VOLUNTARY BREATHHOLDING. III. THE RELATION OF THE MAXIMUM TIME OF BREATHHOLDING TO THE OXYGEN AND CARBON DIOXIDE TENSIONS OF ARTERIAL BLOOD, WITH A NOTE ON ITS CLINICAL AND PHYSIOLOGICAL SIGNIFICANCE [1]

By EUGENE B. FERRIS, GEORGE L. ENGEL, CHARLES D. STEVENS, AND JOSEPH WEBB

(From the Departments of Internal Medicine and Psychiatry, University of Cincinnati, College of Medicine)

(Received for publication April 22, 1946)

By means of underwater weighing during breathholding, after preliminary inhalation of gas mixtures containing varying concentrations of oxygen, it has been shown that the diffusion of oxygen from the lungs is influenced by the pO_2 of the inspired air (1). It was also shown (2) that the duration of the maximum voluntary breathholding time was related to the pO_2 of inspired air. Others have shown that alveolar pCO_2 plays an important role in altering the breathholding time (3 to 5). Thus, it is evident that both pO_2 and pCO_2 are factors which influence the time that the breath can be held. Several investigators (6, 3) have studied alveolar gases during breathholding, and at the end of the apneic period produced by hyperventilation, but to our knowledge, the changes in the arterial blood have not been investigated. Despite the lack of knowledge concerning the physiologic changes which occur during breathholding, it is being used with increasing frequency as a clinical test (7 to 9).

In order to clarify the influence of oxygen and CO_2 in regulating the breathholding time, arterial blood gases have been studied during breathholding and at the time when breathing is forced. These data throw considerable light on the interrelation of oxygen and CO_2 as factors which influence respiration under the conditions studied, and on the factors which influence pulmonary diffusion of oxygen and CO_2 during breathholding.

[1] The work described in this paper was done under a contract, recommended by the Committee on Medical Research, between the Office of Scientific Research and the University of Cincinnati.

METHODS

Since it was known that the pO_2 of the gas breathed just before breathholding markedly influence the duration of breathholding and the rate of pulmonary diffusion of oxygen, 4 standard conditions were used for study: *1.* Breathholding at ground level after breathing (*a*) ambient air, or (*b*) commercial oxygen (approximately 100 per cent); *2.* Breathholding at 16,000 feet (412 mm. Hg) after breathing (*a*) ambient air, or (*b*) commercial oxygen. Oxygen was given by mask with constant flow.

The subjects were medical students and physicians. All subjects were supine, and the breathholding procedure was initiated after approximately 15 minutes' rest during exposure to the desired pO_2 to be tested. The experiments were conducted in the morning, but without reference to meals. Puncture of the femoral artery was made with an 18-gauge needle which remained in place, obturated, throughout the experiment.

After a time interval sufficient for the subject to relax from the rigors of the arterial puncture, a control arterial sample was collected. The subject then exhaled maximally, inhaled maximally, and held his breath as long as he could. Consecutive arterial samples were taken throughout the breathholding period in some instances, and in others, a sample was collected just before the end of the period. It was not possible to collect samples at the instant that breathholding terminated, but by having the subject signal, samples were collected as close to the breaking time as possible. Samples of 10 to 15 ml. of blood were taken in syringes under 3 to 5 ml. of mineral oil, and immediately transferred to mercury storage vessels containing 0.1 ml. of 30 per cent potassium oxalate, and were stored in a refrigerator until analyzed. One ml. samples were analyzed in duplicate for oxygen and CO_2 content by 2 different analysts, using the Van Slyke manometric apparatus by the method of Van Slyke and Neill (10). Determinations of pH at 36 to 38° C. were made with a MacInnes glass electrode, and Leeds and Northrup potentiometer, using 0.05 molar U. S. Bureau of Standards potassium acid phthalate as reference standard (pH 4.03 at 38° C.). Wintrobe hematocrit tubes were centrifuged 1 hour at 2500 r.p.m. to determine the percentage by volume of red cells in the blood.

The pCO_2 values were calculated using the nomogram of Hastings and Shock (11) except when the percentage of saturation of the hemoglobin with oxygen dropped below 90 per cent. In such cases, the method of calculation of Van Slyke and Sendroy (12) was employed. The percentage of saturation of the hemoglobin and the pO_2 values were calculated, using the oxygen solubility factors of Sendroy *et al.* (13) and the dissociation curves of normal human blood (14). No corrections for the oxalate were made.

RESULTS

1. *Breathholding after inhalation of room air (pO_2, 154 mm. Hg). Seven subjects.*

The results are shown in Table I and Figure 1. The marked ventilatory effect of the initial deep breath is indicated by the initial fall in CO_2 and rise in pH (cases 3, 5 and 7). Between 40 and 60 seconds was required for the CO_2 to rise above control values. After this, there was a steady rise in CO_2 and fall in pH, until breathholding was terminated. The oxygen content of arterial blood fell only slightly, except in those subjects who held the breath for relatively long periods of time. The minimum oxygen saturation was 85 per cent after 135 seconds of breathholding. The ventila-

