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DIAPHRAGM ACTIVITY AND THORACOABDOMINAL MECHANICS DURING POSITIVE PRESSURE BREATHING

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FOREWORD

Dr. Emilio Agostoni was Principal Investigator for the research documented in this report. Significant contributions were made by Dr. Rodolfo Margaria and Dr. E. J. M. Campbell. The investigations were conducted by the Instituto di Fisiologia umana, Universita di Milano, Milano, Italy, under the terms of Grant Number AF-EOAR 62-95, administered by the European Office of Aerospace Research (AF EOAR). Major C. H. Kratochvil was the Project Officer representing EOAR. The Research was accomplished during the period from 1 February 1962 - 1 February 1963.

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PUBLICATION REVIEW

This technical report has been reviewed and is approved.

WAYNE H. McCANDLESS
Technical Director
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SECTION II

ABSTRACT

The electrical activity of the diaphragm and the mechanical contribution of the thorax and the abdomen through the breathing cycle have been investigated in man during positive pressure breathing (PPB). The electrical activity of the diaphragm persists even at values at which inspiration should be completely passive according to the pressure volume diagram of the thorax and lung. The transdiaphragmatic pressure decreases as the value of PPB increases, but is still appreciable at values of PPB at which the inspiration appears to be completely passive by an analysis based on transthoracic pressure measurements alone. The transdiaphragmatic pressure becomes zero only at a PPB of about 30 cm water. The persistent activity of the diaphragm during PPB is counterbalanced by an activity of the abdominal muscles in excess of that of the expiratory muscles as given by transthoracic pressure measurements. Owing to the persistence of a thoracoabdominal pressure gradient the venous return, and therefore the cardiac output, should be less reduced than in the case of a passive inspiration. The activity of the abdominal muscles is not necessarily initiated by the respiratory control system. Similarly, during PPB, the activity of the abdominal muscles could be a tonic reflex against the background of which the diaphragm behaves in its usual way. The electrical activity of the diaphragm during breath holding has been studied. After a period of no, or only slight, tonic activity a marked discharge is recorded, this is followed by others at a progressively higher rate up to the breaking point. The action of the diaphragm, not balanced by antagonist muscles, causes a fall of the intrathoracic pressure. The standard error (SE) of alveolar P_{CO_2} values determined at the onset of diaphragm activity in groups of three similar tests is <0.5 mm Hg. Arterial P_{CO_2} in the brain stem at the onset of diaphragm activity has been estimated. In three subjects breathing O_2 the mean values $\pm$SE were respectively, 46.2 ± 0.3, 46.4 ± 0.2, and 50.2 ± 0.2. The onset of diaphragm activity does not seem affected by neurogenic factors related to lung volume or respiratory movements. An alveolar $P_{CO_2} - P_{O_2}$ curve at the onset of diaphragm activity has been determined.

SECTION I

Diaphragm activity and thoracoabdominal mechanics during positive pressure breathing

INTRODUCTION

DURING POSITIVE PRESSURE BREATHING (PPB) inspiration becomes passive and expiration active, as illustrated by the pressure-volume diagram of the respiratory system (1). Endopulmonary or intrathoracic pressure measurements, however, cannot inform us whether the inspiratory and expiratory muscles are acting simultaneously; they give, in fact, only the resultant of all the muscular forces acting upon the system. Furthermore, no direct evidence of the activity of the respiratory muscles during PPB is available.

It is the purpose of this research to investigate in man during PPB *a*) the electrical activity of the diaphragm and *b*) the mechanical relationships between thorax and abdomen, as given by measuring the transdiaphragmatic, transthoracic, and transabdominal pressures through the breathing cycle (2).

METHODS

The subject breathed from a large tank (760 liters) in which the pressure was kept above atmospheric by means of a pump and an adjustable outlet. The pressure in the tank was constant during the test within 1 cm H_2O, the respiratory oscillations ranging from 1 to 3 cm H_2O. The positive pressure in the tank to which the observations will be referred is that at the end of expiration. Experiments were made with pressures up to 30 cm H_2O. In all experiments the subject was in the same sitting position, rebreathing from the tank through a low-resistance pneumotachograph (0.3 cm H_2O/liter/sec) and a large three-way stopcock. The instrumental dead space was 120 ml. The CO_2 in the tank near the connecting tube was lower than 0.1% after 10 min of rebreathing. The records were taken 4–5 min after connecting the subject to the positive pressure. External compression of the abdomen was avoided.

Observations on the electrical activity of the diaphragm were carried out on six subjects (five men and one woman) aged 20–32 years; a bipolar esophageal lead was used, as previously described (3), except that in order to improve the contact the drop-shaped electrodes were replaced by rings, tightly fitted around the esophageal tube.

The differential pressure across the resistance of the pneumotachograph was measured by a Statham strain gauge; its output was amplified by a Sanborn strain-gauge amplifier and recorded, simultaneously with the diaphragm action potentials, on a Cossor double-beam cathode ray oscillograph.

The experiments on the thoracic and abdominal pressures were carried out on two of the above subjects who were particularly accustomed to respiratory procedures, including pressure breathing.

The relaxation volume-pressure curve of the respiratory system as well as that of the chest (rib cage and abdomen) (P_{i_C}) and that of the lung (P_{i_L}) were preliminarily determined; the volume-pressure curve of the lung was also determined during PPB. The end-expiratory and end-inspiratory levels at different values of PPB were then determined. The changes in volume were measured by a recording spirometer. The esophageal pressure was measured through a standard esophageal balloon by a Statham strain gauge and its output amplified and recorded on a Sanborn direct-writing oscillograph. The gastric pressure was measured with the same technique. The esophageal or gastric pressures were then recorded simultaneously with the flow. Since the level of pressure in the tank oscillated with the breathing cycle, the pressure measurements were made relative to the tank pressure; the value of positive pressure in the tank at the end of expiration was then added to the recorded values.

The pressures on the thoracic side of the diaphragmatic dome were assumed to be equal to the esophageal pressure, while those on the abdominal side were obtained from the gastric pressure, as previously described (2, 4).

From the beginning of inspiration and expiration the flow curve was integrated at intervals of 0.2 sec and the corresponding changes in volume obtained. The lung volume, as per cent of the vital capacity (VC), was then plotted against the pressures on the thoracic (P_i) and abdominal (P_{ab}) sides of the diaphragm.

RESULTS AND DISCUSSION

Electrical activity of diaphragm during PPB. The general pattern of the electrical activity of the diaphragm during PPB is similar to that recorded while breathing at am-

bient pressure (Fig. 1); it reaches a maximum toward the end of inspiration and persists during the first part of expiration. The activity seems to increase a little as the

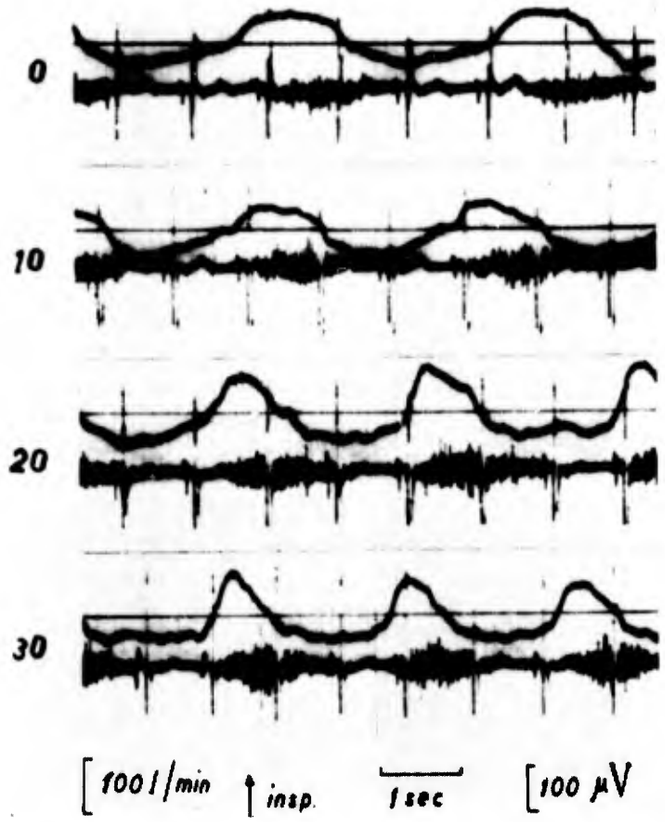

FIG. 1. Respiratory flow and electrical activity of the vertebral part of the diaphragm while breathing at ambient pressure and at positive pressures of 10, 20, and 30 cm H_2O (*subj. 1*).

positive pressure increases, but this increase might be due to the muscular fibers coming closer to the electrodes, since the esophageal hiatus is probably narrowed during PPB when the diaphragm is lower. Owing to the limitations of the technique, the changes of electrical activity during PPB cannot be quantitatively evaluated; nevertheless, it seems likely that the electrical activity does not decrease markedly when the positive pressure is increased. This finding shows, therefore, that the activity of the diaphragm in conscious man persists even when the positive pressure applied to the airways is sufficient to overinflate the lung, as at PPB from 20 to 30 cm H_2O. Furthermore, it shows that in conscious man a sustained distention of the lung does not inhibit the inspiratory activity.

The regulation of breathing during PPB has scarcely been investigated. In the anesthetized animal a moderate degree of PPB is sufficient to cause apnea (5, 6), while this is not the case for the unanesthetized man and dog (7). The conclusions obtained from PPB experiments on anesthetized animals cannot therefore be extended to conscious human subjects. Whether other inspiratory muscles besides the diaphragm are active during PPB is not known. The finding of electrical activity of the intercostal region will not provide a clear-cut answer, because this activity is not necessarily inspiratory in nature.

