Distribution of Ventilation; Clinical Evaluation by Rapid CO₂ Analysis

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THIS ARTICLE DEALS WITH THE MEASUREMENT OF THE DISTRIBUTION OF VENTILATION IN THE CLINICAL PULMONARY FUNCTION LABORATORY, AS A PART OF THE ROUTINE EVALUATION OF THE PATIENT. THE USE OF THIS MEASUREMENT IN MASS EXAMINATIONS OR FIELD SURVEYS WILL ALSO BE CONSIDERED.

Methods used in research laboratories, particularly those using radioisotopes, have attained a high degree of accuracy but are not applicable routinely.

Other methods, using relatively modest equipment, have been used for years and have yielded valuable information, but offer certain disadvantages. They are the seven minute pulmonary nitrogen wash-out test expressed as a “nitrogen index” (Courand, et al.), and the single-breath test (Comroe and Fowler). In both cases, a continuous measurement of nitrogen concentration at the mouth is obtained with a rapid nitrogen meter. The patient inhales “pure” oxygen in order to displace nitrogen from the alveoli. If oxygen is unevenly distributed to different areas of the lung, and if poorly ventilated areas of the lung empty last, abnormally great differences in nitrogen concentration will be observed:

(a) between the beginning and the end of a prolonged expiration (single-breath test); (b) between abnormal and a forced expiration at the end of seven minutes of oxygen breathing (nitrogen washout test).

In these “nitrogen tests” several assumptions are made, but so far no definite evidence has supported them; in recent field surveys, the single-breath test has given improbable results.

Carbon dioxide could be used as the test gas, since good rapid CO₂ analyzers are available, and since uneven ventilation can be expected to result in different CO₂ concentrations in different areas of the lung. It is such a test which we would like to propose here.

In this test, the level of end-tidal CO₂ at rest is carefully determined. Maximum expiration starting from the level of a normal inspiration is then given, at the end of which a second concentration of CO₂ is determined by rapid infra-red analysis. The difference between those two concentrations expresses the degree of heterogeneity of alveolar CO₂, the significance of which will be discussed. Using accepted symbols, this could be called ΔPET-MXCO₂ and will be referred to in this article as ΔCO₂ test.

In the present paper, the technique will be described, and results will be reported in two groups of similar age, one of normal subjects, the other of patients with obstructive respiratory disease of moderate severity. In some individuals, both this CO₂ test and the single breath N₂ test were done simultaneously.

Selection of Subjects

ΔCO₂ Test

Eighteen subjects, hospital employees without evidence of respiratory disease and without obesity, formed the normal group. Their vital capacity (VC) was on the average 100 per cent, and their maximum voluntary ventilation (MVV=MBC) 114 per cent of the predicted values according to the regression equations and the nomogram of the VA-Army Cooperative Study. The average residual volume/total lung capacity ratio (RV/TLC) was 43 per cent (Table 1).

Twenty-five men with chronic obstructive pulmonary disease formed the group of

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* A preliminary paper has been submitted to VA-Armed Forces Research Conference. Presented at the VIII International Congress on Diseases of the Chest, Mexico City, October 11-15, 1964. **Chief, Pulmonary Function Laboratory, Veterans Administration Center.
patients (Table 1). They were consecutive cases with moderate emphysema observed over a short period of time. Their average age was the same as that of the normals, 42. All had a history of several years of cough and expectoration; most had shortness of breath on exertion. None was in acute distress at the time of examination, and the arterial oxygen saturation was normal or slightly below normal (92 per cent or above). For the group the average VC was 73 per cent, the average MVV 48 per cent of predicted; they all had air trapping during MVV. The average RV/TLC was 50 per cent. We considered them as having a marked obstructive syndrome, a slight restrictive syndrome and moderate pulmonary emphysema without respiratory failure at the time of the study.

