JCI The Journal of Clinical Investigation

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J Clin Invest. 1940;19(4):609-618. https://doi.org/10.1172/JCI101163.

Research Article

STUDIES ON THE INTRAPULMONARY MIXTURE OF GASES. III. AN OPEN CIRCUIT METHOD FOR MEASURING RESIDUAL AIR

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(Received for publication March 12, 1940)

In the preceding paper, the use of the closed rebreathing circuit for measuring residual air was discussed and tested to determine the possible error due to imperfect gas mixture within the lungs. It was found that such an error was probably present not only in all cases of severe pulmonary emphysema, but also in some normal subjects with large residual air. Some of the reasons for the inadequacy of the closed circuit measurements are apparent from analysis of the essential features of such a circuit. In the first place, the inspiratory gas mixture is always changing. Thus there would appear to be no sustained equilibrium between spirometer and lungs. As soon as equilibrium is approached for one concentration of the breathing mixture, the inspiratory gas has already changed. This change is most marked when the spirometer volume is allowed to diminish as oxygen is absorbed. McMichael's technique of replacing the oxygen, as tested by us, did not remove the discrepancies due to poor mixing within the lungs. Furthermore, such a procedure introduces further technical difficulty and fails to change the fact that the inspiratory gas is still varying, at the start, until approximate equilibrium is reached. In our experience, the adjustment of a proper flow of oxygen for replacement was difficult even in normal subjects. In subjects with arterial oxygen unsaturation, the maintenance of a constant volume in the closed circuit was practically impossible due to the oxygen deficit and resultant changing rate of oxygen replacement necessary.

The second difficult feature of closed circuit measurements is the exact calculation of the oxygen absorbed. The tracings in abnormal and even in some normal subjects are often so irregular that an exact base line cannot be drawn, yet the calculation demands accuracy in this detail.

Thirdly, with the usual closed circuit technique the net change in lung nitrogen concentration is rarely more than three-tenths of an atmosphere. With such a figure, any error in alveolar measurement (or in the assumed values) is magnified at least three-fold in the final residual air value.

To avoid these three points of difficulty, an open circuit method has been devised, with pure oxygen as the breathing mixture. In such a procedure, the subject is allowed to breathe oxygen for a period of time sufficient to wash practically all the nitrogen out of the lungs. For this period all the expired gases are collected and finally measured and analyzed for nitrogen. It will be seen that the inspiratory gas is absolutely uniform throughout and that there is no need to obtain a smooth breathing curve once the oxygen breathing has been started at a definite point in the breathing cycle. As in the closed circuit, the concentrations of gases in the pulmonary spaces at start and end are estimated by alveolar specimens, yet here the simpler features of the procedure make these measurements less subject to error. Furthermore, since the net change in alveolar nitrogen is approximately eight-tenths of an atmosphere, the effect of errors in these measurements will not be greatly magnified in the course of calculation.

Thus the only errors that are to be anticipated in this method are those due to failure of the alveolar measurements to represent the mean value of residual air nitrogen. It is possible to predict the probable direction of such error. Except in unusual circumstances, the alveolar specimens in cases of poor distribution will tend

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to represent the well aerated portions of the lungs, and to neglect the relatively poorly aerated regions. Thus, in estimating the lung nitrogen concentration on room air breathing at the start, the alveolar specimen obtained may be lower in nitrogen than the average in the lung. Similarly, the alveolar specimen after a period of oxygen breathing may fail to tap some nitrogen still present in the poorly aerated regions and so be somewhat too low as measured. If breathing is continued long enough, the latter error should be gradually reduced, since it is obvious that eventually all the nitrogen will be washed out. The expression used in the calculation is the difference of the two alveolar values, "alv. $\bar{a}$ − alv. $\bar{p}$." The likely error in each is a negative one. If the errors are equal, they will cancel each other. However, since that in "alv. $\bar{p}$" is probably very slight, the expression "alv. $\bar{a}$ − alv. $\bar{p}$" may be too small. Since this expression is the denominator of a fraction in the calculation, the final value for functional residual air by this method could be somewhat too large.

To take an example, an alveolar specimen in a case of emphysema might give a value of 82 per cent of nitrogen, when the average of all residual air nitrogen is actually 84 per cent. At the end of the period of oxygen breathing, let us say that the mean nitrogen of the residual air is 6 per cent. If the alveolar specimen as measured gives 4 per cent of nitrogen, then the alveolar *difference* (0.82 − 0.04) will be the same as the true difference of nitrogen concentrations in the residual air (0.84 − 0.06), the two errors thus cancelling. It is difficult to see how an error of method larger than 5 per cent would be likely from this source.