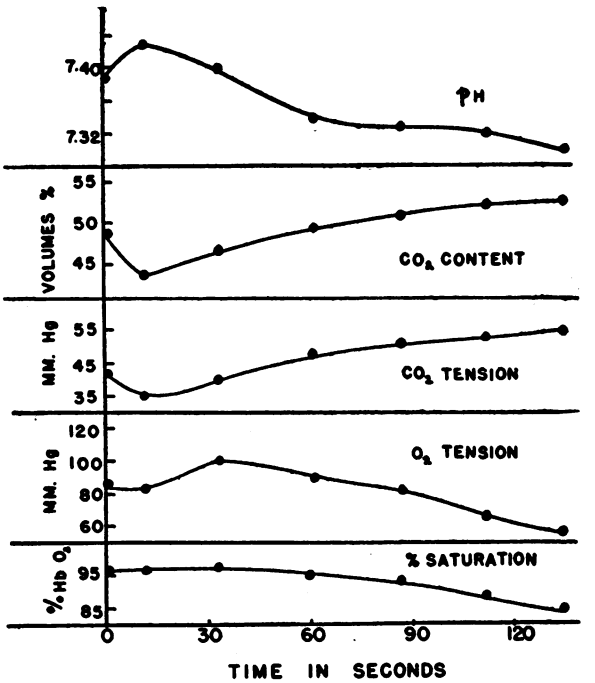

FIG. 1. SERIAL CHANGES IN ARTERIAL BLOOD GASES AND pH DURING MAXIMUM VOLUNTARY BREATHHOLDING FOLLOWING PRELIMINARY BREATHING OF ROOM AIR (pO_2, 154 MM. Hg)

TABLE I

Arterial blood gases in breathholding after initial inhalation of room air (pO_2 = 154 mm. Hg)

Subject number	Mean time from onset of breath-holding	Sampling time	Maximum breath-holding time	CO_2 content	pH	Oxygen content	Oxygen saturation of hemo-globin	pO_2 (calculated)	pCO_2 (calculated)
	seconds	*seconds*	*seconds*	*vol. per cent*		*vol. per cent*	*per cent*	*mm. Hg*	*mm. Hg*
1	Control			44.8	7.41	20.0	94	77	39
	103	25	120	47.9	7.35	19.4	91	70	48
2	Control			46.1	7.33	20.1	98	123	46
	120	10	120	49.6	7.32	19.0	93	77	51
3	Control			45.0	7.33	19.6	93	79	51
	13	19		39.8	7.44	19.8	94	81	35
	63	12	75	46.5	7.32	19.6	93	79	54
4	Control			46.3	7.39	19.9	98	115	41
	103	15	110	50.3	7.32	19.3	96	70	52
5	Control			49.1	7.38	19.2	100	82	43
	21	9		42.1	7.47	18.7	98	64	32
	35	12		47.3	7.40	19.1	100	80	40
	57	7		49.1	7.40	18.9	99	74	41
	81	9		50.0	7.35	18.8	98	76	48
	109	8	105	50.6	7.35	18.6	97	74	47
6	Control			49.7	7.37	18.6	98	115	46
	145	10	155	53.9	7.31	17.0	90	66	57
7	Control			48.5	7.39	17.3	96	86	42
	11	12		44.1	7.43	17.2	96	84	35
	33	14		47.0	7.40	17.5	97	100	40
	61	15		49.5	7.34	17.2	95	90	48
	87	19		51.0	7.33	16.9	94	82	51
	112	16		52.1	7.32	16.1	89	67	53
	135	11	141	52.6	7.30	15.4	85	58	55

TABLE II

Arterial blood gases in breathholding after initial inhalation of ambient air at 16,000 feet (pO_2 = 85 mm. Hg)

Subject number	Mean time from onset of breath-holding	Sampling time	Maximum breath-holding time	CO_2 content	pH	Oxygen content	Oxygen saturation of hemo-globin	pO_2 (calculated)	pCO_2 (calculated)
	seconds	*seconds*	*seconds*	*vol. per cent*		*vol. per cent*	*per cent*	*mm. Hg*	*mm. Hg*
1	Control			43.6	7.41	16.4	78	43	38
	79	22	91	46.2	7.40	14.0	67	34	41
2	Control			48.1	7.41	15.2	75	41	41
	83	10	88	49.6	7.40	14.5	72	38	43
3	Control			46.1	7.42	13.9	66	34	43
	12	16		40.7	7.48	17.6	84	46	33
	56	12	62	46.1	7.40	13.6	65	34	44
5	Control			45.1	7.48	16.0	84	40	33
	59	8	65	47.3	7.44	14.1	74	34	36
6	Control			48.8	7.42	14.0	74	40	40
	12	10		45.4	7.49	17.0	88	50	32
	37	14		49.8	7.41	14.5	77	43	42
	63	18		51.0	7.41	12.6	67	34	43
	91	18		51.5	7.41	10.8	57	29	44
	122	24	140	53.3	7.40	8.4	44	24	46
7	Control								
	16	8		47.6	7.42	12.0	67	34	38
	84	13	90	51.1	7.39	8.3	46	25	42
8	Control			48.5	7.41	15.0	70	35	46
	67	10	72	49.9	7.39	13.9	65	33	49
9	Control			45.6	7.43	15.9	83	49	41
	65	16	75	49.4	7.41	14.4	75	41	47
10	Control			47.8	7.43	14.2	80	44	41
	60	10	68	49.8	7.43	12.0	68	34	44

tory effect of the initial deep breath is barely evident in so far as oxygen content is concerned, presumably because the resulting increase in pO_2 has little effect in increasing the oxygen content.

