−10.5 ±0.6
Mean brain capillary blood						
P_{O_2} (mm. Hg)	−14.2 ±0.7	−18.6 ±1.9	−12.2 ±0.5	− 4.4 ± 1.6†	+ 1.8 ±0.6*	+ 6.4 ±1.6*
Internal jugular venous blood						
P_{CO_2} (mm. Hg)	−4.2 ±0.3	−15.1 ±1.5	− 3.6 ±1.2*	−10.9 ±1.5	+ 0.7 ±1.3†	+11.5 ±1.9
pH	+ 0.038 ±0.007	+ 0.129 ±0.015	+ 0.024 ±0.007*	+ 0.091 ±0.015	− 0.014 ±0.008†	− 0.105 ±0.018
P_{O_2} (mm. Hg)	− 7.7 ±0.5	−16.7 ±1.1	− 4.9 ±0.3	− 9.1 ±0.8	+ 2.8 ±0.6*	+11.8 ±0.9
Hb saturation %	−11.7 ±0.8	−26.9 ±1.8	− 6.8 ±0.7	−15.2 ±1.2	+ 5.0 ±0.8	+20.1 ±1.3
Arteriovenous difference						
P_{O_2} (mm. Hg)	−38.9 ±5.4	− 5.1 ±6.4†	−41.9 ±5.3	+33.8 ±3.1	− 2.9 ±0.7*	−36.8 ±3.0
O_2 content (vol. %)	+ 0.5 ±0.3†	+ 5.8 ±0.4	− 0.5 ±0.3†	+ 5.2 ±0.2	− 1.0 ±0.2	− 6.3 ±0.2
Cerebral blood flow index	− 0.08 ±0.05†	− 0.47 ±0.03	+ 0.09 ±0.05†	− 0.40 ±0.02	+ 0.17 ±0.03	+ 0.57 ±0.03

Phase I = Natural respiration, breathing air at 1.0 atmosphere.
Phase II = Natural respiration, breathing O_2 at 147 mm. Hg ambient pressure.
Phase III = Voluntary hyperventilation, breathing O_2 at 147 mm. Hg ambient pressure.
Phase IV = Natural respiration, breathing CO_2 in O_2 at 147 mm. Hg ambient pressure.

Probability was determined by use of Fisher's t-test (Snedecor, G. W. Statistical methods, 4th ed. Ames, Iowa: Iowa State College Press, 1937). $P < .01$ except that values marked by dagger are not significant and for those marked by asterisk, $P < .05$ and $> .01$.

index. The findings will be described by comparing the average values obtained in the different experimental phases.

Phase I (natural respiration, breathing air at 1.0 atmosphere) versus phase II (natural respiration, breathing O_2 at 147 mm. Hg ambient pressure). Ascent to 39,000 feet simulated altitude,[2] breathing 100 percent O_2 without positive pressure, produced relative hypocapnia and moderate anoxia. The arterial P_{CO_2} fell from 43.5 to 40.3 mm. Hg. Arterial P_{O_2} decreased from 103 to 56 mm. Hg, the arterial hemoglobin saturation from 96.9 to 87.1 percent. Mean brain capillary P_{O_2} fell 14 mm. Hg (from 54 to 40 mm. Hg); the cerebral venous P_{O_2} and hemoglobin saturation fell from 37 to 29 mm. Hg and from 64.6 to 52.9 percent, respectively. The small increase in the arteriovenous O_2 content difference and consequent lowering of cerebral blood flow index were not statistically significant.

Phase II (natural ventilation, breathing O_2 at 147 mm. Hg ambient pressure) versus phase III (voluntary hyperventilation, breathing O_2 at 147 mm. Hg ambient pressure). Active hyperventilation caused a fall in arterial P_{CO_2} from 40.3 to 21.7 mm. Hg. There was nearly an equal rise in arterial P_{O_2} (from 56 to 81 mm. Hg). Because of the effect on hemoglobin of the marked rise in arterial pH (from 7.390 to 7.576), the arterial hemoglobin saturation in phase III returned to its sea level value of 96.9 percent. Mean brain capillary P_{O_2} fell from 39.5 to 35.1 mm. Hg ($0.1 > P > .05$) and internal jugular venous P_{O_2} and hemoglobin saturation declined markedly (from 29 to 20 mm. Hg and from 52.9 to 37.7 percent, respectively). The decrease in mean brain capillary and cerebral venous oxygenation, which occurred concomitantly with improvement in arterial oxygenation, was caused by the removal of a larger amount of oxygen from each milliliter of blood passing through the brain capillaries. This is reflected by the nearly twofold increase in arteriovenous oxygen difference (from 6.8 to 12.0 vol. percent). Since the levels of anoxemia produced in phase III have been shown not to decrease brain oxygen consumption (33, 34), and since little change in brain oxygen consumption appears to occur during hyperventilation (35, 36, 37), the observed change in A-V O_2 content difference was probably caused almost entirely by a reduction in brain blood flow. The change in cerebral blood flow index from 0.91 to 0.51 suggests that brain blood flow was reduced to approximately one-half its normal value.

Phase III (voluntary hyperventilation, breathing O_2 at 147 mm. Hg ambient pressure) versus phase IV (natural ventilation, breathing CO_2 in O_2 at 147 mm. Hg ambient pressure). When voluntary hyperventilation was terminated and the subjects were given 30 percent CO_2 in O_2 to breathe, arterial P_{CO_2} returned from 21.7 to 43.0 mm. Hg, approximately the same value as seen while breathing air at 1.0 atmosphere. Arterial P_{O_2} fell 25 mm. Hg (from 81 to 56 mm. Hg), coming to the P_{O_2} found during natural ventilation breathing 100 percent O_2 at altitude. Arterial hemoglobin saturation fell from 96.9 to 86.4 percent. Notwithstanding the large decrease in arterial P_{O_2} brought about by displacement of alveolar oxygen with CO_2, mean brain capillary and internal jugular venous P_{O_2} each rose markedly (from 35 to 42 mm. Hg and from 20 to 32 mm. Hg, respectively). These elevations of mean capillary and internal jugular venous P_{O_2} occurred because less oxygen was removed from each milliliter of blood passing through the brain capillaries. This is shown by the lowering of Δ A-V O_2 content from 12.0 to 5.7 vol. percent, with a resultant increase in cerebral blood flow index from 0.51 to 1.07. Again, since it is improbable that changes in the rate of cerebral oxygen consumption occurred, the decrease in A-V O_2 difference most likely reflects a restoration of brain blood flow to near normal.

