THE EFFECTS OF ACTIVE AND PASSIVE HYPERVENTILATION ON CEREBRAL BLOOD FLOW, CEREBRAL OXYGEN CONSUMPTION, CARDIAC OUTPUT, AND BLOOD PRESSURE OF NORMAL YOUNG MEN [1]

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The physiological effects of hyperventilation, long a subject of considerable interest to clinicians as well as physiologists, recently assumed a new practical importance in connection with military aviation. Here, in numerous situations, overbreathing may be encountered because of emotions or pain, or it may be induced voluntarily, and the results may be favorable or unfavorable, depending on circumstances. At altitudes at which anoxemia can be completely prevented by inhala- of O_2, hyperventilation not only would exhaust the available supply of O_2 at an unduly rapid rate, but also would have an adverse effect on the ability of the flyer to meet the exigencies of combat aviation (1, 2). But, at altitudes above 35,000 feet, where inhalation even of 100 per cent O_2 cannot keep the alveolar oxygen tension from falling below the sea level normal, anoxemia can be prevented only by raising the pressure of the inhaled gas above the ambient pressure, or by making room for more O_2 in the alveoli by blowing off CO_2. If equipment for the former of these alternatives is not available, proves insufficient, suddenly becomes ineffective, or must be abandoned, the second may be the only possible means of avoiding incapacitating anoxemia. The relative dangers of anoxemia and acapnia then become a matter of immediate practical importance in connection with flight at extreme altitudes. If the cabin of the airplane is pressurized, the possibility of sudden decompression or the necessity for abandoning the plane at an altitude at which hyperventilation may be necessary for survival, must always be borne in mind. If the plane is not pressurized the altitude tolerated by the flyer might be increased, or the time during which he could take effective action at a given high altitude might be prolonged, by means of hyperventilation. Finally, the flyer's ceiling can be increased by simply raising the pressure of O_2 in the mask to a level higher than the ambient pressure, and this can be done by application of the added pressure either continuously or intermittently. The latter procedure is less uncomfortable than the former, but it is likely to cause considerably more hyperventilation.

For these reasons, not only the training of personnel for flight at extreme altitudes, but also the selection and procurement of equipment for such flight have called for fairly exact information concerning the physiological derangements brought about by hyperventilation. Meanwhile the importance of the same considerations in relation to the use of mechanical resuscitating devices has increased not only because of the greater need for resuscitation in connection with the current vogue of intravenous anesthesia, but also because of the recent availability of a number of more efficient devices for this purpose. Although a large amount of experimental work has been done in this field, both on laboratory animals and on man, the data hitherto available are not adequate for the present purpose. Thus, although passive hyperventilation is known to cause a profound fall in blood pressure in anesthetized animals (3) and man (4), due presumably to a decrease in vasomotor tone, voluntary hyperventilation by unanesthetized subjects apparently has no such effect (5). Whether this difference is due to the anesthetic or to the exercise involved in the voluntary process is unknown. Corresponding statements can be made

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about the effects on cardiac output, on which little information is available (6). One of the important effects claimed for hyperventilation is constriction of cerebral blood vessels, but the methods used to demonstrate this in man (increase in the femoral artery—internal jugular vein oxygen difference (7), increase in temperature in an artificially heated thermocouple inserted into an internal jugular vein (8), and decrease in the rate of displacement of cerebrospinal fluid during obstruction of both jugular veins in the neck (9)) are all open to criticism (10).

With the recent development of a method for measuring quantitatively the volume of blood flowing through the brain of an intact unanesthetized man (11), together with the ballistocardiographic method for estimating cardiac output (12) and standard means for determining arterial blood pressure, we had at our disposal for the first time the implements for securing unequivocal evidence on all of the points mentioned above. We could also calculate the amount of O_2 used by the brain from the cerebral arteriovenous O_2 difference, once the volume of cerebral blood flow was known. The total O_2 uptake was readily measured, and the proportion of this represented by cerebral metabolism then could easily be determined. The corresponding figure for the proportion of cardiac output represented by total cerebral blood flow also could be computed from the ballistocardiogram and the measured volume of cerebral blood flow.

We have carried out these measurements in normal young men in the recumbent position at sea level and under 3 conditions, *viz.*, at rest, during voluntary hyperventilation, and during approximately equal hyperventilation produced by a positive pressure resuscitating device, the General Electric Pneumolator. The experiments have been extended subsequently to conditions other than hyperventilation, which was chosen for first study because of the possible immediate military value of the information.

METHODS

Subjects. These were normal young men (conscientious objectors) 23 to 31 years of age. They reported about 9 A.M., without breakfast, and lay quietly on the ballistocardiographic bed for approximately an hour before the experiment began. Seven different subjects were used but complete data (*i.e.*, under the 3 conditions noted above) could be obtained only in 5.

Cerebral blood flow measurements. The nitrous oxide method was used substantially as already described (11), the concentration of N_2O in the inhaled mixture being 15 per cent and that of O_2 21 per cent in all cases. The balance was nitrogen. The period of measurement was 10 minutes. Samples of femoral arterial, and internal jugular venous blood were collected at 1, 3, 5, and 10 minutes after the start of the N_2O inhalation, the collections being accurately timed and synchronized. One such set was collected during quiet breathing, another (after about 5 minutes of quiet breathing and 10 minutes of hyperventilation with room air) during voluntary or passive hyperventilation. The other type of hyperventilation was tested on another day, after a rest period of 2 weeks or more. Each set of observations during hyperventilation, therefore, had its own set of control measurements during quiet breathing. Calculation of cerebral blood flow was carried out from the cerebral arteriovenous N_2O difference substantially as described in our earlier report (11). The $\int_0^t (A - V)dt$ was measured simply from the area between the arterial and venous curves for N_2O content, thus avoiding any assumptions as to the shape of these curves.[2]

Cardiac output. The horizontal ballistocardiograph was used (12). Records were made as follows: (*1*) after the subject had rested for about an hour and before the needles had been inserted; (*2*) during the last 5 minutes of the control cerebral blood flow determination; (*3*) during the last 5 minutes of the cerebral flow determination during hyperventilation; (*4*) during the minute immediately following discontinuance of passive hyperventilation. The calculations of cardiac output from these records have been corrected for dimensions of the living aorta (13). The complexes were distorted at the start of the inspiratory phase of breathing during passive hyperventilation, and the measurements were made from parts of the tracing that were free from obvious artefacts of this character.