2. Breathholding after inhalation of ambient air at 16,000 feet (pO_2, 85 mm. Hg). Ten subjects.

The results are shown in Table II and Figure 2. The maximum breathholding time of each subject is definitely shorter than that after preliminary inhalation of ambient air. In 7 subjects who had both tests, the average breathholding time after inhalation of room air was 120 seconds, and after inhalation of ambient air at 16,000 feet, was 90 seconds. The ventilatory effect of the initial deep breath is now evident not only with respect to arterial CO_2 and pH, but also with respect to oxygen content. The control values for arterial oxygen saturation averaged 80.5 per cent at this altitude, so that changes in pO_2 resulting from the deep breath produced larger changes in the oxygen content of arterial blood. The total change in arterial CO_2 and pH was less than after inhalation of room air, because of the shortened breathholding time, but the rate of rise in CO_2 content was essentially the same. The oxygen content, however, fell consistently at a much faster rate than after initial inhalation of room air, and reached levels as low as 46 per cent saturation in 84 seconds.

3. Breathholding after inhalation of 100 per cent oxygen at an altitude of 16,000 feet (pO_2, 410 mm. Hg). Four subjects.

The results are shown in Table III. The rate of change in CO_2 content and pH appears to be similar to the above categories. However, higher levels of CO_2 and lower levels of pH were reached because of the longer periods of breathholding.

TABLE III

Arterial blood gases in breathholding after initial inhalation of 100 per cent oxygen at 16,000 feet (pO_2 = 410 mm. Hg)

Subject number	Mean time from onset of breath-holding	Sampling time	Maximum breath-holding time	CO_2 content	pH	Oxygen content	Oxygen saturation of hemo-globin	pO_2 (calculated)	pCO_2 (calculated)
	seconds	*seconds*	*seconds*	*vol. per cent*		*vol. per cent*	*per cent*	*mm. Hg*	*mm. Hg*
3	Control			45.5	7.31	21.1	100	130	54
	12	20		40.7	7.42	20.9	100	120	38
	67	21	100	47.0	7.31	21.0	100	130	56
8	Control			44.8	7.42	21.8	100	121	42
	118	19	130	50.9	7.32	22.2	100	260	60
9	Control			41.7	7.50	21.1	100		32
	205	16	215	53.0	7.31	21.0	100		64

Despite the relatively long periods of breathholding, there was no measurable change in the arterial oxygen content after periods of breathholding up to 205 seconds.

4. Breathholding after inhalation of 100 per cent oxygen at ground level (pO_2, 740 mm. Hg). Four subjects.

The results are shown in Table IV, Figure 3. As compared to breathholding after inhaling room air, the breathholding time was prolonged in each subject (average of 114 seconds after inhalation of room air, and of 214.5 seconds after inhalation of 100 per cent oxygen on the ground). The rate of change in CO_2 content and pH were again similar to the other categories; however, the oxygen content and saturation remained unchanged after periods of breathholding as long as 241 seconds.

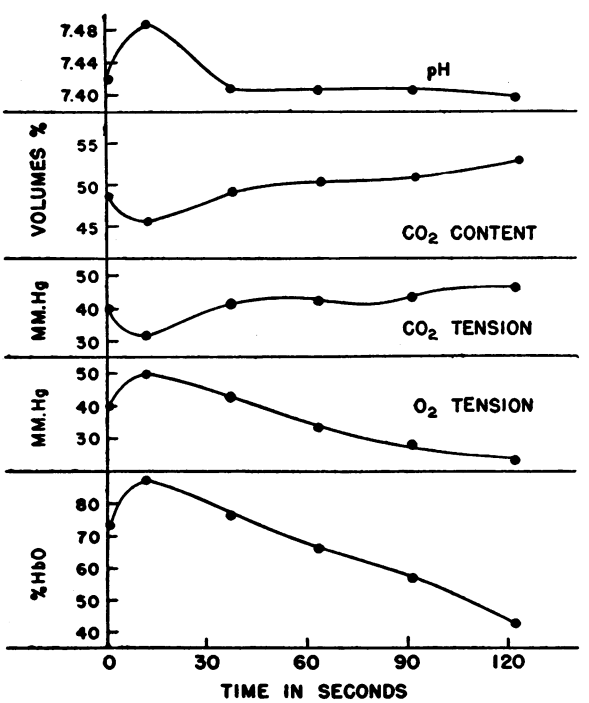

FIG. 2. ARTERIAL BLOOD CHANGES DURING BREATHHOLDING AFTER INHALATION OF AMBIENT AIR AT 16,000 FEET (pO_2, 85 MM. HG)

