# 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]

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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.

## 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-
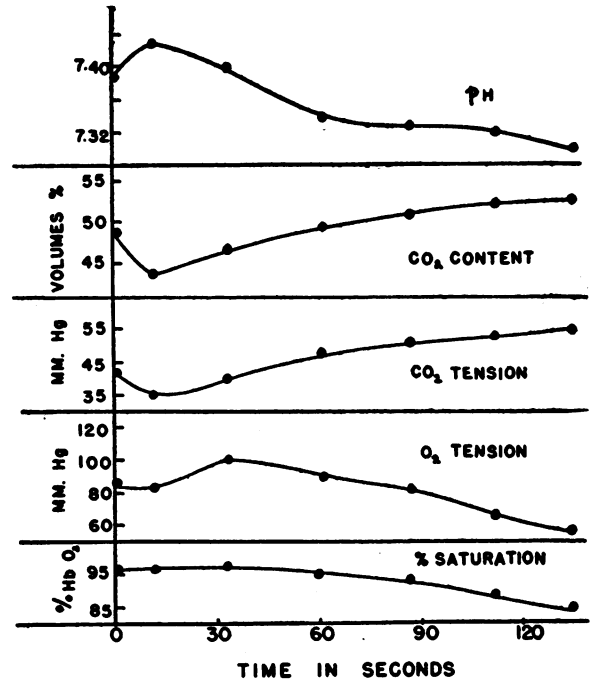


FIG. 1. SERIAL CHANGES IN ARTERIAL BLOOD GASES AND pH DURING MAXIMUM VOLUNTARY BREATHHOLDING FOLLOWING PRELIMINARY BREATHING OF ROOM AIR (pO$_2$, 154 MM. HG)

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 hemoglobin | 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 | CO₂ content | pH | Oxygen content | Oxygen saturation of hemo-globin | pO₂ (calculated) | pCO₂ (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
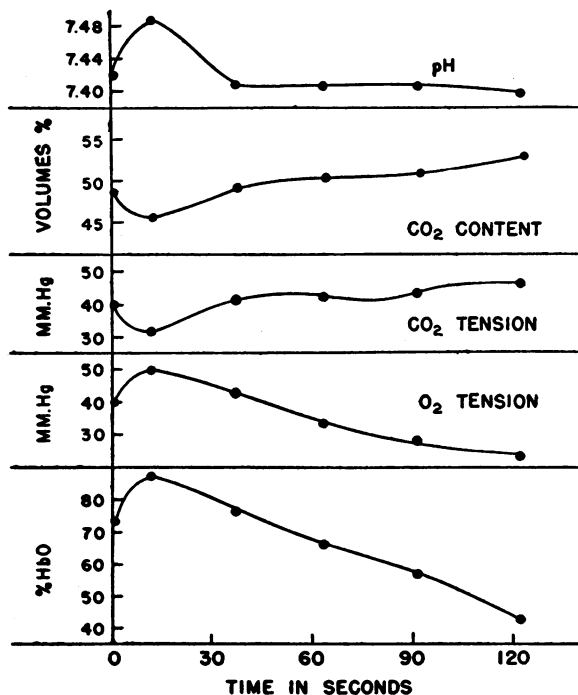


FIG. 2. ARTERIAL BLOOD CHANGES DURING BREATHHOLDING AFTER INHALATION OF AMBIENT AIR AT 16,000 FEET ($pO_2$, 85 MM. HG)
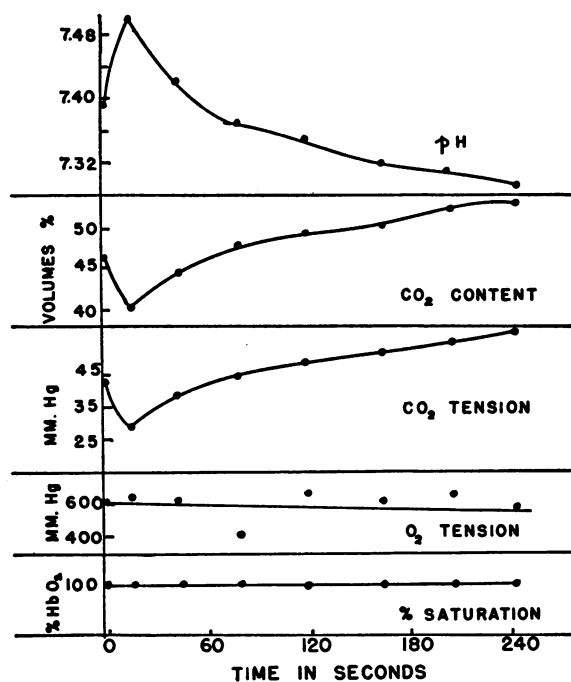


FIG. 3. ARTERIAL BLOOD CHANGES DURING BREATHHOLDING AFTER PRELIMINARY INHALATION OF 100 PER CENT OXYGEN ($pO_2$, 740 MM. HG)

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.