An attempt has been made to test for the presence of such an error. This test, analogous to that used for the Christie method in a previous paper, consists of a similar type of experiment in which the expired gases are collected during a period of breathing room air immediately following prolonged oxygen breathing. In other words, first all the nitrogen is washed out of the lungs; then, during a subsequent period of room air breathing, the amount of retained nitrogen in the lungs is measured.

Such a procedure is really a reversal of the oxygen breathing experiment, in so far as the direction of the nitrogen shift is concerned. In this case, errors in alveolar measurement will cause an effect of opposite sign in the value obtained, as can be seen from analysis of the factors involved. Here the expression "alv. $\bar{p}$ − alv. $\bar{a}$" is the denominator of a fraction in the calculation. Alv. $\bar{a}$, measuring the small nitrogen concentration after oxygen breathing, may possibly neglect nitrogen still trapped in the poorly aerated regions. Thus it is too low, if at all wrong. Similarly, alv. $\bar{p}$, taken after a subsequent period of room air breathing, may be too high in nitrogen, since there may be some higher oxygen mixture still in the poorly aerated lung spaces. Thus the difference, "alv. $\bar{p}$ − alv. $\bar{a}$," may be definitely too high, and from this, the residual air value too low. In contrast to the oxygen breathing experiment, from predictions in this case a cancellation of errors in alveolar measurements will be unlikely. Therefore it may be expected that this second open circuit method will be more likely to give erroneous results than the first method.

The test of the open circuit procedures will be a comparison of residual air values obtained by the two methods. If they differ, it will be evidence that the factor of poor mixing, as it influences alveolar samples, is still a possible source of error in the measurements. If they agree, one may consider the value obtained probably not significantly affected by erroneous alveolar measurements. It will be of special interest to compare this evidence with that obtained in the same subjects by the analogous test procedure in the closed circuit, reported in a previous paper.

PROCEDURE [2]

The apparatus for the open circuit methods was the same as that used for nitrogen excretion measurements in the first paper of this series. The diagram is reproduced here. The arrangement consists essentially of two open breathing circuits fitted with flutter valves (F_1, F_2, F_3, F_4) connected adjacent to the mouthpiece (M) at the valve (V_1), which can be used to shift the breathing from one circuit to the other. One circuit, the main circuit, is attached on its inspiratory side to a rubber anesthesia bag (B_1), this in turn to an oxygen tank. The expiratory side

[2] In collaboration with Dr. Eleanor D. Baldwin, we have recently devised a simplification of this open circuit method, based on results in 200 cases studied. In the new technique, alveolar sampling is eliminated, the only gas analysis necessary being that from the spirometer. This will be reported in a subsequent paper.