**Combined $\Delta CO_2$ and Single-Breath $N_2$ Test**

This was studied in ten normals and ten patients (Table 2). The patients had severe obstructive syndrome, moderate restrictive syndrome, and severe emphysema.

**Method**

$\Delta CO_2$ Test

A Beckman rapid infra-red CO$_2$ analyzer with a microcatheter cell† and an Esterline-Angus recorder‡ were used.

†Beckman Instruments, Inc., Spinco Division, Palo Alto, California.

‡Esterline-Angus Co., Inc., Indianapolis, Indiana.

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**Table 1—Comparison of $\Delta CO_2$ in Normals and Patients with Pulmonary Emphysema**

<table>
<thead>
<tr>
<th></th>
<th>Normals</th>
<th>Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>18</td>
<td>25</td>
</tr>
<tr>
<td>$P_{x CO_2}$</td>
<td>33.8±2.88</td>
<td>30.5±5.2</td>
</tr>
<tr>
<td>$P_{x x CO_2}$</td>
<td>39.17±5.54</td>
<td>39.0±5.7</td>
</tr>
<tr>
<td>$\Delta CO_2$</td>
<td>5.35±1.54</td>
<td>8.30±2.45*</td>
</tr>
<tr>
<td>VC</td>
<td>100</td>
<td>73</td>
</tr>
<tr>
<td>MVV</td>
<td>114</td>
<td>48</td>
</tr>
<tr>
<td>RV/TLC</td>
<td>32</td>
<td>50</td>
</tr>
<tr>
<td>Age</td>
<td>42</td>
<td>42</td>
</tr>
</tbody>
</table>

The symbols are defined in the text.

*Significantly different from normal, P<0.001.

Microfilm or photostat of Table 1, giving additional values for $P_{x CO_2}$, $P_{x x CO_2}$ and $\Delta CO_2$ for the 18 normals, and Table 1b, giving the above values for the 25 patients will be available at moderate cost from the American Documentation Institute (ADI), Library of Congress.

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**Table 2—Comparison of $\Delta CO_2$ and the Single-Breath Test $N_2$ in Patients and Normals**

<table>
<thead>
<tr>
<th></th>
<th>Normals</th>
<th>Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>$P_{x CO_2}$</td>
<td>36.2±2.6</td>
<td>35.9±5.2</td>
</tr>
<tr>
<td>$P_{x x CO_2}$</td>
<td>40.6±2.8</td>
<td>45.2±6.8</td>
</tr>
<tr>
<td>$\Delta CO_2$</td>
<td>4.4±.8</td>
<td>9.3±2.6*</td>
</tr>
<tr>
<td>$\Delta N_2$</td>
<td>.99±.6</td>
<td>7.5±1.0*</td>
</tr>
<tr>
<td>VC</td>
<td>101</td>
<td>64</td>
</tr>
<tr>
<td>MVV</td>
<td>105</td>
<td>25</td>
</tr>
<tr>
<td>RV/TLC</td>
<td>30</td>
<td>69</td>
</tr>
<tr>
<td>Age</td>
<td>44</td>
<td>56</td>
</tr>
</tbody>
</table>

The symbols are defined in the text.

*Significantly different from normal, P<0.001.

Microfilm or photostat of Table 2a, giving individual values for $P_{x CO_2}$, $P_{x x CO_2}$, $\Delta CO_2$ and $\Delta N_2$ for the ten normals and ten patients will be available at moderate cost from the American Documentation Institute (ADI), Library of Congress.

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Noseclip and mouthpiece were put in place after ten minutes of rest in the sitting position. Through a needle inserted in the wall of the mouthpiece, inspired and expired air were sampled continuously. Quiet breathing was recorded for about half a minute, at the end of which a maximal expiration, starting from the level of a normal inspiration, was given. Then a vital capacity maneuver was performed, starting with a maximal inspiration followed by a maximal expiration. If the end-tidal CO$_2$ concentrations during the period of quiet breathing increased or decreased, showing that the patient was not in a steady state, or if the inspiration preceding the maximal expiration was larger than those during quiet breathing or if the expiration did not appear maximal, the test was considered unsatisfactory and was repeated after a period of rest. We will see later why it is so important that the inspiration preceding the maximum expiration be "normal." The analyzer was calibrated with at least four known CO$_2$ gas concentrations before each test and a calibration curve was drawn.

