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A COMPARISON OF METHODS OF OBTAINING ALVEOLAR AIR *

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The recent advances in our knowledge of the physiology of respiration and of the mechanism by which the normal reaction of the blood is maintained have opened wide fields for study in clinical medicine. In many of the problems which present themselves it is essential to have information regarding the tension of gases in the alveolae of the lungs. While it is comparatively simple to obtain satisfactory samples of alveolar air from trained workers, it is a much more difficult task when dealing with the average hospital patient, for unfortunately all the methods yet devised depend in part on the cooperation of the subject himself. Lack of intelligence, lack of interest, pain, dyspnea, restlessness, toxemia, unconsciousness and the natural disinclination of the sick person to take part in any active performance are among the many factors which interfere with the taking of reliable samples of alveolar air. Preliminary, therefore, to the study of alveolar air in pathological conditions, we have considered it necessary to make a comparative study of the various methods of obtaining alveolar air in order to determine the advantages and disadvantages of each method, the conditions under which a given method is best applicable, and in general to decide on which methods are most reliable for the study of clinical cases. The present report is based on approximately five hundred observations, on hospital patients, as well as on laboratory workers, most of whom were untrained in the methods of taking alveolar air.

THE HALDANE METHOD

The method as devised by Haldane[1] consists in the use of a ¾-inch hose about 4 feet long fitted with a glass mouthpiece at one end. The subject, after five minutes' normal breathing, gives the greatest possible expiration through the tube. This should be done rapidly to ensure the displacement of the air in the hose. At the end of the expiration the subject closes the mouthpiece with his tongue, and the sample of air is drawn from the beginning of the tube. Two samples should be taken—

* From the Surgical and Medical Services of the Peter Bent Brigham Hospital.

1. Haldane and Priestley: Jour. Physiol., 1905, xxxii, 225.

one from an expiration beginning at the end of normal inspiration, the other from an expiration beginning at the end of normal expiration. The values of the two samples are averaged.

This method is without doubt the best and simplest for the trained subject. For an untrained person, and especially for one of moderate intelligence, the use of the tongue in closing the mouthpiece presents an almost insurmountable difficulty. To overcome this we have modified the technic by introducing a specially constructed valve.

THE HALDANE METHOD WITH A SPECIALLY DESIGNED VALVE

The general objection to the use of a valve is that currents and eddies of air are formed which probably introduce a real element of uncertainty. While this is certainly true of the ordinary valve, we believe that the one to be described effectually overcomes this difficulty, and greatly increases the usefulness of the Haldane method.

The valve is a hollow copper cylinder about 4 inches in diameter and 1 inch long, closed at both ends. Set into each end of the cylinder, and opposite each other, are two brass tubes of ¾-inch diameter. Inside the main cylinder is another cylinder, ground so as to fit accurately, which revolves through an arc of about 45 degrees. The inside cylinder is pierced by two ¾-inch tubes, one of which is open at both ends, and so placed that when set opposite the two tubes previously mentioned a mouthpiece and straight tube about 4 inches long is formed. The far end of the tube is attached to a rubber hose 4 feet long, as in the ordinary Haldane alveolar air-tube. A single, almost instantaneous movement by means of a handle throws the second tube of the inner cylinder into communication with the mouthpiece. This tube is open at the side and closed at the far end, an arrangement which allows the subject to breathe naturally through the mouthpiece to the outside air with a dead space of not over 20 cm.

The apparatus is used as follows: The subject breathes naturally for five minutes through the mouthpiece directly to the outside air. At a given signal, at the end either of inspiration or of expiration, the observer turns the handle quickly and puts the subject into communication with a 4-foot tube that is perfectly straight and smooth. At the same instant the subject expires as deeply and rapidly as possible, and at the very end of the expiration the observer turns the handle back. The subject now breathes to the outside air and the alveolar air is sealed in the rubber tube. The sample is then quickly drawn into the sampling-pipet.

