

# Value of measurement of alveolo-arterial gradient of $\text{Pco}_2$ compared to pulmonary scan in diagnosis of thromboembolic pulmonary disease<sup>1</sup>

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The alveolo-arterial gradient of  $\text{Pco}_2$  was measured and the percentage of ventilated but unperfused alveoli was derived from Severinghaus's formula in 312 patients divided into five groups according to clinical symptoms, biological, radiographic, scintigraphic or pathological data—87 patients with proved thromboembolic disease, 41 with probable thromboembolic disease, 67 with possible thromboembolic disease, 101 with non-embolic pulmonary disease, and 16 cases of miscellaneous cardiac diseases. After all capnographic curves without an alveolar plateau had been eliminated, 223 capnograms (71%) were examined.

In 59% of the patients with proved thromboembolic disease, the percentage of ventilated but unperfused alveoli was abnormal ( $>15\%$ ). In this group the mean percentage of ventilated but unperfused alveoli (16.3%) was significantly different from the value obtained in the remaining groups. This test was positive in 40% of the patients with probable thromboembolic disease but it was also positive in 22.5% of the cases of miscellaneous pulmonary and cardiac non-embolic diseases.

Compared to the lung scan, this method was less sensitive but also less equivocal in patients with preexisting cardiopulmonary disorders. Estimates of the pulmonary vascular defect by these two methods did not always correspond.

The clinical diagnosis of pulmonary thromboembolic disease can be difficult and all the laboratory aids have disadvantages. A comparison of the relative values of these aids is timely.

At present a lung scan or pulmonary angiography are the most specific diagnostic procedures.

The perfusion lung scan is usually difficult to interpret in patients with chronic cardiopulmonary disease; it is not possible to obtain a pulmonary angiogram in every case of suspected thromboembolic pulmonary disease because of cardiorespiratory distress.

The alveolo-arterial gradient of  $\text{Pco}_2$  was suggested 15 years ago as a simple test for pulmonary embolism (Severinghaus and Stupfel, 1957; Robin, Julian, Travis and Crump, 1959) but this is still not used in daily practice.

In the present paper, the results obtained by this last method are compared with those of the lung scan.

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## METHODS

The alveolo-arterial gradient of carbon dioxide pressure ( $\text{Pco}_2$ ) is the difference between  $\text{Paco}_2$  and  $\text{Paco}_2$ . The  $\text{Paco}_2$  of blood drawn from the brachial artery after local anaesthesia was determined by the Astrup apparatus. When arterial blood had been taken  $\text{Paco}_2$  was measured with the Godart capnograph (Van Weerden, 1961). The principle of this apparatus is the absorption of infrared rays by  $\text{CO}_2$ . Mean  $\text{Paco}_2$  was calculated from each available plateau during blood withdrawal.

Arterial  $\text{Pco}_2$  can be measured accurately but the measurement of alveolar  $\text{Pco}_2$  is more difficult as it depends on the accuracy of the infrared analysis and on a relatively normal distribution of ventilation in the lung. The latter problem was overcome by discarding a significant number of observations in which a plateau was not clearly seen. Figure 1 shows an example of an acceptable capnograph tracing (in which alveolar  $\text{Pco}_2$  in the expired air reaches a plateau from which  $\text{Paco}_2$  can be measured) and of a discarded one (in which no alveolar plateau is available). It is very important to measure  $\text{Paco}_2$  from the alveolar plateau of the  $\text{CO}_2$  concentration of the expired air curve rather than from the end-tidal

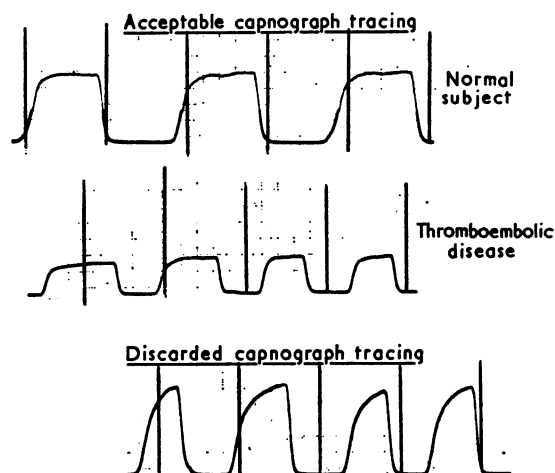


FIG. 1. See text.