From the CO$_2$ curve, CO$_2$ concentrations were measured at three points: at the
end of a quiet expiration representative of mean end-tidal CO₂ for the period of quiet breathing, and at the end of each of the two maximal expirations. Concentrations (Fco₂) were converted into partial pressures in the usual fashion: (Pco₂=Fco₂ x (barometric pressure minus 47)mm.Hg. Thus three variables were obtained. They are shown in Fig. 1, which is to be read from right to left:

Peto₂, mm.Hg=mean end-tidal CO₂ Point A; Pmxco₂, mm.Hg=end-maximal expiration CO₂, Point B; Pvcco₂, mm.Hg= end-vital capacity CO₂, Point C.

The gradient of CO₂ tensions at the end-tidal level and at the maximal expiration level (Peto₂-Pmxco₂) was taken as the index of distribution and is our proposed test, ΔCO₂.

Pvcco₂ was not used in the calculation of ΔCO₂. It served only as a control. If it was higher than Pmxco₂, the test was considered unsatisfactory because the first maximal expiration was probably not maximal. In a large number of tests correctly performed we have not seen a single Pvc that was higher than the preceding Pmx, and in only four or five instances were the two equal.

**Combined ΔCO₂ and Single-Breath N₂ Test**

This more complex procedure was used in order to compare the ΔCO₂ test with the better known N₂ test.

A nitrogen meter† was used, and its output recorded on photographic paper in an oscillographic recorder.†† Simultaneously a CO₂ tracing was obtained from a rapid CO₂ analyzer.§

Two needles inserted in the wall of the mouthpiece at diametrically opposed points took the sampled air to the analyzers. In rapid N₂ analysis, it is necessary to use a "contrasting gas," pure oxygen, which brings the N₂ concentration to zero at the start of expiration.

†Waters Co., Rochester, Minnesota.
††Electronics for Medicine, White Plains, New York.
§Godard Mijnhardt N. V., De Bilt, Holland and Instrumentation Associates, New York, N. Y.

**Figure 1:** CO₂ curve from rapid infra-red CO₂ analyzer for measurement of end-tidal maximal expiration CO₂ difference (Δ). Read from right to left. A=end-tidal CO₂ (the early part of the period of quiet breathing is not shown); B=maximal expiration CO₂; C="vital capacity" CO₂. Note that duration of inspiration is reasonably constant during quiet breathing and just before B—it is increased during the vital capacity maneuver, between B and C. The slope is markedly greater before C than before B, and CO₂ is lower at C than at B. See text. Upper tracing=normal subject, Δ is small. Lower tracing=patient with emphysema, Δ is large.
For half a minute, quiet breaths, inspiring room air, served to establish PETO₂.

Then a valve was turned allowing the patient to inspire pure oxygen. As in the ΔCO₂ test, care was taken that a normal inspiration, essentially equal to the inspirations of the preceding minute, was taken.

During the following maximal expiration both the CO₂ and the N₂ curve were recorded (Fig. 2, read from left to right).

ΔCO₂ was measured as explained above. The nitrogen difference was measured in the accepted manner as the difference in N₂ concentration at 750 and 1,250 ml. of expiration.

RESULTS

ΔCO₂ Study

In Table 1 are shown the mean values and standard deviations of PETO₂, PMXO₂, and ΔPET-MXO₂ (or ΔCO₂) as defined above. Other tests of pulmonary function and age are included.

The mean ΔCO₂ was 5.35±1.54 mm. Hg in the normal group and 8.30±2.45 in the patients. The difference was statistically significant: P<.001.