Blood pressure. The femoral arterial needle was connected to the manifold, containing the battery of syringes used for collecting blood samples, by an annealed silver tube provided with an extra opening to which a mercury manometer was connected. This was heavily damped and was used for the direct measurement of mean blood pressure. Systolic and diastolic pressures were also estimated in the arm by the usual auscultatory method. These measurements were made at about the same time as the ballistocardiograms.

Oxygen consumption. This was estimated from a spirogram made with a conventional small basal metabolism

[2] In some of the most recent experiments, it has been found that all assumptions as to the shape of the curves during the first minute of N_2O inhalation can be avoided by taking an additional pair of samples at a slow constant rate throughout this period. The arteriovenous N_2O difference in this pair immediately gives $\int_0^1 (A - V)dt$.

outfit over a period of 3 to 5 minutes immediately after the period of measurement of cerebral blood flow. During hyperventilation, these spirograms were too erratic to yield valid measurements of oxygen consumption.

Pulmonary ventilation. The spirograms from which oxygen consumption was measured gave reasonably accurate information on this point during quiet breathing and voluntary hyperventilation. During passive hyperventilation, the corresponding measurements were attempted by noting the time required for the exhalation of 65 liters into an accurately balanced spirometer. This method proved unsatisfactory because of a slight but steady leak of gas through the pneumolator during a considerable though variable part of the expiratory phase. Consequently, we have no data on this point.

Collection and analysis of blood samples. Steel needles of 18 gauge were introduced into an internal jugular vein and a femoral artery after infiltration of the tissues with 1 per cent procaine. They were filled with sterile heparin solution (Abbott) by means of a syringe and promptly connected to the tube and manifold system. The latter was provided with a heparin-containing syringe by means of which fresh blood was drawn into relation with the collecting syringe just before the sample was collected and was replaced with a heparin-blood mixture just afterward. The usual aseptic precautions were observed throughout. The syringes used to collect the samples were of 10 ml. size, all glass construction. Each contained a mercury seal amounting to about 1 ml. and a little heparin. After some early experiments showed extraordinarily low figures for arterial pH and pCO_2, we took special pains to be certain that all traces of acid were removed from the freshly washed mercury before it was used.

The blood samples, measuring about 6 to 8 ml. and rendered incoagulable with heparin, were analyzed for N_2O content by the method previously used (11) and for O_2 and CO_2 content by the manometric method of Van Slyke (14). Separate 2 ml. samples were used for N_2O. Analyses for O_2 and CO_2 were made on at least the first and last pair of samples of each cerebral flow determination, and the values reported represent the respective averages. The hydrogen ion concentration of the samples was determined on the whole blood by means of a MacInnes-Belcher glass electrode and a Leeds and Northrup electronic potentiometer. These readings were made at 38° C., and with their aid it was possible to calculate the CO_2 tension (pCO_2) by means of the nomograms of Peters and Van Slyke (14). The blood samples were kept on ice between the time of collection and the time of completion of the analyses. The estimations of O_2, CO_2 content, and pH were begun at once, and all analyses were completed within 12 hours of the collection of the sample.

Other observations. In every experiment, attempts were made to determine the degree of mental alertness by noting the responses to questions and by observing the promptness with which instructions were followed. Signs of tetany were watched for during hyperventilation. The presence of indwelling needles in the internal jugular vein and the femoral artery precluded the use of the usual tests for cerebral functions.

The course of a typical experiment was as follows: The subject, who had had no food since the preceding evening, clad himself in light operating clothes and lay down on the ballistocardiographic bed. About an hour later ballistocardiogram I was recorded. The face mask was then applied and connected to a T-piece through which instantaneous shift could be made between ambient air and the N_2O–O_2–N_2 mixture. The needles were then inserted in the jugular vein and femoral artery and connected to their respective manifolds. The subject was assured that no other disquieting procedures would be carried out and the first (control) 10-minute period of measurement of cerebral blood flow was then begun; after the pair of blood samples had been collected at 5 minutes, the ballistocardiogram and blood pressure measurements were repeated. After the final (10-minute) pair of blood samples was collected, the inhalation of N_2O was discontinued in favor of room air, and when a few more minutes had elapsed, the control spirogram was made. Following this, hyperventilation with room air was begun and was continued for 10 minutes. Voluntary hyperventilation was carried out in time to a bell ringing every 10 seconds, the subject being instructed to take a comfortably deep inspiration and to exhale at a rate that would complete the cycle before the next signal. Passive hyperventilation was carried out with a positive pressure of 150 mm. (6 inches) H_2O which was found by experience to produce about the same degree of alkalosis as the described voluntary procedure. The gas used for this purpose was ambient air compressed in tanks of the same type as those containing the N_2O–O_2–N_2 mixture. At the end of this 10 minutes of hyperventilation with air, an extra sample of jugular blood was collected to give the base-line for the next N_2O period. Then the N_2O–O_2–N_2 mixture was substituted for room air, and the second period of blood flow measurement was begun; the hyperventilation was maintained as nearly constant as possible during this time. Again the ballistocardiographic and blood flow estimations were carried out during the latter 5 minutes of this period. At the end of this time, room air was substituted for the N_2O–O_2–N_2 mixture with the hyperventilation continuing as nearly constant as possible, and the second spirogram was made. Then the hyperventilation was discontinued, and the subject was instructed to relax completely. Usually, there was a brief apnea at this time and in some cases another ballistocardiogram was made as the subject began to breathe again. The total elapsed time was about 3 to 3½ hours, of which about half was comprised in the periods of experimental observations. The hyperventilation period lasted 20 to 30 minutes; hence, the voluntary hyperpnea had to be only of moderate intensity, which the passive process was adjusted to resemble.