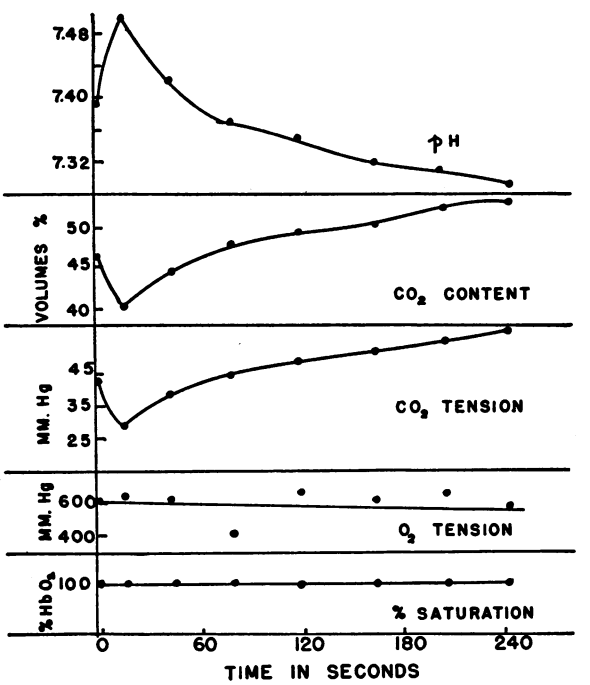

FIG. 3. ARTERIAL BLOOD CHANGES DURING BREATHHOLDING AFTER PRELIMINARY INHALATION OF 100 PER CENT OXYGEN (pO_2, 740 MM. HG)

The above results may be summarized as showing that during breathholding after inhalation of

TABLE IV

Arterial blood gases in breathholding after initial inhalation of 100 per cent oxygen at ground level (pO_2 = 740 mm. Hg)

Subject number	Mean time from onset of breath-holding	Sampling time	Maximum breath-holding time	CO_2 content	pH	Oxygen content	Oxygen saturation of hemo-globin	pO_2 (calculated)	pCO_2 (calculated)
	seconds	*seconds*	*seconds*	*vol. per cent*		*vol. per cent*	*per cent*	*mm. Hg*	*mm. Hg*
1	Control								
	213	25	227	52.3	7.25	22.1	100	440	63
2	Control			46.4	7.39	21.5	100	430	41
	200	10	205	51.6	7.29	22.0	100	310	55
4	Control			46.7	7.37	21.8	100	610	43
	18	15		40.3	7.50	21.9	100	650	29
	44	18		45.4	7.42	21.8	100	630	38
	80	25		48.0	7.37	22.2	100	410	45
	121	22		49.7	7.35	21.9	100	660	49
	163	35		50.1	7.32	21.8	100	620	51
	207	27		52.1	7.31	21.9	100	650	55
	241	22	256	52.4	7.29	21.7	100	580	58
5	Control			44.6	7.45	20.6	100	257	35
	161	12	170	51.5	7.31	20.8	100	330	53

varying pO_2, the arterial CO_2 content and pH rise steadily, and that the final value reached depends upon the duration of breathholding. The arterial oxygen content falls rapidly to very low levels during breathholding after inhalation of 10 per cent oxygen, falls less rapidly after inhaling 21 per cent oxygen, and falls little, if any, after inhalation of supra-normal mixtures, despite the fact that the breath is held for progressively longer periods of time.

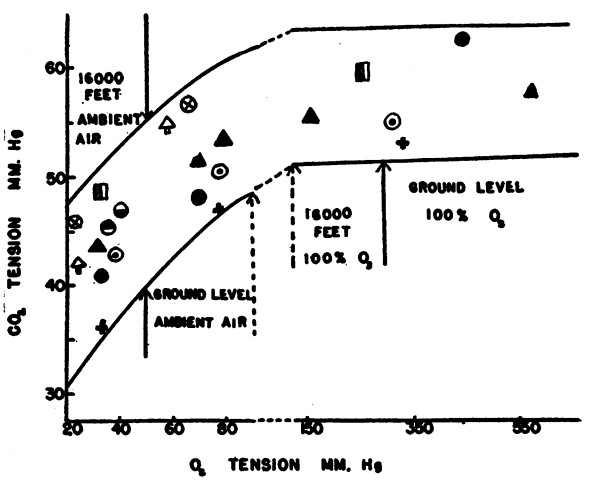

FIG. 4. THE INTERRELATION OF ARTERIAL BLOOD pO_2 AND pCO_2 AT THE TERMINATION OF MAXIMUM VOLUNTARY BREATHHOLDING, AFTER PRELIMINARY BREATHING OF VARIABLE TENSIONS OF OXYGEN

Each type of symbol represents an individual subject.

The arterial blood gas levels at the end of voluntary breathholding are consistent with the alveolar gas tensions which Douglas and Haldane (6) obtained at the end of the apneic period induced by hyperventilation. They noted that at alveolar pO_2 values above 120 mm. Hg, the apnea terminated when the pCO_2 reached 45 to 50 mm. Hg, while at pO_2 levels below 120 mm. Hg, the pCO_2 at the end of apnea varied with the pO_2.

