Clinically suspected acute pulmonary embolism: a comparison of presentation, radiological features and outcome in patients with and without PE

A.R. AKRAM¹, G.W. COWELL¹, L.J.A. LOGAN¹, M. MACDOUGALL², J.H. REID³, J.T. MURCHISON⁴ and A.J. SIMPSON¹

From the ¹Respiratory Medicine Unit, University of Edinburgh, Edinburgh, EH16 4SA, ²Public Health Sciences, University of Edinburgh Medical School, Teviot Place, Edinburgh, EH8 9AG, ³Department of Radiology, Borders General Hospital, Melrose, TD6 9BS and ⁴Department of Clinical Radiology, Royal Infirmary of Edinburgh, Edinburgh, EH16 4SU, Scotland, UK

Received 22 November 2008 and in revised form 16 March 2009

Summary

Background: Relatively little is known about prognosis in patients for whom suspected pulmonary embolism (PE) is refuted by imaging.

Aim: This prospective study of suspected PE therefore compared clinico-radiological features and outcome in patients with and without PE.

Design and Methods: Computed tomographic pulmonary angiography (CTPA) confirmed or refuted PE in consecutive patients. Clinical, laboratory and radiological features were recorded at baseline, and mortality at 1 year determined. Univariate and multivariate analyses identified variables associated with PE.

Results: PE was diagnosed in 45 patients and refuted in 141. The PE and ‘non-PE’ groups were similar with regard to extravascular radiology (though consolidation was significantly more common in the PE group [present in 24 (53%) of the PE group and 42 (30%) of the non-PE group, P<0.01]), comorbidities (no significant differences), and baseline characteristics (only serum D-dimer concentrations were independently associated with PE by multivariate analysis, P=0.001). Right ventricular dimensions were significantly higher in the PE group, [right ventricular to left ventricular ratio was 0.98 (range 0.64–2.48) in the PE group and 0.92 (range 0.66–1.95) in the non-PE group, P<0.05]. In the PE group, right ventricular dimensions rose sharply when 10 or more segmental pulmonary arteries were occluded. One year all-cause mortality was 6.7% in the PE group and 13.5% in the non-PE group (no significant difference, P=0.218).

Conclusion: Among a cohort of patients presenting with clinically suspected PE, clinical characteristics, co-morbidities and radiological features were similar when comparing groups with CTPA-proven or CTPA-refuted PE. However RV dimensions, radiological consolidation on imaging and D-dimer levels were significantly higher in the PE group. Patients with suspected PE have a poor prognosis irrespective of whether PE is confirmed. This appears accentuated in patients without PE, a finding possibly under-recognized in clinical practice.
Introduction

The annual incidence of acute pulmonary embolism (PE) has been estimated at up to 70/100,000 placing a massive strain on health resources.\(^1\,^2\) Acute PE has been estimated to cause over 50,000 deaths per annum in the USA.\(^3\)

However, the clinical diagnosis of acute PE remains notoriously difficult.\(^4\) Among patients with clinically suspected PE who proceed to diagnostic imaging, objective evidence for thrombus in the pulmonary arteries is typically found in around 20%. Clinical outcomes after confirmed PE have been carefully characterized in previous studies.\(^5\)–\(^12\)

However, less is known about the clinical features and outcomes of patients in whom diagnostic imaging refutes PE. By definition these patients present with clinical features mimicking PE. While this heterogeneous subgroup has been studied with respect to the risk of subsequent venous thromboembolism,\(^13\)–\(^15\) few studies have characterized clinico-radiological features and all-cause mortality in detail.

With this in mind, our primary aims were to establish whether patients presenting acutely with suspected PE have a worse outcome if PE is proven, and also whether co-morbidities or radiological changes in the lungs (assessed at CTPA) were differentially distributed in the PE and non-PE groups. CTPA allows detection of pulmonary emboli to the level of sub-segmental arteries and the extent of thrombus in the pulmonary arterial tree can be quantified, along with measurements of cardiac dimensions.\(^16\)–\(^19\) Secondary aims of the study were therefore (i) to compare right ventricular dimensions in patients with and without PE, and (ii) to assess the relationship between right ventricular dilatation, thrombus load and outcome within the group of patients with confirmed PE.