This method has proved itself to be of great value and we invariably use the valve when we are taking alveolar air by the Haldane method.

The relative accuracy of the Haldane method with and without the valve is shown by the following observation:

April 9, 9 a. m.; B.: With valve: Inspiration, $CO_2 = 41.1$ mm.; expiration, $CO_2 = 41.3$ mm. Without valve: Inspiration, $CO_2 = 39.9$ mm.; expiration, $CO_2 = 40.1$ mm.

The Haldane method in one of its various modifications should be classed as the standard method of taking samples of alveolar air since it undoubtedly gives the most accurate values when used under proper conditions. Its clinical applicability is limited to patients who are in comparatively good health. To obtain satisfactory samples it is necessary not only that the expiration should be as complete as possible, but also that it be rapid and forcible. A slow prolonged expiration is not sufficient. Many sick patients are unable, on account of pain or dyspnea or weakness, to give an expiration of enough force and depth. In these and in patients of distinctly low intelligence the method is unreliable. We have found, moreover, that even among intelligent, healthy persons it frequently takes considerable training before satisfactory results are obtained.

THE LINDHARD METHOD

Lindhard[2] has recently described the following very ingenious way of obtaining alveolar air: The subject breathes through a Krogh glass valve with rubber flaps and dead space of from about 40 to 50 c.c. Through an opening directly opposite the mouth is passed a small flexible lead tube with an interior bore of about 1 mm. This lead tube passes back into the pharynx so far as possible for comfort. The samples of air are drawn with a sampling-tube in 3 or 4 c.c. amounts at the end of a normal expiration. Accordingly to Krogh and Lindhard, this is reliable in subjects breathing 600 c.c. or over per respiration. The essential point in this method is the exact time at which the samples are taken, and this is somewhat difficult for the observer. If taken either just too early or too late alveolar air is not obtained. The movement of the rubber valve-flaps is an aid in timing.

We have made an extensive trial of this method and have found it to check up with the Haldane method if the subject breathed deeply. In the ordinary person 300 or 400 c.c. is the normal expired air; therefore, we were obliged to have the subject exhale about double his usual amount on a given signal; we repeated these deep exhalations about every forty-five seconds.

In order to determine more accurately the influence of the depth of expiration on this method of taking alveolar air, the valves were attached to a recording spirometer, and the volume measured of those expirations, at the end of which the samples were taken.

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2. Linhard: Jour. Physiol., 1911, xlii, 337.

March 10, 3:30 p. m.; P.: Volume of expiration = 399 c.c.; alveolar CO_2 = 29.9 mm. Volume of expiration = 440 c.c.; alveolar CO_2 = 34.5 mm.
Control by two Haldane samples (valve) = 41.3 mm. and 38.9 mm.; 40.1 mm.

It is thus evident that samples taken at the end of normal expirations are not alveolar air. The percentage of carbon dioxid is much lower than it should be. The following experiments show the results which may be obtained when samples are taken at the end of deeper expirations:

April 3; P.: Volume of expiration = 880 c.c.; alveolar CO_2 = 40.2 mm.
Volume of expiration = 1,200 c.c.; alveolar CO_2 = 39.5 mm.
Volume of expiration = 1,650 c.c.; alveolar CO_2 = 36.5 mm.
Volume of expiration = 870 c.c.; alveolar CO_2 = 36.5 mm.
Volume of expiration = 1,000 c.c.; alveolar CO_2 = 38.8 mm.
Volume of expiration = 1,250 c.c.; alveolar CO_2 = 40.1 mm.
Control by two Haldane samples (valve); inspiration, CO_2 = 41.1 mm.
expiration, CO_2 = 41.6 mm.