$PCO_2$ . In cases of hyperpnoea, or when ventilation distribution is abnormal, no alveolar plateau is available. Therefore, whenever possible, it is useful to carry out a forced expiration at the end of the test in order to detect possible abnormalities of ventilation distribution. Tulou (1966) demonstrated that if the difference between  $PCO_2$  during normal expiration and forced expiration is higher than 7 mmHg there is an abnormal ventilatory distribution. When respiration is very slow,  $PACO_2$  must be measured from the beginning of the alveolar plateau. Reichel (1960) demonstrated that  $PACO_2$  at the end of a long expiration might be higher than  $PACO_2$ .

The accuracy of the infrared analyser is checked regularly (at least once a month) by means of  $CO_2$  tubes with precisely known concentration.

The alveolo-arterial gradient of  $CO_2$  becomes abnormal when the physiological dead space increases because of well-ventilated but unperfused alveoli. When this occurs, the unperfused alveoli no longer release  $CO_2$  into the expired air; therefore the  $CO_2$  concentration of the expired air is much lower than that of arterial blood. The gradient is abnormal when it is greater than 5 mmHg (Lacoste, Tufik-Simao, Nikly, and Saunier, 1960).

The percentage of well-ventilated but unperfused alveoli is derived from the formula of Severinghaus, Stupfel, and Bradley (1957):

$$\frac{P(a-A) CO_2}{Paco_2} \times 100.$$

The percentage of ventilated but unperfused alveoli was considered abnormal whenever it exceeded 15%.

At the beginning of this study, the lung scan was done by intravenous injection of iodine-131 ( $^{131}I$ ) macroaggregated albumin and later by intravenous injection of technetium-99m ( $^{99m}Tc$ ) albumin micro-spheres.

Only anterior views of the scans were quantitatively studied; the defects were estimated by planimetry according to the method of Tow and Wagner (1967) and recorded as percentages of the whole pulmonary precapillary bed. Defects corresponding to a radiological opacity, such as condensations and pleural fluid, were subtracted from the total vascular defect; therefore the defects due to pulmonary infarcts were eliminated.

A defect less than 5% of total pulmonary perfusion was considered as non-pathological because of the mean age of the studied patients, which exceeded 62 years.

Statistical evaluations of the differences between the groups of subjects were carried out by variance analysis after angular transformation of the original percentage data in order to obtain homogeneous variances and normal distributions (Snedecor, 1956).

#### MATERIAL

Our study was done on 312 patients divided into five groups (Table I) either according to the pathological findings or according to symptoms and other investigations (chest radiograph, ECG, bilirubin, LDH, lung scan, blood gases, pleural fluid analysis, pulmonary angiography in 29 cases) without taking into account the alveolo-arterial gradient of  $CO_2$ .

TABLE I

Group	No. of Patients	Male	Female	Mean Age (yr)
I Proved thromboembolic disease	87	38	49	65
II Probable thromboembolic disease	41	22	19	68
III Possible thromboembolic disease	67	34	33	64
IV Non-embolic pulmonary diseases	101	76	25	59
V Miscellaneous cardiac diseases	16	9	7	59
Total	312	179	133	

GROUP I (87 patients with proved thromboembolic disease) In 38 cases necropsy was performed and confirmed the diagnosis. In the others, the diagnosis was established by very suggestive clinical evidence as well as by other investigations. The mean age was 65 years; 38 patients were male and 49 female.

GROUP II (41 cases of probable thromboembolic disease) The diagnosis of thromboembolic disease was the most probable but could not be unequivocally documented. The mean age was 68 years; 22 patients were male and 19 female.

GROUP III (67 cases of possible thromboembolic disease) Alternative diagnoses in these patients were inflammatory disease, cardiac failure or coronary insufficiency. The mean age was 64 years; 34 patients were male and 33 female.