DISCUSSION

It has been shown that during breathholding the rate of exchange of gas between the lungs and the blood is relatively constant. When the arterial gas findings during breathholding after inhalation of varying pO_2 are considered together, it is clear that the oxygen is falling, and the CO_2 and pH are rising, the former at a rate dependent chiefly upon the pO_2 of inspired air and the oxygen dissociation curve of arterial blood, and the latter 2 at a more constant rate, dependent chiefly on CO_2 production and the CO_2 dissociation curve, once the transient effect of the initial deep breath is over. Since the breathholding time (breaking point) varies with the pO_2 of inspired air (2), we are, in effect, studying the interrelation of arterial oxygen and CO_2 as respiratory stimulants with both variables changing: CO_2 at a relatively constant rate under all conditions studied, and oxygen at a variable rate, dependent upon

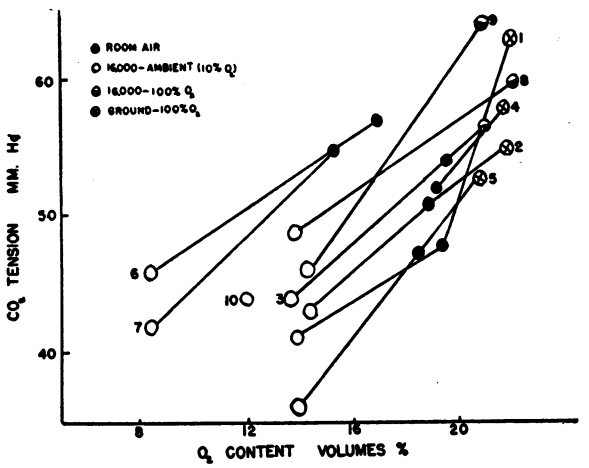

FIG. 5. THE INTERRELATION OF ARTERIAL BLOOD OXYGEN CONTENT AND pCO_2 AT THE TERMINATION OF MAXIMUM VOLUNTARY BREATHHOLDING

The lines joining the symbols represent individual subjects numbered according to the tables.

both the pO_2 of inspired air and the arterial oxygen dissociation curve.

When the arterial pCO_2 and pO_2 at the breaking point are related as factors in inducing breathing (Figure 4), there appears to be some interrelation at arterial pO_2 below 100 mm. Hg, but very little at higher pO_2. However, when the arterial pCO_2 is plotted against oxygen *content* of arterial blood, instead of pO_2 (Figure 5), a series of parallel lines are obtained, which indicate a fairly constant interrelation of pCO_2 and oxygen content to the breaking point, regardless of the pO_2 of initially inspired air. Inspection of the curve denoting the relationship of the pO_2 of initially inspired air to the breathholding time (2, Figure 2) shows that its shape is roughly like that seen in Figure 4. If the values for pO_2 of inspired air (2, Figure 2) are calculated in terms of the approximate oxygen content of whole blood to be expected, and this plotted against breathholding time, again the relationship of oxygen content of whole blood to the breathholding time becomes a relatively constant one at all pO_2's breathed (Figure 6).

By utilizing varying amounts of hyperventilation, Mirsky and Grinker (15) have recently tested the effect of variable initial pCO_2 at relatively constant initial pO_2 of inspired air, on the breathholding time, and have found that the breathholding time varies with the amount of hyperventilation. Others (3 to 6) have also demonstrated the effect of CO_2 on the breathholding time; in fact, hyperventilation is an age-old method for lengthening the breathholding time.

It would appear, then, that in so far as breathholding time is concerned, arterial oxygen and CO_2 are interrelated as factors which initiate breathing, regardless of the range of the pO_2 and pCO_2 of the inspired air and blood, but that the influence of pO_2 becomes less and less as it rises above normal (about 100 mm. Hg). The interrelation becomes a reasonably constant one if the oxygen is considered in terms of oxygen content of whole arterial blood, and hence, of the ability of the blood to deliver a given volume of oxygen to the tissues in order to maintain an adequate pO_2 there. Such a relation is quite consistent with the concept that the stimulus to breathe is dependent on the metabolic state of the cells of the respiratory centers, and that pO_2 and pCO_2 in the blood influence respiration to the extent that they influence the metabolic requirements of the centers. Higher pO_2 of inspired air and blood become less and less effective in increasing the breathholding time, because once the hemoglobin is saturated, additional oxygen can be delivered to the tissues only to the extent that it dissolves in blood plasma.

THE CLINICAL AND PHYSIOLOGICAL SIGNIFICANCE OF BREATHHOLDING

Since the observations presented in the 3 papers of this series include related phases of the phenomenon of breathholding, it is perhaps well to discuss the clinical and physiological significance of these findings together. Of particular significance are those findings related to diffusion of gas through the lungs, and those concerned with the interrelation of oxygen and CO_2 in stimulating the taking of a breath.

During breathholding over the periods of time utilized in these experiments, it is evident that the bellows effect of breathing is eliminated, and the passage of oxygen and CO_2 between the pulmonary dead space and the arterial blood is essentially a phenomenon of diffusion. Since, under normal conditions, the tensions in the alveoli are essentially