RESULTS

The essential data from 12 successful experiments are presented in Tables I, II, and III, and

TABLE I

Effects of active and passive hyperventilation on arterial and cerebral venous blood constituents

Subject		Pulmonary ventilation		Blood CO_2 content				Cerebral A-V difference		Blood O_2 content				Cerebral A-V difference		Cerebral R.Q.		Blood pH			
				Arterial		Internal jugular		CO_2		Arterial		Internal jugular		O_2				Arterial		Internal jugular	
		C	H	C	H	C	H	C	H	C	H	C	H	C	H	C	H	C	H	C	H
		liters per minute		*volumes per cent*				*volumes per cent*		*volumes per cent*				*volumes per cent*							
I Active hyperventilation	S. H.	8.2	25.3	51.4	37.9	55.4	47.7	4.0	9.8	17.0	18.4	11.0	9.4	6.0	9.0	0.67	1.09	7.30	7.44		
	A. C.	8.6	12.1	51.7	42.5	55.6	53.9	4.0	11.4	17.8	18.8	12.0	8.2	5.8	10.6	0.69	0.98	7.29	7.52		
	L. E.	7.0	12.3	49.4	41.9	54.5	52.8	5.1	10.9	17.5	17.4	11.8	6.6	5.7	10.8	0.90	1.01	7.39	7.52	7.36	
	M. H.	7.9	7.6*	52.2	48.7	58.4	58.0	6.2	9.3	17.0	17.6	10.9	8.1	6.1	9.5	1.02	0.98	7.43	7.53	7.41	7.46
	D. M.	7.5	15.2	49.1	39.3	53.8	49.1	4.7	9.8	18.7	19.4	12.6	8.4	6.1	11.0	0.77	0.89	7.38	7.57	7.35	7.45
	W. H.	9.1	20.2	50.0	40.5	55.0	51.6	5.0	11.1	18.5	19.4	12.1	8.4	6.4	11.0	0.78	1.01	7.39	7.56	7.34	7.46
	W. G.			51.1	45.1	57.3	55.7	6.2	10.6	18.0	18.8	11.4	7.8	6.6	11.0	0.94	0.97				
	Mean	8.1	15.5	50.7	42.3	55.7	52.7	5.0	10.4	17.8	18.5	11.7	8.1	6.1	10.4	0.82†	0.99	7.37	7.53	7.36	7.46
II Passive hyperventilation	S. H.	6.5		45.7	37.4	53.2	48.3	7.5	10.9	17.7	18.5	10.6	7.8	7.1	10.7	1.05	1.02	7.43	7.58	7.42	7.49
	L. E.	8.1		51.1	40.1	58.4	52.1	7.3	12.0	17.6	18.7	9.4	7.0	8.2	11.7	0.89	1.03	7.42	7.60	7.34	7.49
	M. H.	6.8		49.2	44.3	55.7	54.7	6.5	10.4	16.7	17.2	9.5	6.3	7.2	10.9	0.90	0.96	7.35	7.50	7.30	
	D. M.	6.5		49.7	41.4	56.0	53.7	6.3	12.3	19.8	20.1	13.0	7.6	6.8	12.5	0.93	0.98	7.37	7.51	7.31	7.40
	W. H.	7.8		50.5	40.8	57.9	51.8	7.4	11.0	18.2	18.8	11.5	7.7	6.7	11.1	1.10	0.99	7.38	7.63	7.34	7.58
	Mean	7.1		49.2	40.8	56.2	52.1	7.0	11.3	18.0	18.7	10.8	7.3	7.2	11.4	0.97	1.00	7.39	7.56	7.34	7.49

C = control. H = hyperventilation. R.Q. = respiratory quotient. Further data in Table III.

* This subject became drowsy during the period of hyperventilation and had to be reminded regularly of what was expected of him. Even though the respiratory minute volume seems to have decreased there was, by virtue of the slower and deeper respiration in this period, a real increase in effective ventilation as shown by the blood changes.

† In this group of determinations oiled syringes were not used with consequent slight loss of CO_2 sufficient, however, to depress the R.Q. in some cases. This defect was corrected in subsequent experiments.

TABLE II

Effects of active and passive hyperventilation on cardiac output, pulse and blood pressure

Subject		Stroke volume				Cardiac output				Pulse rate				Mean arterial blood pressure direct				Auscultatory blood pressure			
		I	II	III	IV	I	II	III	IV	I	II	III	IV	I	II	III	IV	I	II	III	IV
		ml.				*liters per minute*								*mm. Hg*				*mm. Hg*			
I Active hyperventilation	S. H.	77	76	75		5.5	4.9	5.6		72	64	75		83		97					
	A. C.	72	63	56		6.5	5.2	5.3		90	82	94			86	96			117/80	130/95	
	L. E.	71	70	70		5.8	4.9	4.6		82	70	65		92		93		118/70		120/70	
	M. H.	70	69	64		4.1	4.5	3.8		58	65	59		90	88	97		105/78	105/78	105/90	
	D. M.														95	93			112/80	100/74	
	W. H.	68	74	60		4.5	4.9	5.7		66	66	95			86	112			100/70	135/105	
	Mean	72	70	65		5.3	4.9	5.0		74	69	78		88		98		110/76		118/87	
II Passive hyperventilation	S. H.	68	63	49	62	3.6	3.4	3.1	3.4	53	54	64	55		85	86		95/75	95/65	90/70	
	L. E.	71	63	55	63	5.4	5.3	4.3	4.8	76	84	79	76		94	95					
	M. H.	70	70	53	53	4.5	4.2	3.8	3.9	64	60	71	73		84	91			110/65	105/75	
	D. M.	74	70	65	71	5.7	4.9	4.8	5.1	77	70	74	72		94	99		105/80	112/85	102/95	
	W. H.	76	70	53		4.3	4.5	3.8		56	65	71			104	125			115/95	120/95	
	Mean	72	67	55	62	4.7	4.5	4.0	4.3	65	67	72	69	92		99		107/78		104/84	

I = control period (just before start of control blood flow measurement); II = latter 5 minutes of period of control blood flow measurement; III = latter 5 minutes of period of blood flow measurement during hyperventilation; IV = during first minute after cessation of hyperventilation.