Analysis of thoracoabdominal mechanics during PPB. Tracings of the respiratory flow and the gastric pressure during PPB are shown in Fig. 2; the scale of the gastric pressure has been corrected in order to read directly the pressure on the abdominal side of the diaphragm referred to ambient pressure. As the value of PPB increases, the average abdominal pressure increases progressively; furthermore, a progressively increasing peak in the expiratory phase and a progressively decreasing peak in the inspiratory phase is observed. The former indicates the increasing mechanical contribution of the expiratory muscles; the latter, the decreasing contribution of the diaphragm. The persistence of an increase of abdominal

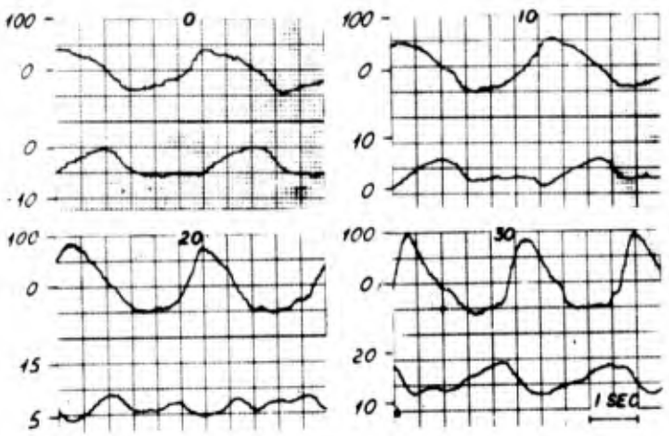

FIG. 2. Respiratory flow and pressure on the abdominal side of the diaphragmatic dome while breathing at ambient pressure and at positive pressures of 10, 20, and 30 cm H_2O. In each quadrant the *upper tracing* refers to the flow expressed in liters/min (inspiration upwards), the *lower tracing* to the abdominal pressure expressed in cm H_2O. Zero pressure corresponds to atmospheric pressure (*subj. 2*).

pressure during the inspiratory phase suggests, however, that the diaphragm is still mechanically active at values of PPB at which inspiration could be completely passive. The curves showing the end-expiratory and end-inspiratory lung volumes at different values of PPB are drawn in Fig. 3, where the lung volume, as per cent of the VC, is plotted against the endopulmonary pressure. Part of the relaxation pressure curve of the respiratory apparatus is also drawn. The end-inspiratory curve crosses the relaxation curve at about 20 cm H_2O; therefore in this subject, to which all other diagrams refer, inspiration should be completely passive when breathing at a positive pressure of 20 cm H_2O or higher. In the other subject examined, this point was at about 15 cm H_2O, a value which is closer to the mean value previously found on a large number of subjects (1).

In Fig. 4 the lung volume, as per cent of the VC, is plotted against the intrathoracic pressure due to the elasticity of the lung (P_{i_L}) or to that of the relaxed chest (P_{i_C}). The shape of the volume-pressure curve of the lung at different values of PPB was not found appreciably changed, confirming previous observations of Ting et al. (8). A family of curves was, therefore, drawn in Fig. 4 parallel to P_{i_C} and shifted to the right by the amount of positive pressure applied ($P_{i_{L+5}} \cdots P_{i_{L+30}}$); these curves

give the static intrathoracic pressures at different values of PPB. The intrathoracic pressures found at the end of expiration at each value of PPB are indicated by the points; the continuous line joining them represents the end-expiratory intrathoracic pressure curve. For a given value of PPB or lung volume the horizontal distance between this curve and P_{ic} indicates the contribution of the expiratory muscles and corresponds to the distance between the end-expiratory curve and the total-relaxation pressure curve of Fig. 3. The abdominal pressure at the end of expiration was found to be similar to the intrathoracic pressure for each value of PPB; these points are, therefore, superimposed on the intrathoracic ones, and the broken line represents the end-expiratory abdominal pressure curve.

The diagrams of Fig. 5 illustrate the pathways of the

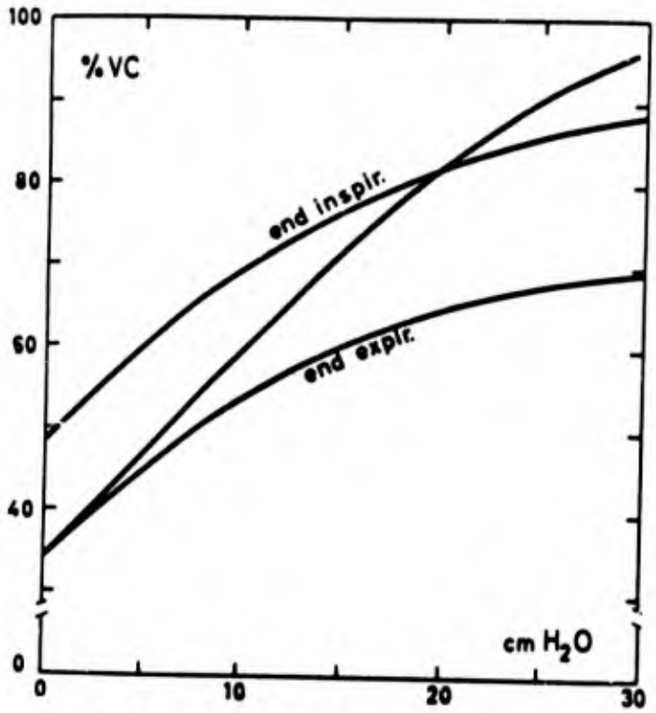

FIG. 3. Lung volume as per cent of the vital capacity against endopulmonary pressure. The end-expiratory and end-inspiratory curves during positive pressure breathing as well as the positive part of the relaxation pressure curve of the respiratory apparatus are drawn. Zero pressure corresponds to atmospheric pressure (*subj. 2*).

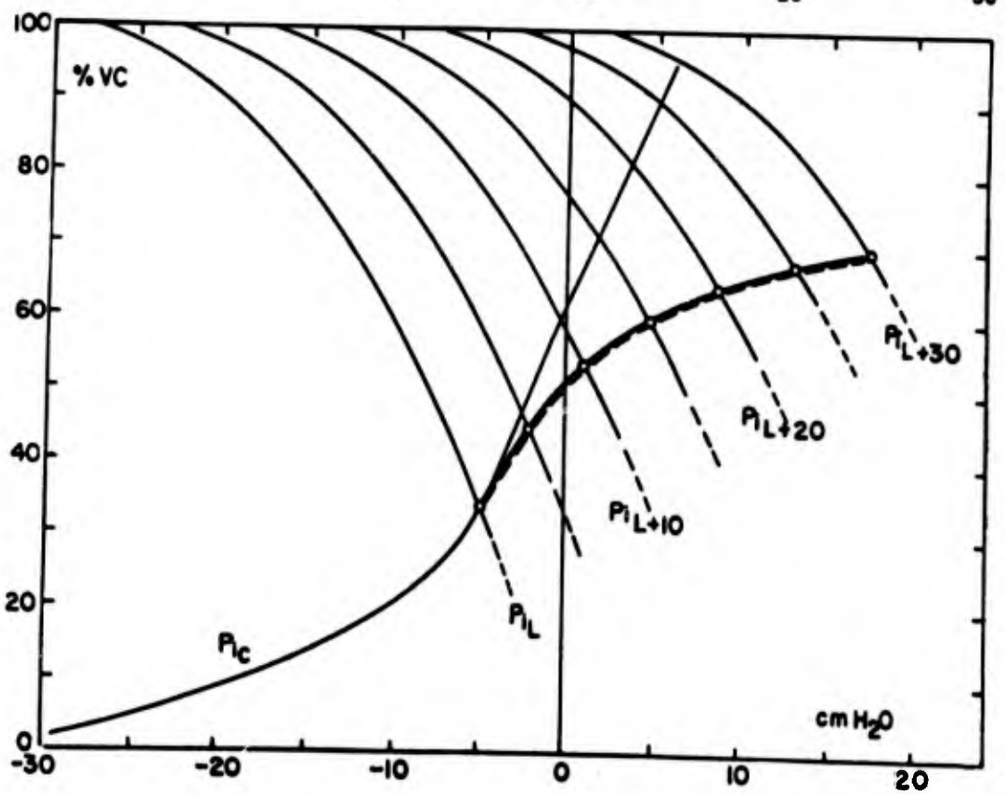

FIG. 4. Lung volume as per cent of vital capacity against intrathoracic pressures due to the elasticity of the relaxed chest (P_{ic}) and the lung (P_{iL}); the curves parallel to P_{iL} indicate the intrathoracic pressures due to the elasticity of the lung plus the amount of pressure applied to the airways at different values of positive pressure breathing. The *points* indicate the pressures on both the thoracic and abdominal side of the diaphragmatic dome at the end of expiration while breathing at ambient pressure and at a positive pressure of 5, 10 . . . 30 cm H_2O; the heavy *continuous* and *broken lines* represent, respectively, the end-expiratory intrathoracic and abdominal pressure curves during positive pressure breathing. Zero pressure corresponds to atmospheric pressure (*subj. 2*).

