alone and that zinc should be given to patients who do not respond to cupriuretic treatment.

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Observations on the mechanism of hypoxaemia in acute minor pulmonary embolism

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Abstract

An automated computer analysis of ventilation-perfusion lung scans was used to derive graphical data from lung scans of 11 patients with acute minor pulmonary embolism, free of pre-existing cardiorespiratory disease, and with no evidence of intrapulmonary complication or pleural effusion. In each case the analysis showed the presence of areas of lung, remote from those affected by the pulmonary embolism, that had a pathological disturbance of ventilation-perfusion matching with relative overperfusion. Such a disturbance would cause hypoxaemia. When the extent of the mismatching was calculated in terms of relative blood flow and alveolar ventilation it correlated well with the degree of arterial hypoxaemia.

It is proposed that in acute minor pulmonary embolism the development of ventilation-perfusion mismatching in areas of lung unaffected by the embolic event may be an important mechanism of hypoxaemia.

Introduction

Acute pulmonary embolism is usually accompanied by hypoxaemia.[1-3] There is no obvious reason, however, why an area of reduced perfusion should result in blood traversing the lungs without being oxygenated, and despite several hypotheses the mechanism remains unresolved. We have developed an automated computer analysis of ventilation-perfusion lung scans that permits quantitative estimation of the distributions of ventilation and perfusion in the lungs. We used this to look for possible pathophysiological mechanisms for the hypoxaemia observed with acute minor pulmonary embolism.

Patients and methods

PATIENT SELECTION

We examined the case notes of several hundred patients whose diagnosis at discharge from this hospital from January 1975 to August 1982 had included pulmonary embolism. Criteria for inclusion in the study were: (1) A firm clinical diagnosis of acute minor pulmonary embolism. This was defined as the sudden onset of dyspnoea—with or without cough, haemoptysis, or pleuritic chest pain—that could not be accounted for by any other mechanism on clinical and chest x ray examination. (2) No known pre-existing cardiovascular or respiratory disease. (3) A predisposing factor to the development of thromboembolic disease. (4) The presence on examination of tachypnoea and tachycardia. (5) A ventilation-perfusion lung scan taken within seven days after the acute event that was independently reported as supporting the diagnosis of acute minor pulmonary embolism. (6) Arterial blood gas tensions obtained within 24 hours of the lung scan and with the patient breathing room air. (7) A chest x ray film taken within 24 hours of the lung scan that showed no intrathoracic radiological abnormality.

Only 11 cases satisfied all these criteria. Table I gives further details of these cases.

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VENTILATION-PERFUSION LUNG SCAN

Lung scans were performed using krypton-81m for ventilation and technetium-99m macroaggregated albumin for perfusion. Details of the method of computer analysis have been reported elsewhere.[4-6]

TABLE I—*Clinical characteristics of 11 patients with acute minor pulmonary embolism (clinical observations made at time of acute event)*

Case No	Age (years)	Sex	Smoking history (pack years*)	Predisposing factor	Respiratory rate (breaths/min)	Pulse (beats/min)	Blood pressure (mm Hg)	Jugular venous pressure (cm)	Pleural rub	Chest x ray findings	Other findings
1	27	F	0	5 days postoperatively	30	140	130/80	0	—	Normal	Pulmonary angiography positive; tender left calf
2	65	F	0	6 days postoperatively	Raised	120	110/70	0	—	Normal	Leg phlebography positive
3	58	F	0	Previous deep vein thrombosis	Raised	100	120/90	+2	—	Normal	Leg phlebography positive
4	70	F	0	2 weeks' bed rest	25	90	140/75	0	—	Normal	
5	84	M	0	Carcinoma of bladder	Raised	100	110/70	0	+	Over-inflated lung fields	Lung function tests normal 6 weeks later
6	59	M	8	5 days postoperatively	20	110	120/80	0	+	Normal	Pleuritic pain
7	30	M	5	Gross obesity	Raised	92	120/80	0	+	Normal	Pleurisy and haemoptysis; leg phlebography positive
8	53	M	0	7 days postoperatively	Raised	98	140/85	0	+	Normal	
9	64	M	0	Carcinoma of ureter	18	106	140/80	0	—	Normal	Leg phlebography positive
10	54	M	4	Thrombophlebitis	Raised	90	130/80	0	—	Normal	Leg phlebography positive
11	68	M	0	Previous deep vein thrombosis	22	120	130/75	0	—	Normal	Leg phlebography positive

*One pack year = one packet (20 cigarettes) a day for a year.