Combined ΔCO₂ and Single-Breath N₂ Test

In Table 2 it is shown that the normals had a mean ΔCO₂ of 4.4±.8 mm.Hg and a mean ΔN₂ of .99±.6 per cent. The patients had a mean ΔCO₂ of 9.3±2.6 mm. Hg and a mean ΔN₂ of 7.5±1.0 per cent. The differences were statistically significant: P<.001.

Fig. 3 shows the same data on a diagram, with the single-breath test on the horizontal axis, the ΔCO₂ test on the vertical axis. The normals are close together in the left lower corner, the patients with severe obstructive emphysema are scattered well away from the normal zone. The coefficient of rank correlation for these data was .85 per cent.

DISCUSSION

In order to consider ΔCO₂ as a reliable test of distribution, one may be satisfied with the significant difference (P<.001) between the group of normals and the group of patients with emphysema in this study. Emphysema is known to be a major source of abnormal distribution, as is demonstrated by accurate methods of measurement of the volume and turnover rate of well and poorly ventilated spaces.

Another point in favor of ΔCO₂ is the concordance of the N₂ and CO₂ tests in the normals, as well as the patients. This can be seen in Table 2 and Fig. 3. All N₂ tests are well below the generally accepted upper limit of normal, 1.5 per cent and we take 7 mm.Hg as the upper limit of normal in the CO₂ test (Tables 1 and 2). Both
tests clearly separate the two groups. As for the justification of the single-breath test, Comroe and Fowler base it on a comparison with the seven minute nitrogen washout test of Courand et al. They admit that there is no absolute standard against which to compare either the seven minute or the single breath tests, yet both tests have been very useful in the study of respiratory function in health and disease.

Recently, Anderson has described the "end-expiratory-end-tidal CO₂ difference" as a "simple test of abnormal ventilation/perfusion relationships." This is essentially the same test we have been using, but our interpretation is different. We agree that changes in the V/Q ratio, such as brought about by changes of position, can change ΔCO₂; we have observed this in the laboratory; but there are situations in which ΔCO₂ would be normal although V/Q would be abnormal. Comroe et al. have indeed pointed out that if expiration proceeds synchronously from all areas of the lung, a constant CO₂ concentration will be observed at the mouth, however different CO₂ concentrations may be in different alveoli. Therefore, ΔCO₂ should not be considered to be a test of ventilation/perfusion relationships.

We have studied possible correlations of the ΔCO₂ test with other variables of pulmonary function. We found that there was a correlation with the RV/TLC ratio, such that there is an increase of about 3 mm.Hg of ΔCO₂ per 10 per cent increase in RV/TLC (Fig. 4).

Place of the ΔCO₂ test in Pulmonary Function Testing

The test takes a few minutes to perform and calculate. It is easy to incorporate in a routine evaluation. We have obtained close to 3,000 such measurements in six years, with a number of subjects tested repeatedly over the years. On the basis of this experience, we consider as slightly abnormal distribution of ventilation values of 7 to 10 mm.Hg; moderately abnormal, 10 to 13; and markedly abnormal, above 13 mm.Hg. The highest values recorded are in the 22 to 24 mm.Hg range.

Some authors have reported CO₂ in quiet and forced expirations in normals and patients.

DuBois et al. have been the first to report the increased slope of the CO₂ curve during prolonged expiration in the emphysematous patient.

Values for ΔCO₂ can be calculated from the data of Sivertson and Fowler. In normal subjects ΔCO₂ would be 3.1
mm.Hg, in moderately severe emphysema 8.6, and in severe emphysema 10 mm.Hg.

From the data of Sakamoto and Murao, \( \Delta CO_2 \) would be 3.3 mm.Hg in normals and 13.9 in emphysematous patients.

Anderson found that the upper limit of normal in his subjects was about 5 to 6 mm.Hg; the majority of patients have a \( \Delta CO_2 \) between 8 and 14 mm.Hg.