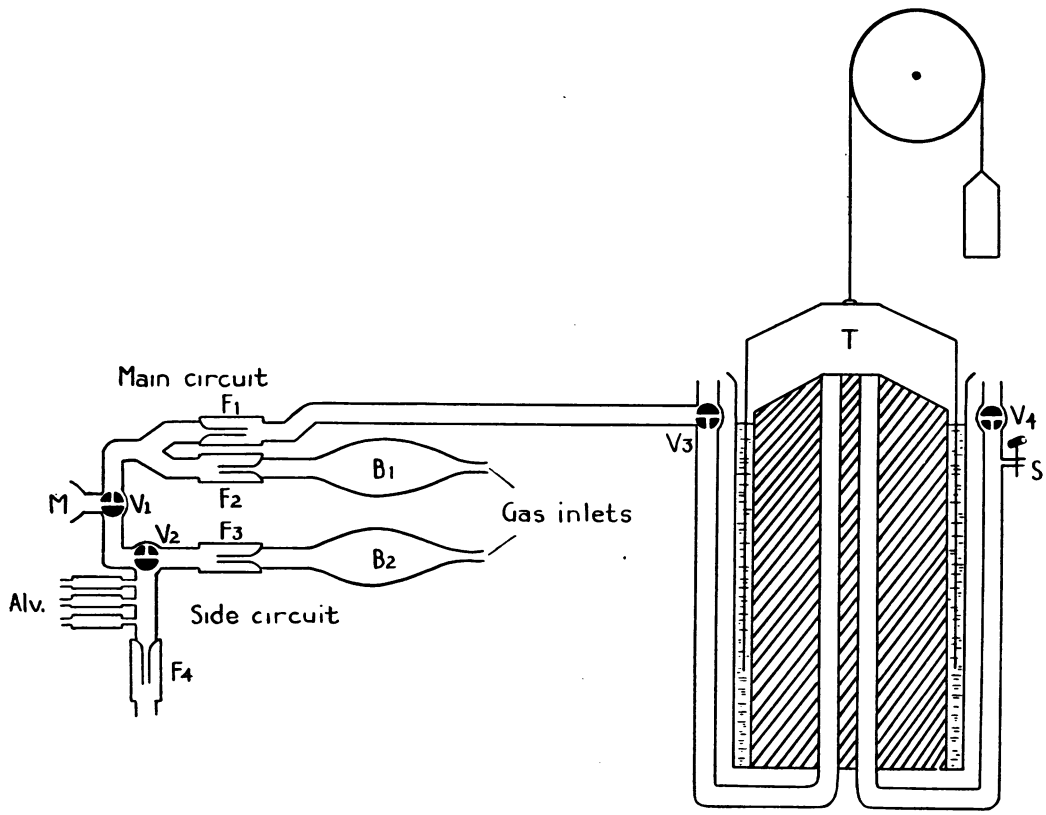

FIG. 1. OPEN CIRCUIT APPARATUS FOR MEASUREMENT OF RESIDUAL AIR

M, mouthpiece. *Alv.*, group of three evacuated gas sampling tubes. V_1, V_2, V_3, V_4, three-way respiratory valves. F_1, F_2, F_3, F_4, one-way rubber flutter valves. B_1, B_2, small rubber anesthesia bags. *T*, one-hundred liter (Tissot) gasometer. *S*, valve and attachment for obtaining gasometer samples. For further explanation, see text.

leads to a Tissot gasometer of 100-liter capacity. On the side circuit there is an additional valve (V_2) with which the inspiratory gas flow can be cut off during alveolar sampling. The inspiratory arm of this circuit leads to an anesthesia bag (B_2) and oxygen tank, which were replaced by a tube leading from outside air when atmospheric air was the desired breathing mixture. On the expiratory arm evacuated sampling tubes labelled "alv." are inserted close to the valve (V_2). The dead space from mouthpiece to these tubes is about 100 cc.

The procedure for a determination of functional residual air by the open circuit method was started with V_1 turned to the side circuit. The main circuit and gasometer were thoroughly washed out with oxygen. Six successive washings of 10 to 20 liters each were found adequate. After the washing, V_3 was opened to connect the main circuit to the open room and a flow of 4 to 5 liters per minute of oxygen maintained in this circuit. The bag (B_2) in the side circuit was replaced by a room inlet tube. Then with V_1 unchanged, the subject, under basal conditions, was attached to the mouthpiece. When breathing quietly, he was instructed to exhale maximally for an alveolar sample. At the same time, the valve (V_2) was turned to close the inspiratory side of the circuit. The alveolar sample was taken at the end of approximately five seconds of expiration and V_2 then reopened. This sample, designated "alv. $\bar{a}$," was thus a Haldane-Priestley alveolar sample and represented an attempted measure of average lung gas concentration on room air breathing.

Following this sampling, at least two minutes of room air breathing were allowed in order to restore quiet breathing. Then V_3 was turned to direct the oxygen flow of the main circuit into the gasometer and V_1 was turned to the main circuit at exactly the end of a normal expiration. By watching carefully the respiratory rhythm for the few previous breaths, this latter valve turn could be made accurately at the desired moment.

For the next seven minutes of oxygen breathing the expired gases were collected in the gasometer. During this time, the oxygen flow was maintained to keep the bag (B_1) about one-half full. The period of seven minutes was the standard one used. Results of trials with longer periods will be presented to show that seven minutes is probably adequate.

At the conclusion of the seven minutes, the valve (V_1) was again turned to the side circuit, this time at any point

during expiration, preferably near the beginning. At the same time, the subject was instructed to expire fully for an alveolar sample. For this, as for all alveolar sampling, the valve (V_3) had been turned to close the inspiratory arm of the side circuit. This alveolar sample, designated "alv. $\bar{p}$," was taken at approximately five seconds of expiration as before.

Following this, the patient was disconnected and the main circuit flushed out with 5 to 10 liters of oxygen, the wash gas being allowed to mix in the gasometer with the collected expired gases. The valve (V_3) was next turned to close the entire gasometer contents, whose volume and the temperature were then recorded. A sample was taken from the gasometer for analysis within one to two minutes, after first flushing out the inlet and outlet pipes of the gasometer proper with the collected gases. This sample will be designated as "Tissot" sample in future references.

An approximation of the dead space of the gasometer was necessary for the final calculation. It will become apparent from the calculation to be discussed that this need only be an approximation. With the procedure as outlined, the effective dead space consisted only of the gas space under the bell when fully lowered. The dimensions of this space were measured and its volume calculated geometrically. The volume of the tubing did not need to be considered, since it was filled with oxygen at both the start and the end of the experiment.