The analysis enables the numerical values derived from the posterior view of each lung scan to be plotted superimposed on the normal range (mean ±2SD) for the subject's age and sex (fig 1). The analysis divides the vertical axis of the ventilation and perfusion scans for each subject into 50 equal intervals, scans each interval for abnormal values, and
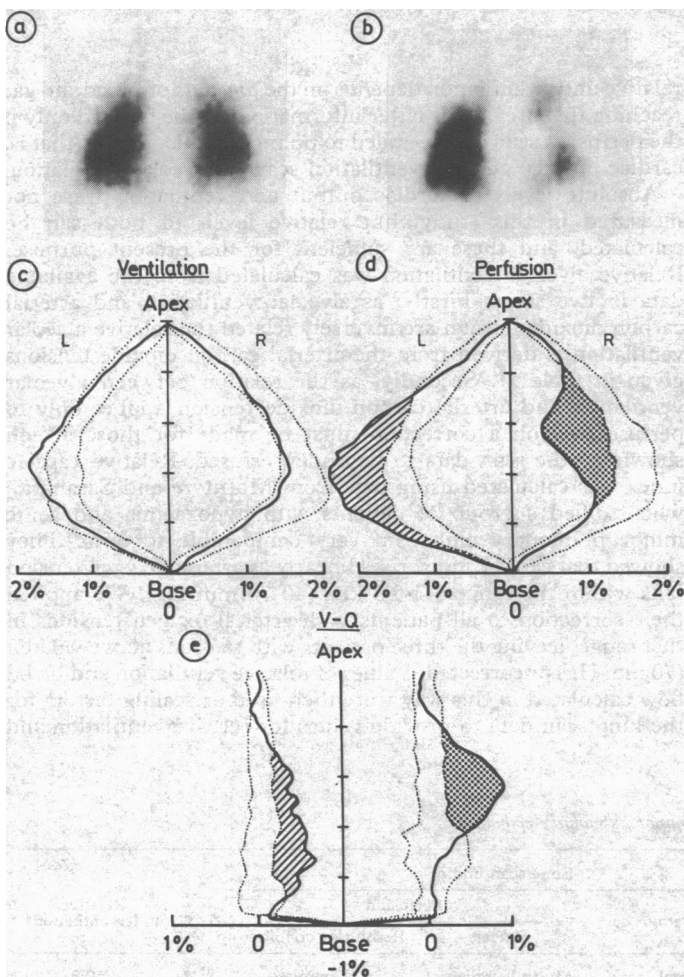

FIG 1—Posterior ventilation (a) and perfusion (b) images (case 10) analysed and presented graphically as ventilation (c), perfusion (d), and ventilation minus perfusion (e). In c, d, and e the data are presented as a solid line with normalised lung length on the vertical axis and counts, expressed as a percentage of total counts, on the horizontal axis. The dotted lines indicate the range (±2SD) in normal subjects matched for age and sex. The stippled areas in d and e are where perfusion counts fall below the normal range (regions of underperfusion and therefore high V-Q), and the hatched areas are where perfusion counts lie above the normal range (regions of overperfusion and low V-Q).

sums low and high values separately. Thus the dotted region of underperfusion in the right lung in fig 1 (d), for example, is calculated as an area with the units percentage activity × fractional lung length. The analysis also compares corresponding values of ventilation and perfusion at each interval down each lung, expressing them as a ratio (V/Q) and as a difference (V-Q). Both these are variables of ventilation-perfusion matching in the lungs. The ratio V/Q, though familiar, has a disadvantage for the present study in that it shows very wide scatter at the apices and bases, an effect of taking ratios between two small numbers of counts both of which are subject to statistical variability. In the present study we therefore used V-Q as an index of matching, as the normal limits are relatively narrow throughout the lung (fig 1 (e)). V-Q moves in the same direction as V/Q when mismatching occurs; thus low values of V-Q correspond to low values of V/Q and indicate relative underventilation. This type of mismatching (hatched area in fig 1 (e)) produces venous admixture and arterial hypoxaemia.

