Usefulness of D-dimer, blood gas, and respiratory rate measurements for excluding pulmonary embolism

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Abstract

***Background*—A study was undertaken to assess the usefulness of the SimpliRED D-dimer test, arterial oxygen tension, and respiratory rate measurement for excluding pulmonary embolism (PE) and venous thromboembolism (VTE).**

***Methods*—Lung scans were performed in 517 consecutive medical inpatients with suspected acute PE over a one year period. Predetermined end points for objectively diagnosed PE in order of precedence were (1) a post mortem diagnosis, (2) a positive pulmonary angiogram, (3) a high probability ventilation perfusion lung scan when the pretest probability was also high, and (4) the unanimous opinion of an adjudication committee. Deep vein thrombosis (DVT) was diagnosed by standard ultrasound and venography.**

***Results*—A total of 40 cases of PE and 37 cases of DVT were objectively diagnosed. The predictive value of a negative SimpliRED test for excluding objectively diagnosed PE was 0.99 (error rate 2/249), that of Pa_{O_2} of ⩾80 mm Hg (10.7 kPa) was 0.97 (error rate 5/160), and that of a respiratory rate of ⩽20/min was 0.95 (error rate 14/308). The best combination of findings for excluding PE was a negative SimpliRED test and Pa_{O_2} ⩾80 mm Hg, which gave a predictive value of 1.0 (error rate 0/93). The predictive value of a negative SimpliRED test for excluding VTE was 0.98 (error rate 5/249).**

***Conclusions*—All three of these observations are helpful in excluding PE. When any two parameters were normal, PE was very unlikely. In patients with a negative SimpliRED test and Pa_{O_2} of ⩾80 mm Hg a lung scan is usually unnecessary. Application of this approach for triage in the preliminary assessment of suspected PE could lead to a reduced rate of false positive diagnoses and considerable resource savings.**

(*Thorax* 1998;**53**:830–834)

Keywords: pulmonary embolism; deep vein thrombosis; D-dimer; blood gas; respiratory rate

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Received 2 January 1998
Returned to authors
10 March 1998
Revised version received
30 March 1998
Accepted for publication
15 April 1998

Pulmonary embolism (PE) and deep vein thrombosis (DVT) are disorders of importance in most areas of medicine. The clinical presentation of PE is notoriously non-specific and may mimic many other acute cardiorespiratory illnesses. In cases of suspected PE the ventilation perfusion (VQ) lung scan is a commonly requested examination. A normal VQ scan effectively excludes PE, and a high probability VQ scan in an appropriate clinical setting offers good but not incontrovertible evidence that PE has occurred.[1] However, in practice up to 70% of lung scans show non-specific abnormalities, and additional tests, including pulmonary angiography, are often required.[2] Furthermore, the VQ scan is a relatively expensive and technology dependent screening procedure, and more selective utilisation of this test has been advocated.[3] For example, the recently published British Thoracic Society guidelines suggested that a normal D-dimer level (measured by ELISA) excludes PE, as does a respiratory rate of <20/min and the absence of pleuritic pain and hypoxaemia.[4] These suggestions, while plausible, remain relatively untested.

D-dimer is a product of fibrinolysis. Levels of D-dimer are raised in many conditions including trauma, infection and inflammation and consequently cannot be used to establish the diagnosis of venous thromboembolism (VTE) except as part of a decision analysis-based strategy.[5] However, provided a sensitive ELISA assay system is used, a normal D-dimer level usually excludes VTE.[6 7] Other D-dimer testing systems are available that are less time consuming and more convenient than ELISA tests. In this study we have chosen to investigate a commercial assay based on the agglutination of red blood cells—the SimpliRED test.[8]