Each experiment required the analysis of three gas samples, two "alveolar" and one "Tissot." In addition, the contents of each new oxygen tank required analysis for the small amount of inert gases. All gases were analyzed with a Haldane gas analysis apparatus. In the case of the samples of very high oxygen content, the dilution method was employed, as described in the first paper of this series. (The Van Slyke-Neill manometric apparatus can also be used for gas analysis.) Analysis of the alveolar specimens required an accuracy of only 0.1 to 0.2 per cent, so that possibly a simpler method might be employed. However, a high degree of accuracy was necessary in the analysis of the Tissot sample. In all cases the analyses were done in duplicate to check within 0.05 per cent. All analyses were reported as decimal fractions of an atmosphere of nitrogen, as dry gas.

CALCULATION

The first step in the calculation requires an expression for the total nitrogen in the expired gas in excess over that inspired. The volume of expired gas is known, but that inspired unknown. However, the nitrogen content of the inspired gas is so low that no significant error is involved by assuming that the inspired volume equals the expired volume. The gasometer volume obtained and corrected to dry gas at standard temperature and barometric pressure will be designated as V_0. To this the measured dead space volume ($D.S.$) has been added for the calculation.

Then (1) Total excess N_2 in gasometer

$$= (V_0 + D.S.)(\text{"Tissot" } N_2 - \text{"O}_2 \text{ tank" } N_2).$$

Of this, a part has come from nitrogen originally in the lung spaces, a further part from excreted nitrogen from the blood.

$\therefore$ (2) N_2 from functional residual air (F.R.A.)

$$= (V_0 + D.S.)(\text{"Tissot" } N_2 - \text{"O}_2 \text{ tank" } N_2) - N_2 \text{ excreted.}$$

Also (3) N_2 from functional residual air

$$= \text{F.R.A. Vol. (alv. } \bar{a} - \text{alv. } \bar{p}).$$

$\therefore$ (4) F.R.A. Vol.

$$= \frac{(V_0 + D.S.)(\text{"Tissot" } N_2 - \text{"O}_2 \text{ tank" } N_2) - N_2 \text{ excreted}}{\text{alv. } \bar{a} - \text{alv. } \bar{p}}.$$

From the first paper of this series:

(5) N_2 excreted $= 220 \times \frac{\text{alv. } \bar{a} - \text{alv. } \bar{p}}{0.80}$

(For seven minutes; 10 cc. added to 220 cc. for each minute after seven, if longer period.)

Substituting:

(6) F.R.A.

$$= \frac{(V_0 + D.S.)(\text{"Tissot" } N_2 - \text{"O}_2 \text{ tank" } N_2)}{\text{alv. } \bar{a} - \text{alv. } \bar{p}} - 275.$$

The F.R.A. value here obtained was then corrected to temperature 37° C. and saturation with water vapor to obtain the values reported in our results.

The reversed procedure used to test these results was somewhat more complicated in practice but similar in principle. In this case the bag (B_1) was replaced with an inlet tube from outside air. The bag (B_2) was in place and connected with an oxygen tank. In preparation the main circuit and gasometer were thoroughly washed with room air. The subject was attached to the mouthpiece with valve V_1 open to the side circuit and an oxygen flow of 4 to 5 liters per minute in that circuit. Quiet breathing of oxygen was maintained for ten minutes. At the end of that time, an alveolar specimen was taken in the usual manner and quiet oxygen breathing was resumed in the same circuit for two further minutes. This alveolar specimen was designated as "alv. $\bar{a}$" and considered as a measure of lung gas concentrations two minutes later, since it had been found by a series of tests that the alveolar nitrogen value during oxygen breathing reached a plateau value after ten minutes or less in both normal subjects and patients with emphysema, the maximum change in alveolar nitrogen from tenth to twelfth minute being less than 1 per cent.

At the end of the complete twelve minutes of oxygen breathing, the valve (V_1) was turned to the main circuit exactly at the end of a normal expiration. The expired gases were then collected for a seven-minute period (or longer) of room air breathing, after which an alveolar specimen was taken in the side circuit as before. The tubing of the main circuit was then flushed into the gasometer with 5 to 10 liters of room air, the valve (V_3) closed, and the gasometer volume and temperature read. A gasometer sample was taken promptly as before, after first flushing out the tubing of the gasometer itself with the first part of the collected gas.

As in the previous procedure, there were three gas samples and one volume measurement. In this case, however, the inspiratory volume, as well as the expiratory

volume, needed to be known for the calculation. Since the respiratory quotient was normally less than unity under basal conditions, the inspiratory volume was greater than the expiratory volume by an amount of some 200 to 400 cc. for the seven minutes. Direct measurement of the inspiratory volume with sufficient accuracy was found to be technically cumbersome. In our experience it was simpler to decide upon a correction factor (ΔV) to be added to the expiratory volume in order to determine the inspiratory volume. To do this the carbon dioxide excretion and the oxygen consumption per minute were determined from a six-minute collection of expired air on room air breathing, usually done just before the other tests on the same day. From this, (O_2 absorbed per minute $-$ CO_2 excreted per minute) $\times 7 = \Delta V$ for seven minutes of room air breathing. This would seem to be an accurate correction in subjects with normal arterial oxygen saturation.