**Comparison with other Tests of Distribution of Ventilation**

In the laboratory, \( \Delta CO_2 \) and \( N_2 \) tests appear to be of similar value. The single-breath \( N_2 \) test, correctly performed, is essentially a test of distribution of ventilation and changes in \( V/Q \) are not likely to alter the result. Yet, when the technique cannot be carefully controlled, as may happen in field surveys, the \( N_2 \) test would seem to lose its advantages in favor of the \( \Delta CO_2 \) test.

The experience of Balchum et al. is quite interesting in this respect. Submitting some 1,500 industrial workers to spirometry and single-breath \( N_2 \) tests, they found an abnormal distribution in 60 per cent of the cases, while only 17 per cent were suspected of having chronic respiratory disease on the basis of low one-second forced expiratory volume.

The explanation probably lies, at least in part, in the excessive volume of the inspiration preceding the expiration during which the \( N_2 \) difference is calculated. It has been shown by Kjellmer et al. that the larger the volume inspired, the greater the \( N_2 \) difference in the following expiration. In Balchum's study, only three minutes were allowed for each subject to perform spirometry and test of distribution, and no control of the volume inspired was possible.

In the \( \Delta CO_2 \) test, there is no such danger. There is no need for oxygen. It suffices to make sure that the subject breathes evently, and that the inspiration before the maximum expiration differs in no way from those of the preceding half-minute of recording \( P_{ET CO_2} \).

Other advantages particularly noticeable in field testing are that tanks of oxygen and valves are not required and the volume of expiration need not be recorded.

It must be emphasized that to have a reliable \( \Delta CO_2 \) test, the period of rest before the test is indispensable—the subject must be in a steady state, and the changes in \( P_{ET CO_2} \) during the half-minute of recording must be minimal, not showing an ascending or descending pattern which would make the measurement of \( P_{ET CO_2} \) impossible. The maximal expiration must be really maximal, and \( P_{M CO_2} \) must be higher than \( P_{V CO_2} \) immediately following.

![Figure 4: Correlation of $\Delta CO_2$ and RV/TLC ratio. Normal subjects (x), Patients with several kinds of bronchopulmonary disease (o). The regression line indicates an increase of 3 mm.Hg $\Delta CO_2$ for a 10 per cent increase in RV/TLC.](http://journal.publications.chestnet.org/pdfaccess.ashx?url=/data/journals/chest/21428/)
All this would appear easy to control in the conditions of a field survey. Finally, the calculations on the CO₂ curve are very easy to perform, only Pet and PmXco₂ need to be known and their difference calculated.

SUMMARY

The ΔCO₂ test, measuring the Pco₂ difference at the end-tidal and maximum expiration levels, gives significantly different results in normal subjects and patients with moderate pulmonary emphysema. It correlates well with the single-breath N₂ test. When both tests are performed simultaneously, each test clearly separates the normals from the emphysematous subjects.

Attempts have been made by several authors to incorporate a test of distribution in the study of respiration of individual patients or in field surveys.

These efforts appear worthwhile and in order to determine what help the clinician or epidemiologist may receive from the evaluation of distribution, the ΔCO₂ test seems to offer certain advantages over other tests.

The physiologic and clinical significance of the ΔCO₂ test has been discussed.

Acknowledgment: The advice of Dr. B. Bromberger-Barna, consultant to this laboratory, and the technical help of the laboratory personnel are gratefully acknowledged.

RESUMEN

La determinación ΔCO₂ que mide la diferencia Pco₂ al final de la expiración ordinaria y de la expiración máxima han dado valores distintos en sujetos normales y moderadamente enfisematosos, que se correlacionan bien con los resultados en la prueba de la inspiración única de nitrógeno.