Phase II (natural ventilation, breathing O_2 at 147 mm. Hg ambient pressure) versus phase IV (natural ventilation, breathing 30 percent CO_2 in O_2 at 147 mm. Hg ambient pressure). Administration of 30 percent CO_2 in oxygen at 147 mm. Hg elevated arterial P_{CO_2} from 40.3 to 43.0 mm. Hg.

[2]This condition of reduced ambient pressure will be loosely referred to as altitude.

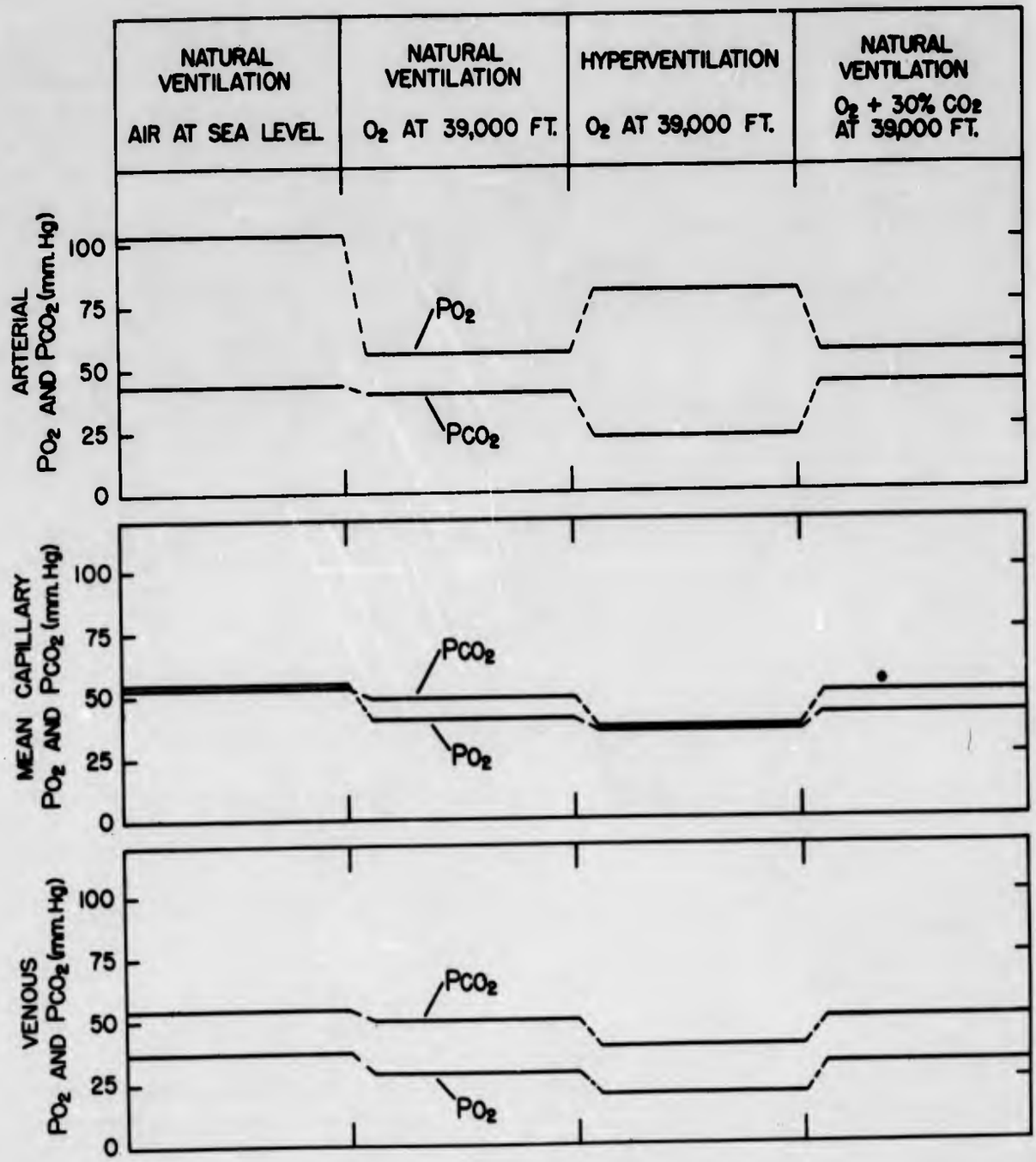

FIGURE 1

Relationship of P_{CO_2} and P_{O_2} of arterial, mean brain capillary, and internal jugular venous blood at 1 atmosphere during air breathing and at 39,000 feet simulated altitude during oxygen breathing with and without induced alteration of alveolar P_{CO_2}.

The dashed lines connecting the several study conditions indicate only that a change occurred and not the rate of its development. For elaboration, see legend of figure 2.