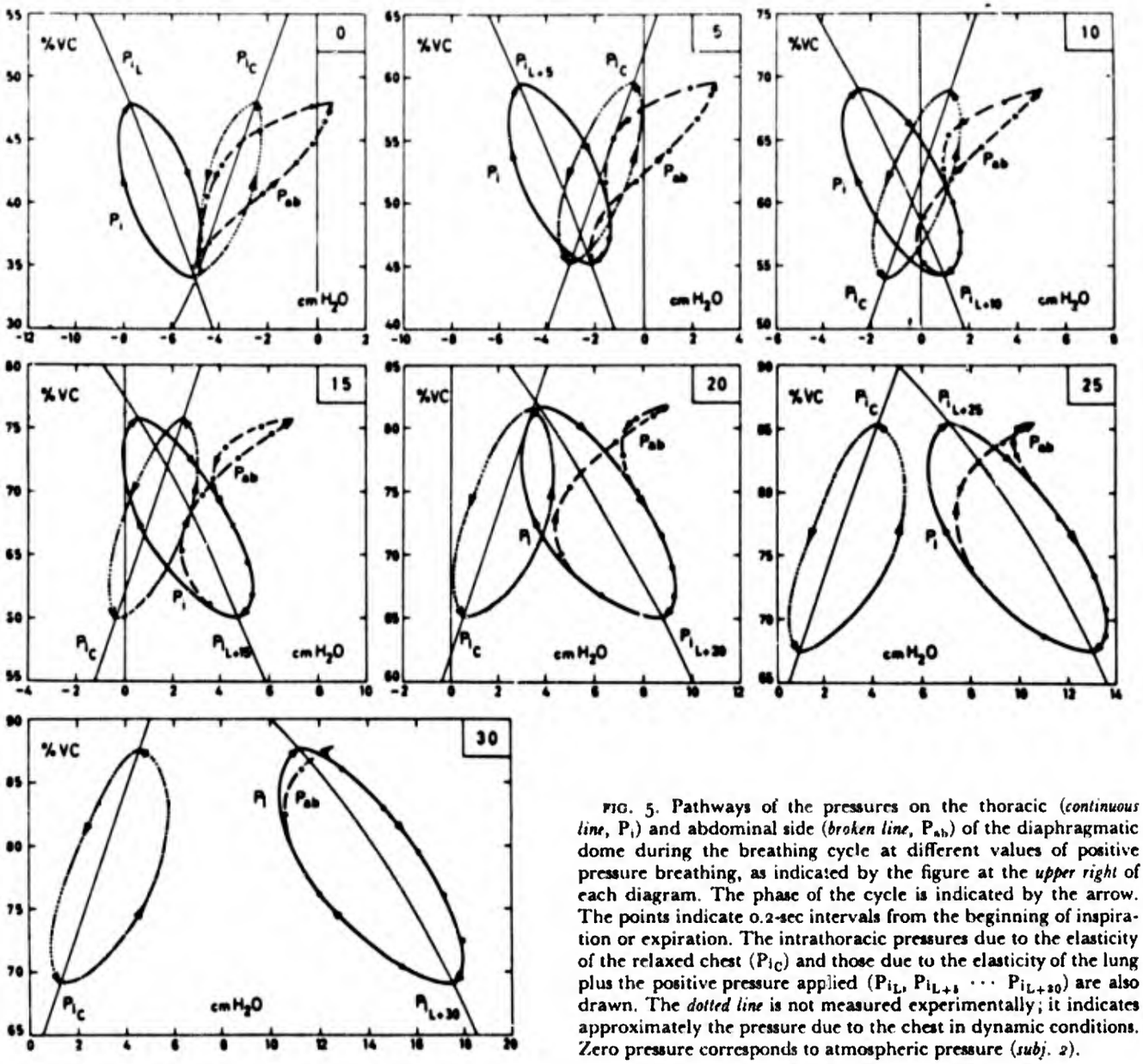

FIG. 5. Pathways of the pressures on the thoracic (*continuous line*, P_i) and abdominal side (*broken line*, P_{ab}) of the diaphragmatic dome during the breathing cycle at different values of positive pressure breathing, as indicated by the figure at the *upper right* of each diagram. The phase of the cycle is indicated by the arrow. The points indicate 0.2-sec intervals from the beginning of inspiration or expiration. The intrathoracic pressures due to the elasticity of the relaxed chest (P_{i_C}) and those due to the elasticity of the lung plus the positive pressure applied (P_{i_L}, $P_{i_{L+5}}$ $\cdots$ $P_{i_{L+30}}$) are also drawn. The *dotted line* is not measured experimentally; it indicates approximately the pressure due to the chest in dynamic conditions. Zero pressure corresponds to atmospheric pressure (*subj. 2*).

intrathoracic (continuous line, P_i) and abdominal (broken line, P_{ab}) pressures during the breathing cycle at different values of PPB. The data, as given in the diagrams, are the means of selected experiments, repeated at intervals of weeks.[3] The changes in contribution of different components of the respiratory apparatus at various levels of PPB can be analyzed in the diagrams. The meaning of P_{i_L}, P_{i_C}, P_i, and P_{ab} curves has been previously given (2). The dotted line indicates approximately the pressure due to the chest in dynamic conditions; it is not measured experimentally; it was drawn assuming that the flow resistance of the thorax is 70% of that of the lung (air and tissues) throughout all the breathing cycle (2). *a*) The pressure corresponding to the flow resistance of the lung is given by $P_{i_L} - P_i$. *b*) The pressure corresponding to the flow resistance of the chest is given by the distance between P_{i_C} and the dotted line. *c*) The distance between P_i and the corresponding dotted line indicates the pressure exerted by the respiratory muscles as can be obtained from transthoracic measurements; when P_i is to the left of the dotted line, this distance indicates the net contribution of the inspiratory muscles; when it is to the right, it indicates the net contribution of the expiratory muscles. *d*) The distance between the broken (P_{ab}) and continuous lines (P_i) gives the transdiaphragmatic pressure.

It is not feasible to separate the muscular contribution from the passive elastic component of the abdominal

[3] The breathing pattern at PPB shows wide variations (9) that are probably due to differences in the voluntary or reflex response to PPB. In the present experiments the breathing frequency was found to increase as the value of PPB was increased; in the two subjects in which the thoracoabdominal mechanics were studied, the breathing frequency, while the subjects breathed at a positive pressure of 30 cm H_2O, was 35% higher than while they breathed at ambient pressure. This increase is within the range of the values found in previous researches (1, 9, 10), though higher than the average. The increase of tidal volume was similar to that previously found, and it could correspond roughly to the increase of dead space brought about by the increase of lung volume and by the possible expansion of the extrathoracic airways induced by the condition of PPB.

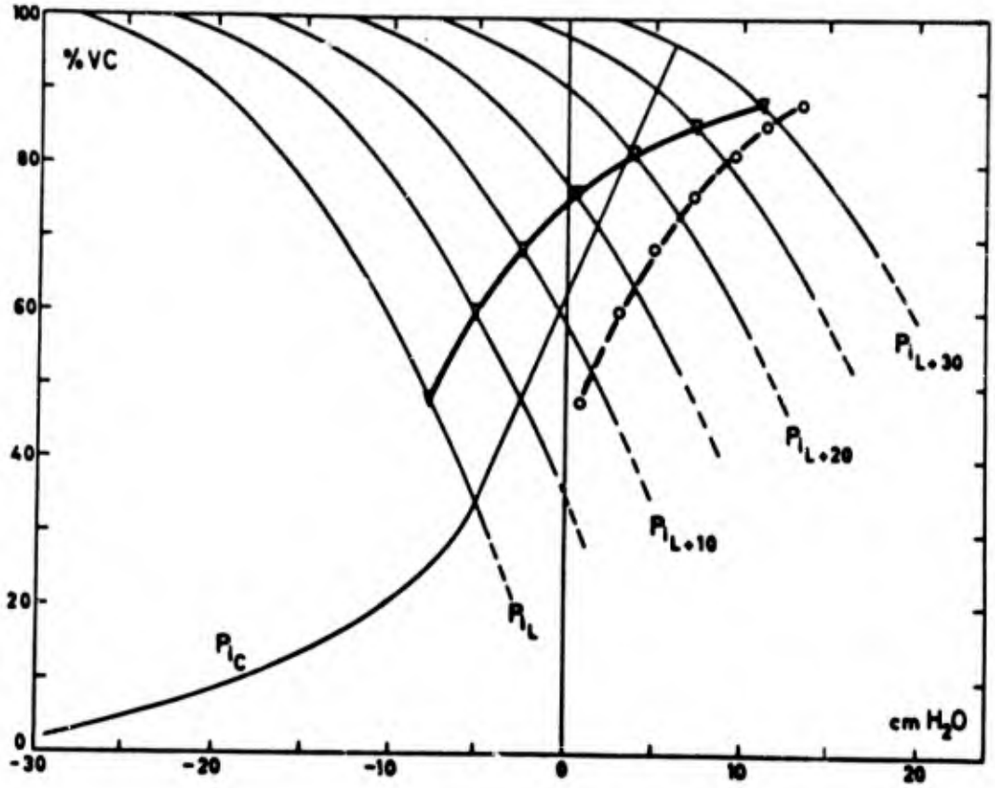

FIG. 6. Pressures on the thoracic (*triangles*) and abdominal (*circles*) sides of the diaphragmatic dome at the end of inspiration while breathing at ambient pressure and at positive pressure of 5, 10 . . . 30 cm H_2O. The heavy *continuous* and *broken lines* represent, respectively, the end-inspiratory intrathoracic and abdominal pressure curves during positive pressure breathing. For further details see legend of Fig. 4 (*subj. s*).

wall, because at a given lung volume the position of the abdominal wall and, therefore, its elastic contribution at relaxation is different from that during breathing. The geometry of the thorax and abdomen is, in fact, different in the two cases. Only when P_i is to the right of the dotted line, i.e., when expiration is active, can the pressure given by P_{ab} (dotted line) be considered as the contribution of the contraction of the abdominal muscles.

The behavior of the transdiaphragmatic pressure at the end of inspiration during PPB is illustrated by the diagram of Fig. 6, in which the end-inspiratory pressures above (continuous line) and below (broken line) the diaphragm are drawn (cf. Fig. 4). The horizontal distance between the continuous line and P_{ic} gives the contribution of the inspiratory or the expiratory muscles, according to whether this curve is to the left or to the right of P_{ic}, respectively.

The diagrams of Figs. 5 and 6 show that the transdiaphragmatic pressure decreases as the positive pressure is increased, but that it is still appreciable at values of PPB at which inspiration appears to be completely passive by an analysis of the transthoracic pressure data alone. The same conclusion applies to the experiments made on the other subjects examined; according to the mechanical features of the respiratory apparatus, inspiration could be made completely passive at a positive pressure of about 15 cm H_2O, but only at 30 cm H_2O was the transdiaphragmatic pressure zero throughout all the breathing cycle. Therefore, from the mechanical point of view, inspiration cannot be considered completely passive until values of PPB up to 30 cm H_2O are reached.