TABLE III

Effects of active and passive hyperventilation on cerebral blood flow and cerebral oxygen consumption

Subject		Age	Weight	Height	Surface area	Blood CO_2 tension: Arterial		Blood CO_2 tension: Internal jugular		Cardiac output		Basal metabolism	Mean arterial blood presure		Cerebral: Blood flow		Cerebral: O_2 consumption		Other effects
						C	H	C	H	C	H		C	H	C	H	C	H	
		years	*pounds*	*inches*	*m²*	*mm. Hg*				*liters per minute*		*ml. of O_2 per minute*	*mm. Hg*		*ml. per 100 grams per minute*				
I Active hyperventilation	S. H.	24	147	69.5	1.82	52	31			4.9	5.6	300	83	97	59	44	3.5	4.0	Lost consciousness at 18′ of H. Facial twitchings. Emotional upset afterwards.
	A. C.	23	147	69	1.80	55	28			5.2	5.3	244	86	96	87	51	5.0	5.4	
	L. E.	26	148	70	1.83	43	29	49		4.9	4.6	252	92	93	70	40	4.0	4.3	
	M. H.	25	160	69.5	1.85	41	32	48	43	4.5	3.8	310	88	97	56	48	3.4	4.6	Inclination to forget to hyperventilate.
	D. M.	31	160	70	1.88	44	24	49	38			245	95	93	69	40	4.2	4.4	Clouded consciousness. Twitchings of head and extremities.
	W. H.	23	155	73	1.91	43	25	50	38	4.9	5.7	252	86	112	79	52	5.1	5.7	Severe carpopedal spasm.
	W. G.	23	150	70	1.83										73	53	4.8	5.8	
	Mean					46	28*	50	40*	4.9	5.0	268	88	98	70	47*	4.3	4.9*	
II Passive hyperventilation	S. H.	24	147	69.5	1.82	38	22	43	34	3.4	3.1	246	85	86	59	40	4.2	4.3	
	L. E.	26	148	70	1.83	42	23	54	36	5.3	4.3	279	94	95	62	44	5.1	5.1	
	M. H.	25	165	69.5	1.90	46	30	57		4.2	3.8	243	84	91	72	47	5.2	5.1	Clouded consciousness toward end of hyperventilation.
	D. M.	31	165	70	1.91	45	27	56	45	4.9	4.8	218	94	99	81	40	5.5	5.0	Lost consciousness toward end of hyperventilation.
	W. H.	23	155	73	1.91	45	22	55	30	4.5	3.8	256	104	125	55	36	3.7	4.0	Carpopedal spasm.
	Mean					43	24*	53	36*	4.5	4.0*	248	92	99	66	41*	4.7	4.7	

C = control. H = hyperventilation. * This represents statistically significant changes.

TABLE IV

Percentile changes induced by active (A) and passive (P) hyperventilation

Subject	Arterial: CO_2 content		Arterial: pCO_2		Arterial: (H^+)		Internal jugular: pCO_2		Cerebral: A-V difference O_2		Cerebral: Blood flow		Cerebral: O_2 uptake		Cardiac output		Blood pressure	
	A	P	A	P	A	P	A	P	A	P	A	P	A	P	A	P	A	P
															per minute			
S. H.	−26	−18	−40	−42	−28	−30		−21	+50	+51	−25	−32	+14	+2	+14	− 9	+17	+ 1
L. E.	−15	−22	−33	−45	−27	−34		−33	+90	+43	−43	−29	+ 7	0	− 6	−19	+ 1	+ 1
M. H.	− 7	−10	−22	−35	−19	−29	−10		+56	+52	−14	−35	+35	−2	−15	−10	+10	+ 8
D. M.	−20	−17	−45	−40	−36	−28	−22	−20	+80	+84	−42	−51	+ 5	−9		− 2	− 2	+ 5
W. H.	−19	−19	−42	−50	−32	−45	−24	−45	+72	+66	−34	−34	+12	+8	+16	−15	+30	+20
Mean	−17	−17	−36	−43	−28	−33	−19	−30	+70	+59	−32	−36	+15	0	+ 2	−11	+12	+ 8

A = active (voluntary). P = passive (pneumolator).

the most significant effects of hyperventilation are summarized in Table IV. The gaps in the tables are due to lack of pertinent information for various reasons. The estimations of pH and pCO_2 in the blood in the first 2 experiments (Tables I and III) were invalidated by failure to wash the mercury completely free of acid after cleansing it in towers of dilute nitric acid and distilled water in the usual manner; as a result, the pH values were abnormally low, but this oversight was remedied for the subsequent experiments. The relatively high values for arterial CO_2 content and tension during quiet breathing (Table I and III) are most probably referable to

the dead space of the mask. The actual figures for the N_2O content of the various blood samples are omitted from the tables for the sake of simplicity, but representative examples are shown in Figure 1.

The intensity of the hyperventilation can be judged better from the changes in CO_2 content and acidity of the arterial blood than from the figures given for pulmonary ventilation. This is glaringly evident in the case of active hyperventilation by M. H. (Table I), which indicates that the values listed for pulmonary ventilation should not be regarded as precise criteria of the degree of alkalosis involved in these experiments. The reason for this discrepancy is our practice of measuring the ventilation at a period different from that involved in the collection of the blood samples. The degree of voluntary hyperventilation could not be kept constant throughout the entire period which lasted more than 20 minutes. In the case of passive hyperventilation, we have to depend entirely on the blood changes for orientation on this point.