In cases with arterial oxygen unsaturation, however, there is an excess oxygen absorption during the first few minutes of oxygen breathing. Following resumption of room air breathing after oxygen, there is a diminished oxygen intake until the arterial unsaturation is reestablished. It may be assumed with sufficient accuracy for the present purpose that the excess oxygen intake in one instance equals the diminution in the other. Accordingly, in such cases the oxygen deficit of the subject was estimated from respiratory tracings taken with a recording spirometer. This oxygen deficit was subtracted from the ΔV value obtained above, giving a corrected ΔV.

The calculation proceeded in an analogous manner to that in the first method. In this instance there was nitrogen retained in the lungs instead of washed out.

(1) N_2 retained in lung

$= (V_0 + D.S. + \Delta V)0.791 - (V_0 + D.S.)$ Tissot N_2 $- N_2$ absorbed into blood.

Also (2) N_2 retained in lung = F.R.A.(alv. $\bar{p} -$ alv. $\bar{a}$) and

(3) N_2 absorbed into blood $= 220 \times \frac{\text{alv. } \bar{p} - \text{alv. } \bar{a}}{0.80}$.

$\therefore$ (4) F.R.A.

$$= \frac{(V_0 + D.S.)(0.791 - \text{"Tissot" } N_2) + 0.791 \times \Delta V}{\text{alv. } \bar{p} - \text{alv. } \bar{a}} - 275.$$

RESULTS

The subjects for this study were selected by the same criteria as those in the preceding paper. There were four normal subjects, including the two in whom the closed circuit method gave doubtful results. In all there were ten patients with severe pulmonary emphysema, of whom six were included in the series of the previous paper. These six were studied by both of the new methods described. The remaining four were tested only by the first of the two new methods, which is the one proposed as a practical test.

It will be apparent, from the two preceding papers of this series as well as this present one, that this new method for residual air has been devised primarily for the study of cases of abnormal, unequal, or ineffective pulmonary ventilation, in which previous methods, such as that of Christie, have been found inaccurate. It is on the basis of such unusual or extreme cases that any new method must be judged. If in these cases, or at least in a fair proportion of them, the method can provide a reasonably accurate and consistent measure of residual air, then the method can perhaps be considered worthy of further trial.

The results should be examined, therefore, case by case, rather than by any attempt at statistical analysis.

The results of tests on these subjects may be compared in several ways.

(1) Comparison of results by each of the two open circuit techniques (Table I). This will demonstrate whether the slowness or poorness of distribution of respiratory gases, in any given case, is sufficient to invalidate the technique used.

TABLE I

Functional residual air determinations by open circuit methods

Subject	Length of test	Number of determinations	Decreasing lung N_2		Increasing lung N_2		Ratio of average values*	
			Average	Range	Average	Range	Open circuit	Closed circuit†
NORMAL SUBJECTS								
	minutes							
J.L.		5	1220	(1140–1300)	1060	(1005–1090)	0.87	0.98
A.C.		2	2055	(2015–2095)	1930	(1880–1980)	0.94	1.02
R.C.D.		3	2890	(2695–3000)	2770	(2410–3090)	0.96	0.83
D.W.R.		2	3450	(3250–3650)	3355	(3310–3400)	0.97	0.72
SUBJECTS WITH PULMONARY EMPHYSEMA								
M.K.		2	4065	(4030–4100)	3845	(3760–3930)	0.95	0.72
Ant.C.		2	3225	(3080–3370)	3245	(3760–3250)	1.01	0.88
F.H.		1	2670		2540		0.95	0.64
J.C.	7	3	5980	(5940–6050)	5450	(5250–5740)	0.91	0.83
	10	1	6250		5765		0.92	0.87
D.H.	7	4	3325	(3050–3590)	2855	(2805–2910)	0.86	0.81
	10	1	3395		3290		0.97	
H.K.	7	4	2960	(2895–3140)	2095	(1700–2560)	0.71	0.59
	10	3	3080	(2855–3285)	2490	(2445–2520)	0.81	0.52

* Ratio = average value by increasing lung nitrogen method ÷ average value by decreasing lung nitrogen method.

† Figures computed from Paper II of this series.

(2) Comparison of the relative agreement between the two open circuit techniques, with the relative agreement between the two closed circuit techniques. This is given by the two ratios, in the last two columns of Table I.