April 4; P.: Volume of expiration = 650 c.c.; alveolar CO_2 = 38.0 mm.
Volume of expiration = 670 c.c.; alveolar CO_2 = 35.3 mm.
Volume of expiration = 840 c.c.; alveolar CO_2 = 37.8 mm.
Volume of expiration = 690 c.c.; alveolar CO_2 = 37.6 mm.
Volume of expiration = 840 c.c.; alveolar CO_2 = 39.6 mm.
Volume of expiration = 1,460 c.c.; alveolar CO_2 = 39.4 mm.
Volume of expiration = 880 c.c.; alveolar CO_2 = 39.2 mm.
Volume of expiration = 540 c.c.; alveolar CO_2 = 38.2 mm.
Volume of expiration = 800 c.c.; alveolar CO_2 = 38.3 mm.
Volume of expiration = 1,500 c.c.; alveolar CO_2 = 39.2 mm.
Control by two Haldane samples (valve); CO_2 = 38.5 mm.
CO_2 = 38.5 mm.

Inasmuch as these were the results obtained in a series of consecutive experiments with a subject who was not particularly well trained, it will be noted that they are in close accord with the results by the Haldane method. In the instances in which the carbon dioxid is low, beyond the limit of error, the timing of taking the samples was undoubtedly at fault. It is thus quite possible to obtain accurate samples of alveolar air by the Lindhard method even with persons whose respiration is normally shallow, if they are made to give occasional moderately deep expirations, and if a series of small samples are taken at exactly the end of such expirations.

Early in our studies we became impressed with the fact that untrained persons, and especially sick persons, were greatly inconvenienced by the use of valves. Indeed, the use of a simple mouthpiece may quite change the type of respiration, making it deeper than normal and more labored. This is especially the case with patients having a tendency to dyspnea. We therefore attempted to develop a method for obtaining alveolar air with as little as possible of the disturbing apparatus. The result is a modification of the Lindhard method.

THE LEAD TUBE METHOD

The subject breathes through his mouth, the nose as usual being closed by a nose-clip. A small flexible lead tube of 1 mm. bore is introduced into the mouth, and the end passed as far back as is possible without bothering the patient. At a point about 3 cm. from the mouth a small feather is attached to the tube to serve as an index of the phases of respiration. The other end of the lead tube is attached to one of the sampling-pipets used by Krogh, with an easy working tap at the top, but none at the bottom. The opening at the bottom of the tube must be wide so that the mercury falls rapidly and the sample is taken quickly. The subject breathes naturally and at a word given at the end of an inspiration gives a deep forcible expiration of at least 600 or 800 c.c. At almost the end of the expiration the tap on the sampling-tube is turned quickly and from 3 to 5 c.c. of air taken into the tube from the back of the mouth. Deep expirations are given at intervals until a large enough sample is obtained for analysis. The following examples illustrate the probable accuracy of the method:

April 13; Miss B.: CO_2 in successive samples A. (1) 38.8 mm.; (2) 40.9 mm.; (3) 39.1 mm.; (4) 38.8 mm. B. (1) 40.8 mm.; (2) 42.0 mm.; (3) 43.1 mm.;
Controls by Haldane method: Inspiration, $CO_2 = 41.8$ mm.
Expiration, $CO_2 = 41.9$ mm.

These figures present some interesting points for study. It is probable that the tension of carbon dioxid in the alveolar air of this patient was practically 42 mm. Series A was taken by one of us and Series B by the other. We have frequently seen a slightly lower average by one observer than by the other. We attribute this to the difficulty of exactly timing the opening of the tap, and do not consider that it represents an actual change in the alveolar air. The following experiments were done by the same method:

April 14; F.: CO_2 in successive samples = (1) 40.4 mm. (2) 41.3 mm.; (3) 41.3 mm.; (4) 40.5 mm. Average = 40.8 mm.

Controls by Haldane method: Inspiration, $CO_2 = 39.1$ mm. Expiration, $CO_2 = 41.3$ mm. Average = 40.2 mm.

April 15; B.: CO_2 in successive samples = (1) 38.2 mm.; (2) 40.0 mm.; (3) 39.2 mm.; (4) 38.2 mm. Average = 38.9 mm.