ARTERIAL BLOOD GAS TENSIONS

Arterial blood was taken during the acute illness, within 24 hours of the lung scan, with the patient breathing room air. Values of pH and arterial oxygen and carbon dioxide tensions were obtained with a Corning 165 or 168 blood gas analyser. Predicted normal values of arterial oxygen tension were calculated from the data of Sorbini et al.[7]

Results

Figure 1 shows posterior views of a ventilation-perfusion lung scan in a patient with acute minor pulmonary embolism, together with the computer analysis. The same pattern was seen in all cases, although the extent of the perfusion disturbances varied. All patients showed an area, or areas, of localised underperfusion without an appreciable disturbance of ventilation, which gave an area where the V-Q graph was high (that is, the area of embolism—for example, the right mid-zone in fig 1). In addition, there were other areas where the perfusion was high and therefore there was relative underventilation (left lower zone in fig 1 (d), hatched area in fig 1 (e)).

Table II gives the arterial blood gas tensions, the nature of the perfusion defects, and the extent of relative underventilation. In all cases the extent of relative underventilation far exceeded the normal limit of 30 units derived from 55 normal subjects.

Figure 2 shows the extent of relative underventilation and the arterial partial pressure of oxygen (measured within 24 hours of the scan) for each patient. The two quantities were strongly correlated (r = −0.68).

Discussion

This study presents findings derived from quantitative analysis of ventilation-perfusion lung scans in a series of patients carefully selected to represent acute, uncomplicated minor pulmonary embolism.

This method of analysing ventilation-perfusion lung scans highlights two main features. Firstly, the region of the embolus is shown as an area where the perfusion graph is below the normal range, ventilation remains normal, and the V-Q graph is above the normal range (for example, the right mid-zone in fig 1). Such a pattern is typical of pulmonary embolism.[8] [9] The second feature—that of relative overperfusion of those areas not affected by embolism (the left lower zone in fig 1)—is less familiar but occurs because if cardiac output is maintained pulmonary blood flow will be redistributed to regions of lung unaffected by embolism. In acute minor pulmonary embolism uncomplicated by pre-existing cardiovascular or respiratory disease or cardiac failure, cardiac output remains stable or, if the patient has hypoxaemia, rises.[1] [2] [10] As none of our patients had hypotension or oliguria and only one had a minor rise in jugular venous pressure, we believe that cardiac output remained normal or was raised in all of them. The perfusion scan, therefore, reflects the redistribution of pulmonary blood flow to non-embolised regions of lung, and as ventilation is not redistributed to these areas mismatching occurs with relative underventilation.

Areas of relative underventilation are a potential cause of hypoxaemia, and the relation shown in figure 2 suggests such a mechanism in our patients. This may be misleading, however, as the lung scan shows only the *distribution* of blood and inhaled gas, while the severity of the hypoxaemia caused by an area of

FIG 3—Arterial oxygen tension in 11 patients with acute minor pulmonary embolism plotted against index of relative underventilation calculated to take account of cardiac output and alveolar ventilation as described in the Discussion. Linear regression yielded $y = -0.012x + 69.96$; $r = -0.81$, $p < 0.01$.
   Conversion: SI to traditional units—Arterial oxygen tension: 1 kPa ≈ 7.5 mm Hg.

relative underventilation depends on the *amounts* of blood and gas reaching that area. This latter information can be derived only if the perfusion scan can be scaled to pulmonary blood flow (that is, cardiac output) and the ventilation scan to alveolar ventilation.