Disturbances in blood gas tensions and respiratory rate are commonly observed both in PE and in a number of other respiratory disorders. In the absence of these disturbances PE is probably less likely, but we are not aware of any prospective studies to investigate this hypothesis. Szucs *et al*,[9] in a study of 36 patients, suggested that an arterial oxygen tension (Pa_{O_2}) of more than 80 mm Hg (10.7 kPa) while breathing air effectively excluded PE; however, more recent studies have suggested that between 15% and 25% of patients with proven PE will have a Pa_{O_2} of more than 80 mm Hg depending on the prevalence of other cardiopulmonary disease.[10] It was observed in the Urokinase Pulmonary Embolism trial that only 8% of patients with PE had a respiratory rate of less than 16 breaths/min.[11] In the Prospective Investigation of Pulmonary Embolism Diagnosis (PIOPED) tachypnoea was the commonest sign observed, but 30% of those with PE had a respiratory rate of less than 20 breaths/min.[12] Tachypnoea

associated with PE is thought to be caused by reflex mechanisms unrelated to hypoxaemia.[13 14]

The aim of the present investigation was to evaluate prospectively the use of the D-dimer test, blood gas tensions, and respiratory rate in excluding PE with a view to reducing the need for lung scans.

Methods

SELECTION OF SUBJECTS AND LUNG SCANS

The study was conducted over a one year period from July 1996 at Christchurch Hospital. This is a tertiary level 600 bed institution which has the only nuclear medicine facility serving a region of 375 000. Approximately 700 lung scans are performed annually. The subjects of the study were consecutive patients of general medical, coronary care, emergency department, or specialist medical physicians who were referred for a lung scan to assist in the diagnosis of suspected acute PE. This excluded any patients under the care of surgical or intensive care specialists at the time a lung scan was requested.

This was an observational study in which no attempt was made to influence the process of referral for lung scans, subsequent tests, or management. All lung scans performed to assist in the diagnosis of suspected acute PE in the specified patient groups were evaluated. Lung scans which were performed for the routine follow up of previously diagnosed PE or to evaluate chronic progressive dyspnoea or chronic pulmonary hypertension were not included. When a symptomatic recurrence of suspected VTE led to a further lung scan, this was treated as a new episode.

INVESTIGATIONS

The doctor requesting the lung scan was asked to complete a specially designed referral form comprising a tick box questionnaire identifying risk factors, and also asking the question "In your opinion, based on history and examination, is there a high likelihood of pulmonary embolism in this case?" (Question 1). For the purposes of this study a YES answer to this question was defined as a high pretest probability and a NO answer defined a group who did not have high pretest probability. A 5 ml citrated venous blood sample was taken for the SimpliRED test. In order to preserve blinding the test was performed at the laboratory on an uncentrifuged sample. However, it can also be performed at bedside on capillary blood in approximately two minutes. The SimpliRED result was not divulged to the participating clinicians. Arterial blood gas measurements performed breathing air whenever possible were also obtained, and the referring doctor was also asked to count and record the respiratory rate over one minute.

Aerosol ventilation studies using 99m-technetium DTPA were usually performed immediately before a standard perfusion study. Criteria established in the PIOPED study were used for interpreting lung scans and pulmonary angiograms.[1] Pulmonary angiograms were selective digital subtraction studies performed at the discretion of physicians caring for the patients. Standard venography or B mode ultrasound criteria were used to diagnose DVT.[15]

DATA ANALYSIS AND ADJUDICATION

Following discharge of the patient, diagnostic outcomes were assessed by examination of the case records. The following predetermined end points, in order of precedence, were taken as objective evidence of pulmonary embolism: (1) a post mortem diagnosis, (2) a positive pulmonary angiogram, (3) a high probability VQ scan when the pretest probability was also high.

When a high probability VQ scan was reported but the pretest probability was not classified as high by the referring doctors, the case was presented to a panel of three physicians for reconsideration of pretest probability. They were unaware of the blood gas tension, respiratory rate, or D-dimer result. The panel estimated both the pretest probability and the final overall probability of PE, and a unanimous opinion was considered final.

The study received approval from the ethics committee of the Southern Regional Health Authority (Canterbury), and all subjects gave written informed consent prior to inclusion.