Methods

This was a prospective, observational, non-interventional cohort study performed in a single university teaching hospital over 4.5 months. Eligible patients were those presenting acutely to hospital in whom admitting physicians were sufficiently suspicious of acute PE to request a computed tomographic pulmonary angiogram (CTPA), completion of which triggered entry into the study. The route of entry to the study was designed to be pragmatic and to reflect ‘real life’, i.e. CTPA requests were not influenced by the study team and use of pre-test prediction models was entirely at the discretion of the referring physician. Patients who were already in-patients when clinical features suggestive of PE arose were not included.

CTPAs were performed using a multislice CT scanner (Aquilion 16, Toshiba Medical Systems Ltd) and 1 mm collimation with images viewed on a Vitrea Workstation (Toshiba Report Direct V500). CTPAs were reported by the hospital’s diagnostic service. However all scans were independently reviewed by an experienced pulmonary radiologist (JTM). The study design stipulated that discrepancies in opinion between the study radiologist and the diagnostic service would be discussed and the final diagnosis reached by consensus. The study design also stipulated that CTPAs deemed to be indeterminate for technical reasons were excluded from analysis. The study radiologist assessed cardiac dimensions in all patients, and quantified the degree of pulmonary arterial occlusion in patients with PE. Cardiac dimensions were assessed using axial images to determine the maximum end-diastolic dimension of the right and left ventricular (RV and LV) chambers, expressed as a ratio (RV:LV ratio) (Figure 1). Thrombus load was quantified according to criteria described by Miller, adjusted for CTPA by Bankier et al.\(^16\)\(^,\)\(^17\) This generates a modified Miller score (MMS) of 0–16, whereby the segmental pulmonary arteries (nine on the right, seven on the left) are observed and a score of one is attributed to each artery occluded by thrombus. Any more proximal occlusion scores the number of segmental branches distal to the occlusion.

Evidence of other cardiopulmonary diseases detectable at CTPA (e.g. consolidation, pleural effusions, emphysema etc.) was also systematically

Figure 1. CTPA demonstrating pulmonary embolism and associated right ventricular dilatation. Black arrows demonstrate the maximal end-diastolic dimensions of the right ventricle (RV) and left ventricle (LV), showing RV dilatation and septal (S) bowing. White arrow demonstrates a segmental right lower lobe thrombus.
recorded. Co-morbidities and results of investigations performed at presentation (before CTPA) were recorded. All patients provided a short history covering co-morbidities/potential risk factors for PE.

Dates of discharge from hospital or death in hospital were recorded. Mortality data relating to the period after hospital discharge were obtained from the National Registry Office for Scotland. Patients’ details were matched to the national registry of deaths occurring in Scotland by name, date of birth, sex and postcode. Matching was considered to be adequate if at least three of these characteristics concurred with a death recorded in the registry, and under these circumstances the patient’s death was considered confirmed.

Patients were excluded if case records were unavailable throughout hospital admission or if the presence or absence of acute PE could not be confidently diagnosed at CTPA. If more than one CTPA was performed during the study period, only data from the first scan were included. Patients were excluded if they had a CTPA in the 3 months prior to the study period and had a follow-up CTPA during the study period that did not relate to a new presentation.

The study was approved by the ethical review process for medical student projects in our institution.

Statistical analysis

The distribution of gender, previous PE and previous deep vein thrombosis (DVT) in the PE and non-PE groups was compared using the chi-squared test. Comparison of numeric variables in the PE and non-PE groups was performed using the Mann–Whitney U-test. A significance level of 0.05 was used.