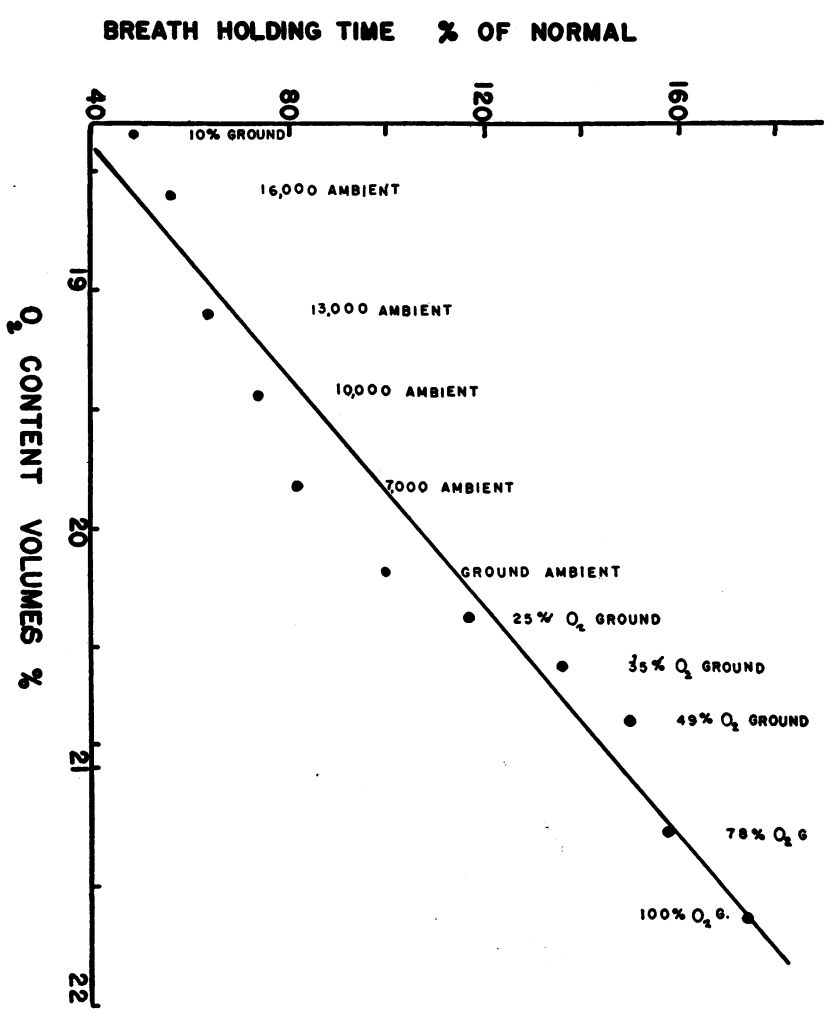

FIG. 6. THE RELATION OF THE BREATHHOLDING TIME TO THE INITIAL OXYGEN CONTENT OF WHOLE ARTERIAL BLOOD

Calculated from the pO_2 of the inspired air preliminary to breathholding. The calculations were made from the data in Paper II.

the same as in arterial blood,[2] the pulmonary diffusion gradient can be assumed to lie largely between the pulmonary dead space and the alveoli. Therefore, for purposes of this discussion, pulmonary diffusion will be treated as a phenomenon of gaseous diffusion within the tubular structures of the lung. Since, at most, only a minor portion of the total pulmonary diffusion gradients for CO_2 and oxygen can lie between the alveoli and arterial blood (membrane diffusion), the neglect of this factor, by assuming arterial and alveolar tensions to be equal, will not alter the basic principles to be evolved from the data at hand.

In analyzing the fate of oxygen and CO_2 in both lungs and arterial blood, and the factors which influence their passage during breathholding, it is necessary to consider whether oxygen consumption and CO_2 production by the tissues is significantly altered under the conditions studied. Variations of pO_2 over the range of these experiments apparently does not influence significantly either oxygen consumption or CO_2 production (16, 17). The similarity in the rates of arterial CO_2 retention at the different pO_2 of inspired air, likewise

[2] The similarity between alveolar and arterial pCO_2 is well established; however, only recently has it been demonstrated that there is no significant physiological difference between alveolar and arterial pO_2 (22).

suggests that variations in oxygen consumption and CO_2 production are not of importance in influencing the results of these experiments.

Likewise, variations in cardiac output, due either to mechanical or chemical factors, can scarcely be of importance in influencing our results. Since the technique of breathholding was similar under all conditions, mechanical effects on cardiac output cannot explain the variations caused by altering the pO_2 of inspired air. Although variations in cardiac output, pulse rate and blood pressure may result from breathholding, these effects are relatively insignificant, except in the so-called group of hyper-reactors (7).

It has generally been assumed that CO_2 diffuses much more rapidly than oxygen through the body. This is undoubtedly true as it applies to diffusion of CO_2 in solution in body fluids (18). However, these studies show conclusively that in so far as gaseous CO_2 is concerned, it diffuses much more slowly through the lungs than does oxygen, not only when the pO_2 of inspired air is normal or supranormal, but even when it is reduced. There are 2 reasons for this. First, CO_2 has a larger molecular weight than oxygen, and hence its coefficient of diffusion is less. ($CO_2 = 0.139$ sq. cm. per second; oxygen = 0.178 sq. cm. per second.) Second, when one compares the relative diffusion gradients of CO_2 and oxygen between the pulmonary dead space and the alveoli under the conditions of these experiments, it is evident that the diffusion gradient for CO_2 may be much less than that for oxygen.

The gaseous diffusion gradient in the lungs, P_d, equals $P_1 - P_2$, where $P_1(CO_2)$ is the pCO_2 in the alveolus (or arterial blood), and $P_2(CO_2)$ is the pCO_2 in the pulmonary dead space. $P_1(O_2)$ is the pO_2 in the pulmonary dead space, and $P_2(O_2)$ is the pO_2 in the alveolus (or arterial blood).