Results

SUBJECTS AND INITIAL INVESTIGATIONS

The commonest single indication for requesting a lung scan was pleuritic chest pain which was documented in about 70% of cases. Although patients currently under the care of surgical specialists were excluded, 70 of the study population (14%) had undergone surgery with a general anaesthetic within the previous two days to one month and were subsequently readmitted to hospital for suspected PE. Forty four cases (8.5%) were referred by doctors from the Emergency Department and were discharged home following the lung scan.

Of 558 consecutive lung scans, 30 could not be included because of early discharge or clerical errors which prevented acquisition of key data (n = 15) or refusal of consent (n = 15). None of the excluded scans was performed on patients who received a final diagnosis of VTE. Routine follow up scans of previously diagnosed PE (n = 6) were excluded, as were scans requested to evaluate chronic pulmonary hypertension or chronic progressive dyspnoea (n = 5). This left a total of 517 scans for analysis. Thirty two (6%) were reported as high probability VQ scans, four (1%) were "high probability" perfusion only, 135 (26%) were non-diagnostic (indeterminate), 182 (35%)

Table 1 Pretest probability, SimpliRED, blood gas tension, and respiratory rate findings in 517 cases referred for a lung scan for suspected acute pulmonary embolism

Observation made	*Proportion of cases**	*%*
High pretest probability	216/515	42
SimpliRED negative	249/499	50
Pao_2 ≥80 mm Hg	160/471	34
Respiratory rate ≤20/minute	308/509	61

*The denominator represents the number of cases in which observations were available.

Table 2 Method of diagnosis of PE and the number with negative SimpliRED results

Method of diagnosis	*No. of cases*	*SimpliRED negative*
Post mortem	0	0
Pulmonary angiogram	8	1
High probability VQ and high pretest probability	28	1
Adjudication by panel	4	0

were low probability, 154 (30%) were normal, and 10 (2%) had missing data and were unable to be classified.

Table 1 lists the results for pretest probability, SimpliRED test, and respiratory recordings. Blood gas tensions were measured while breathing air in 434 patients (85%).

DIAGNOSTIC OUTCOMES

A total of 27 subjects (5%) died within 10 days of undergoing a lung scan. A post mortem examination was performed in five cases but no pulmonary emboli were observed in any of these. In two cases PE had been diagnosed clinically prior to death, but the pathologist considered the cause of death to have been warfarin induced lung haemorrhage and pneumonia, respectively. Twenty four pulmonary angiograms were performed, of which eight (33%) showed evidence of PE.

Adjudication was required in four cases with high probability VQ scans in which the pretest probability was not high, and in six further cases with "high probability" perfusion only scans or scans which were difficult to classify. The committee agreed with the initial pretest assessment in eight cases (six NO and two YES), but in the other two cases changed the NO to a YES. Considering all the available evidence, the committee judged that PE was proven in four of the cases which came to adjudication, but unlikely in the other six.

VALIDITY AND RELIABILITY OF THE PRETEST PROBABILITY ASSESSMENT

A YES answer to question 1 was associated with a risk ratio of 12.3 for objectively diagnosed PE (95% CI 4.4 to 34.0). As previously stated, there was agreement for both YES and NO answers to question 1 between the original doctor and the expert panel in eight of 10 cases which came to adjudication. When comparing our YES/NO answers to question 1 with the admitting doctors' responses we found agreement in 45 out of 50 consecutive cases (90%). Furthermore, 75% of the cases in which the YES box had been ticked were commenced on heparin prior to the lung scan, and only five cases in which the NO box had been ticked went on to receive a final objective diagnosis of PE.

D-DIMER RESULTS IN OBJECTIVELY DIAGNOSED CASES

The criteria used to diagnose PE are shown in table 2, together with the cases of PE in which the SimpliRED test was negative. PE was diagnosed without satisfying the criteria of objectivity in a further 68 cases who were excluded from further consideration.