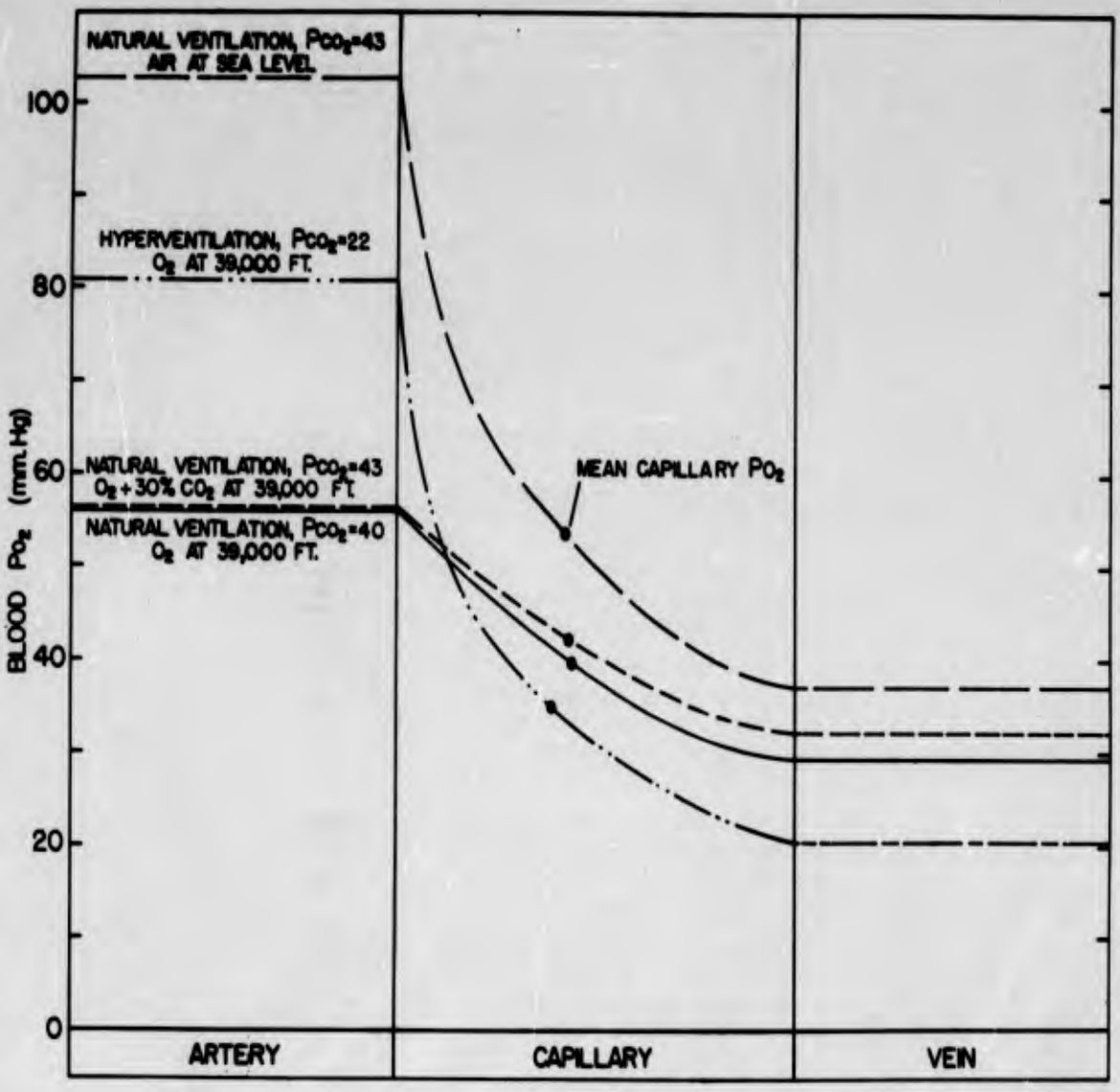

FIGURE 2

Changes in P_{O_2} of blood in passage through the brain (from average data obtained on arterial and internal jugular venous blood).

During air breathing while resting at 1.0 atmosphere, P_{O_2} falls from a value near 100 mm. Hg in the arterial blood entering the brain to approximately 40 mm. Hg in the internal jugular venous blood. Within the brain capillary (indicated in the figure by capillary length or transit time), a uniform rate of removal of oxygen would result in the pattern of fall in P_{O_2} shown. Mean brain capillary P_{O_2} (see methods) is the integral of the change from the arterial to venous level.

Oxygen breathing at the reduced ambient pressure of 39,000 feet simulated altitude resulted in a greater lowering of arterial and mean capillary P_{O_2} than of brain venous P_{O_2}.

Voluntary pulmonary hyperventilation while breathing oxygen at altitude raised arterial P_{O_2} prominently above the value found when oxygen was inhaled without voluntary overbreathing. Although hyperventilation raised arterial P_{O_2}, both mean capillary and venous P_{O_2} were lowered.

Addition of carbon dioxide to the oxygen inspired at altitude displaced oxygen in the alveolar gas and thus lowered arterial P_{O_2} from the value obtained by hyperventilation. Although arterial P_{O_2} fell, mean capillary and brain venous P_{O_2} were elevated, being restored to levels close to those previously associated with the breathing of pure O_2 at rest.

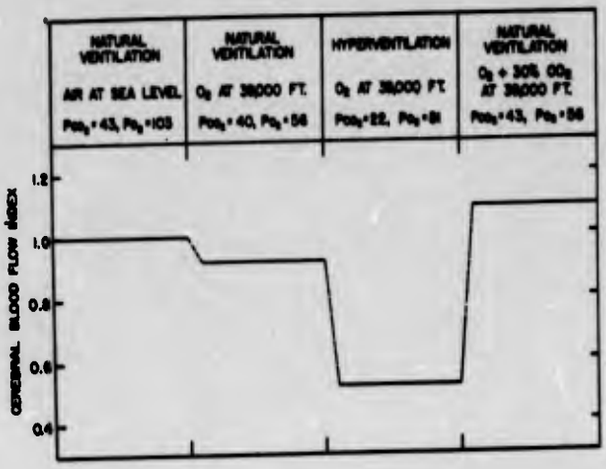

FIGURE 3

Changes in brain blood flow index at 147 mm. Hg ambient pressure during natural respiration breathing O_2, voluntary hyperventilation breathing O_2, and natural respiration breathing 30 percent CO_2 in O_2.

Brain blood flow index (see methods) suggests a slight lowering of cerebral blood flow below normal when O_2 was breathed while resting at 39,000 feet simulated altitude. This occurred in spite of a reduction of arterial Po_2.

When hypocapnia was induced by voluntary hyperventilation during O_2 breathing at reduced ambient pressure, brain blood flow index decreased to about 50 percent of the normal resting value.