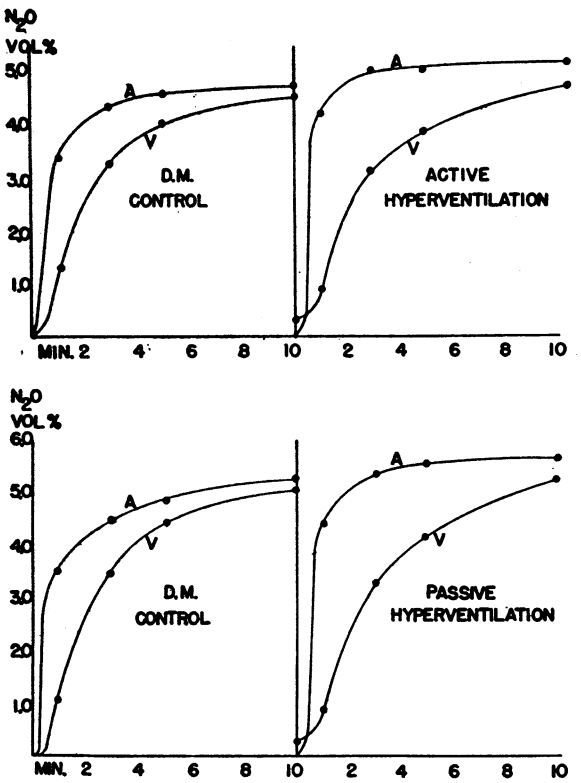

FIG. 1. NITROUS OXIDE CONCENTRATION CURVES FOR ARTERIAL AND INTERNAL JUGULAR BLOOD FROM WHICH CEREBRAL BLOOD FLOW IS CALCULATED

Two typical experiments on the same subject (D. M.) performed 3 weeks apart are illustrated. There is a lapse of about 20 minutes between the control and hyperventilation periods, during which nitrous oxide is cleared completely from arterial and almost completely from cerebral venous blood. Cerebral blood flow is calculated as previously derived (11) from $\frac{100\,S(V_{10} - V_0)}{\int_0^{10}(A - V)dt}$ the constant S being a partition coefficient for nitrous oxide between brain and blood. It is apparent by inspection that during hyperventilation, the area between the arterial and venous curves $\left(\int(A - V)dt\right)$ increases considerably indicating a decrease in cerebral blood flow.

DISCUSSION

The data presented in the tables afford a considerably deeper insight into the physiological readjustments evoked by hyperventilation in normal man than had been possible hitherto because they include actual figures for the behavior of cerebral blood flow. They also permit a set of calculations, previously impossible, of the fractions of the total cardiac output and total oxygen consumption that are accounted for by the blood flow and oxygen uptake of the brains of normal intact men. The importance of each of these items of information is attested by the existence of a considerable literature bearing upon it. We believe, therefore, a full discussion of an interpretation of the probable significance of our findings to be justified.

The validity of these findings rests upon the competence of the methods employed. With the exception of the measurements of cerebral blood flow and cardiac output, these were standard procedures that call for no further comment. Our method for measuring cerebral blood flow, as pointed out elsewhere (11), has been subjected to calibration against direct measurement of cerebral blood flow in monkeys and has back of it, therefore, an assurance of fundamental accuracy that is rare among methods advanced for clinical use. Further experience with the method has led to several improvements in detail but to no fundamental change in principle or interpretation. The ballistocardiographic method for measuring cardiac output has been considered in detail in a recent symposium (15) where a full account of its strengths and weaknesses was presented. The

consensus appears to be that the results obtained are probably trustworthy, provided that neither hypotension nor tachycardia is present. Our experiments clearly fall into this category.

Changes in composition of blood. The actual data are given in Table I, and the percentile changes are summarized in Table IV. The most significant findings are those for cerebral arteriovenous differences for O_2 and CO_2, which underwent a consistent and considerable increase during hyperventilation of either type. Since mean blood pressure never fell and usually rose at the same time (Table II), this particular effect cannot be ascribed to depression of the general circulation but must have been due either to an increase in the rate of cerebral metabolism, or to an intrinsic diminution in the volume of blood passing through the brain, *i.e.,* cerebral vasoconstriction, or perhaps to both. The data shown in Table III indicate that the second of these was the dominant factor. These findings and their interpretation are fully confirmatory, therefore, of those of others (7, 25, 26).[3] The indicated diminutions in CO_2 content and hydrogen ion concentration in both arterial and venous bloods are as expected, as are also the slight increases in arterial O_2 content (in view of the high resting arterial CO_2 content, which was attributed to the dead space of the mask).

The behavior of the cerebral respiratory quotient deserves a brief comment. This factor was practically the expected 1.0 in all cases except 4 out of the first series of resting (control) observations (Table I). The first 2 of these probably can be discounted because they were the instances of failure to remove all traces of acid from the mercury used to seal the syringes. The other 2 may have been related to the avoidance of oil to lubricate the syringes for fear that it would dissolve significant amounts of N_2O out of the blood samples. After these low values were obtained, we investigated this possibility and found it to be insignificant. From this time on, the syringes were lubricated and no more low respiratory quotients were obtained. The behavior of CO_2 naturally was not as important for our purposes as was that of N_2O.

Cerebral blood flow. The data are presented in Table III and are expressed on a percentile basis in Table IV. Without exception, cerebral blood flow diminished during hyperventilation. The degree of the change is somewhat surprising when it is remembered that these hyperpneas were only moderately intense. Definite signs of tetany were seen in only 4 of the 11 experiments and in only 3 of the 7 subjects, which may be taken as evidence that we were not dealing with an extreme alkalosis or acapnia. Yet the diminutions in cerebral blood flow during voluntary hyperpnea ranged from 14 to 43 and averaged 32 per cent, while during passive hyperventilation, the corresponding range in the same subjects was 29 to 51, and the average was 36 per cent. A change of this magnitude can scarcely be ignored in allocating responsibility for deterioration in cerebral functions during hyperventilation. As shown in Table III, signs of impairment of cortical activity were evident during hyperventilation in 5 of the experiments even by the crude methods which we used to detect such changes. The use of more exact tests for cerebral performance was precluded by the experimental conditions (particularly the indwelling needles and the mask).