GROUP IV (non-embolic pulmonary diseases such as chronic bronchitis, emphysema, silicosis, neoplasm or tuberculosis) This group included 101 patients, 76 males and 25 females. The mean age was 59 years.

GROUP V (miscellaneous cardiac diseases such as myocardial infarction, angina pectoris, and cardiac failure, without pulmonary complications) There were 16 patients, 9 males and 7 females. The mean age was 59 years.

RESULTS

The alveolo-arterial gradient of CO<sub>2</sub> and the percentage of ventilated but unperfused alveoli were calculated from 223 capnograms in which an acceptable plateau could be demonstrated, i.e., in 71% of the total number performed (Table II, Figure 2).

TABLE II

Group	Available Capno-grams	P(a-A)CO <sub>2</sub> > 5 mmHg (no. of cases)	% Unper-fused Alveoli	Unper-fused Alveoli > 15% (no. of cases)
I Proved thromboembolic disease	68 (78%)	37 (54%)	16.3 (0-82)	40 (59%)
II Probable thromboembolic disease	35 (85%)	15 (43%)	7.4 (0-33)	14 (40%)
III Possible thromboembolic disease	54 (81%)	12 (22%)	4.9 (0-50)	13 (24%)
IV Non-embolic pulmonary diseases	52 (51%)	15 (29%)	5.5 (0-52)	11 (21%)
V Miscellaneous cardiac diseases	14 (87.5%)	5 (36%)	6.9 (0-41)	4 (29%)
Total	223			

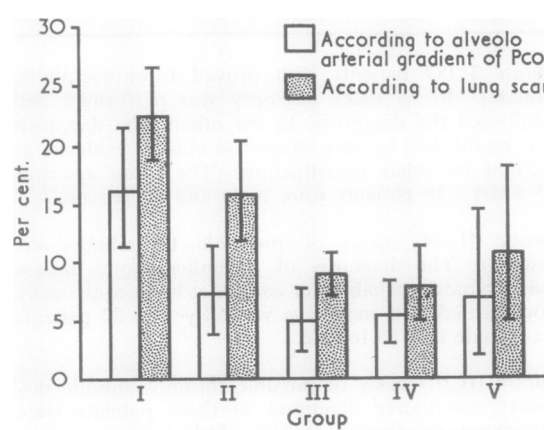


FIG. 2. Mean vascular defect percentages measured for the five groups under study.

In the group with proved thromboembolic disease, 68 capnograms (78%) were available. The mean alveolo-arterial gradient of CO<sub>2</sub> was 5.90 mmHg; 37 patients had an alveolo-arterial gradient of CO<sub>2</sub> higher than 5 mmHg. The mean percentage of the ventilated but unperfused alveoli was 16.3 (range 0-82) which is significantly different from the value obtained in the remaining groups (6.0, range 0-52) (p<0.001). In 40 cases (59%) the percentage of ventilated but unperfused alveoli was abnormal and higher than 15%.

In the group with probable thromboembolic disease, 35 capnograms (85%) were available. The mean alveolo-arterial gradient of CO<sub>2</sub> was 2.67 mmHg; in 15 cases (43%) it was higher than 5 mmHg. The mean percentage of ventilated but unperfused alveoli was 7.4 (range 0-33), which is not significantly different from the mean percentage of ventilated but unperfused alveoli in the following three groups (5.5, range 0-52). In only 14 cases (40%) was the percentage of ventilated but unperfused alveoli higher than 15%.

In the group of patients with possible thromboembolic disease, 54 capnograms (81%) were available. The mean alveolo-arterial gradient of CO<sub>2</sub> was 1.69 mmHg; in 22% of the cases (12 patients) the alveolo-arterial gradient of CO<sub>2</sub> was higher than 5 mmHg. The mean percentage of ventilated but unperfused alveoli was 4.9 (range 0-50); in 13 cases (24%) the percentage of ventilated but unperfused alveoli was abnormal.

In the group of patients without embolic pulmonary disease only 52 capnograms were available (51%), because of frequent uneven ventilation. The mean alveolo-arterial gradient of CO<sub>2</sub> was 2.89 mmHg; in 15 cases (29%) the alveolo-arterial gradient of CO<sub>2</sub> was abnormal. The mean percentage of ventilated but unperfused alveoli was 5.5 (range 0-52); in 11 cases (21%) the percentage of ventilated but unperfused alveoli was higher than 15%.