Controls by Haldane method: Inspiration, $CO_2 = 37.2$ mm. Expiration, $CO_2 = 41.5$ mm. Average = 39.3 mm.

April 16; B.; CO_2 in successive samples = (1) 38.6 mm.; (2) 39.8 mm.; (3) 40.0 mm.; (4) 40.1 mm. Average = 39.6 mm.

Controls by Haldane method: Inspiration, $CO_2 = 38.9$ mm. Expiration, $CO_2 = 41.0$ mm. Average = 39.9 mm.

April 16; F.: CO_2 in successive samples = (1) 41.3 mm.; (2) 42.6 mm.; (3) 42.6 mm.; (4) 42.8 mm. Average = 42.1 mm.

Controls by Haldane method: Inspiration, $CO_2 = 40.0$ mm. Expiration, $CO_2 = 42.9$ mm. Average = 41.7 mm.

May 27; W. (patient): CO_2 in successive samples = (1) 42.4 mm.; (2) 43.0 mm. Average = 42.7 mm.

Controls by Haldane method: Inspiration, $CO_2 = 43.0$ mm. Expiration, $CO_2 = 41.4$ mm. Average = 42.2 mm.

June 2; S. (patient): CO_2 in successive samples = (1) 33.6 mm.; (2) 36.6 mm.; (3) 35.5 mm.; (4) 36.6 mm. Average = 35.6 mm.

Controls by Haldane method: Inspiration, $CO_2 = 35.3$ mm. Expiration, $CO_2 = 34.9$ mm. Average = 35.2 mm.

The chief disadvantage of the method is the difficulty of taking samples at exactly the right time. If they are taken too early or too late, the carbon dioxid values fall too low. It is thus advisable to take several tubes. Occasionally one analysis falls so far below the others that it is obviously incorrect and it must be discarded. The advantages of the method lie first in the fact that the valves or mouthpiece which upset the subject's natural respiration are discarded. Troublesome accumulation of saliva is avoided, as the tube can be removed from the mouth at any moment, and the subject allowed to swallow. Secondly, it is possible to obtain samples of alveolar air with less deep and forcible expirations than by the Haldane method because a number of small samples are taken from a series of expirations, rather than one large sample from a single expiration. In clinical work the method has proved to be of especial value with toxic or unconscious patients, in whom the alveolar ventilation is great. It is impossible to make these patients breathe as one desires, and their respiration is often changed when they are forced to breathe through a mouthpiece. Moreover, it is sometimes difficult to prevent leakage round a mouthpiece. The small lead tube can be passed into the mouth almost without the patients being aware of its presence, and the samples are taken at the end of expiration. The following analyses show the results obtained in a case of severe diabetic coma:

Oct. 2; B.: CO_2 in successive samples = (1) 6.2 mm.; (2) 6.2 mm.; (3) 5.5 mm.

Control by Plesch-Higgins method: $CO_2 = 6.7$ mm.

Oct. 3; B.: CO_2 in successive samples = (1) 11.0 mm.; (2) 10.8 mm.

Controls by Plesch-Higgins method: CO_2 = (1) 10.8 mm.; (2) 10.5 mm.

THE PLESCH METHOD

The principle of this method of determining the carbon dioxid tension of the alveolar air is quite different from that of the methods described above. Instead of attempting to obtain actual samples of air from the alveoli by means of deep expirations, Plesch[3] has suggested the rebreathing of a limited volume of air until it is in equilibrium with the air in the alveoli. Porges[4] and his associates have found this method satisfactory in series of clinical investigations. Porges states that the carbon dioxid diffuses so rapidly that an equilibrium is established before a single complete circulation of the blood has taken place. The apparatus, as we have used it, is the same in principle, and differs only in details of construction from that of Porges. The form was devised by Mr. H. L. Higgins, of the Carnegie Nutrition Laboratory, Boston. To a copper disk of about 20 cm. is soldered on the under side a flange 2 cm. wide. In the center of the same (under) side of the disk