The possible effects of hyperventilation on cerebral functions are so numerous and so poorly understood that it is impossible at present to evaluate the part played by any single factor with even approximate accuracy. Alkalosis, diminution in pCO_2, changes in the cerebral O_2—glucose ratios and respiratory quotients, all are elicited concurrently during hyperventilation (25, 26), and there is insufficient evidence by which to assess the relative importance of any of these. One group has found during hyperventilation a better correlation of electroencephalographic patterns and impaired consciousness with lowered pCO_2 in the internal jugular vein than with lowered pO_2 (25, 26). Nevertheless, it seems to us that a diminution in cerebral blood flow of the order of 30 per cent, while cerebral O_2 consumption is unchanged or increased (Tables III and IV), should

[3] It is noteworthy, however, that actual calculations of cerebral metabolism in these experiments showed it to undergo a consistent and significant increase during active hyperventilation with no appreciable change during the passive process (Tables III and IV). This is a concrete example of the untrustworthiness of the cerebral arteriovenous oxygen difference as a criterion of the behavior of either cerebral metabolism or cerebral blood flow, as pointed out in an earlier publication (18).

be capable of leading to a diminution in mean cortical pO_2 sufficient to constitute a major factor in the concurrent deterioration of cortical functions. If one assumes that the relation of cerebral venous pO_2 to mean cortical pO_2 remains unchanged during hyperventilation, one can estimate the diminution in the latter from the observed decrease in the former. The observed mean changes in cerebral venous O_2 content (Table I) were from 11.7 to 8.1 volumes per cent during voluntary and from 10.8 to 7.3 volumes per cent during passive hyperventilation—decreases of 31 and 32 per cent. The corresponding changes in pO_2 on the nomogram of Peters and Van Slyke (14) are from 35 to 22 and from 33 to 19 mm. Hg respectively—decreases of 37 and 42 per cent.

We have as yet no direct information concerning the relation of cerebral venous pO_2 to cortical pO_2 in man. According to recent studies made with an oxygen electrode applied to the exposed brain of the cat, cortical pO_2 varies over a wide range, depending both on the proximity of the electrode to a blood vessel (16) and the state of functional activity of the underlying tissue (17), but there was a clear tendency for the pO_2 in the cortex to be lower than that in the cerebral veins (16). If a similar relation existed in our subjects, the observed decreases in cerebral venous pO_2 would signify that cortical pO_2 had fallen to an even lower level and signs of anoxia would not be surprising. As a matter of fact, our figures both for mean cerebral venous O_2 content during hyperventilation (7.7 volumes per cent) and its decrease below the control level (32 per cent) are practically identical with the corresponding values (7.9 and 32 volumes per cent respectively) reported (7) from experiments on subjects inhaling mixtures having an O_2 content of only 6 to 8 per cent. The associated cerebral anoxia undoubtedly was less severe in our subjects than in theirs because of the higher level of pO_2 at the arterial end of the capillaries in ours, but the severity of the systemic anoxemia required to elicit such a drop in cerebral venous O_2 content at least indicates that this change was not inconsequential. Even though we are unable to estimate the part played by cortical anoxia due to diminution in cerebral blood flow in the deterioration in cerebral functions associated with hyperventilation, it seems proper to point out that a major physiological adjustment is involved in addition to the biochemical changes evident in the blood.

Since the mean blood pressure either was unchanged or rose during hyperventilation (Table II), it is clear that the recorded decreases in cerebral blood flow must have been due to some change localized in the brain, and by far the most likely cause is constriction of cerebral blood vessels. These findings, therefore, lend strong support to the already prevalent belief (7, 8, 10, 20) that the cerebral vessels are specifically regulated by the CO_2 tension to which they are exposed. This attractive and seemingly well-founded conception was recently called into question (10, 18) because the first quantitative measurements of cerebral blood flow ever to be made under conditions approaching the normal (18, 19) indicated that the cerebral circulation as a whole is influenced much more strongly by changes in pO_2 than in pCO_2, and no evidence could be obtained that the response to pCO_2 was marked enough to warrant confidence in a specific regulating function by this agent. The measurements of total cerebral blood flow were made on monkeys, whereas those on which the belief in the specificity of CO_2 was based were semi-quantitative observations on the pial or cortical circulation in cats.

The possibility of a species difference has not yet been evaluated, but the most important question, *viz.*, the behavior of man, is answered unequivocally by our present data: the total cerebral circulation of man resembles the pial or cortical circulation of the cat and not the total cerebral circulation of the monkey in its response to hypocapnia. The possible implications of this surprising conclusion will not be discussed further at this time than to point out that the most obvious interpretation—that the intrinsic control by pCO_2 is better developed in the cat than in the monkey—is not necessarily justified. It may be that the effects on the subcortical areas in the monkey are equal but opposite to those in the cortex, and thus the total blood flow does not change while flow in the cortex does. It is possible that the response to pCO_2 is more highly developed and, therefore, more subject to derangement by narcosis and experimental manipulations in the monkey

than in the cat. Comparisons of the adequacy of the methods used in these various studies strongly favor the monkey experiments because in these total cerebral blood flow was actually measured, whereas in the cat experiments, changes in blood flow were inferred either from changes in the caliber of pial blood vessels (20), or from changes in temperature of a special thermocouple inserted in the cortex (21). The limitations of these methods are considered elsewhere (10). The possible influence of anesthesia on the cerebral vasoconstriction associated with acapnia will have to be settled by appropriate studies on man; it is unlikely that corresponding data can be obtained in animals before and after the induction of anesthesia.