The progressive decrease of the transdiaphragmatic pressure, in spite of the fact that the electrical activity of the diaphragm is about the same with increasing values

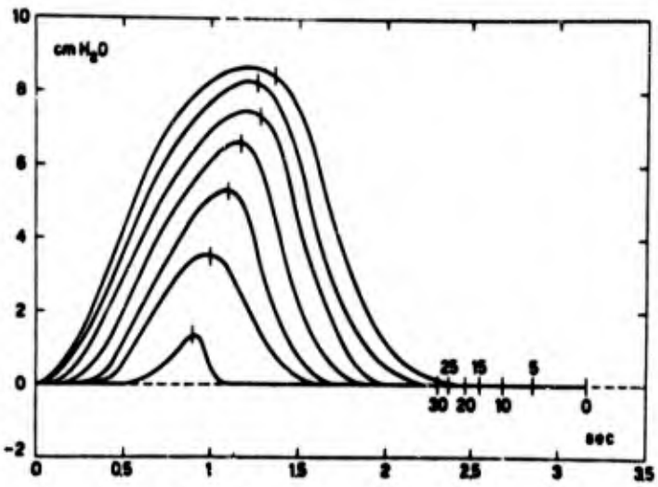

FIG. 7. Transdiaphragmatic pressures in a single breathing cycle against time at different values of positive pressure breathing. From top to bottom the *lines* indicate the transdiaphragmatic pressure when breathing at ambient pressure and at pressures of 5, 10 . . . 30 cm H_2O, respectively. Zero time corresponds to the beginning of inspiration; the *bars* indicate the end of inspiration and expiration (*subj. s*).

of PPB, is not easily understood. The energy produced by the active fibers could be expended to overcome the internal resistances to the shortening of the whole muscle. However, this event may occur only at a high speed of shortening and seems to be not the case as, at PPB of 30 cm H_2O, the peak of the inspiratory flow is only doubled. Furthermore, this explanation does not apply to the beginning of expiration when there is still activity of the diaphragm and there is no shortening but lengthening of its fibers. It could be thought that, as the lung volume is increased by the positive pressure, the geometry of the diaphragm changes in such a way that, for a given ter n

of its fibers, the transdiaphragmatic pressure becomes progressively smaller. On the other hand, it has been shown (4) that the transdiaphragmatic pressure during maximum inspiratory efforts as well as during maximum expulsive efforts is about the same at all lung volumes. As a consequence, unless during maximum efforts the strength of contraction changes at different lung volumes, the hypothesis does not seem to explain the phenomena observed.

As shown by Rahn et al. (1), during PPB the lung volume does not increase as much as would be expected from the mechanical properties of the thoracopulmonary system, a reflex activity coming into play to counteract the inflation (cf. Fig. 3). The present findings show that during part of the breathing cycle the abdominal muscles provide an opposition to the expansion larger than that calculated on the transthoracic pressure measurements alone; this difference of pressure between the abdominal and thoracic cavities is sustained by the persistent activity of the diaphragm. The persistence of an abdominal-thoracic pressure gradient at values of PPB, at which otherwise it would be zero, partially prevents the reduction of the venous return from the abdomen and therefore the reduction of cardiac output elicited by the increased intrathoracic pressure. In Fig. 7 the transdiaphragmatic pressure in a breathing cycle at different values of PPB is plotted against time. The average transdiaphragmatic pressure throughout the breathing cycle while breathing at 20 cm H_2O is still 42% of the value found while breathing at ambient pressure; the venous return from the abdominal cavity should therefore be less reduced than in the case of a completely passive inspiration. As the reduction of cardiac output seems to be the main limiting factor in PPB (11), the previously described phenomenon should give the possibility of tolerating a higher level of PPB, the limit being probably set by the reduction to zero of the average transdiaphragmatic pressure gradient.

Bjurstedt (6) presented some evidences that the vagi may afford special reflex pathways to increase the tone of the abdominal wall and facilitate the venous return to the heart during PPB; these results, however, obtained on anesthetized, apneic, and supine dogs, can hardly be extrapolated to the conditions of conscious man. Furthermore, above resting volume and in the erect posture, only the contraction of the diaphragm provides an abdominal-thoracic pressure gradient and is therefore the conditioning factor in facilitating the venous return.

Besides its mechanical interest, the persistent activity of the diaphragm during PPB raises a problem concerning the regulation of breathing. Campbell et al. (12), studying the response of the abdominal muscles to threshold expiratory loading, found that in anesthetized subjects there was no contraction of the abdominal muscles, but increased activity of the inspiratory muscles and increased inflation of the chest, so that the extra force required to overcome the resistance was provided by elastic recoil. In conscious subjects no activity of the abdominal muscles was found unless the expiratory pressure exceeded 10 cm H_2O; this threshold was even higher when pulmonary ventilation was increased (13). On the basis of these and other findings (14) Campbell suggested that the activity of the abdominal muscles may not be purposefully directed from the respiratory center and that the active phase of breathing in man is always inspiration. The present finding of the persistent activity of the diaphragm during PPB could fit in Campbell's view. The contraction of the abdominal muscles during PPB is not necessarily initiated by the respiratory control system; it could be a tonic reflex against the background of which the diaphragm behaves in its usual way.

It could be that during PPB in the conscious man the activity of the inspiratory muscles persists at about the same extent as during quiet breathing at ambient pressure. The mechanical effect of this activity is counterbalanced by an extra activity of the expiratory muscles, besides that required to counteract PPB as indicated by the pressure-volume diagram of the thorax and lung (cf. Fig. 3). This extra contribution of the expiratory muscles, as well as the contribution of the inspiratory, cannot be detected on such a diagram based on transthoracic pressure measurements; in fact, at the level of the thoracic cage both inspiratory and expiratory muscles act on the same structures, and, therefore, whenever these muscles act simultaneously, there is no way to deal separately with the mechanical contribution of either of them. At the level of the abdomen, on the contrary, this distinction can be made, as the measure of the transdiaphragmatic pressure gives the contribution of the inspiratory component alone, even when the expiratory muscles contract simultaneously.

SUMMARY

The electrical activity of the diaphragm and the mechanical contribution of the thorax and the abdomen through the breathing cycle has been investigated in man during positive pressure breathing (PPB). The electrical activity of the diaphragm persists even at values at which inspiration should be completely passive according to the pressure volume diagram of the thorax and lung. The transdiaphragmatic pressure decreases as the value of PPB increases but is still appreciable at values of PPB at which the inspiration appears to be completely passive by an analysis based on transthoracic pressure measurements alone; the transdiaphragmatic pressure becomes zero only at PPB of about 30 cm H_2O. The persistent activity of the diaphragm during PPB is counterbalanced by an activity of the abdominal muscles in excess of that of the expiratory muscles as given by transthoracic pressure measurements. Owing to the persistence of an abdominothoracic pressure gradient, the venous return and therefore the cardiac output should be less reduced than in the case of a passive inspiration.

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SECTION II

Influence of chemical and nervous stimuli on the resurgence of the activity of the diaphragm during voluntary apnea

INTRODUCTION

After a certain time from the beginning of the voluntary apnea, there is a resumption of the diaphragmatic activity: the alveolar pressure of CO_2 ($P_{A\,co_2}$) at this moment has a remarkably constant value (ref. 1). However, to study the hypercapnic stimulus, it is necessary to know the value of P_{co_2} in the arterial blood at the central level at the beginning of the diaphragmatic activity ($P'a_{co_2}$).

To calculate $P'a_{co_2}$, it is assumed that $P_{A\,co_2} = P'a_{co_2}$, and that the average time of circulation between the lungs and the respiratory chemoreceptor center is 9 seconds. Then, by any type of test, the curve of $P_{A\,co_2}$ versus time of apnea is determined. On this curve $P'a_{co_2}$ is determined, taking into consideration the delay (about 3 seconds) between the beginning of the activity of the diaphragm and the analysis of the alveolar carbon dioxide.

METHODS

Tests were performed on three patients in sitting position. The resurgence of the diaphragmatic activity appeared during the registration of the electric activity of the diaphragm or the intrathoracic pressure. On the resumption of the activity of the diaphragm, the patient was asked to exhale, and the CO_2 in the exhaled air was analyzed with an infra red CO_2 meter conected to an oscillograph.

To study the influence of the pulmonary volume, tests were performed at 80% and 25% of the vital capacity (VC). In the first case, the patient entered into apnea after a maximal inhalation followed by a short exhalation up to 80% of the vital capacity. In the second, after hyperventilation in such a way that the $P_{A\,co_2}$ was brought to about 30 mm Hg, the patient exhaled down to 25% of the VC. To eliminate the influence of a possible hypoxic stimulus, oxygen was breathed in both tests.

To make the hypoxic stimulus evident, comparative tests were run between respiration in air and in O_2. The patient hyperventilated in a way to maintain $P_{A\,co_2}$ at about 30 mm Hg for 4 to 5 minutes and entered into apnea at the end of a normal exhalation. Considering that there is a certain variability in the value of $P'a_{co_2}$ from day to day, the comparative tests were performed during the same session.

RESULTS AND DISCUSSION

The values obtained with the individual patients at different pulmonary volume are reported in table I. In patient no. 3 a higher hypercapnic stimulus is necessary to overcome the voluntary inhibition of the inspiratory muscles (see also table II). This can be due to a higher threshold for CO_2, or to a stronger inhibition. In patients no. 1 and 2, the values for $P'a_{co_2}$ are similar at both volumes, whereas in patient no. 3, $P'a_{co_2}$ at 25% of the VC is 1.6 mm Hg higher than at 80%. The difference, although small, is statistically significant ($p<0.02$). These results justify the assumption that the afferent impulses tied to the pulmonary expansion and which inhibit the inspiratory activity (Hering-Breuer reflex) do not inhibit the diaphragmatic activity. On the other hand, the effect of these afferent impulses could be disguised by another factor that works in the opposite direction, whose existence seems to be likely by the results obtained with patient no. 3.

In the patient who is released during the apnea at 25% of the VC, the intrathoracic pressure is about −8 cm H_2O, whereas it is 2 cm H_2O at 80%. This difference of about 10 cm H_2O can influence the venous return and eventually the conditions of irrigation of the respiratory center. To check this hypothesis, experiments were performed in which the patient, in apnea of 25% of the VC, maintained such a respiratory tonus that the intrathoracic pressure was about 2 cm H_2O. The values of $P'a_{co_2}$ under these conditions showed, however, the same results as those obtained in the same session in the released patient. One can, therefore, exclude the possibility that the difference in intrathoracic pressure has an influence upon the value of $P'a_{co_2}$.