Prevention of hypocapnia during hyperventilation, by addition of CO_2 to the O_2 inspired at the simulated altitude, restored brain blood flow index at least to the normal value for air breathing at rest.

While 30 percent inspired carbon dioxide at altitude is equivalent in Pco_2 to approximately 6 percent CO_2 at 1.0 atmosphere, the change in arterial Pco_2 produced at altitude was no greater than that associated with breathing 2 percent CO_2 in 21 percent O_2 in N_2 at sea level (32). Carbon dioxide breathing at altitude did not change arterial oxygenation, arterial Po_2 remaining at about 56 mm. Hg. Mean brain capillary Po_2 was increased, however, from 40 to 42 mm. Hg and internal jugular venous Po_2 from 29 to 32 mm. Hg. At the same time, venous hemoglobin saturation was elevated from 52.9 to 57.9 percent. The improvement in capillary and venous oxygenation was again related to removal of less oxygen from each unit of blood traversing the brain. Thus, A-V O_2 content difference was reduced from 6.8 to 5.7 vol. percent, presumably as a result of a return of brain blood flow to normal.

Changes in respiration

The small average increases in respiratory rate, depth, and minute volume on ascent to 39,000 feet simulated altitude while breathing O_2 were not significant. The voluntary increases in respiratory parameters at altitude represent conditions of the study rather than results. Finally, administration of 30 percent CO_2 in O_2 at altitude increased respiratory rate, tidal volume, and minute volume above the values observed during air breathing at 1.0 atmosphere and during natural respiration with oxygen at altitude.

4. DISCUSSION

When no inert gas is present in the gas inspired, total alveolar gas tension is equal to the

$$\text{Total inspired gas pressure} = P_{H_2O} + P_{CO_2} + P_{O_2}.$$

The level of alveolar oxygen pressure is then largely dependent upon the alveolar P_{CO_2} (itself determined by balance among such factors as rate of metabolic CO_2 production, alveolar ventilation, and the partial pressure of CO_2 inspired). In this situation a lowering of alveolar P_{CO_2} secondary to an increase in alveolar ventilation (or other cause) will improve arterial oxygenation, and an increase of alveolar P_{CO_2} will lower arterial P_{O_2}.

While a fall in arterial P_{O_2} produces the chemoreflex effects of anoxemia, consideration of arterial blood alone is not sufficient to make a judgment on the presence, absence, or degree of cellular anoxia. Oxygenation of the brain is affected not only by arterial P_{O_2} and O_2 content, but also by the rate of blood (oxygen) flow through brain tissue. At a particular O_2 capacity and entering (arterial) P_{O_2}, the rate of blood flow relative to oxygen utilization of the brain determines the rate of fall of oxygen tension as blood passes through the capillary network. Since the level of arterial P_{CO_2} exerts a prominent influence on the rate of brain blood flow (34, 37, 38, 39), the same factors which alter *arterial* oxygen tension in one direction may change *brain* oxygenation in the other. It is evident, then, that the end result of an induced or an accidental change in alveolar P_{CO_2} during oxygen breathing will depend upon the interaction of the effects of high and low P_{CO_2} and P_{O_2}. These and other aspects of tissue oxygenation are discussed elsewhere (40-43).

The interactions of P_{CO_2} and P_{O_2} having greatest significance to the present study are those affecting (a) the flow of blood through brain tissue, (b) the control of respiration by central and chemoreflex mechanisms, and (c) the uptake of oxygen by hemoglobin. These will be discussed in relation to the several experimental situations studied.

Oxygen breathing at altitude

The primary physiologic event on exposure to reduced ambient pressure was the considerable (nearly 50 mm. Hg) lowering of arterial and alveolar oxygen tension. In view of the well-known cerebral vasodilator effect of anoxemia (37, 38), it might be expected that an increase in brain circulation would follow. This can be considered not to have occurred, since in a previous study anoxic cerebral vasodilatation could not be detected until the P_{O_2} of arterial blood fell below about 50 mm. Hg (lower than in any phase of the present study) (13, 42). Actually, as shown by the drop in cerebral blood flow index, there appears to have been not a rise but a decrease of nearly 10 percent in the rate of brain blood flow. This was most probably an indirect effect of the arterial anoxemia. It presumably resulted from the anoxemic chemoreflex respiratory stimulation, lowering of arterial P_{CO_2} and, hence, hypocapneic cerebral vasoconstriction. During this part of the study, the development of anoxia was indicated by lowering of oxygen tension not only in arterial blood but in the mean capillary and brain venous blood as well. The use of an arterial "oximeter" as a warning device in this condition would properly indicate the development of anoxia.

Active hyperventilation while breathing oxygen at altitude

In this situation the initial effects of hyperventilation can be considered to be the changes in alveolar P_{O_2} and P_{CO_2}. Arterial P_{O_2} was raised by the increased alveolar ventilation, and, with the additional influence of alkalosis, arterial oxygen saturation actually returned to normal. Arterial oximetry (44) would indicate this change also as a complete restoration of normal oxygenation, even though arterial P_{O_2} was still 22 mm. Hg below normal. More important, figure 1 shows that such an oximeter indication of arterial percentage of Hb saturation would undoubtedly be erroneous in terms of brain oxygenation, since the halving of brain flow caused both mean capillary and internal jugular venous blood P_{O_2} to fall. Again, the influence of the observed change in arterial

P_{O_2} upon the brain vessels can be considered negligible and the reduction in blood flow attributed to the powerful vasoconstrictor effect of hypocapnia. Thus, excessive pulmonary ventilation and hypocapnia during oxygen breathing at high altitude can lead to exaggerated central anoxia, even while diminishing arterial anoxemia.

Several consequences of the changes in opposite directions observed in arterial and central P_{O_2} deserve attention in relation to the capacity for effective performance at low ambient pressures. First, the rise in arterial P_{O_2} (and the fall in P_{CO_2}) should lead to diminished bombardment of the brain by the chemoreflex impulses which normally provide a powerful arousal mechanism in isotonic anoxia (42, 45). Loss of this form of central nervous system stimulation, coinciding with central alkalosis and an exaggeration of central anoxia, may be an important factor predisposing the individual to loss of consciousness when anoxia is accompanied by excessive alveolar ventilation (42, 45).