Cerebral metabolism. From the cerebral arteriovenous O_2 difference and the volume of cerebral blood flow, the cerebral O_2 uptake can, of course, be computed directly. The values obtained are shown in Table III, and the percentile changes during hyperventilation are given in Table IV. One of the most interesting results of these studies is the difference in this respect between the two types of hyperventilation; though active hyperpnea was associated with a consistent and statistically significant increase in cerebral O_2 uptake, passive hyperventilation of approximately the same degree and in the same subjects was not. Since the indicated increase in cerebral O_2 uptake occurred only when the hypocapnia was induced voluntarily, this cannot have been a simple experimental artifact related to imperfect understanding of the true contours of the arterial and venous N_2O curves, nor can it have been due entirely to an acceleration of cerebral metabolism by alkalosis or by a subnarcotic concentration of N_2O. The most probable cause appears to be an actual increase in cerebral O_2 uptake associated with the voluntary hyperpnea. If the relatively mild cortical activity, involved in maintaining an arbitrary respiratory cycle in accordance with a signal bell ringing every 10 seconds, is sufficient to produce a measurable increase in the total amount of O_2 used by the brain, a high degree of lability in this function is indicated. If the cerebral arteriovenous O_2 difference during passive hyperventilation can change so as to counterbalance precisely the associated decrease in blood flow, the delicacy with which these two factors are adjusted in relation to cerebral metabolism (18) becomes evident.

The absence of significant decrease in cerebral O_2 consumption associated with a mild diminution in cerebral blood flow in these experiments places them in the same category with the first effects of mild hemorrhage in anesthetized monkeys (18). In both cases, the decrease in volume flow of blood was fully compensated by an increase in the arteriovenous O_2 difference, and the total amount of O_2 taken up by the brain did not fall. In the monkeys, there were no signs of cerebral deterioration at this time, but the criteria (wink reflex, unimpaired respiratory activity) were relatively crude, and the presence of anesthesia would already have brought about the counterpart of the more subtle derangements of which signs were evident in our human subjects. When the cerebral ischemia became too marked to be compensated by increasing the arteriovenous O_2 difference, marked deterioration of cerebral and medullary functions rapidly ensued in monkeys (18), but we have not made any comparable experiments on man.

The coincidence of mild impairment of cerebral functions with undiminished or actually increased cerebral O_2 consumption may be accounted for in several ways. It is possible that the metabolism associated with consciousness constitutes a relatively small fraction of the total cerebral O_2 uptake, and its behavior is obscured therefore by that of the great mass of brain tissue. This interpretation is not in accord with our finding of a significant increase in total cerebral O_2 uptake during voluntary hyperventilation. A more probable explanation is that the average pO_2 to which the cortical cells were subjected was significantly diminished during hyperventilation, since the cerebral venous pO_2 then was 37 to 42 per cent lower than before (p. 114), and the arterial pO_2 was not appreciably increased. Even though the product of the decreased blood flow by the increased arteriovenous O_2 difference indicated no change, or even an increase, this in itself means that the venous blood leaving the brain had to be considerably lower in O_2 content and tension than before. A corresponding change in pO_2 within the actively metabolizing cells of the cortex

seems reasonable to assume. Finally, it is possible that the cortical and subcortical areas behave differently, perhaps oppositely. Our method is incapable of detecting any but the total change in blood flow or in O_2 uptake in the brain, and there seems no point in further speculation along these lines at present.

It is interesting to note (Table IV) that the fall in pCO_2 in cerebral venous blood during hyperventilation was considerably less than that in arterial. This is undoubtedly a reflection of the concomitant diminution in blood flow, which tends to conserve the CO_2 produced by cerebral metabolism and thus partially to compensate for the profound arterial hypocapnia (26).

Cardiac output. It is seen in Tables II and IV that cardiac output per minute was not significantly changed during voluntary hyperpnea but showed a consistent fall averaging 11 per cent during passive hyperventilation. In each type of hyperventilation, stroke volume was the function primarily depressed, the heart rate increasing in both, but, in the case of the active process, to a degree sufficient to keep the minute volume from falling. The decrease in cardiac minute volume during passive hyperventilation is statistically significant. Examination of the ballistocardiograms discloses the fact that the decrease in stroke volume occurs during the inspiratory phase when the thorax is being expanded by a positive intrapulmonary pressure. This would be expected to cause a sharp decrease in venous return to the right side of the heart which would shortly be reflected in a decrease in left ventricular output. The fact that in period IV (Table II), immediately after the cessation of overbreathing, the outputs per beat and per minute both tend to revert nearly to the control value is evidence that the changes in cardiac output are the result of the mechanical factors associated with the hyperventilation rather than the chemical alterations in the blood; the latter would not change appreciably in so short a time after the cessation of overbreathing.

These results are at variance with the striking increase in cardiac output during active hyperventilation found with the acetylene method (22). They confirm recent studies (23) made by the direct Fick method in which cardiac output was found to fall about 13 per cent during passive hyperventilation of the type used here. The two types of hyperventilation employed in these experiments could have different effects on cardiac output for two reasons: the active type entails voluntary muscular exertion that is lacking in the passive one, while the latter contains a positive intrapulmonary pressure factor that is lacking in the former. Evaluation of these influences is beyond the scope of the present investigation. Other effects on the ballistocardiogram of changing intrathoracic pressures are the subject of a separate report (24).

Blood pressure. Both the mean and the auscultatory values (Tables II and IV) showed a moderate but not statistically significant rise during either type of hyperventilation. In no case was there a fall comparable with that observed in anesthetized animals (3) and humans (4). This discrepancy is probably due to a depression by the narcotic drug of the reactivity of cerebral blood vessels to the constrictor influence of acapnia. The brain cells then suffer a drop in pCO_2 when acapnia is produced because the diffusion gradient for CO_2 is increased, and there is no effective compensation by restriction of the volume of blood irrigating them.

Magnitude of cerebral blood flow and metabolism. Since our calculations of cerebral blood flow are based on the percentage content of N_2O in the arterial and cerebral venous blood and the solubility coefficient of the gas in the brain, they yield a figure for blood flow per unit weight and are reported in terms of 100 grams of brain. A reasonable approximation to the total values can be obtained by adopting an acceptable average figure for brain weight in normal adult males, and a calculation of this type employing the factor 1400 grams is shown in Table V. These figures represent the means of the two series of control estimations (Table III), and they pertain solely to the then existing state of physical and mental inactivity in the recumbent position.