TABLE I

Values of $P_{A_{CO_2}}$ and duration of apnea obtained with individual patients at different pulmonary volumes. Uncertainty expressed as ± one standard deviation of the mean.

	80% Vital Capacity					25% Vital Capacity				
Patient	No. of tests	Time of apnea (seconds)	P_{ACO_2} (beginning)	P_{ACO_2} (final)	P_{ACO_2} (mm Hg)	No. of tests	Time of apnea (mm Hg)	P_{ACO_2} (beginning)	P_{ACO_2} (final)	P'_{aCO_2} (mm Hg)
1	6	64.5±2.6	32.6±0.2	47.7±0.4	46.5±0.3	6	62.2±1.8	32.8±0.4	48.4±0.1	46.7±0.1
2	6	59.7±4.8	31.7±0.5	47.6±0.5	46.0±0.5	6	48.7±1.3	33.7±0.3	47.7±0.2	46.0±0.2
3	6	61.2±3.0	32.3±0.6	50.2±0.3	48.8±0.4	6	88.0±5.4	33.7±0.6	51.9±0.5	50.4±0.3
Average		61.8±1.4	32.2±0.3	48.4±0.9	47.1±0.9		66.3±11.5	33.4±0.3	49.3±1.3	47.7±1.4

TABLE II

Data on duration of apnea and $P_{A_{CO_2}}$ values in individual patients breathing air and oxygen. Uncertainty expressed as ± one standard deviation of the mean.

	Air					Oxygen				
Patient	No. of tests	Time of apnea (seconds)	P_{ACO_2} (beginning)	P_{ACO_2} (final)	P_{ACO_2} (mm Hg)	No. of tests	Time of apnea (mm Hg)	P_{ACO_2} (beginning)	P_{ACO_2} (final)	P'_{aCO_2} (mm Hg)
1	15	34.5±1.8	31.0±0.2	44.0±0.2	41.7±0.2	15	60.4±2.6	31.7±0.2	46.8±0.2	45.5±0.2
2	6	34.2±2.9	30.6±0.5	43.4±0.4	41.3±0.4	6	50.0±2.6	31.5±0.5	46.5±0.2	45.0±0.2
3	6	76.2±2.7	31.5±1.1	48.5±0.2	47.0±0.3	6	89.3±2.6	31.8±0.3	51.9±0.3	50.5±0.2
Average		48.3±13.9	31.0±0.2	45.3±1.6	43.3±1.8		66.5±11.8	31.6±0.1	48.4±1.7	47.0±1.7

Table II shows the values obtained in the individual patients in the tests where air was breathed and those in which O_2 was breathed. The value of P'_{aCO_2}, markedly lower in the experiments in air, shows the influence of the hypoxic stimulus on the resumption of diaphragmatic activity. The values of alveolar P_{O_2}, measured in any experiment, were within the range of 65 to 70 mm Hg.

In some experiments, the patient breathed mixtures of different oxygen content. Thus, one could draw a graph P_{CO_2} versus P_{O_2} of the alveolar values at the rise of the activity of the diaphragm. The results show that the hypoxic stimulus stops at values for $P_{A_{O_2}}$ of 115 to 120 mm Hg. This curve corresponds to the one of Douglas and Haldane (ref. 2), based on values of $P_{A_{CO_2}}$ and $P_{A_{O_2}}$ during apnea, at the resurgence of the "desire to breathe." Thus, the sensation defined by Douglas and Haldane seems to correspond to the resumption of diaphragm activity as shown in these experiments.

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SECTION III

Diaphragm activity during breath holding: factors related to its onset

INTRODUCTION

After a period of breath holding, a feeling similar to that produced by inspiratory efforts is commonly experienced. No information, however, is available on the activity of the respiratory muscles in such conditions. The study of the activity of the respiratory muscles or of related mechanical events during breath holding should contribute to the understanding of breathing control. To this end the study of the activity of the diaphragm seems particularly significant, because *a*) the diaphragm is the principal inspiratory muscle, *b*) ordinarily its activity is not postural in nature (1), *c*) its activity is not masked by that of other respiratory muscles.

In this research therefore the activity of the diaphragm during breath holding has been studied, and its onset related to alveolar P_{CO_2}.

METHODS

The electrical activity of the diaphragm and of the muscles of the abdominal wall (external oblique), as well as the intrathoracic pressure, were recorded during breath holding. The electrical activity of the diaphragm was recorded through a bipolar esophageal lead as previously described (2, 3). That of the external oblique was recorded through two surface electrodes, 2 cm in diameter, placed along the direction of the fibers at a distance of about 5 cm. The intrathoracic pressure was measured through a standard esophageal balloon by means of a Statham transducer connected to a Sanborn strain gauge amplifier.

Alveolar CO_2 was determined by means of an infrared CO_2 meter, whose output was fed into a Sanborn oscillograph. The CO_2 meter was calibrated before each test with three mixtures ranging from 4.5 to 7.5% CO_2 in air: the effects due to the water vapor and, when breathing O_2, that due to the different properties of the background gas were determined and taken into account. The gas flow and the input pressure in the analyzer during calibration were similar to those occurring during expiration.

In a series of tests the alveolar P_{O_2} was also measured: as soon as the alveolar plateau on the capnogram was reached, expired air was sampled in a small rubber bag and then analyzed in duplicate with a Scholander apparatus.

The apnea was initiated in different experiments: *1*) at the end of a normal expiration, resting volume; *2*) after a full inspiration followed by an expiration to 80% of the vital capacity (VC), monitored by a recording spirometer; *3*) at the end of an expiration down to 25% VC. Oxygen, air, or different mixtures of O_2 in N_2 were breathed. Before the apnea the subject breathed normally or hyperventilated. During the apnea the subject was invited to relax.

The experiments were performed on three subjects in sitting position. Their characteristics and lung volumes are reported in Table 1; *subjects 1* and *2* were particularly trained to experiments on respiratory physiology.

TABLE 1. *Age, body measurements, and lung volumes of subjects*

Subj.	Age, yr	Height, cm	Weight, kg	VC, liters$_{BTPS}$	RV, liters$_{BTPS}$	FRC, liters$_{BTPS}$
1	22	174	66	5.6	1.4	3.2
2	32	178	78	4.8	1.7	3.3
3	23	179	71	5.9	1.7	3.7

RESULTS AND DISCUSSION

Diaphragm activity during breath holding. When the breath is held, the activity of the diaphragm stops or only a slight tonic activity may be recorded; then a marked discharge is recorded, which is followed by others at a progressively increased rate up to the breaking point (Figs. 1–3). The durations of single bursts and the intervals between them may change even in the same subject for the same type of apnea; the patterns shown by Figs. 1 and 2 represent the limits of this variability in one subject.

During breath holding the activity of the muscles of the abdominal wall is negligible (Fig. 2), i.e., the action of the diaphragm is not balanced by an activity of its antagonist muscles. As a consequence the intrathoracic pressure is lowered at each contraction of the diaphragm (Fig. 3). The onset of diaphragm activity may thus be simply monitored by a record of intrathoracic pressure. Only in one subject the change of intrathoracic pressure was so marked as shown by Figs. 3 and 4; in the other two it was about one third, but equally clear. In a fourth subject the onset of diaphragm activity was not sharp enough on either the electromyographic or the esophageal pressure records; the activity increased progressively becoming marked toward the end of breath holding.

These results suggest that when the respiratory stimuli reach a given level, voluntary inhibition of impulses to the inspiratory muscles is overcome. From this point on up to the breaking point, the respiratory act is impeded only by the voluntary closure of the airways. The period of breath holding may thus be divided into two parts: the first, characterized by voluntary inhibition of the inspiratory muscles activity, and the second, by involuntary inspiratory efforts.

Significance of $P_{A_{CO_2}}$ at the onset of diaphragm activity. At the onset of diaphragm activity the subject was asked to breathe out and the $P_{A_{CO_2}}$ was determined (Fig. 4): three tests were repeated in each session and the mean with its standard error calculated. The apnea was started at the end of a normal expiration after breathing O_2. The data obtained from the groups of tests performed, over a long period of time, on *subject 1* are given in Table 2. The first column refers to the time of apnea up to the onset of diaphragm activity; the second refers to the value of $P_{A_{CO_2}}$ at the beginning of apnea, i.e., the value recorded at the end of the alveolar plateau of the last expiration before apnea; the third refers to the value of $P_{A_{CO_2}}$ about 3 sec after the onset of diaphragm activity; the 3-sec lag is due to the monitoring and expiration time (Fig. 4).