At the beginning of breathholding after a deep breath, $P_1(CO_2)$ is about 34 mm. Hg (see charts), and $P_2(CO_2)$ can be assumed to be zero or greater. As the breath is held, $P_1(CO_2)$ gradually rises, but is less than 60 mm. Hg, even after 4 minutes of breathholding. During this period $P_2(CO_2)$ probably rises slowly, but cannot fall; hence, the maximum CO_2 diffusion gradient during breathholding is less than 60 mm. Hg, and is probably of the order of 34 mm. Hg, under all the conditions of these experiments. Since $P_2(CO_2)$ cannot be less than zero, the limitation of the CO_2 diffusion gradient is largely controlled, therefore, by the CO_2 dissociation of blood, which allows the CO_2 being produced to dissolve in the blood with a relatively small increase in $P_1(CO_2)$.

After the initial deep breath $P_1(O_2)$ is about 700 mm. Hg after 100 per cent oxygen inhalation, 150 mm. Hg after inhalation of room air, and 85 mm. Hg after inhalation of air at 16,000 feet. All these pressures are much higher than $P_1(CO_2)$. As for $P_2(O_2)$ it is roughly 400 to 500 mm. Hg after 100 per cent inhalation of oxygen, 100 mm. Hg after inhalation of room air, and 50 mm. Hg after inhalation of air at 16,000 feet. While a decrease in $P_2(CO_2)$ is limited by the fact that it cannot fall below zero, $P_2(O_2)$ can be decreased markedly, depending on the oxygen dissociation curve of whole blood and the oxygen consumption. At normal or higher pO_2 of inspired air $P_2(O_2)$ can fall greatly with relatively slight change in oxygen content. Thus, as compared to CO_2, the initial pulmonary oxygen diffusion gradient is high, and the arterial oxygen dissociation is such that a relatively high pO_2 gradient can readily be maintained during breathholding. Since the rate of change in lung volume during breathholding, which is largely due to oxygen diffusion, is constant (1), it may be assumed that the oxygen diffusion pressure gradient established at the beginning of breathholding remains relatively constant throughout.

Both these diffusion factors, diffusion gradient and diffusion coefficient, tend to cause oxygen to diffuse more rapidly than CO_2 through the lungs, and offer an explanation of why, during breathholding, oxygen diffuses out of the lungs infinitely more rapidly than CO_2 diffuses into the lungs. Moyer and Beecher (19) came to a similar conclusion with respect to inhalation of 100 per cent oxygen in dogs anesthetised with barbiturates, when they found that the CO_2 content of arterial blood rose, while the oxygen saturation remained normal, during depressed breathing. Our observations would suggest that even at normal pO_2 of inspired air (21 per cent oxygen), oxygen can be taken in more effectively than CO_2 can be eliminated, when the need arises. This is consistent with many observations, indicating that, under physiologic conditions, respiratory ventilation is influenced more by changes in pCO_2 of in-

spired air and arterial blood, than by comparable changes in pO_2, for during homeostasis, breathing must be adjusted primarily to equilibrate the least diffusible gas, namely CO_2. It does not necessarily mean, however, that the respiratory centers are more sensitive to changes in CO_2 than to oxygen, as many observers have concluded. As our data indicate, the error in this reasoning lies in the fact that the pCO_2 and pO_2 in the tissues is related to the tension of these gases in the alveoli and blood principally, according to the capacity of the blood to carry these gases in quantities consistent with metabolic demands.

Because of the fact that respiration serves as a homeostatic mechanism, and the bellows effect of breathing adjusts itself to maintain the blood and tissue gas tensions at optimum levels for tissue function, the blood gases do not reflect functional changes in pulmonary exchange until an extreme degree of impairment is present. While such clinical measurements as respiratory rate, tidal air, vital capacity, lung volume, complemental and supplemental air, and respiratory minute volume are undoubtedly of great clinical value in estimating pulmonary function, yet a clear understanding of the significance of these tests in terms of diffusion capacity of the lungs is lacking. Direct measurements of changes in lung volume and/or arterial blood gases during breathholding should lead to a better understanding of the diffusion capacity of the lungs in health and disease.

The specific effects of oxygen and CO_2 on the breathholding time suggest, also, that the duration of voluntary breathholding may offer a simple means for studying respiratory factors in unanesthetized man. The finding that oxygen and CO_2 are reciprocally interrelated with respect to respiratory activity in an organized fashion over a wide range of pO_2 and pCO_2, tends to clarify a great deal of the controversy concerning the relative effects of oxygen lack and CO_2 as respiratory stimulants. Recent reviews of this subjects have been written by Bernthal (21) and Schmidt (22). Our observations indicate that in so far as respiratory activity after breathholding is concerned, the composite respiratory mechanism has no true threshold for either oxygen or CO_2 nor is there any particular point where oxygen lack or CO_2 alternately take over control of respiration, when considered in the light of the capacity of the blood to carry oxygen and CO_2 to and from the respiratory centers. In so far as the breathholding time is concerned, the effects of oxygen and CO_2 (or pH) on it can best be explained by their alteration of the tonic activity of the respiratory tissues in response to metabolic need.

In utilizing the breathholding time as an index of respiratory activity, it must be recognized that there are many factors which influence it, some related to chemical factors, and some probably not.