In the group of patients with cardiac diseases, 14 capnograms (87.5%) were available. The mean alveolo-arterial gradient of CO<sub>2</sub> was 3.57 mmHg; in five cases (36%) the alveolo-arterial gradient of CO<sub>2</sub> was higher than 5 mmHg. The mean percentage of ventilated but unperfused alveoli was 6.9 (range 0-41); in four cases (29%) the percentage of ventilated but unperfused alveoli was abnormal.

Two-hundred-and-seventeen pulmonary scans were studied for vascular defects (Table III, Figure 2).

In the group with proved thromboembolic disease 74 scans were done. The mean defect

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TABLE III

Group	Lung Scan	Mean Defect (%)	Defect > 5% (no. of cases)
I Proved thromboembolic disease	74	22.7 (0-60)	66 (89%)
II Probable thromboembolic disease	31	16.1 (0-52)	27 (87%)
III Possible thromboembolic disease	53	9.1 (0-36)	33 (63%)
IV Non-embolic pulmonary diseases	47	8.1 (0-50)	21 (45%)
V Miscellaneous cardiac diseases	12	10.7 (0-50)	9 (75%)
Total	217		

the precapillary pulmonary circulation was 22.7% of the whole precapillary surface (range 0-60); this is significantly different from the values obtained in the patients belonging to all the other groups ( $P < 0.001$ ). In 66 cases (89%) the defect was higher than 5%.

In the group with probable thromboembolic disease 31 scans were done. The mean defect of the precapillary pulmonary circulation was 16.1% (range 0-52); this is significantly different from the groups of patients with proved thromboembolic disease ( $0.02 < P < 0.05$ ) but also from the value obtained in all the other patients (sum of the other groups) ( $0.01 < P < 0.02$ ). In 27 cases (87%) the scan was abnormal.

Between the mean circulatory defects of each

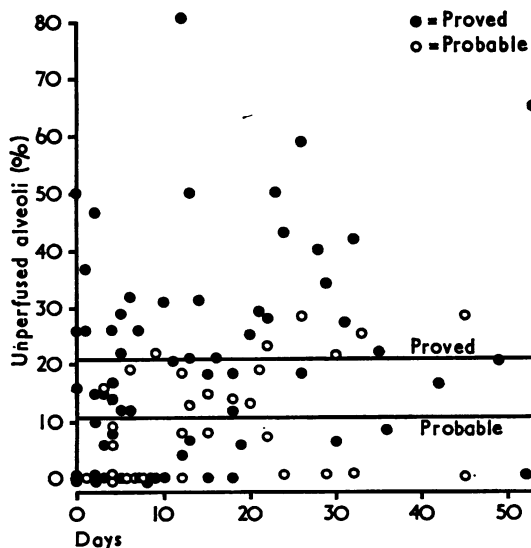


FIG. 3. Relation between percentage of unperfused alveoli and time between onset of symptoms and measurement of the alveolo-arterial gradient of  $PCO_2$ .

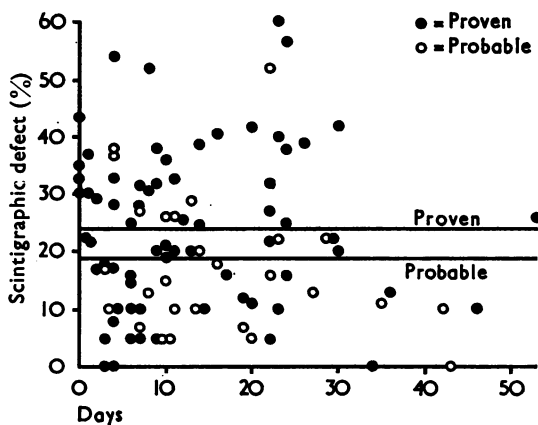


FIG. 4. Relation between scintigraphic defect and time between onset of symptoms and lung scan.

of the last three groups there was no significant difference.