The $P_{A_{CO_2}}$ at the onset of diaphragm activity is remarkably constant, as shown by the standard errors of groups of three tests performed in the same session. The reproducibility of the data was similar in *subjects 2* and *3*. The mean $P_{A_{CO_2}}$ value of one group of tests may differ significantly ($P < 0.05$) from the mean value of a similar group of tests performed in another session: the values of the second and third groups are significantly higher than that of the fifth. These differences seem unrelated to time of day or other known factors, and suggest that uncontrolled changes of the conditions of the subjects may facilltate or inhibit the onset of diaphragm activity. Owing to this variability, when two types of tests have to be compared, they must be performed on the same session or a great number of tests should be performed. The value of $P_{A_{CO_2}}$ at the onset of diaphragm activity may increase with training; however, after some training, such a value does not increase progressively over a long period of time (Table 2). The reproducibility of $P_{A_{CO_2}}$ suggests that the onset of diaphragm activity during breath holding may be a more direct and reliable monitor than the breaking point in studying breathing control and voluntary inhibition. In fact: *1*) it is difficult to decide when further apnea is impossible, especially when the subject must exhale for an analysis of alveolar air; *2*) an apnea up to the onset of diaphragm activity is a

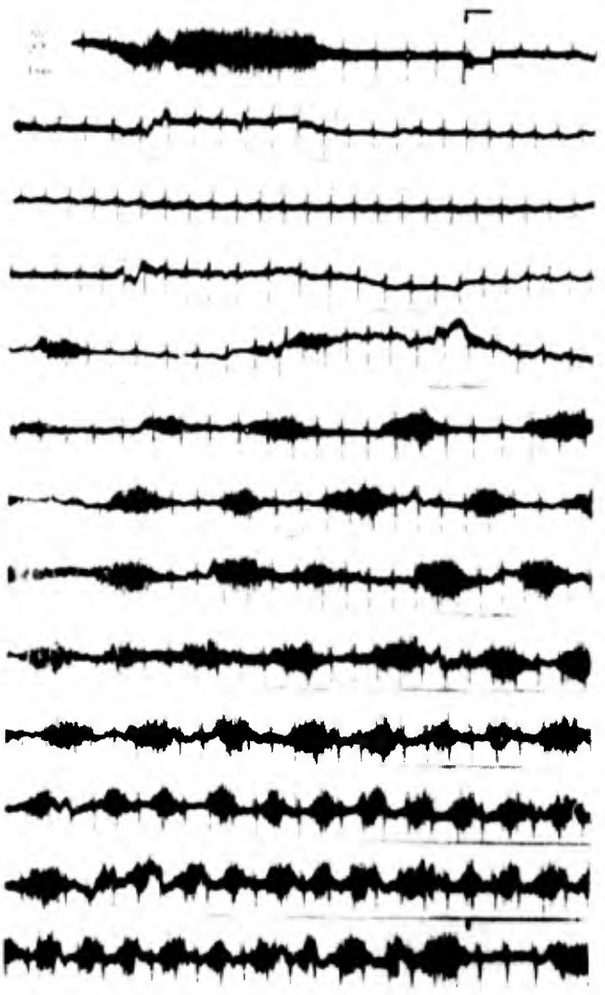

FIG. 1. Electrical activity of the diaphragm during breath holding at 80% VC breathing O_2; beginning and ending of apnea are indicated by the arrows. Before apnea the subject made a full inspiration followed by an expiration to 80% VC. At the breaking point the subject made a quick expiration for an analysis of alveolar CO_2 (*subj. 1*).

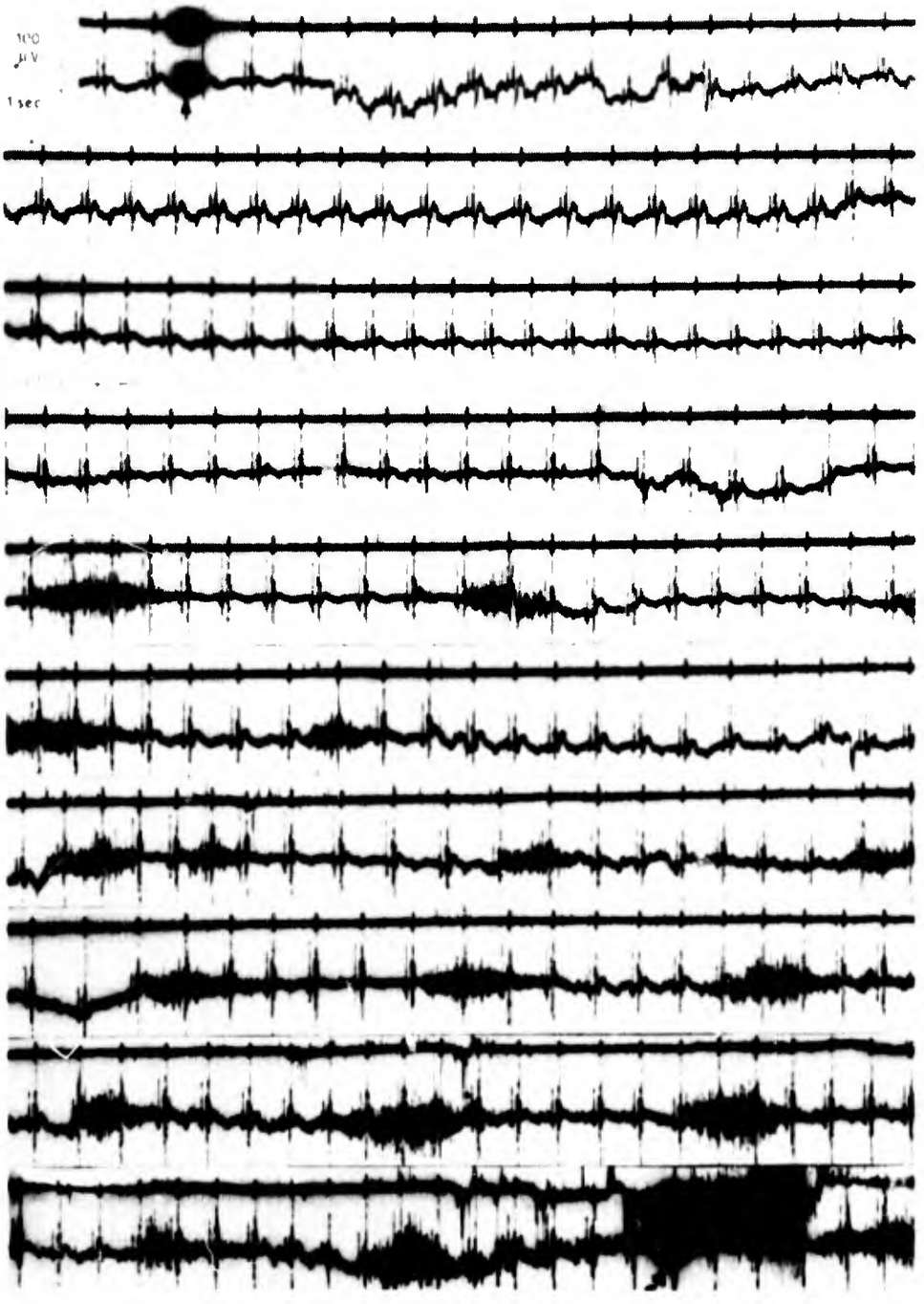

FIG. 2. Electrical activity of the diaphragm (lower tracing) and of the external oblique (upper tracing) during breath holding at resting volume after breathing O_2. Beginning and ending of apnea are indicated by the light signals and by the arrows. At the breaking point the subject made a quick expiration for an analysis of alveolar CO_2 (*subj. 1*).

less crude interference in respiration and circulation than an apnea up to the breaking point. Although in trained subjects $P_{A_{CO_2}}$ at the breaking point is fairly constant, the standard error of its mean value was found to be higher than that of the mean value found at the onset of diaphragm activity. Since, however, the onset of diaphragm activity and the breaking point represent two phenomena, the study of respiratory stimuli at these two moments of apnea may be profitably integrated.

Fink et al. (4) correlated $P_{A_{CO_2}}$ with the disappearance and recovery of the diaphragmatic activity produced in anesthetized patients by artificial increase and decrease of ventilation. They could thus determine the respiratory center threshold to CO_2 in their patients. This approach is evidently different and the results cannot be compared: in fact, besides the different sensitivity of an anesthetized subject, in their experiments the activity of the respiratory muscles was involuntarily stopped by passive hyperventilation and the respiratory movements did not come to a complete stop.

The $P_{A_{CO_2}}$ at the onset of diaphragm activity is only an indirect index of the CO_2 stimulus acting on the cells of the respiratory center and on the glomus cells at the onset of diaphragm activity. To compare different types of apnea it is necessary to know the value of arterial P_{CO_2} in the brain stem at the onset of diaphragm activity ($P'a_{CO_2}$). To calculate approximately this parameter it has been assumed that $P_{A_{CO_2}} = Pa_{CO_2}$ and that the mean circulation time from the lung to the respiratory center is 9 sec (5, 6). The relationship between $P_{A_{CO_2}}$ and the time of apnea was then determined for each kind of apnea by having the subject breathe out after different periods of breath holding and Pa_{CO_2} was then calculated on this curve taking into account the circulation time and the lag between the diaphragm's first discharge and the alveolar CO_2 record (Fig. 5). The values of $P'a_{CO_2}$ so obtained are reported in the fourth column of Table 2.

Table 3 shows the mean values of two groups of tests performed, on comparable sessions, at resting volume, breathing O_2 at normal rate or hyperventilating in such a

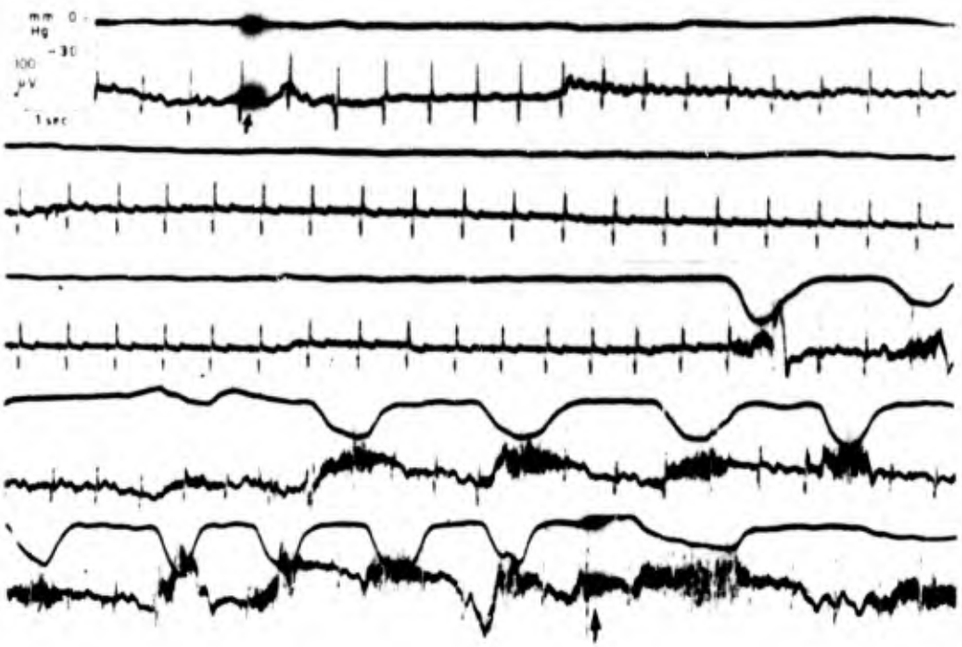

FIG. 3. Intrathoracic pressure (upper tracing) and electrical activity of the diaphragm (lower tracing) during breath holding at resting volume after breathing air. Beginning and ending of apnea are indicated by the light signals and by the arrows (*subj. 1*).

way as to maintain $P_{A_{CO_2}}$ at 30–32 mm Hg for 4–5 min. The value of $P'a_{CO_2}$ in *subject 3* is higher than in *subjects 1* and *2*: a higher hypercapnic stimulus is necessary in that subject to overcome voluntary inhibition of the inspiratory muscles. This could be due either to a higher threshold or to a stronger inhibition.