For instance, under controlled conditions with respect to preliminary breathing, oxygen content of inspired air, learning, etc. the breathholding time has varied from 56 to 167 seconds among our normal subjects. In some of our subjects, it has varied significantly from time to time. When the breath is held after an initial inspiration, the breathholding time is longer than after an initial expiration. Breathholding time appears to correlate poorly with vital capacity (5) and exercise tolerance tests (20). Schneider (5) feels that psychological factors play an important role in determining the breathholding time. Mirsky and Grinker (15) have compared the breathholding time in normal controls with that of patients suffering from anxiety states. They found that the mean breathholding time was significantly lower in the anxious group than in the normals. Whether these differences in the breathholding time of normal and anxious individuals are related to differences in metabolic requirements in the 2 groups, or to differences in their ability consciously or unconsciously to withstand the increasingly unpleasant sensations incident to breathholding, cannot be established at this time.

The variability of the breathholding time within and among individuals does not preclude it as a useful clinical test, but does indicate the restrictions which must be placed on its use as a means of studying respiratory mechanisms in conscious human subjects, and the need to learn more about the factors which control the breathholding time.

SUMMARY AND CONCLUSIONS

1. Serial measurements of oxygen, CO_2, and pH of arterial blood throughout the period of maximum voluntary breathholding have been made, after preliminary inhalation of oxygen mixtures varying from pO_2 of 85 to 740 mm. Hg.

2. Oxygen and CO_2 are interrelated as factors which influence the breathholding time, regardless of the relative tensions of either of these gases in the blood. The effectiveness of supra-normal pO_2 in lengthening the breathholding time is lessened, not because oxygen loses its action on respiratory tissues, but because once the hemoglobin is saturated, the blood is less effective in delivering additional oxygen to the tissues.

3. The observations presented in these 3 papers suggest that breathholding technics may be applied to the study of pulmonary diffusion, and of factors related to respiratory control in man.

We are indebted to Jane K. Friedlander for her technical assistance.

BIBLIOGRAPHY

1. Stevens, C. D., Ferris, E. B., Webb, J. P., Engel, G. L., and Logan, M., Voluntary breathholding. I. Pulmonary gas exchange during breathholding. J. Clin. Invest., 1946, **25**, 723.
2. Engel, G. L., Ferris, E. B., Webb, J. P., and Stevens, C. D., Voluntary breathholding. II. The relation of the maximum time of breathholding to the oxygen tension of inspired air. J. Clin. Invest., 1946, **25**, 729.
3. Hill, L., and Flack, M., The effects of excess carbon dioxide and of want of oxygen upon the respiration and circulation. J. Physiol., 1908, **37**, 77.
4. Haldane, J. S., and Priestley, J. G., Respiration. Yale University Press, New Haven, 1935.
5. Schneider, E. C., Observations on holding the breath. Am. J. Physiol., 1930, **94**, 464.
6. Douglas, C. G., and Haldane, J. S., The regulation of normal breathing. J. Physiol., 1909, **38**, 420.
7. Ayman, D., and Goldshine, A. D., The breath-holding test. A simple standard stimulus of blood pressure. Arch. Int. Med., 1939, **63**, 899.
8. Friedman, M., Studies concerning the etiology and pathogenesis of neurocirculatory asthenia. Am. Heart J., 1945, **30**, 557.
9. Gubner, R., Silverstone, F., and Ungerleider, H. E., Range of blood pressure in hypertension. J. A. M. A., 1946, **130**, 325.
10. Van Slyke, D. D., and Neill, J. M., The determination of gases in blood and other solutions by vacuum extraction and manometric measurement. J. Biol. Chem., 1924, **61**, 523.
11. Hastings, A. B., and Shock, N., Studies of the acid-base balance of the blood. II. A nomogram for calculation of acid-base data for blood. J. Biol. Chem., 1934, **104**, 575.
12. Van Slyke, D. D., and Sendroy, J., 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., 1928, **79**, 781.
13. Sendroy, J., Dillon, R. T., and Van Slyke, D. D., Studies of gas and electrolyte equilibria in blood. XIX. The solubility and physical state of uncombined oxygen in blood. J. Biol. Chem., 1934, **105**, 597.
14. Bock, A. V., Field, J., Jr., and Adair, G. S., The oxygen and carbon dioxide dissociation curves of human blood. J. Biol. Chem., 1924, **59**, 353.
15. Mirsky, I. A., and Grinker, R., Breathholding time in anxiety states. Fed. Proc., 1946, **5**, 74.
16. Lusk, G., Science of Nutrition. W. B. Saunders, Philadelphia, 4th Edition, 1928.
17. Dubois, E. F., Basal Metabolism in Health and Disease. Lea and Febiger, Philadelphia, 3rd Edition, 1936.
18. Krogh, A., The rate of diffusion of gases through animal tissues, with some remarks on the coefficient of invasion. J. Physiol., 1919, **52**, 391.
19. Moyer, C. A., and Beecher, H. K., Effects of barbiturate anesthesia (evipal and pentothal sodium) upon the integration of respiratory control mechanisms. J. Clin. Invest., 1942, **21**, 429.
20. Karpovich, P. V., Relation between breathholding and endurance in running and the Harvard step-up test score. Fed. Proc., 1946, **5**, 53.
21. Bernthal, T., Respiration. Ann. Rev. Physiol., 1944, **6**, 155.
22. Schmidt, C. F., Respiration. Ann. Rev. Physiol., 1945, **7**, 231.