Absolute levels of cardiac output and ventilation were not measured in this study, but relative levels of both can be calculated, and these are sufficient for the present purpose. Relative alveolar ventilation was calculated from the available data in two steps. Firstly, as alveolar ventilation and arterial carbon dioxide tension are inversely related the relative alveolar ventilation is derived from the arterial carbon dioxide tensions given in table II. Secondly, as the relation between alveolar ventilation and arterial carbon dioxide tension applies only to perfused alveoli a correction must be made for those alveoli shown by the scan data to be underperfused. Relative cardiac index was calculated using data from McIntyre and Sasahara,[2] who studied a group of patients with hypoxaemia and acute minor pulmonary embolism very comparable to ours. They showed that cardiac index rises linearly as arterial oxygen tension falls within the range 5.3-9.3 kPa (40-70 mm Hg). We applied their correction to all patients with arterial oxygen tensions in that range, leaving the three patients with tensions above 9.3 kPa (70 mm Hg) uncorrected. Values of relative ventilation and blood flow calculated in this way were then used as scaling factors for the lung scan data to provide values for relative ventilation and
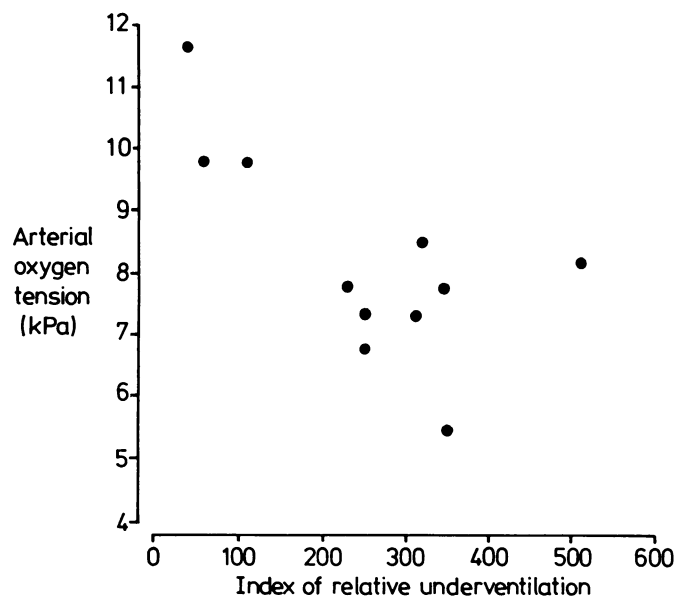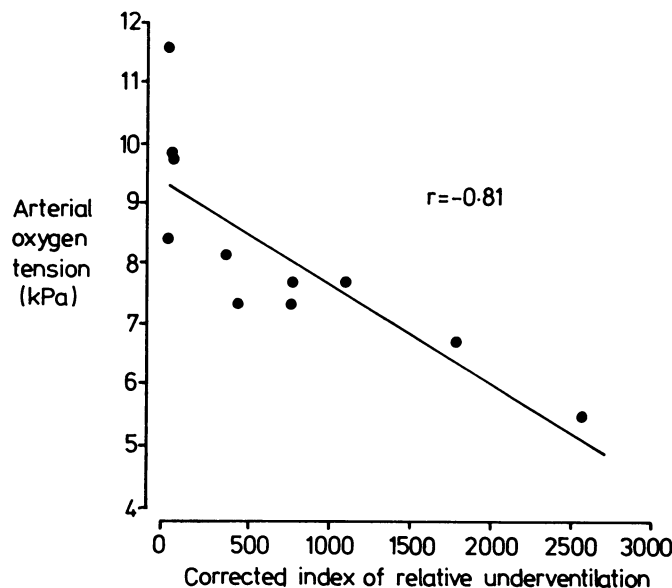

FIG 2—Arterial oxygen tension plotted against index of relative underventilation in 11 patients with acute minor pulmonary embolism. For units of index of underventilation see Patients and methods.
   Conversion: SI to traditional units—Arterial oxygen tension: 1 kPa ≈ 7.5 mm Hg.

TABLE II—Blood gas tensions and lung scan characteristics of 11 patients with acute minor pulmonary embolism