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3. Plesch: Ztschr. f. exper. Pathol. u. Therap., 1909, iii, 380.
4. Porges, Leimdorfer and Markovi: Ztschr. f. Klin. Med., lxxiii.

is soldered an ordinary ¾-inch three-way brass valve. Near this is soldered a small brass tap suitable for the attachment of small rubber tubing for taking samples of air. Over the top of the disk is stretched a woman's rubber bathing-cap, held in place on the flange by a large rubber band. The subject, with his nose clamped, breathes through a mouthpiece which is attached by a short piece of wide-bore rubber tubing to the three-way tap in the bottom of the copper disk. The tap is at first turned so that the subject breathes to the outer air. It is then turned so that the subject breathes in and out of the bag for a given length of time. The tap is then turned again, the bag is closed and a sample of air taken from the bag for analysis. Porges begins with the bag empty, lets the subject take a deep inspiration, and at the height of the inspiration turns the tap so that the subject expires into the bag and then rebreathes. Experiments with this technic, however, show that the tension of the carbon dioxid in the bag varies considerably with the depth of the initial inspiration, and thus with the amount of air in the system of respiratory tract plus bag. In the following the time and number of respirations were constant:

March 13; B.: Moderately deep initial inspiration: $CO_2 = 43.2$ mm.
Deeper initial inspiration: $CO_2 = 41.5$ mm.
Very deep initial inspiration: $CO_2 = 38.2$ mm.
Controls by Haldane method: Inspiration, $CO_2 = 41.2$ mm.
Expiration, $CO_2 = 41.2$ mm.

This source of error is to some degree at least avoided if one follows the suggestion of Higgins and fills the bag with a constant volume of air. The tap is then turned at the end of a normal expiration, and the patient begins by inspiring from the bag. This is the method which we have adopted, but instead of filling the bag with 600 c.c. of air (Higgins) we find it more satisfactory to fill with 1,000 c.c. of air, and thus allow the subject to take a deeper inspiration. The air is forced into the rubber bag through the small tap by water displacement from an ordinary flask.

The time during which breathing takes place is of considerable importance. Porges[4] states that after from twenty to thirty seconds there is very little change in the composition of the air. His experiments, however, show that practically there may be a considerable rise in the carbon dioxid tension if the same air is rebreathed for twenty-five-second periods after various intervals. We have performed a similar experiment and have found that after breathing from the bag four times in twenty seconds the carbon dioxid tension of the air in the bag was 39.5 mm. After an interval of three and one-half minutes the same air was rebreathed for two periods of twenty seconds each, the periods separated by an interval of one minute. The carbon dioxid tension in the bag was then 45.9 mm. After rebreathing for two more similar periods the carbon dioxid tension had risen to 46.4 mm. There may also be a rise in the carbon dioxid tension if the length of the single periods is prolonged. Thus successive determinations with the same patient gave the following results:

Four respirations in 20 seconds: $CO_2 = 45.2$ mm.
Six respirations in 30 seconds: $CO_2 = 47.4$ mm.
Eight respirations in 40 seconds: $CO_2 = 48.6$ mm.

The element of time is therefore an important one, and we have found, in agreement to Porges, that from twenty to thirty seconds, and preferably twenty-five seconds, is the optimum.

The question of the rate and depth of respiration while rebreathing is of some moment. Within certain limits, however, they seem to play a lesser rôle than one might anticipate. The following successive determinations were made on the same person (P.) the rate and depth of the respirations being varied:

Five	respirations in 25 seconds.	Moderately deep	$CO_2 = 46.4$ mm.
Sixteen	respirations in 25 seconds.	Shallow	$CO_2 = 45.9$ mm.
Five	respirations in 25 seconds.	Very deep	$CO_2 = 46.3$ mm.
Seventeen	respirations in 25 seconds.	Shallow	$CO_2 = 45.4$ mm.
Five	respirations in 25 seconds.	Natural	$CO_2 = 39.0$ mm.
Five	respirations in 25 seconds.	Moderately deep	$CO_2 = 45.1$ mm.