RESPIRATORY FINDINGS IN OBJECTIVELY DIAGNOSED CASES

Respiratory data were recorded in 39 of 40 objectively diagnosed cases of PE. Amongst these, a Pa_{O_2} of $\geqslant$80 mm Hg was observed in five (13%) and a respiratory rate of $\leqslant$20/min in 14 (36%). A "normal" value for one or other of these findings was present in 17 (45%) of this group, but in only two cases (5%) were both parameters simultaneously "normal". In both of the subjects with a Pa_{O_2} of $\geqslant$80 mm Hg and respiratory rate of $\leqslant$20 the alveolar-arterial gradient was also normal. The SimpliRED test was positive in both these cases.

INVESTIGATIONS FOR DVT

Femoral B mode compression ultrasound examinations, with Doppler studies in selected cases, were performed on 164 patients with suspected PE either to investigate leg symptoms or, in most cases, to further evaluate patients with abnormal lung scans. Thirty seven above knee DVTs were diagnosed by ultrasound, the remaining 127 examinations (78%) were normal. No normal ultrasound studies were subsequently repeated in order to detect propagation of possible below knee thrombosis. Contrast venography was performed in six patients including three who also had ultrasound examinations. In two of the three cases in which both investigations were performed there was conflicting evidence and the venographic findings were given precedence. This led to the conclusion that one ultrasound was false positive and one false negative. In the other three cases in which venography was employed the test was normal. This gave a total of 37 objectively diagnosed DVTs. Another nine diagnoses of DVT were made without imaging support. These cases did not satisfy our criteria of objectivity

Table 3 Predictive value of a negative SimpliRED, Pa_{O_2} $\geqslant$80 mm Hg, and respiratory rate $\leqslant$20/min for excluding objectively diagnosed pulmonary embolism (PE) and venous thromboembolism (VTE) in 517 cases

Observation made	*Condition excluded*	*Correct exclusions*	*Predictive value* (95% CI)*
Negative SimpliRED	PE	247/249	0.99 (0.981 to 0.999)
Negative SimpliRED	VTE**	244/249	0.98 (0.962 to 0.997)
Pa_{O_2} $\geqslant$80 mm Hg	PE	155/160	0.97 (0.942 to 0.996)
Respiratory rate $\leqslant$20	PE	294/308	0.95 (0.931 to 0.978)
Negative SimpliRED and Pa_{O_2} $\geqslant$80mm Hg	PE	93/93	1.00 (0.968 to 1.000)
Negative SimpliRED and respiratory rate $\leqslant$20	PE	168/170	0.99 (0.972 to 1.000)
Pa_{O_2} $\geqslant$80 mm Hg and respiratory rate $\leqslant$20	PE	106/108	0.98 (0.956 to 0.999)
Negative SimpliRED and Pa_{O_2} $\geqslant$80mm Hg and respiratory rate $\leqslant$20	PE	72/72	1.00 (0.959 to 1.000)

*The predictive value is calculated as the number of correct exclusions divided by the number of observations made. For example, in a total of 249 negative SimpliRED tests, 247 subjects did not have objective evidence of PE.
**VTE comprises objectively diagnosed PE or DVT or both.

and were excluded. DVT was objectively diagnosed in 10 of the 40 cases in whom PE was also objectively diagnosed. Three of the objectively diagnosed DVTs (8%) had a negative SimpliRED test. These included a case of isolated calf vein thrombosis, one involving the superficial femoral vein, and a third with extensive thrombosis of the femoral and popliteal veins.

The predictive value of a negative SimpliRED test for excluding PE or VTE, alone or in combination with the other observations, is given in table 3. Expressed from the more conventional standpoint of diagnosing PE, the sensitivity of the SimpliRED test (true positives/true positives + false negatives) was 38/40 (95%) and the specificity (true negatives/true negatives + false positives) was 247/459 (54%).

Discussion

The SimpliRED test, Pa_{O_2}, and respiratory rate were all useful for excluding PE. The best single parameter was the SimpliRED test. If clinicians had accepted the validity of a negative result, 249 lung scans (50%) and 10 pulmonary angiograms could have been avoided at the cost of missing two cases of PE. The best combination was that of a negative SimpliRED and Pa_{O_2} of $\geqslant$80 mm Hg. In this study 93 subjects (18% of the study population) had this combination of findings. Thirty four of these (37%) had been judged to have a high pretest probability, but none of the 93 had high probability VQ scans and none went on to receive an objective diagnosis of PE.