(3) Average values by the open circuit method can be compared with average values in the same subject by the closed circuit method of Christie (Table III). This will provide, for any given case, a criterion as to whether the various sources of error in the Christie method do actually cancel out, leaving a residual air value comparable with that of the open circuit method. In this comparison it will be important to note not only the difference of average results, but also to compare the range or reproducibility of results by the two methods.

Table I presents the first type of comparison, listing the average open circuit results, the range, and number of determinations. In the two columns on the right are listed also the ratio of the two values by the open circuit methods parallel with the ratio of the two closed circuit results in the same subjects.

Among the four normal subjects, it will be seen that all agree within 200 cc. These include the two subjects, D. W. R. and R. C. D., who showed 500 and 900 cc. difference, respectively, with the two closed circuit methods. Thus it may be seen that in this group of normal subjects there is no evidence of serious error due to maldistribution in the open circuit methods.

It may be noted that the open circuit methods in the case of J. L. give somewhat poorer agreement than the closed circuit. The reason for this is not entirely clear. It seems probable, however, that the error lies in the increasing lung nitrogen method. In the case of small subjects, the assumed ΔV factor in this method has a much larger relative influence on the result than in larger subjects.

Considering now the six abnormal subjects, it will be seen that the first four show satisfactory agreement between the two methods. Agreement within 10 per cent may be considered satisfactory. The fifth subject, D. H., showed a 13 per cent difference by the standard seven-minute test. Using a twelve-minute period, however, there was good agreement. It should be noted that the only significant change by the twelve-minute test was an increase in the result by the second method. This is a part of the evidence which leads to the tentative conclusion that a seven-minute period is adequate for the decreasing lung nitrogen method.

The sixth subject is the only one in whom agreement could not be reached. This case will be discussed in detail later.

The striking difference between the open and closed circuit methods, tested by analogous procedures, is shown in the last two columns, which may be considered as comparative indices of the influence of poor mixing on the results. It will be seen that, in every instance among the abnormal subjects, the index shows much better agreement by the two open circuit techniques.

Table II presents in detail the results on the subject H. K., the sixth one in Table I, in whom agreement could not be reached. This subject was a man of sixty-five with a history of increasing cough and dyspnea for twelve years. The etiology of his condition was unknown. There was no evidence of tuberculosis. There were diffuse asthmatic rales, but no improvement with the use of adrenalin. Roentgenogram of the chest showed increased hilar markings and dark areas at the periphery suggesting emphysematous bullae. His arterial oxygen saturation was 85 per cent. At the time of testing, he was practically bedridden because of dyspnea, though this symptom varied considerably from day to day.

TABLE II

Functional residual air by open circuit methods

Subject—H. K.

Date	Decreasing lung N_2 method			Increasing lung N_2 method		
December 15, 1938	2895			2385		
December 16, 1938	3095			1700		
December 20, 1938	3140			2560		
December 24, 1938	3110*			2510*		
December 27, 1938	3285†			2520†		
January 17, 1939	2700			1735		
	2855†			2445†		
		S.D.	S.E.$_m$		S.D.	S.E.$_m$
Mean 7-minute value	2960	130	65	2095	510	255
Mean 11-minute–12-minute value	3080	275	160	2490	50	29

* 11 minutes. † 12 minutes.

As shown in Table II, there was a considerable variation in values obtained for functional re-

sidual air in this subject in experiments continued over a month's time. It will be noted, however, that the figures by the decreasing lung nitrogen technique are rather consistent, considering that the subject's clinical state varied considerably from one day to the next. It was the increasing lung nitrogen technique which gave the wider variations, and these figures generally are lower than the other group. This is the type of error which is to be expected (see above) with the increasing nitrogen technique, when intrapulmonary mixture is extremely poor. Furthermore, by prolonging the period of breathing such an error should become less, and Table II, in the second column, shows a clear tendency for the figures in the eleven- and twelve-minute period to be higher than the seven-minute period. In the first column, little difference is noted with prolongation of the breathing period.

Table III presents the data for comparison of open and closed circuit techniques in the same subjects, listing the results by the standard Christie procedure, calculated with alveolar specimens, and by the open circuit method, using the decreasing lung nitrogen technique.