It is interesting to note that according to these calculations about one-fifth of the total cardiac output and about one-quarter of the total O_2 consumption were required to satisfy the needs of the brains of these subjects under these circumstances. Their average weight was approximately 70 kgm., and, therefore, the estimated brain weight repre-

TABLE V

Total cerebral blood flow and cerebral oxygen consumption (assuming a brain weight of 1400 grams) and their respective fractions of cardiac output and total oxygen consumption

Subject	Cerebral blood flow		Cerebral oxygen consumption	
		Fraction of cardiac output		Fraction of total O_2 uptake by body
	ml. per minute	*per cent*	*ml. per minute*	*per cent*
S. H.	826	20.2	55	20.1
L. E.	925	18.2	64	24.0
M. H.	896	20.4	60	21.6
D. M.	1050	21.4	69	29.8
W. H.	938	20.0	62	24.4
Mean	927	20.0	62	24.0

The figures used for these calculations are the averages of the two resting (control) values in each subject.

sents 2 per cent of the total. These figures speak for themselves as far as the magnitudes of cerebral blood flow and metabolism relative to the rest of the body are concerned. The changes which they would undergo under conditions of altered cerebral, muscular, and visceral activity and under the influence of drugs and other agencies are at present matters for conjecture, as are also the variations to be expected between the sexes, at different ages, and under the influence of various pathological processes involving the brain, the cardiovascular system, the metabolism, and the blood. Our findings in monkeys (18) indicated that the "physiological" range for cerebral O_2 uptake (*i.e.*, the range of variation that could be undergone without engendering irreversible or slowly reversible changes in cerebral functional activity) was from about half to nearly double the resting "normal." No comparable values for man are at present available, and even those for the monkey are subject to the restrictions imposed by the experimental procedures (anesthesia, extensive operation, systemic anticoagulants and diversion of the cerebral arterial stream into a system of glass and rubber tubing). Any of these is a potential source of reduction in cerebral blood flow and metabolism, and the effectiveness of the anesthetics in this regard was clearly demonstrated (18).

For these reasons, we suggested (18) that the highest "normal" values in the monkey were probably the proper ones to use as the basis for expectations in intact man. These values in monkeys were, for cerebral blood flow and O_2 consumption, 74 and 4.5 ml. per 100 grams per minute, which would amount to 1040 and 63 ml. per minute in a 1400-gram brain. The corresponding normal resting values obtained in the present experiments on men were 59 to 75 (mean 66) and 3.9 to 4.9 (mean 4.4) ml. per 100 grams per minute; the means for a 1400 gram brain would be 927 and 62 ml. per minute (Table V). Since the monkey experiments involved no assumptions as to the measurement of cerebral blood flow, the fact that even one of them yielded results that were as high as those obtained by a less direct method in intact men indicates that our present estimates in man probably are not excessive. It also confirms the validity of the inferences drawn from the monkey experiments.

As far as we are aware, the figures in Table V are the first of the kind to become available. They are presented as a first step toward the establishment of a new set of normals, but they are also an example of the possibilities with respect to clinical medicine of some of the methods that have been employed in recent researches related to the war effort. It is to be hoped that the collaboration among various types of laboratory workers and clinicians which has made possible the development, and utilization for specific military problems, of new technics for the quantitative measurement of various functions in normal young men, will be continued after the incentive and financial support related to the war have ceased to operate. In the opinion of the authors, one of the greatest possibilities for securing an advantage to human welfare out of the wastage of the present war lies here, for in the past advances in clinical medicine have invariably followed the introduction of new methods, and the number of these developed during the past few years is without precedent.

SUMMARY AND CONCLUSIONS

1. Hyperventilation of moderate intensity was produced either voluntarily or passively in 5 normal young men lying recumbent at sea level. The effects on the following functions were studied:

cerebral blood flow (by the N_2O method (11)), cerebral arteriovenous O_2 difference, cerebral O_2 consumption, cardiac output (by the ballistocardiograph (12)), arterial blood pressure, pulse rate, pulmonary ventilation, and total O_2 consumption.

2. Cerebral blood flow invariably diminished, the mean decreases during active and passive hyperventilation being 33 (range 12 to 44) and 35 (range 29 to 51) per cent of the control value. Cardiac output was reduced significantly (2 to 19, average 11 per cent) during passive hyperventilation, but during the active process it was maintained by a concomitant tachycardia. Blood pressure did not fall in any case and tended to rise in most, though not significantly. The cerebral arteriovenous O_2 difference invariably increased (41 to 84, average 58 per cent). Cerebral O_2 consumption showed a consistent and significant increase during active hyperventilation (5 to 35, average 15 per cent), no change during passive. Definite signs of impairment of cerebral functions were observed in 5 instances, of tetany in 3.

3. These findings support the belief that cerebral vasoconstriction is one of the important results of hyperventilation, carried out voluntarily or passively with 21 per cent O_2 in normal young men lying at rest at sea level.

4. The increase in cerebral O_2 consumption during active hyperventilation is attributed to an actual increase in cerebral metabolic activity, since no corresponding change was associated with passive hyperventilation to the same extent.

5. The mean findings for cerebral blood flow and O_2 consumption at rest, recalculated on a basis of a 1400-gram brain, came to 927 and 62 ml. per minute, which are practically identical with the highest "normal" values (1040 and 63 ml.) calculated from direct measurements in monkeys (18). This indicates that the present estimates probably are not excessive. According to these mean values, about 20 per cent of the total cardiac output and about 24 per cent of the total O_2 consumption are dedicated to the requirements of the brain (about 2 per cent of the body weight) in normal young men at physical and mental rest at sea level. The mean Qo_2 for the normal resting human brain in these subjects was 13.2 (range 11.7 to 14.7).

The collaboration of Dr. Isaac Starr in conjunction with the use of the ballistocardiograph and the interpretation of the records is gratefully acknowledged, as is that of Dr. C. K. Friedland in the performance of some of the experiments. The seven conscientious objectors used as subjects in the present study proved to be willing, cooperative, highly motivated, and unusually intelligent, and we are glad to record our appreciation of their superlative qualities for such purposes.

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