Thus with the exception of the fifth determination, in which the subject was breathing naturally, quietly and superficially, the values of the carbon dioxid tension agreed well, whether the respirations were very deep or were shallow and rapid. Gentle, superficial respiration does not suffice to bring about complete diffusion of gases. The same has been found to be true of very rapid, superficial, panting breathing, which also gives too low values for the carbon dioxid tension. Respirations of moderate depth, however, seem to bring about as complete diffusion as very deep respirations. The results of a large number of determinations lead us to agree with Porges in feeling that the best results are obtained if five rather deep respirations are taken in the twenty-five seconds.

In regard to the accuracy and reliability of this method of taking alveolar air, one must first consider the constancy of the results obtained by the method and then the relation of the results obtained to those found by other methods. A comparatively large number of observations have now been made on patients and more or less experienced laboratory workers. The results depend, of course, in some degree on the experience of the subjects and on their intelligence in understanding what is required of them. In general, however, it has been striking that reliable observations have been obtained with comparative ease from almost all hospital patients. At least two experiments are made for each determination. The results very frequently agree within 1 mm. tension of carbon dioxid. Almost always they agree within about 2 mm. tension. While this is perhaps not the highest degree of accuracy, it must be remembered that it is extremely difficult to achieve greater accuracy in obtaining samples of alveolar air by any method except in trained subjects, so that on the whole the results are satisfactory as far as their constancy is concerned. A series of observations has also been made comparing those obtained by the Plesch method with those obtained by the Haldane method in the same subject and at the same time. The relation is, of course, a variable one, but the Plesch method almost always gives a higher value for carbon dioxid tension. On the average it is approximately from 1 to 4 mm. higher, but sometimes it is less and sometimes a little more.

The advantages in the use of the Plesch method are obvious. From the point of view of the subject it is extremely simple, and satisfactory results can be obtained from almost any one with a minimum of training. It is frequently extremely difficult to make a sick person or, in fact, many healthy persons, give an expiration of maximum depth, but almost any one can easily breathe deep enough to give reliable results by the Plesch method. Moreover, the technic required of the observer is so simplified that it is readily acquired and needs very little skill. The chief disadvantage of the Plesch method is that it is not quite so accurate as the Haldane method. This, however, seems to be only with regard to highly trained subjects. In a person of experience and intelligence it is possible to obtain constant and accurate results by the Haldane method, but in the average run of persons the results obtained by the Plesch method are on the whole more satisfactory. The Plesch method is worked out on a more empirical basis, but it gives very constant values, and values which are extremely satisfactory for comparative studies.

SUMMARY

As a result of an extensive comparative study of various methods for obtaining the tension of gases in the alveolar air, with especial reference to the use of these methods in clinical work, we have arrived at the following conclusion:

The Haldane method gives results which approximate closely the average gaseous composition of the alveolar air. It is the most reliable and accurate method when used on intelligent and experienced subjects. The necessity, however, of obtaining very deep and very forcible expirations limits its usefulness when working with untrained or sick persons.

The Lindhard method, and the modification of it described here, give values analogous to those of the Haldane method. The method has

the advantage, however, of not requiring such deep expirations as the Haldane method. The technic of taking the samples is, however, much more difficult for the observer. In certain types of pathological cases, notably in unconscious or very sick patients with a large alveolar ventilation, the method is useful and the technic simple.

The Plesch method gives values for the carbon dioxid tension which are higher than those obtained by the Haldane and Lindhard methods. Successive determinations give sufficiently constant values. The technic of the method both for the observer and for the subject is so simple that the method is especially useful for routine clinical work.

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