| Case No | Arterial blood gases | | | Lung scan findings | | | Relative underventilation* |
| | pH | Oxygen (kPa) | Carbon dioxide (kPa) | Ventilation | Perfusion | | |
					Defects	Resolution on follow up	
1	7.45	5.5	3.7	Normal	Multiple, bilateral	Complete	352.7
2	7.39	8.1	3.5	Normal	Multiple, bilateral	No follow up	510.9
3	7.55	7.3	4.1	Normal	Multiple, bilateral	Partial	250.6
4	7.44	8.4	2.7	Normal	Multiple, bilateral	Complete	322.5
5	7.51	6.8	4.7	Normal	Multiple, bilateral	No follow up	252.1
6	7.33	7.7	5.4	Normal	Multiple, right side	No follow up	234.1
7	7.43	11.6	4.6	Normal	Multiple, bilateral	Complete	43.9
8	7.40	9.8	4.8	Normal	Multiple, bilateral	No follow up	113.7
9	7.39	9.7	4.8	Normal	Multiple, left side	Partial	58.8
10	7.44	7.7	4.5	Normal	Single, left side	Complete	347.3
11	7.46	7.3	3.5	Normal	Multiple, bilateral	No follow up	319.5

*For units see Patients and methods.
   Conversion: SI to traditional units—Blood gas tensions: 1 kPa ≈ 7.5 mm Hg.

blood flow in each part of the lungs. From this, values of relative underventilation (summed for both lungs) were calculated and plotted against arterial oxygen tension for each patient (fig 3). The extent of the relative underventilation correlated well with the degree of arterial hypoxaemia. A slight refinement of allowing for the age dependence of normal arterial oxygen tension in calculating the degree of hypoxaemia attributable in each patient to the pulmonary embolism further improved this correlation.

In view of the above considerations we postulate that the development of ventilation-perfusion mismatching in regions of non-embolised lung was an important cause of hypoxaemia in our patients. There has been no general agreement about the cause of hypoxaemia in acute pulmonary embolism in man, and evidence has been provided for right to left intrapulmonary shunting[1] [11] and impairment of gas diffusion.[12] These results are not necessarily incompatible with ours. Localised atelectasis and prolonged breathing of oxygen may produce shunting. We were at pains to exclude these in the present study, whereas one or more of them appears to have been present in most patients in other studies.[1] [11] [12] Furthermore, other mechanisms of hypoxaemia might be operating in massive pulmonary embolism accompanied by appreciable haemodynamic disturbances, which were not detected in our mild cases.

One possible way of exploring the relative roles of mismatching and shunting would be to use 100% oxygen breathing as a discriminatory test.[13] Observations of this kind do not appear to have been reported to date and were not possible in the present series because we studied the patients retrospectively.

Finally, some support for our hypothesis may be drawn from animal studies in which pulmonary embolisation with autologous clot[14] [15] or gas bubbles[16] caused hypoxaemia by disturbing ventilation-perfusion ratios in the direction that we postulate.

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Persistent fetal haemoglobin and falsely high glycosylated haemoglobin levels

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Abstract

Some of the routine methods of measuring glycosylated haemoglobin depend on its difference in charge from haemoglobin A and do not distinguish between glycosylated haemoglobin and fetal haemoglobin. Two insulin dependent diabetics showed persistent discrepancies between their capillary blood glucose values and their glycosylated haemoglobin values measured by agar gel electrophoresis: the blood values were normal but the glycosylated haemoglobin values were raised. In one patient increases in insulin dose in response to the glycosylated haemoglobin results repeatedly produced hypoglycaemia. Both patients were found to have higher than normal concentrations of fetal haemoglobin; and when measured by the thiobarbituric acid reaction their glycosylated haemoglobin levels were almost normal.

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This problem may be avoided by using a method that distinguishes between fetal and glycosylated haemoglobin or by testing glycosylation of hair or serum albumin if discrepancies arise. This is particularly important during pregnancy, when some women have an increase in fetal haemoglobin.

Introduction

Glycosylated haemoglobin is widely used as a measure of diabetic control in insulin treated patients, often in conjunction with home blood glucose monitoring. Some of the methods routinely used for measuring glycosylated haemoglobin depend on its separation from haemoglobin A by a difference in charge—for example, column techniques and agar gel electrophoresis. With all of these methods fetal haemoglobin (HbF) will migrate with glycosylated haemoglobin and, if present, give a falsely high reading.[1]

Case 1

A 24 year old research assistant had been diabetic for 15 years. She adjusted her dose of twice daily quick and intermediate acting insulins according to home blood glucose concentrations measured by BM 20-800 strips and confirmed by filter paper capillary blood glucose measurement. These consistently showed normal or near