In the group of patients with possible thromboembolic disease 53 scans were done; the mean circulatory defect was 9.1% (range 0-36); in 33 cases (63%) the scan was abnormal.

The group of patients with non-embolic pulmonary diseases included 47 scans. The mean circulatory defect was 8.1% (range 0-50); in 21 cases (45%) perfusion was abnormal.

In the group of patients with miscellaneous cardiac diseases 12 scans were done; the mean circulatory defect was 10.7% (range 0-50) and in nine cases (75%) scintigraphic abnormalities were evident.

Figures 3 and 4 demonstrate the lack of relation between the importance of the vascular defect (evaluated by the alveolo-arterial gradient of  $CO_2$  measurement or by the scan) and the duration of the disease from the first symptoms to the date of the measurement of the alveolo-arterial gradient of  $CO_2$  or of the scan.

Figure 5 shows the relation between the percentage of the ventilated but unperfused alveoli, estimated by the measurement of the alveolo-arterial gradient of  $CO_2$  (abscissae), and by lung scan (ordinates). It should be noted that although the two procedures were not performed simultaneously, only the cases where the interval between them was less than 48 hours were retained. The regression line is significantly different from the horizontal ( $0.001 < P < 0.01$ ) as well as from the bisecting line ( $P < 0.001$ ) (which corresponds to a perfect relation between both measurements of circulatory defect).



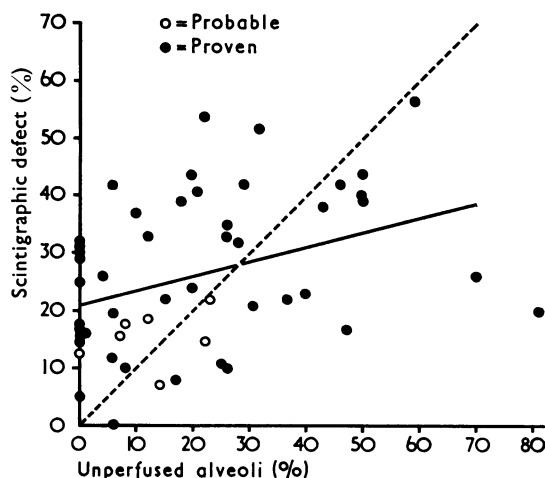


FIG. 5. Relation between scintigraphic defect and percentage of unperfused alveoli.

#### DISCUSSION

Many authors have attempted to find a simple diagnostic test for thromboembolic disease. The classical triad of elevated bilirubin, elevated LDH, and normal SGOT—SGPT is of limited value because it is not often positive (12% of the cases for Szucs *et al.* (1971)). The ECG is pathognomonic in only a few cases—nearly always when emboli are massive. A lowered  $\text{PaO}_2$ , although present in most cases (Szucs *et al.*, 1971), is not a sufficiently selective test.

The clinical advantage of the measurement of the alveolo-arterial gradient of  $\text{PCO}_2$  for the diagnosis of thromboembolic disease was first emphasized by Robin *et al.* (1959, 1960). Previously, in animal experiments Severinghaus and Stupfel (1957) had provoked large alveolo-arterial gradients by artificial emboli. These studies were confirmed by other authors (Julian, Travis, Robin, and Crump, 1960; Levy *et al.*, 1965; Stein, Forkner, Robin, and Wessler, 1961; Thomas *et al.*, 1964); there is a clear parallelism between the importance of the gradient and the area of the obliterated vascular bed (Julian *et al.*, 1960). In 1968, temporary pulmonary artery occlusion in man with an intraluminal balloon during cardiac catheterization showed similar results (Janota, Widimsky, Hurych, and Stanek, 1968). Except for the work of MacKeen, Landrigan, and Dickson (1961) there has been no clinical study in which the alveolo-arterial gradient of  $\text{PCO}_2$  has been measured in a large series of patients. However, some authors confirmed the clinical value of the alveolo-arterial gradient of  $\text{PCO}_2$  for the diagnosis

of thromboembolic disease (Llamas and Swenson, 1965; Mostyn and Luft, 1967; Nutter and Massumi, 1966; Robin *et al.*, 1959, 1960). Other authors (Jones and Goodwin, 1965; Nikodymovskaya, Daum, Stiksa, and Widimsky, 1968) measured the alveolo-arterial gradient of  $\text{PCO}_2$  in order to study the late sequelae of pulmonary embolism; the mean alveolo-arterial gradient of  $\text{PCO}_2$  was not clearly abnormal but was, however, a little higher than in normal subjects. Nadel, Gold, and Burgess (1968) studied eight patients with dyspnoea due to obliteration of peripheral branches of the pulmonary artery; six of the eight cases had an abnormal alveolo-arterial gradient of  $\text{PCO}_2$ .