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 | CO2 content | pH | Oxygen content | Oxygen saturation of hemoglobin | pO2 (calculated) | pCO2 (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
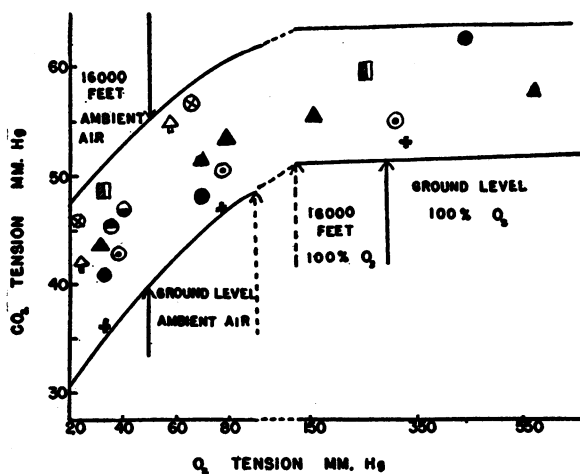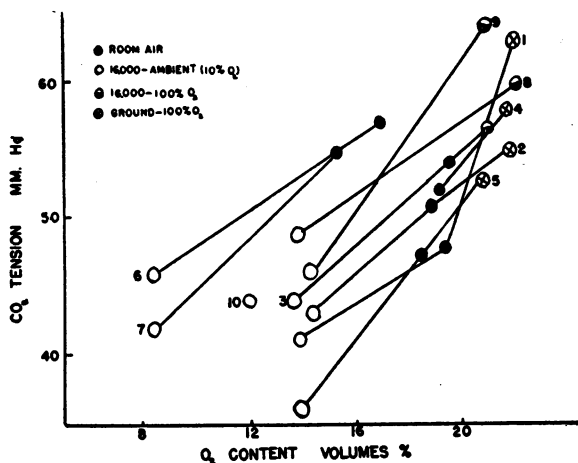
FIG. 5. THE INTERRELATION OF ARTERIAL BLOOD OXYGEN CONTENT AND $pCO_2$ AT THE TERMINATION OF MAXIMUM VOLUNTARY BREATHHOLDING

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
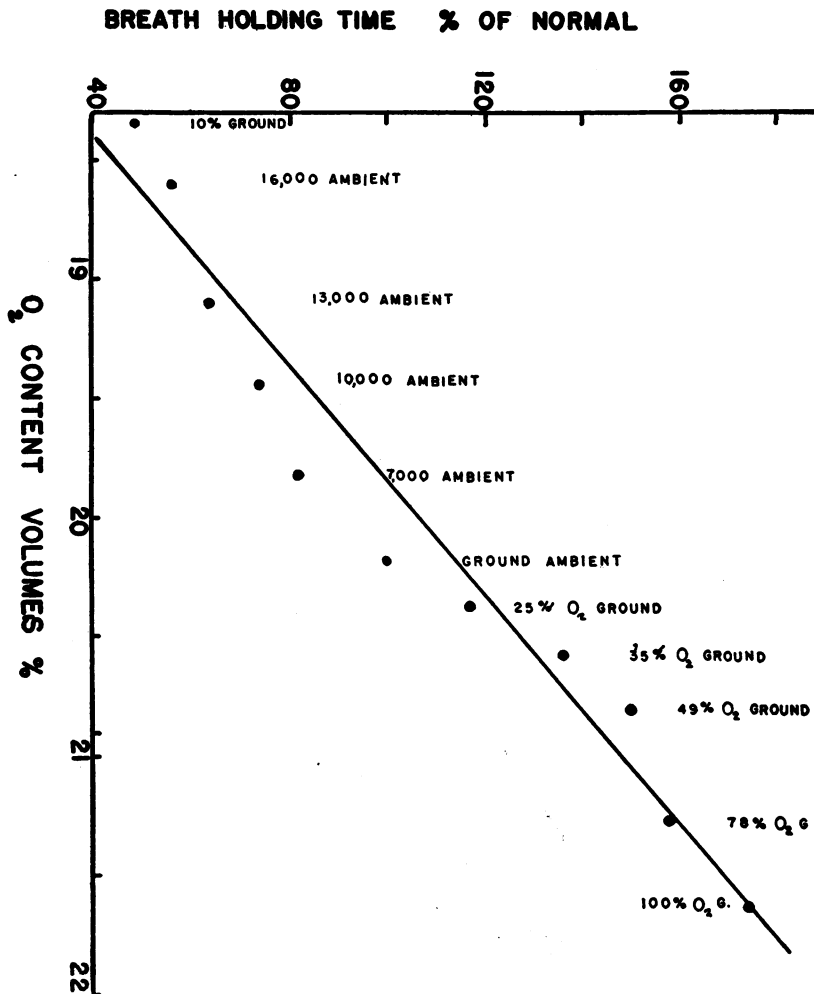
**BREATH HOLDING TIME    % OF NORMAL**



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

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[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.

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