Cuando ambas determinaciones se practican simultáneamente sus resultados separan netamente los sujetos normales de los enfisematosos. Varios autores han intentado introducir pruebas de distribución en los estudios de la función respiratoria individuales o colectivos. Estas tentativas son de valor para determinar la utilidad de la evaluación de la distribución para el clínico y el epidemiólogo. En este terreno la determinación del ΔCO₂ parece ofrecer ciertas ventajas sobre los otros métodos.

La significación clínica y fisiológica de la prueba del ΔCO₂ es analizada por los autores.

Résumé

Le diagnostic par le test au CO₂ mesurant la différence des niveaux terminaux de l'expiration courante et maximum, donne des résultats nettement différents chez les sujets normaux et la maladie atteint d'emphysème pulmonaire modéré. Les résultats sont comparables à ceux du test de mixique au cours d'une expiration unique, mesurant la concentration d'azote après inspiration d'oxygène. Lorsque les deux tests sont pratiqués simultanément, chaque test sépare clairement les sujets normaux des sujets emphysématiques.

Des essais ont été faits par plusieurs auteurs pour incorporer un test de distribution dans l'étude de la respiration des malades pris individuellement ou lors d'examens systématiques.

Ces efforts semblent en valoir la peine, et pour déterminer quelle aide le clinicien ou l'épidémiologiste peut recevoir de l'évaluation de la distribution, le diagnostic par le test au CO₂ semble offrir certains avantages sur les autres tests.

La signification clinique et physiologique du test au CO₂ est discutée.

ZUSAMMENFASSUNG

Bei normalen Versuchspersonen und Patienten mit mässig schwerer Lungenemphysema gibt der ΔCO₂-Test, der die Pco₂ Differenz am Ende des ausatmens und der maximalen Ausatmungszeit mißt, beträchtlich voneinander abweichende Werte. Er stimmt gut überein mit dem N₂ Atmegenommen, so trennt jeder Test deutlich die normale Teste. Werden beide Proben gleichzeitig von den emphysématise Versuchspersonen. Es wurden Bemühungen von verschiedenen Autores unternommen, um einen Test über die Atmung bei Patienten oder bei Massenuntersuchungen.

Diese Untersuchungen dürften sich lohnen, und der Δ CO₂-Test scheint gewisse Vorteile über andere Methoden zu haben, um zu ermitteln, welche Unterstützung die Kliniker oder der Epidemiologe von der Erhebung des Mischverhältnisses gewinnen kann.

Die physiologische und klinische Bedeutung des Δ CO₂-Tests wird diskutiert.

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ROENTGENOLOGIC PICTURE OF PULMONARY CHANGES IN WEGENER'S GRANULOMATOSIS

On the basis of pertinent literature and personal observation, the authors discuss the nature of the principal pathologic-anatomic changes occurring in the lungs in Wegener's granulomatosis. A description is given of the most characteristic alterations in the x-ray picture which consist of the appearance of multiple macrofocal shadows in both lungs, frequently with disintegration therein. The authors describe rarely encountered x-ray changes in the lungs: microfocal bilateral disemination, solitary spherical formations, involvement of the pleura with the development of effusion, enlargement of intrathoracic lymph nodes. Tsyplion, A. M. and Ruisen, E. V.: "The Roentgenologic Picture of Pulmonary Changes in Wegener's Granulomatosis," *Clin. Med. (USSR)*, 43:35, 1965.

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LOCATION OF CORONARY OCCLUSIONS

Postmortem and clinical data for 127 patients dying of acute myocardial infarction were correlated to determine the relationship between primary branch occlusions and cardiogenic shock. The relative frequency of shock was significantly greater in patients with branch occlusions than in those with main stem occlusions or infarction without fresh occlusion. Branch occlusions in the distribution of the left circumflex coronary artery had a particularly high association with shock. A reflex mechanism, with receptor sites in the primary branches of the coronary arteries, may be implicated in the pathogenesis of shock in certain cases of acute myocardial infarction, as has been demonstrated in the experimental animal. Shock also occurs in patients with myocardial infarction who have had main stem occlusion or no occlusion at all.