TABLE III

Comparison of functional residual air values by Christie, modified Christie, and new open circuit methods

Subject	Closed circuit: Modified Christie method			Open circuit: Decreasing lung N_2			Ratio of Mean Values
	Number	Mean	Range	Number	Mean	Range	
NORMAL SUBJECTS							
J.L.	12	1320	(1170–1485)	5	1220	(1140–1300)	1.08
A.C.	2	2235	(2155–2315)	2	2180	(2100–2265)	1.02
D.W.R.	3	3540	(3200–3770)	2	3450	(3250–3650)	1.02
R.C.D.	5	3250	(2890–3545)	3	2890	(2695–3000)	1.13
SUBJECTS WITH PULMONARY EMPHYSEMA							
Ant.C.	2	3240	(3140–3340)	2	3225	(3080–3370)	1.00
A.M.	6	2750	(2290–3435)	4	2570	(2550–2600)	1.07
K.H.	2	3255	(3240–3270)	2	3590	(3580–3600)	0.91
D.H.	2	3140	(3070–3210)	5	3355	(3050–3590)	0.94
J.C.	4	6570	(5980–7760)	4	6050	(5940–6250)	1.08
J.S.	2	3630	(3615–3645)	1	3515		1.03
F.H.	1	3020		1	2670		1.13
H.K.	3	3835	(3560–4060)	7	3010	(2855–3285)	1.27
M.S.	6		(2230–3750)	8		(2420–3570)	
M.K.	10		(2245–5260)	12		(2130–4100)	

Among the *normal* subjects, the first two gave results in close agreement by the modified Christie and the new methods, as expected from the fact that previous analysis indicated both methods were reliable. In the case of the third subject, D. W. R., with whom the closed circuit could not be proved reliable, still the two circuits gave practically the same results. It is apparent here that in the standard closed circuit method there must have been a fair balance of the various errors which were mentioned.

In the case of the fourth subject, R. C. D., in whom also the closed circuit gave doubtful results, the open circuit gave significantly lower results with less variability on successive tests, and with a good agreement with both open circuit techniques. Thus it would seem here that the standard closed circuit method gave an erroneously high value.

The group of *abnormal* subjects includes ten patients. The last two of these were unusual cases, however, and will be presented in detail in a later tabulation.

Considering for the moment the first eight subjects only as far as a comparison of the average results, it will be seen that the first six show insignificant differences between average open and closed circuit results. As before, a difference of less than 10 per cent is considered insignificant. In the seventh case, F. H., and more markedly in the eighth case, H. K., the closed circuit values are significantly higher.

It is probably important that these two subjects had the greatest pulmonary disability of the group.

Let us next note the reproducibility of results by the two methods in these same eight patients. In two of them, A. M., and J. C., the open circuit shows much less difference in successive tests. The other subjects either showed a similar range or else the data are insufficient to determine the range. It should be mentioned that the range of values in many of the subjects probably reflects not only the accuracy of the method, but also the actual volume variation from day to day.

Table IV presents the detailed results on the two remaining subjects, M. S., and M. K. They are considered together because of their similar clinical pictures and comparable results on residual air determinations. They were both men of slightly under forty years of age, with prolonged histories of nearly constant asthma and bronchitis. Each had marked arterial anoxemia and secondary polycythemia. M.K. had had

TABLE IV

Functional residual air

Date	Closed circuit Modified Christie method	Open circuit Decreasing lung N_2
Subject—M. S.		
October 19	2285	
	3295	
October 24		2420
		3110
October 30		3570
		3220
		2815
		3070
November 8	2590	
	2230	
November 18*	3750	3140
	3310	3210
December 26*	2450	2850
	2805	2410
Subject—M. K.		
May 7, 1938	3890	
May 13, 1938	3550	
May 17, 1938	2710	
	3125	
September 21, 1938		4030
September 22, 1938		4100
October 19, 1939	4250	
	5260	
October 21, 1939		3230
		2780
October 26, 1939		2240
		2130
		3050
October 28, 1939		3605
		4050
		3450
November 15, 1939*	2530	2920
	2245	2760
December 28, 1939*	3220	2975
	2955	2660

* Tests on these dates performed after the use of "Vaponefrin" bronchodilator spray.

several bouts of right-sided cardiac decompensation with massive edema, but was compensated at the time of these measurements. M. S. had slight cardiac weakness only, and had had one episode of mild edema. Each of these patients had a large element of bronchial spasm in his disability, as shown by partial relief with adrenalin. However, free of asthma with adrenalin, they still had arterial anoxemia.

A striking feature in both these subjects was the extreme variability of their respiratory disability, and likewise their extremely irregular respiratory curves. In the case of M. K., on one occasion following a cough, a sudden shift of 1000 cc. was noted in the base line of a respiratory tracing. This variability of actual residual air volume would seem to be indicated in the measurements taken up to the last two days of tests in each case. Whether either method is also in error cannot be deduced from such variable data.