The relation of the blood P_{O_2} at various locations to the oxygenation of individual brain cells also must be considered in appraising the observed effects of hyperventilation. When P_{O_2} is measured with an oxygen electrode, the oxygen pressure of the brain tissue is found to vary with the proximity of the sensing electrode to a blood vessel: the P_{O_2} is higher near an artery than near a vein (40, 41). In this study certain brain cells can be considered to have been strongly affected by the reduction of central oxygen tension which resulted from slowing of brain blood flow. These include: (a) those brain cells in which the O_2 supply depends chiefly upon a P_{O_2} gradient from the venous end of a capillary, (b) those cells furthest removed from the capillary, and (c) those cells most actively metabolizing. Actually, brain cells supplied with oxygen from the arterial end of the capillary were probably rendered *less* anoxic by the increase in arterial P_{O_2}, even though hyperventilation led to cerebral vasoconstriction and a lowering of P_{O_2} further along the brain capillary bed.

At this point attention must be given to the interpretation of changes in "mean brain capillary P_{O_2}." Since P_{O_2} varies not only from arterial to venous end of the capillary but also in relation to the distance of a cell from oxygen source, mean capillary P_{O_2}, like mean brain P_{O_2}, is not a measurable quantity (31, 40, 41). Presumably, it must even vary at different sites within the metabolizing cell. The fall in calculated mean brain capillary P_{O_2} observed during hyperventilation in the present study represents the integrated mean effect of improved oxygenation in some regions and diminished oxygenation in others. Hence, it does not provide a useful quantitative index of change in cellular oxygenation. Circumstances can be visualized in which there is no change in the calculated mean capillary P_{O_2} even though prominent physiologic changes have occurred, e.g., exaggerated increase in arterial P_{O_2} with limited decrease in brain-blood flow. For this reason, most attention should be given to changes in oxygenation of the brain venous blood. These will be considered representative of the maximal levels of intravascular P_{O_2} available for supplying the oxygen tension gradient to certain brain cells (46, 47). Since it has been found that a lowering of internal jugular P_{O_2} below 19 or 20 mm. Hg is associated with development of unconsciousness (46, 47), the actively hyperventilating subjects of this study probably came close to losing consciousness.

Administration of carbon dioxide with oxygen at altitude

By none of the standards of measurement employed did the addition of 30 percent CO_2 to the oxygen breathed at altitude reduce oxygenation below that associated with inhalation of pure oxygen at the same ambient pressure. The rise in alveolar P_{CO_2} was too small to reduce arterial oxygen tension detectably, although a decrease probably was produced. The elevation of arterial P_{CO_2}, equivalent in degree to that produced by administration of 2 to 3 percent CO_2 in 21 percent O_2 in N_2 at 1.0 atmosphere, caused only the slight, and not distressful, respiratory stimulation which would be expected (31). Actually, the small increase in

respiration produced by administration of 30 percent CO_2 in O_2 represents the major measured difference between the state of the resting subjects breathing CO_2 in O_2 and that of those breathing O_2 alone. Therefore, at the ambient pressure studied, the greatest influence of added carbon dioxide can be considered to be the prevention of cerebral anoxia and alkalosis in subjects showing excessive alveolar ventilation rather than improvement in the oxygenation of the normally breathing subject.

The role of increased inspired P_{CO_2} in preventing central anoxia in hyperventilation appears related entirely to the restoration of brain blood flow to an adequate level (table II; fig. 3). This effect, reflecting the well-known and powerful influence of carbon dioxide upon cerebral vessels (34, 35), is related more to changes in P_{CO_2} than to changes in pH of the circulating blood (39, 48). This action of carbon dioxide may be an expression of the changes in pH produced within vascular smooth muscle cells as the P_{CO_2} of blood is altered (39, 48). Except during severe central nervous system stimulation (48), the action of carbon dioxide upon brain vessels has also been more clearly correlated to changes in the arterial blood (i.e., at the arteriolar location) than to changes in the venous blood or tissues (13, 17, 36, 42). It is primarily on this basis that the background control of brain circulation has been considered, not an active process as often proposed, but a passive consequence of the influence of alveolar ventilation on arterial P_{CO_2} (42).

Carbon dioxide also affects the mechanisms of respiratory control in anoxia. The existence of a prominent respiratory stimulant effect of anoxemia in the absence of hypocapnia has been well documented (42, 49, 50, 51), although the mechanism of the effect is far from clear. Studies employing "CO_2 sensitivity" curves indicate a greater overall respiratory reactivity to CO_2 at low alveolar P_{O_2} than at high P_{O_2} (49, 50, 51). However, an induced change in the alveolar carbon dioxide tension does not necessarily cause the same magnitude of change in central P_{CO_2} (31, 32), which is grossly altered by the anoxic dilatation of brain vessels (42). It is, therefore, not even certain whether the O_2-CO_2 interaction occurs at the peripheral chemoreceptors or in a central location.

During inhalation of 30 percent CO_2 in O_2, both the average arterial P_{O_2} (56 mm. Hg) and the central venous P_{CO_2} were the same as during oxygen breathing at rest. Thus, the higher ventilation when breathing 30 percent CO_2 in O_2 would appear to be related to an effect of the restoration of *arterial* P_{CO_2} from a slightly subnormal to a normal level. As an effect of change only in arterial P_{CO_2}, the resulting 9-liter difference in ventilation indicates an action of CO_2 upon the peripheral chemoreflex mechanism rather than upon cells of the central nervous system.

Limitations

At any altitude addition of small amounts of carbon dioxide to the oxygen breathed should prevent the alkalemia and central alkalosis which normally result from alveolar hyperventilation. This will be true regardless of whether the carbon dioxide is autogenous or is a constituent of a compressed gas supply. Added carbon dioxide will also somewhat exaggerate the hyperventilation related to the chemoreflex stimulation of arterial anoxemia. However, it should not increase a hyperpnea based on the involuntary respiratory overdrive of excitement.