Measurement of the respiratory rate and blood gas tensions has been specifically recommended in this context.[4] However, in practice doctors often fail to recognise the importance of these observations, which were omitted in 50% of cases referred for lung scans in a previous study.[16] One or other of these observations was also omitted prior to the lung scan in approximately 30% of cases in the present study.

Since the aim of this study was to investigate methods of accurately excluding PE, it was crucial to avoid false positives in our objective diagnostic end points. A high probability VQ scan without consideration of other factors is associated with at least 14% of false positives and would probably not have been adequate for our purposes.[17] In the PIOPED study when doctors assessed the "clinical probability" of PE as being "higher than 80%", the false positive rate was only 4%.[18 19] Conversely, when the clinical probability was "20% or lower" the positive predictive value of a high probability VQ scan for angiographically detectable emboli fell to around 50%.[20]

We chose not to follow this aspect of the PIOPED methodology in the present study because we considered it potentially confusing and insufficiently validated. We were also unable to find a satisfactory definition of "high pretest probability"in the literature. For the purposes of this study we adopted an operational definition, which was the act of ticking the YES box for question 1. This judgement was based on the signs and symptoms and other relevant data including previously documented risk factors. In all cases this assessment was made prior to the lung scan.

Most of the cases of DVT diagnosed during this study were by means of femoral ultrasound which may provide a less than ideal objective end point. Doubts have been raised about the accuracy of this method in asymptomatic cases.[21 22] It could be considered desirable to verify a diagnosis of DVT established by ultrasound, but this was done in only three cases.

A possible weakness of the present investigation is that PE was objectively diagnosed in only 40 out of 517 suspected cases (8%) compared with 68 (13%) which were diagnosed by non-objective methods. It is surprising that objective verification was not sought more frequently in the diagnosis of this disease, particularly in view of the risks associated with anticoagulant therapy. The low prevalence of well documented PE in the suspect population further emphasises the need for a more focused application of lung scanning.

It has been established in five previous prospective trials involving approximately 1000 patients that the SimpliRED test has a negative predictive value for VTE of approximately 0.95.[23–27] However, previous studies have focused on DVT rather than PE, where the D-dimer is more likely to be raised, since fibrinolysis is probably more intense in the pulmonary arteries than in the veins of the lower limbs.[28] However, it is unlikely that any single test or combination of tests will be sufficient to exclude all cases of PE absolutely, given the potential for false positives of all the methods of diagnosis commonly available. For example, one of the patients in this study with a positive pulmonary angiogram and a negative SimpliRED test had malignant lymphoma. Tumour emboli are relatively common[29] and may not cause changes in D-dimer levels.

In designing this study we were interested in finding an inexpensive, simple, and robust system for triage to reduce the need for lung scans. This study and the cumulative evidence of previous studies provides strong support for the value of a negative SimpliRED test in excluding VTE. The value of normoxaemia and a low respiratory rate in excluding PE has also been demonstrated. Accepting that the diagnosis of PE is almost always a probability based exercise, we conclude that a negative SimpliRED test virtually excludes PE, a negative SimpliRED test coupled with a Pa_{O_2} of more than 80 mm Hg is even more conclusive and these patients do not require a lung scan. In patients with abnormal lung scans the finding of a negative SimpliRED test substantially reduces the probability that the abnormalities are due to PE.

The investigators in this study have no connection with the manufacturers of the SimpliRED blood test and have not received any financial support from them.

We sincerely thank Drs J Billings, J Elliott, J O'Hagan, and A Pitchford who helped with the coordination of this study, the physicians and resident staff of Christchurch Hospital who enrolled the subjects, the staff of Medical Records, the Nuclear Medicine Department, and Canterbury Health Laboratories who assisted with data collection, and Dr C Frampton who gave statistical advice.

This study was funded by the University of Otago Research Committee.

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