In order to obtain a more stable condition, each of these subjects was tested in duplicate by both methods, following the use of "Vaponefrin" spray inhalation, or adrenalin by hypodermic injection. The results of these tests are listed on the last two days in each subject. Very little more can be said from these results except that the variability from test to test on the same day seems to be reduced. It is obvious that average values in these two subjects have no meaning. One can only conclude that these subjects are unsuitable for residual air measurements by either the closed or open circuits. Certainly a part of this difficulty is due to actual change in the functional residual air volume itself. It may be that poor intrapulmonary gas mixture is a factor, producing significant errors of measurement. Their extremely slow mixture is shown by their values for alv. $\bar{p}$ nitrogen, which were frequently as high as 10 per cent after seven minutes of oxygen breathing.

DISCUSSION

It is apparent from the results that the new method does not entirely solve the problem of accurate residual air measurement. It has been shown and should be again emphasized that, in severely diseased lungs and probably also in some normal individuals, there is an imperfect mixture of gases within the lungs during breathing. This factor may be an important one in any method involving the estimation of average gas concentrations within the lungs. Since no method without such estimations was found, the aim of the new method was to minimize the effect of these potentially erroneous measurements.

The theoretical advantages of the new method were clear cut. By keeping the inspiratory gas mixture of constant composition, it offered a better chance of adequate intrapulmonary mixing. The "mixing" approached by the procedure is actually a simple process of *emptying* the lung of all, or nearly all, its contained nitrogen. By increasing the net alveolar nitrogen change, the new method reduced the relative error due to erroneous "alveolar" samples. Furthermore, it

avoided the necessity of measuring oxygen consumption from a respiratory tracing. Accuracy in this is necessary in the Christie method, yet often difficult in patients with emphysema or other pulmonary conditions.

The new method, tested on a small group of picked subjects, has shown definite improvement over the closed circuit method, in so far as the probable effect of poor mixing is concerned. The method of testing this effect has been the same as that used for the closed circuit; namely, the repetition of the test with a reversal in the direction of the nitrogen shift, by which the probable error due to poor mixing was also reversed in direction. On the basis of such a test, the new method showed no evidence of error in any normal subjects nor in any but one of the patients with pulmonary disease. Even in this one subject, the trend of repeated tests increasing the breathing time indicated the probable accurate figure. This was a contrast to similar evidence by the closed circuit method where two normal subjects and all subjects with emphysema showed considerable discrepancies due to poor mixing.

With this evidence in its favor, the results by the open circuit method have been compared with the results obtained in the same subjects by the closed circuit. Three normal subjects and six patients with emphysema gave nearly identical values by open and closed circuit methods respectively. One normal subject and two patients with severe emphysema gave significantly higher results by the closed circuit technique. This is in accordance with the prediction offered in the analysis of possible errors of method in the second paper of this series. In addition, two other patients with emphysema showed a considerably wider range of variation in residual air values on successive tests by the closed as compared with the open circuit method.

It is thus apparent that the new method can be used with some assurance of reliability in a larger group of abnormal subjects in whom such measurements are notoriously difficult. It would seem that this point is its chief practical justification, in addition to the theoretical advantages mentioned.

Even in our small group of subjects, however, there were two unusual cases in whom both methods gave variable results. A part of this was undoubtedly due to actual change in the volume, but still it leaves two exceptions in whom the reliability of the method could not be proved. In such cases it would be desirable to have a method in which no problem of mixing is involved.

Our primary interest has been the identification and quantitation of disturbances in mixing. Both an increase in the residual air and a disturbance in mixing may add to the pulmonary disability in cases of emphysema. In cases where the maldistribution factor is large, the closed circuit method may give a value which represents the true functional residual volume plus an increment that is actually an error of method due to poor mixing of intrapulmonary gases. This factor of disturbed distribution is probably a large one in contributing to the pulmonary disability in emphysema. Therefore, it is important to differentiate it from the effect of a mere increase in the residual lung volume. The open circuit method should give a better measure of the latter without serious error from the former. With an accurate measure of the volume, it should be possible to quantitate disturbances in distribution separately.

SUMMARY

1. A new open circuit method of measuring residual air is described.

2. A test for this method is also described, consisting of a reversal of the nitrogen shift in the original procedure.

3. Results of the use of these two procedures are presented on a group of four normal subjects and six patients with severe pulmonary emphysema.

4. A comparison is made between results by the new method and by the modified Christie method on a series of four normal subjects and ten patients with severe pulmonary emphysema.

5. The probable significance of the results is discussed.

CONCLUSIONS

1. The open circuit method for residual air determination offers a better means of avoiding

error due to maldistribution of pulmonary gases than the closed circuit method. This is shown by the test procedure as well as theoretical considerations.

2. The modified Christie method gives erroneously high values for residual air in some cases of severe pulmonary emphysema.

3. It is possible with the new method to distinguish more surely the factor of imperfect gas distribution from that of excessive residual lung volume in the evaluation of the disturbances associated with pulmonary emphysema.

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