While prevention of hypocapnia should sustain central oxygenation, the benefit derived will depend upon the degree of central anoxia actually produced by the cerebral vasoconstriction during oxygen breathing. This is dependent, in part, upon the arterial P_{O_2}, and, hence, upon the ambient pressure and altitude. When breathing oxygen at an altitude of 35,000 feet (179 mm. Hg ambient pressure), the approximate alveolar gas composition can be indicated as: $P_{H_2O} = 47$ mm. Hg, $P_{CO_2} = 40$ mm. Hg, and $P_{O_2} = 92$ mm. Hg. These values are close to the alveolar O_2 and CO_2 tensions normally associated with air breathing at sea level. Some degree of central anoxia can be expected to accompany severe hypocapnia although arterial P_{O_2} is normal when breathing oxygen at

this altitude (12). However, it is at altitudes higher than 35,000 feet that the development of arterial anoxemia can be seriously compounded by the added complication of hypocapneic cerebral vasoconstriction to produce an exaggerated central anoxia. Finally, at an altitude so high that central anoxia is present, even when the rate of brain blood flow is normal or excessive, the increase in carbon dioxide may so exaggerate arterial anoxemia that central oxygenation will also be reduced by CO_2 administration. It may be estimated that this begins at altitudes slightly over 40,000 feet.

REFERENCES

1. Aggazzotti, A. The therapy of aviation sickness, hypobaropathy. Giorn. Med. Milit. 66:183 (1918).

2. Schneider, E. C., D. Truesdell, and R. W. Clarke. The influence of carbon dioxide on man during exposure to reduced barometric pressure. Amer. J. Physiol. 78:393 (1926).

3. Fenn, W. O., H. Rahn, and A. B. Otis. A theoretical study of the composition of the alveolar air at altitude. Amer. J. Physiol. 146:637 (1946).

4. Hall, F. G., and K. D. Hall. Effect of adding carbon dioxide to inspired air on consciousness time of man at altitude. Proc. Soc. Exp. Biol. Med. 76:140 (1951).

5. Gray, J. S. Concerning the use of carbon dioxide to counteract anoxia. USAF School of Aviation Medicine Report 310, Aug. 1944.

6. Gellhorn, E. The effectiveness of carbon dioxide in combating the changes in visual intensity discrimination produced by oxygen deficiency. Amer. J. Physiol. 117:75 (1936).

7. Gibbs, F. A., E. L. Gibbs, W. G. Lennox, and L. F. Nims. The value of carbon dioxide in counteracting the effects of low oxygen. J. Aviation Med. 14:250, (1943).

8. Dill, D. B., and N. Zamcheck. Respiratory adjustments to oxygen-lack in the presence of carbon dioxide. Amer. J. Physiol. 129:47 (1940).

9. Himwich, H., J. Fazekas, H. Herrlich, A. E. Johnson, and A. L. Barach. Studies on the effects of adding carbon dioxide to oxygen-enriched atmospheres in low pressure chambers. J. Aviation Med. 13:177 (1942).

10. Johnson, A. E., M. Eckman, C. Rumsey, Jr., and A. L. Barach. Studies on the effects of adding carbon dioxide to oxygen-enriched atmospheres in low pressure chambers. J. Aviation Med. 13:130 (1942).

11. Otis, A. B., H. Rahn, and L. E. Chadwick. Effects of adding carbon dioxide to inspired oxygen on tolerance to high altitudes. Proc. Soc. Exp. Biol. Med. 70:487 (1949).

12. Sugioka, K., and D. A. Davis. Hyperventilation with oxygen – A possible cause of cerebral hypoxia. Anesthesiology 21:135 (1960).

13. Turner, J. E., C. J. Lambertsen, S. G. Owen, H. Wendel, and H. Chiodi. Effects of .08 and .8 atmospheres of inspired P_{O_2} upon cerebral hemodynamics at a "constant" alveolar P_{CO_2} of 43 mm. Hg. Fed. Proc. 16:130 (1957).

14. Dobeln, W. v. A respiration valve with insignificant dead space. Acta Physiol. Scand. 18:34 (1949).

15. Lambertsen, C. J., and J. M. Benjamin, Jr. Breath-by-breath sampling of end-expiratory gas. J. Appl. Physiol. 14:711 (1959).

16. Kety, S. S., and C. F. Schmidt. The nitrous oxide method for the quantitative determination of cerebral blood flow in man. Theory, procedure and normal values. J. Clin. Invest. 27:476 (1948).

17. Lambertsen, C. J., R. H. Kough, D. Y. Cooper, G. L. Emmel, H. H. Loeschcke, and C. F. Schmidt. Oxygen toxicity. Effects in man of oxygen inhalation at 1 and 3.5 atmospheres upon blood gas transport, cerebral circulation and cerebral metabolism. J. Appl. Physiol. 5:471 (1953).

18. Rosenthal, T. B. The effects of temperature on the pH of blood and plasma in vitro. J. Biol. Chem. 173:25 (1948).

19. Severinghaus, J. W., M. Stupfel, and A. F. Bradley. Accuracy of blood pH and P_{CO_2} determinations. J. Appl. Physiol. 9:189 (1956).

20. Van Slyke, D. D., and J. M. Neill. The determination of gases in blood and other solutions by vacuum extraction and manometric measurement. J. Biol. Chem. 61:523 (1924).

21. Bartels, H., and E. Opitz. *In* Handbook of respiration, WADC Technical Report 58-352, pp. 7 and 8 (1958).

22. Sendroy, J., Jr., R. T. Dillon, and D. D. Van Slyke. Studies of gas and electrolyte equilibria in blood. XIX. The solubility and physical state of uncombined oxygen in blood. J. Biol. Chem. 105:597 (1934).

23. Roughton, F. J. W., R. C. Darling, and W. S. Root. Factors affecting the determination of oxygen capacity, content and pressure in human arterial blood. Amer. J. Physiol. 142:708 (1944).