In *subjects 1* and *2*, the values of $P'a_{CO_2}$ of the hyperventilation tests are significantly lower ($P < 0.02$, $P < 0.01$, respectively) than those after normal breathing. In the respiratory center as in cerebrospinal fluid (7–10), the P_{CO_2}-related changes probably lag behind those in the arterial blood. This slow equilibrium between brain tissues and arterial blood CO_2 is due to: *1*) the changes in cerebral blood flow (11), *2*) the effect of stored CO_2 (12), and *3*) the small permeability of the barrier to bicarbonate ions (7, 9). Therefore at the beginning of apnea in the hyperventilation tests the center tissues might have been not in equilibrium with arterial blood. If the difference of $P'a_{CO_2}$ between "normal" and "hyperventilation" tests is in some way related to such condition of imbalance, then $P'a_{CO_2}$ could be made to vary by changing the degree of imbalance. To control this point, *subject 1*, who was unaware of the problem, performed some tests after normal breathing and after different periods of hyperventilation, in which Pa_{CO_2} was lowered to about 30 mm Hg and maintained at such a value for different periods of time before breath holding to obtain different degrees of imbalance. As shown by Table 4, after a short hyperventilation the value of $P'a_{CO_2}$ is markedly lower than in the normal tests and this difference decreases progressively if hyperventilation is maintained for a longer time, i.e., if a new equilibrium is approached. This finding indicates a relationship between the degree of imbalance at the beginning of apnea and the change of $P'a_{CO_2}$; however, the mechanism underlying this relationship is not clear and it may be that no causality is involved between the two phenomena. At present, no speculation seems worthwhile because of the complexity and lack of knowledge of the kinetics, site and mechanism of action of the CO_2-related stimuli (8, 13, 14),

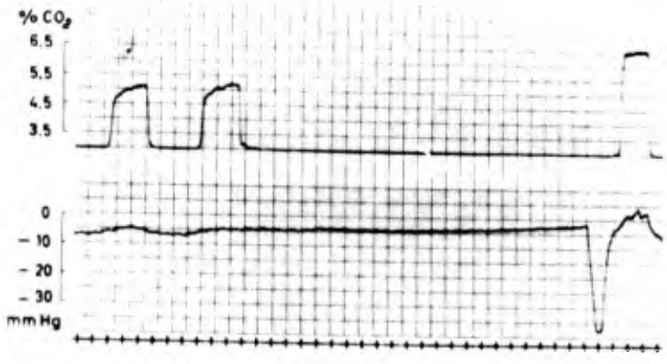

FIG. 4. CO_2-meter record (upper tracing) and intrathoracic pressure (lower record) during voluntary apnea up to the onset of diaphragm activity, monitored by the sharp decrease of the intrathoracic pressure. Time mark in sec. Apnea was started at the end of a normal expiration breathing air: two normal breaths before apnea are shown, at the onset of diaphragm activity the subject was invited to exhale. An increase of the esophageal pressure, presumably due to an increase of the esophageal tonus, was often found during breath holding (*subj. 1*).

TABLE 2. *Alveolar P_{CO_2} at onset of diaphragm activity during voluntary apnea at resting volume after breathing O_2 (subj. 1)*

	Time of Apnea, sec	Initial P_{ACO_2}, mm Hg	Final P_{ACO_2}, mm Hg	Calc. $P'a_{CO_2}$, mm Hg
12/16/61	43.6±4.3	40.5±0.2	48.5±0.4	47.0±0.4
12/16/61	44.0±2.4	40.0±0.3	48.8±0.4	47.3±0.4
12/18/61	46.6±4.6	40.3±0.3	49.0±0.3	47.5±0.3
12/28/61	41.7±2.3	39.2±0.2	48.4±0.3	46.8±0.2
1/8/62	36.6±0.3	40.6±0.3	47.6±0.1	46.1±0.1
Total means	42.5±1.5	40.1±0.3	48.3±0.2	46.9±0.2

Values are means ± SE of 3 tests.

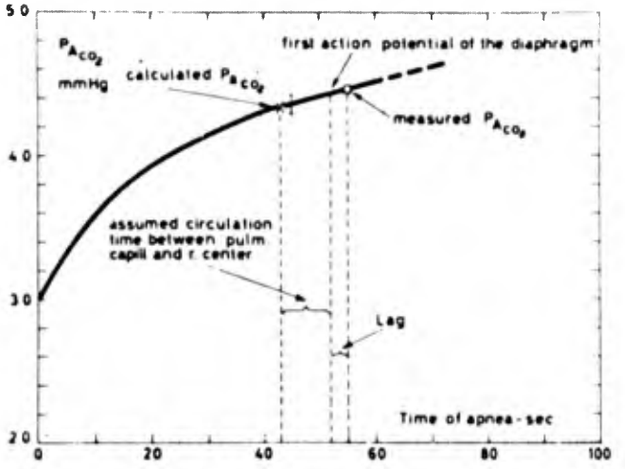

FIG. 5. $P_{A_{CO_2}}$ against time of apnea. Assuming $P_{A_{CO_2}} = P_{a_{CO_2}}$, the diagram illustrates how the value of $P_{a_{CO_2}}$ in the brain stem was estimated at the onset of diaphragm activity. Vertical bar indicates the standard deviation of 3 measurements of $P_{A_{CO_2}}$ made at given time of apnea. The data refer to *subj. 1* holding his breath at resting volume after 4–5 min hyperventilation in O_2.

and of the interplay of hemodynamics and CO_2 store changes.

Neurogenic factors: effect of lung volume. To study the effect of afferent impulses related to lung volume on the onset of diaphragm activity, experiments were performed in the following conditions: *a*) the subject breathed O_2 at a normal rate and the apnea was started after a full inspiration followed by an expiration to 80% VC; and *b*) the subject hyperventilated, in O_2, to reach a $P_{A_{CO_2}}$ value similar to that occurring just before breath holding in the 80% VC tests, and the apnea was started after an expiration down to 25% VC.

As shown by Table 5, the values of $P'a_{CO_2}$ are similar at both volumes in *subjects 1* and *2*, while in *subject 3* $P'a_{CO_2}$ at 25% VC is significantly higher ($P < 0.01$) than at 80%. These results suggest that either the afferent impulses related to such lung volumes do not influence differentially the onset of diaphragm activity, as could be expected from the Hering-Breuer reflex, or that this effect is masked by an opposing factor, that could be prevailing in *subject 3*.

TABLE 3. *Alveolar P_{CO_2} at onset of diaphragm activity during voluntary apnea at resting volume after breathing O_2*

Subj.	Normal				Hyperventilation			
	Time of apnea, sec	Initial $P_{A_{CO_2}}$, mm Hg	Final $P_{A_{CO_2}}$, mm Hg	Calc. $P'a_{CO_2}$, mm Hg	Time of apnea, sec	Initial $P_{A_{CO_2}}$, mm Hg	Final $P_{A_{CO_2}}$, mm Hg	Calc. $P'a_{CO_2}$, mm Hg
1	39.2 ±1.5	39.9 ±0.4	47.9 ±0.2	46.4 ±0.2	65.0 ±4.1	32.3 ±0.2	46.7 ±0.3	45.4 ±0.3
2	25.2 ±2.5	41.6 ±0.5	48.1 ±0.5	46.2 ±0.3	50.0 ±2.6	31.5 ±0.5	46.5 ±0.2	45.0 ±0.2
3	45.3 ±2	41.0 ±0.3	51.9 ±0.3	50.2 ±0.2	89.3 ±2.6	31.8 ±0.3	51.8 ±0.3	50.5 ±0.2
Mean	36.5 ±5.8	40.8 ±0.5	49.3 ±1.3	47.6 ±1.3	68.1 ±11.5	31.9 ±0.2	48.3 ±1.7	46.9 ±1.8

Mean values ± SE of tests (6 each) after normal breathing and after 4–5 min hyperventilation, performed at the same session.

TABLE 4. *Tests after different periods of hyperventilation*

Test No.	Period of Hyperventilation	Time of Apnea, sec	Initia $P_{A_{CO_2}}$, mm Hg	Δ From $P'a_{CO_2}$ of Corresponding Normal Tests,* mm Hg
1	40 sec†	43	30	−4.6
2	1 min + 40 sec	62	30.6	−3
3	4 min + 40 sec	79	30.9	−1.4
4	10 min + 40 sec	82	30.2	−1.2
5	40 min + 40 sec	102	30.9	−0.5

* Differences from the normal value of $P'a_{CO_2}$ found in the same session: all hyperventilation tests could not be made in one session and normal value may change from one session to another, as previously discussed. † Approx. time spent to lower $P_{A_{CO_2}}$ to 30 mm Hg: i.e., in such test the breath was held when $P_{A_{CO_2}}$ reached 30 mm Hg; in the following tests the hyperventilation was continued, for the time indicated, in such a way as to maintain $P_{A_{CO_2}}$ at about 30 mm Hg.