In our series of 103 cases (groups I and II) the diagnosis of thromboembolic disease was confirmed in 59% of the cases of proved thromboembolic disease by the alveolo-arterial gradient measurement with calculation of the percentage of the ventilated but unperfused alveoli. In nearly 48% (49) of the cases (Table IV) this test did not

TABLE IV

Group	$\frac{\text{P(a-a)}\text{CO}_2}{\text{PaCO}_2} \times 100$		Scintigraphic Defect (%)
	Falsely Negative (no. of cases)	Falsely Negative (no. of cases)	Falsely Negative (no. of cases)
I Proved thromboembolic disease	31 (46%)	28 (41%)	8 (11%)
II Probable thromboembolic disease	20 (57%)	21 (60%)	4 (13%)
	Falsely Positive (no. of cases)	Falsely Positive (no. of cases)	Falsely Positive (no. of cases)
IV Non-embolic pulmonary diseases	15 (29%)	11 (21%)	21 (45%)
V Miscellaneous cardiac diseases	5 (36%)	4 (29%)	9 (75%)

lead to diagnosis. A normal percentage of ventilated but unperfused alveoli can be explained in 10 of them by the minimal circulatory defect of the scan (not exceeding 15% of the total perfusion), in 14 others by pulmonary infarction with abolition of ventilation in this region; in other cases a possible cause of erroneous diagnosis is alveolar hypoventilation by bronchoconstriction in avascular areas, which improves the ventilation-perfusion ratio. This bronchoconstriction was demonstrated in animals (Cahill, Attinger, and Byrne, 1961; Nadel, Colebatch, and Olsen, 1964; Severinghaus *et al.*, 1961; Stein *et al.*, 1961; Thomas *et al.*, 1964; Tisi, Wolfe, Fallat, and Nadel, 1970) and in man (Gurewich, Thomas, Stein, and Wessler, 1963; Swenson, Finley, and Guzman, 1961). Finally, another cause of underestimation of the alveolo-arterial gradient of  $\text{PCO}_2$  is the

penetration into unperfused alveoli of CO<sub>2</sub> coming from the anatomic dead space or from the bronchial circulation (Julian *et al.*, 1960).

To correct this underestimation of the vascular defect, Robin *et al.* (1960) calculated the alveolar dead space by applying the following formula:

$$\frac{\text{Pa CO}_2 - \text{PA CO}_2}{\text{Pa CO}_2 - \text{PA CO}_2 + \text{PE CO}_2} \times 100.$$

In this case expired air must be obtained by balloon collection, which complicates the test.

The test was positive in nearly 60% of the cases of proved thromboembolic disease. This percentage is a little lower than in the studies of Robin *et al.* (1959, 1960) in which 11 out of 16 cases (69%) had an abnormal percentage of ventilated but unperfused alveoli. It is much lower than in the study of MacKeen *et al.* (1961) in which 16 out of 17 cases (94%) had an abnormal alveolo-arterial gradient of PCO<sub>2</sub>. Nutter and Massumi (1966) found a higher physiological dead space in 15 out of 20 cases (75%); they measured PACO<sub>2</sub> from a sample of expired air that was considered equivalent to alveolar air; this may overestimate the alveolar dead space in thromboembolic disease and in normal subjects.

On the other hand, there were only 12 cases out of 105 (11%) in which the scan did not confirm the clinical diagnosis of thromboembolic disease (Table IV). In eight of these cases the scintigraphic defect corresponded to pulmonary infarcts demonstrated by radiological opacities and were therefore not retained. In three more cases the emboli were presumably too small to be demonstrated by an investigation of such large scope. Finally, in the last case, the examination was done very late, during treatment, when restoration of the pulmonary circulation was nearly complete.