24. Severinghaus, J. W. Oxyhemoglobin dissociation curve correction for temperature and pH variation in human blood. J. Appl. Physiol. 12:485 (1958).

25. Van Slyke, D. D., and J. Sendroy, Jr. Studies of gas and electrolyte equilibria in blood. XV. Line charts for graphic calculations by the Henderson-Hasselbalch equation, and for calculating plasma carbon dioxide content from whole blood content. J. Biol. Chem. 79:781 (1928).

26. Severinghaus, J. W., M. Stupfel, and A F. Bradley. Variations of serum carbonic acid pK′ with pH and temperature. J. Appl. Physiol. 9:197 (1956).

27. Bohr, C. The specific activity of the lungs during inspiration and its relationship to the diffusion of gas through the alveolar wall. Scand. Arch. Physiol. 22:221 (1909).

28. Barcroft, J. Architecture of Physiological Functions. Cambridge, Eng.: Cambridge University Press, 1934.

29. Houston, C. S., and R. L. Riley. Respiratory and circulatory changes during acclimatization to high altitude. Amer. J. Physiol. 149:565 (1947).

30. Lambertsen, C. J., J. H. Ewing, R. H. Kough, R. Gould, and M. W. Stroud, 3rd. Oxygen toxicity. Arterial and internal jugular blood gas composition in man during inhalation of air, 100% O_2 and 2% CO_2 in O_2 at 3.5 atmospheres ambient pressure. J. Appl. Physiol. 8:255 (1955).

31. Lambertsen, C. J. Carbon dioxide and respiration in acid-base homeostasis. Anesthesiology 21:642 (1960).

32. Lambertsen, C. J., R. H. Kough, D. Y. Cooper, G. L. Emmel, H. H. Loeschcke, and C. F. Schmidt. Comparison of relationship of respiratory minute volume to P_{CO_2} and pH of arterial and internal jugular blood in normal man during hyperventilation produced by low concentrations of CO_2 at 1 atmosphere and by O_2 at 3.0 atmospheres. J. Appl. Physiol. 5:803 (1953).

33. Lambertsen, C. J. Oxygen, carbon dioxide and helium. *In* Drill, V. A. (ed.). Pharmacology in medicine. New York: McGraw-Hill, 1958.

34. Kety, S. S., and C. F. Schmidt. The effects of altered arterial tensions of carbon dioxide and oxygen on cerebral blood flow and cerebral oxygen consumption of normal young men. J. Clin. Invest. 27:484 (1948).

35. Kety, S. S., and C. F. Schmidt. The effects of active and passive hyperventilation on cerebral blood flow, cerebral oxygen consumption, cardiac output and blood pressure of normal young men. J. Clin. Invest. 25:107 (1946).

36. Lambertsen, C. J., S. G. Owen, H. Wendel, M. W. Stroud, A. A. Lurie, W. Lochner, and G. F. Clark. Respiratory and cerebral circulatory control during exercise at .21 and 2.0 atmospheres inspired P_{O_2}. J. Appl. Physiol. 14:966 (1959).

37. Sokoloff, L. The action of drugs on the cerebral circulation. Pharmacol. Rev. 11:1 (1959).

38. Lassen, N. A. Cerebral blood flow and oxygen consumption in man. Physiol. Rev. 39:183 (1959).

39. Lambertsen, C. J., S. J. G. Semple, M. G. Smyth, and R. Gelfand. H^+ and P_{CO_2} as chemical factors in respiratory and cerebral circulatory control. J. Appl. Physiol. 16:473 (1961).

40. Kety, S. S. Determinants of tissue oxygen tension. Fed. Proc. 16:666 (1957).

41. Davies, P. W., and D. W. Bronk. Oxygen tension in mammalian brain. Fed. Proc. 16:689 (1957).

42. Lambertsen, C. J. Respiration. *In* Bard, P. (ed.). Medical physiology, 11th ed., ch. 39. St. Louis: C. V. Mosby, 1961.

43. Lambertsen, C. J. A philosophy of extremes for the gaseous environment of manned closed ecological systems. IAS Proceedings of the Manned Space Stations Symposium, p. 316 (1960).

44. Nilsson, N. J. Oximetry. Physiol. Rev. 40:1 (1960).

45. Heymans, C., and E. Neil. Reflexogenic Areas of the Cardiovascular System. Boston: Little, Brown and Co., 1958.

46. Opitz, E., and M. Schneider. The oxygen supply of the brain and the mechanism of the response to oxygen deficiency. Ergebn. Physiol. 46:126 (1950).

47. Lennox, W. G., F. A. Gibbs, and E. L. Gibbs. Relationship of unconsciousness to cerebral blood flow and to anoxemia. Arch. Neurol. & Psychiat. 34:1001 (1935).

48. Gotoh, F., Y.. Tazaki, and J. S. Meyer. Transport of gases through brain and their extravascular vasomotor action. Exp. Neurol. 4:48 (1961).

49. Nielsen, M., and H. Smith. Studies on the regulation of respiration in acute hypoxia. Acta Physiol. Scand. 24:293 (1951).

50. Loeschcke, H. H., and K. H. Gertz. The influence of inspired Po_2 on the respiratory activity of man at a constant alveolar Pco_2. Arch. ges. Physiol. 267:460 (1958).

51. Lloyd, B. B., M. G. M. Jukes, and D. J. C. Cunningham. The relation between alveolar oxygen pressure and the respiratory response to carbon dioxide in man. Quart. J. Exp. Physiol. 43:214 (1958).

School of Aerospace Medicine, Brooks AF Base, Tex. SAM-TDR-62-70. EFFECTS OF CHANGES IN BLOOD P_{CO_2} ON BRAIN OXYGENATION AT 147 MM. HG AMBIENT PRESSURE (39,000 FEET). June 62, 17 pp. incl. illus.