When the subject relaxes during apnea, at 25% VC the intrathoracic pressure is about −8 cm H_2O, while at 80% VC it is about 2 cm H_2O. A difference of 10 cm H_2O in intrathoracic pressure could influence the venous return, and—hypothetically—the conditions of the respiratory center. To investigate this point, *subjects 1* and *3* performed some experiments at 25% VC, keeping a moderate tone of the expiratory muscles, so as to maintain an intrathoracic pressure of 1–2 cm H_2O. The values of $P'a_{CO_2}$ were similar to those obtained in the tests at relaxation performed on the same session. Within these limits, therefore, the intrathoracic pressure does not seem to play any role.

To avoid the possibility of a time-related interference and to get a more reliable control on the effect of afferent impulses related to lung volume, *subject 1* performed some experiments at 80% VC, in which the full inspiration preceding apnea was made from a bag containing 5–6% CO_2 in O_2 so that the initial $P_{A_{CO_2}}$ was about 40 mm Hg and the time of apnea about 40 sec, as in the normal tests at resting volume. The values of $P'a_{CO_2}$ in such tests, at 80% VC and normal initial $P_{A_{CO_2}}$, were similar to those at resting volume and normal breathing, showing that the effect of afferent impulses related to lung volume on the onset of diaphragm activity is negligible.

These findings agree with others (3, 15), suggesting that in man, especially if conscious, the afferent impulses related to lung volume do not influence the activity of the respiratory muscles as would be expected from the Hering-Breuer reflex. The breaking point, on the contrary, is influenced by afferent impulses related to lung volume: the larger the volume, the larger the tolerance to hypercapnic (5, 16, 17) and to hypoxic (17) stimuli.

Neurogenic factors: effect of respiratory movements. The values of the hypercapnic and hypoxic stimuli at the breaking point of rebreathing are higher than those at the breaking point of breath holding, i.e., the tolerance to such stimuli is higher if respiratory movements are made (18–20). To investigate whether the onset of diaphragm activity is also affected by such a factor,

experiments were performed as follows. The subject made a normal breath-holding test as previously described and, after the onset of diaphragm activity, took 3–4 breaths, as deep as he wanted, from a bag in which the P_{CO_2} was 1–4 mm Hg lower than the value of $P_{A_{CO_2}}$ at the onset of diaphragm activity; then, at resting volume, he held his breath again until the next onset of diaphragm activity. Within 3–6 sec of apnea the diaphragm contracted again, the value of $P_{A_{CO_2}}$ being equal or 0.5 mm Hg higher than that recorded earlier. These findings, along with those above, show that the onset of diaphragm activity during breath holding is due mainly to chemical stimuli, and not to neurogenic factors, as those related to lung volume and respiratory movements. Furthermore, they point out the different nature of the onset of diaphragm activity and of the breaking point of breath holding, and, more generally, the different levels at which the complex mechanism of breath control operates.

Hypoxic stimulus. Table 6 shows the data obtained, at resting volume, after 4–5 min of hyperventilation in air or O_2. The markedly lower value of $P'a_{CO_2}$ when breathing air gives evidence of the effect of the hypoxic stimulus on the onset of diaphragm activity; the corresponding alveolar P_{O_2}, measured in some instances, ranged from 65 to 70 mm Hg.

TABLE 5. *Alveolar P_{CO_2} at onset of diaphragm activity during voluntary apnea at 80% and 25 % of vital capacity after breathing O_2*

Subj.	80% VC				25% VC			
	Time of apnea, sec	Initial $P_{A_{CO_2}}$, mm Hg	Final $P_{A_{CO_2}}$, mm Hg	Calc. $P'a_{CO_2}$, mm Hg	Time of apnea, sec	Initial $P_{A_{CO_2}}$, mm Hg	Final $P_{A_{CO_2}}$, mm Hg	Calc. $P'a_{CO_2}$, mm Hg
1	64.5 ±2.6	32.6 ±0.2	47.7 ±0.4	46.5 ±0.3	62.2 ±1.8	32.8 ±0.4	48.4 ±0.1	46.7 ±0.1
2	59.7 ±4.8	31.7 ±0.5	47.6 ±0.5	46.0 ±0.5	48.7 ±1.3	33.7 ±0.3	47.7 ±0.2	46.0 ±0.2
3	61.2 ±3	32.3 ±0.6	50.2 ±0.3	48.8 ±0.4	88.0 ±5.4	33.7 ±0.6	51.9 ±0.5	50.4 ±0.3
Mean	61.8 ±1.4	32.2 ±0.3	48.4 ±0.9	47.1 ±0.9	66.3 ±11.5	33.4 ±0.3	49.3 ±1.3	47.7 ±1.4

Mean values ± SE of tests (6 each) performed at the same session.

TABLE 6. *Alveolar P_{CO_2} at onset of diaphragm activity during voluntary apnea at resting volume after breathing air or O_2*

Subj.	Air					Oxygen				
	No. of tests	Time of apnea, sec	Initial $P_{A_{CO_2}}$, mm Hg	Final $P_{A_{CO_2}}$, mm Hg	Calc. $P'a_{CO_2}$, mm Hg	No. of tests	Time of apnea, sec	Initial $P_{A_{CO_2}}$, mm Hg	Final $P_{A_{CO_2}}$, mm Hg	Calc. $P'a_{CO_2}$, mm Hg
1	15	34.5 ±1.8	31.0 ±0.2	44.0 ±0.2	41.7 ±0.2	15	60.4 ±2.6	31.7 ±0.2	46.8 ±0.2	45.5 ±0.2
2	6	34.2 ±2.9	30.6 ±0.5	43.4 ±0.4	41.3 ±0.4	6	50.0 ±2.6	31.5 ±0.5	46.5 ±0.2	45.0 ±0.2
3	6	76.2 ±2.7	31.5 ±1.1	48.2 ±0.2	47.0 ±0.3	6	89.3 ±2.6	31.8 ±0.3	51.9 ±0.3	50.5 ±0.2
Mean		48.3 ±13.9	31.0 ±0.2	45.2 ±1.5	43.3 ±1.8		66.5 ±11.8	31.6 ±0.1	48.4 ±1.7	47.0 ±1.7

Values are means ± SE.

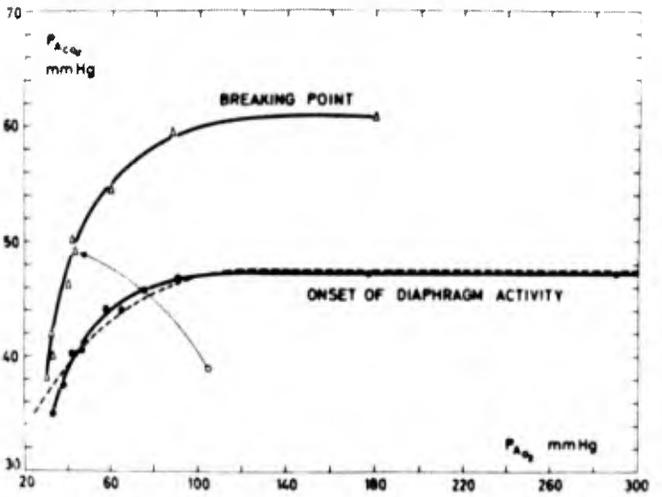

FIG. 6. CO_2–O_2 diagram showing the alveolar air values at the onset of diaphragm activity (points) and at the breaking point (triangles) in breath-holding tests performed after breathing mixtures with various O_2 content, down to about 4%. Open circle indicates the alveolar point at the beginning of breath holding after breathing air at normal rate; dotted line, starting from it, shows the alveolar pathway during apnea. Broken line is reported from Douglas and Haldane (15), and is based on data obtained by analyzing the alveolar air when, during apnea after hyperventilation, "the desire to breathe returned."

Experiments with different values of P_{O_2} in the inspired gas were performed by *subject 1*; $P_{A_{CO_2}}$ and $P_{A_{O_2}}$ at the onset of diaphragm activity and at the breaking point were measured and plotted on a $P_{CO_2}-P_{O_2}$ diagram (Fig. 6). In hypoxic conditions, the two curves become closer: the hypoxic stimulus seems relatively more important in setting the breaking point than in triggering diaphragm activity. The hypoxic stimulus becomes nil when $P_{A_{O_2}}$ is 115–120 mm Hg, while the CO_2 related stimuli becomes negligible when $P_{A_{CO_2}}$ is about 35 mm Hg.

An approach similar to the present one was used by Douglas and Haldane (21), who analyzed the alveolar air during hyperventilation apnea when "the desire to breathe returned." The record of diaphragm activity in the present investigation proved that trained subjects can tell exactly the onset of diaphragm activity during breath holding: hence the desire to breathe corresponds probably to the onset of diaphragm activity. This seems demonstrated by the good fitting of the $P_{A_{CO_2}}-P_{A_{O_2}}$ curve determined by Douglas and Haldane and that corresponding to the onset of diaphragm activity (Fig. 6). Douglas and Haldane believed that the apnea was involuntarily set after hyperventilation, while there is now evidence that there is no hyperventilation apnea in the waking conditions, i.e., in conscious man apnea is always started by a voluntary act (6). The data of Douglas and Haldane therefore do not represent the threshold exciting level, but the level at which voluntary inhibition of the inspiratory muscles activity is overcome.

SUMMARY

The electrical activity of the diaphragm during breath holding has been studied. After a period of no or slight tonic activity a marked discharge is recorded, this is followed by others at a progressively higher rate up to the breaking point. The action of the diaphragm, not balanced by antagonist muscles, causes a fall of the intrathoracic pressure. The period of breath holding, in most subjects, may be divided into two parts: the first, characterized by voluntary inhibition of respiratory muscles activity; the second, by involuntary respiratory efforts. The standard error (SE) of alveolar P_{CO_2} values determined at the onset of diaphragm activity in groups of three similar tests is <0.5 mm Hg. Arterial P_{CO_2} in the brain stem at the onset of diaphragm activity has been estimated: breathing O_2 the mean values $\pm$SE in three subjects were, respectively, 46.2 ± 0.3, 46.4 ± 0.2, and 50.2 ± 0.2. The onset of diaphragm activity seems not affected by neurogenic factors related to lung volume or respiratory movements. An alveolar $P_{CO_2} - P_{O_2}$ curve at the onset of diaphragm activity has been determined.

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