Although they are based on a different approach to the problem of pulmonary perfusion both methods provide significantly correlated results. There is a significant correlation between the vascular defects either measured by lung scan or calculated from the alveolo-arterial gradient of PCO<sub>2</sub> but these methods do not provide identical results (Fig. 5).

This relationship shows that the scan has greater sensibility for the smaller emboli; the normal alveolo-arterial gradient in such cases is probably explained by bronchoconstriction and hypoventilation occurring in pulmonary embolism (Cahill *et al.*, 1961; Gurewich *et al.*, 1963; Nadel *et al.*, 1964; Severinghaus *et al.*, 1961; Stein *et al.*, 1961; Swenson *et al.*, 1961; Thomas *et al.*, 1964; Tisi *et al.*, 1970). On the other hand, the discrepancy

between both estimations of vascular defect could be due to the fact that only the anterior views of the scan were retained for planimetry. The alveolo-arterial gradient of CO<sub>2</sub> can be overestimated when the alveolar plateau is not correctly evaluated although all capnograms without evident plateaus were eliminated. In chronic cardiopulmonary disease the pulmonary scan can lead to overestimation of vascular defects from thromboembolic disease. The presence of pulmonary infarcts would not explain these results: they were not retained for scintigraphic planimetry, and as they cause a ventilatory as well as a circulatory defect they do not impair the alveolo-arterial gradient of PCO<sub>2</sub>.

We found that the delay between the beginning of the symptoms and the investigation (measurement of the alveolo-arterial gradient of PCO<sub>2</sub> or scan) is not critical for the diagnosis of thromboembolic disease. Indeed, without any treatment there seems to be no improvement in perfusion within the first 30 to 50 days, probably because of further embolism and the time needed for recanalization. Therefore these investigations remain useful for the diagnosis of thromboembolic disease even after several weeks.

For comparison, alveolo-arterial gradient of PCO<sub>2</sub> and lung scan were studied in non-embolic diseases (groups IV and V) (Table IV). In 15 cases out of 66 (22.5%) there was an abnormal percentage of ventilated but unperfused alveoli. These included five cases of chronic bronchitis, two cases of massive pleural effusion, and one case each of old tuberculosis, bronchial neoplasm, chronic mediastinitis, pleural thickening, uraemic lung, mitral regurgitation, myocardial infarct and cardiac failure. In some cases the excess of ventilated but unperfused alveoli was due to an abnormal ventilatory distribution with a capnographic plateau which did not correspond to true alveolar air; in other cases vascular obliteration was greater than the ventilatory defect. In 30 cases out of 59 (51%) the lung scan was pathological. In chronic pulmonary diseases such as emphysema, silicosis, and old tuberculosis, ventilatory abnormalities lead to vascular defects; in bronchial neoplasms there may be vascular compression or local thrombosis. In cardiac failure without clinical pulmonary symptoms, the lung scan is always difficult to interpret and may lead to a false diagnosis of thromboembolic disease when the defects are actually due to chronic pulmonary hypertension.

Pulmonary angiography is considered to be the most specific procedure for the diagnosis of thromboembolic disease. Nevertheless it should

be stressed that it cannot reveal emboli in third-order vessels (Dalen *et al.*, 1966; Dalen, 1970).

#### CONCLUSION

The measurement of the alveolo-arterial gradient of  $\text{PCO}_2$  and of the percentage of the ventilated but unperfused alveoli is a simple and rapid test for the diagnosis of thromboembolic disease. Nevertheless the lung scan is more accurate, especially for small emboli. The percentage of ventilated but unperfused alveoli was abnormally high in 59% of our cases of proved thromboembolic diseases. As for the lung scan, this measurement is useful chiefly for patients without other cardiopulmonary disorder.

In both methods, underestimation or overestimation of vascular defects may lead to erroneous results. They must be interpreted together with the clinical data.

If these procedures are used first, pulmonary angiography could be reserved for those cases in which the diagnosis remains in doubt and for those in which surgical or fibrinolytic treatment is being considered.

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