Hyperventilation during the breathing of 100 percent oxygen elevates the P_{O_2} of alveolar gas by the same amount that it lowers its P_{CO_2}. Since the development of arterial hypocapnia causes cerebral vasoconstriction, brain oxygenation is drastically decreased even while arterial oxygenation is improved by the hyperventilation. Administration of 30 percent CO_2 with oxygen at an ambient pressure

1. Physiology
2. Hyperventilation
3. Cerebral circulation

I. AFSC Project 7756, Task 59692
II. Contract AF 41(657)-16
III. E. C. Pierce, Jr., C. J. Lambertsen, M. J. Strong, S. C. Alexander, D. Steele
IV. In ASTIA collection

School of Aerospace Medicine, Brooks AF Base, Tex. SAM-TDR-62-70. EFFECTS OF CHANGES IN BLOOD P_{CO_2} ON BRAIN OXYGENATION AT 147 MM. HG AMBIENT PRESSURE (39,000 FEET). June 62, 17 pp. incl. illus.

Hyperventilation during the breathing of 100 percent oxygen elevates the P_{O_2} of alveolar gas by the same amount that it lowers its P_{CO_2}. Since the development of arterial hypocapnia causes cerebral vasoconstriction, brain oxygenation is drastically decreased even while arterial oxygenation is improved by the hyperventilation. Administration of 30 percent CO_2 with oxygen at an ambient pressure

1. Physiology
2. Hyperventilation
3. Cerebral circulation

I. AFSC Project 7756, Task 59692
II. Contract AF 41(657)-16
III. E. C. Pierce, Jr., C. J. Lambertsen, M. J. Strong, S. C. Alexander, D. Steele
IV. In ASTIA collection

School of Aerospace Medicine, Brooks AF Base, Tex. SAM-TDR-62-70. EFFECTS OF CHANGES IN BLOOD P_{CO_2} ON BRAIN OXYGENATION AT 147 MM. HG AMBIENT PRESSURE (39,000 FEET). June 62, 17 pp. incl. illus.

Hyperventilation during the breathing of 100 percent oxygen elevates the P_{O_2} of alveolar gas by the same amount that it lowers its P_{CO_2}. Since the development of arterial hypocapnia causes cerebral vasoconstriction, brain oxygenation is drastically decreased even while arterial oxygenation is improved by the hyperventilation. Administration of 30 percent CO_2 with oxygen at an ambient pressure

1. Physiology
2. Hyperventilation
3. Cerebral circulation

I. AFSC Project 7756, Task 59692
II. Contract AF 41(657)-16
III. E. C. Pierce, Jr., C. J. Lambertsen, M. J. Strong, S. C. Alexander, D. Steele
IV. In ASTIA collection

School of Aerospace Medicine, Brooks AF Base, Tex. SAM-TDR-62-70. EFFECTS OF CHANGES IN BLOOD P_{CO_2} ON BRAIN OXYGENATION AT 147 MM. HG AMBIENT PRESSURE (39,000 FEET). June 62, 17 pp. incl. illus.

Hyperventilation during the breathing of 100 percent oxygen elevates the P_{O_2} of alveolar gas by the same amount that it lowers its P_{CO_2}. Since the development of arterial hypocapnia causes cerebral vasoconstriction, brain oxygenation is drastically decreased even while arterial oxygenation is improved by the hyperventilation. Administration of 30 percent CO_2 with oxygen at an ambient pressure

1. Physiology
2. Hyperventilation
3. Cerebral circulation

I. AFSC Project 7756, Task 59692
II. Contract AF 41(657)-16
III. E. C. Pierce, Jr., C. J. Lambertsen, M. J. Strong, S. C. Alexander, D. Steele
IV. In ASTIA collection

equivalent to that at 39,000 feet altitude prevented alkalemia and, in spite of hyperventilation, restored central oxygenation to a level at least equivalent to that found when pure oxygen was breathed at rest at the same altitude. The respiratory minute volume during administration of CO_2 with O_2 was greater than when O_2 alone was breathed at the reduced ambient pressure. Since neither arterial P_{O_2} nor central P_{CO_2} values differed in these two experimental situations, the respiratory stimulation may represent the quantitative demonstration in man of a respiratory effect of carbon dioxide which is mediated solely by the chemoreceptors exposed to arterial blood and which acts in the absence of a change in direct central stimulation by CO_2.

equivalent to that at 39,000 feet altitude prevented alkalemia and, in spite of hyperventilation, restored central oxygenation to a level at least equivalent to that found when pure oxygen was breathed at rest at the same altitude. The respiratory minute volume during administration of CO_2 with O_2 was greater than when O_2 alone was breathed at the reduced ambient pressure. Since neither arterial P_{O_2} nor central P_{CO_2} values differed in these two experimental situations, the respiratory stimulation may represent the quantitative demonstration in man of a respiratory effect of carbon dioxide which is mediated solely by the chemoreceptors exposed to arterial blood and which acts in the absence of a change in direct central stimulation by CO_2.

equivalent to that at 39,000 feet altitude prevented alkalemia and, in spite of hyperventilation, restored central oxygenation to a level at least equivalent to that found when pure oxygen was breathed at rest at the same altitude. The respiratory minute volume during administration of CO_2 with O_2 was greater than when O_2 alone was breathed at the reduced ambient pressure. Since neither arterial P_{O_2} nor central P_{CO_2} values differed in these two experimental situations, the respiratory stimulation may represent the quantitative demonstration in man of a respiratory effect of carbon dioxide which is mediated solely by the chemoreceptors exposed to arterial blood and which acts in the absence of a change in direct central stimulation by CO_2.

equivalent to that at 39,000 feet altitude prevented alkalemia and, in spite of hyperventilation, restored central oxygenation to a level at least equivalent to that found when pure oxygen was breathed at rest at the same altitude. The respiratory minute volume during administration of CO_2 with O_2 was greater than when O_2 alone was breathed at the reduced ambient pressure. Since neither arterial P_{O_2} nor central P_{CO_2} values differed in these two experimental situations, the respiratory stimulation may represent the quantitative demonstration in man of a respiratory effect of carbon dioxide which is mediated solely by the chemoreceptors exposed to arterial blood and which acts in the absence of a change in direct central stimulation by CO_2.

UNCLASSIFIED