To obtain an estimate of the relationship between RV:LV ratio and MMS, the RV:LV ratio data for the PE group were tested for outliers. Three extreme outliers >87% higher than the median were eliminated. To minimize roughness caused by measurement uncertainty a smoothing procedure—the LOCALy-WEighted Scatter plot Smoother, LOWESS—was then applied to a plot of RV:LV ratios vs. MMS. Using polynomial regression analysis, a quadratic curve was fitted to the smoothed data using the statistical software package Minitab 14. The resultant polynomial curve fitted to the smoothed data was tested using an F-ratio test with a significance level of 0.05. Using a bivariate model with two outcomes—occurrence or non-occurrence of PE—a binary logistic regression analysis was performed to test for factors differentiating PE and non-PE patients at presentation, adjusting for confounding effects. Variables adjusted for in binary logistic regression included age, sex, previous PE, previous DVT, PaO₂, PaCO₂, SaO₂, hydrogen ion concentration in arterial blood, serum D-dimer, prothrombin time, serum C reactive protein, RV:LV ratio. Logistic regression analysis was performed using the statistical package SPSS 12.0.

Results

One hundred and ninety-four patients were admitted to hospital with suspected acute PE and had CTPA. Eight patients were excluded (two scans were indeterminate for technical reasons, two patients were transferred to another hospital before being seen by study investigators, and four were lost to follow-up after transfer to other hospitals). Therefore data analysis was performed on 186 patients followed through to discharge from hospital or death in hospital.

Forty-five patients (24.2%) had a diagnosis of acute PE at CTPA. With regard to whether PE was present or absent, no discrepancies were found in observations made by the study radiologist and the diagnostic service for any of the 186 scans.

Baseline characteristics for the PE and ‘non-PE’ groups are shown in Table 1. Patients with PE were significantly more likely to be male ($P=0.020$), to have a higher circulating D-dimer ($P<0.0005$), and to have increased RV:LV ratio ($P=0.037$). However, when these factors were entered into binary logistic regression analysis and adjustments made for mutual confounding factors, only elevated serum D-dimer level remained significantly and independently associated with PE (adjusted odds ratio 1.12, 90% confidence intervals 1.06–1.18).

Significant co-morbidities were evenly distributed in patients with and without PE (Figure 2). Chronic obstructive pulmonary disease (COPD) was more common in the non-PE group but this finding did not reach statistical significance ($P=0.101$). Working diagnoses for the 141 patients with no evidence for acute PE are shown in Table 2.

No significant differences were found when comparing major pulmonary and pleural radiological abnormalities in patients with and without PE, with the exception of consolidation which was more common among patients with PE (Figure 3).

There were seven deaths in hospital, all in the non-PE group (no significant difference between the groups). None of these seven patients had a post-mortem examination. In each case bronchopneumonia was listed as a cause of death on the death certificate, though three patients had another significant pathology recorded (idiopathic...
pulmonary fibrosis, left ventricular failure and cancer). At 1 year all-cause mortality in the PE group was 3/45 (6.7%) as compared with 19/141 (13.5%) in the non-PE group (no significant difference, \( P = 0.218 \)). None of the deaths were attributed to PE.

Among patients with PE the median MMS was six (range 1–16) and there was a significant positive correlation between MMS (reflecting thrombus load) and RV:LV ratio. Following LOWESS smoothing, a highly significant quadratic relationship \( (R^2 = 0.99, \ P < 0.0005) \) was observed between

Table 1  Univariate analysis of clinical and laboratory variables in the PE and non-PE groups

<table>
<thead>
<tr>
<th></th>
<th>PE group</th>
<th>Non-PE group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>( n (%) )</td>
<td>( n (%) )</td>
</tr>
<tr>
<td>Sex: Male</td>
<td>30 (66.7)</td>
<td>66 (46.8)</td>
</tr>
<tr>
<td>Previous PE</td>
<td>3 (6.7)</td>
<td>15 (10.6)</td>
</tr>
<tr>
<td>Previous DVT</td>
<td>7 (15.6)</td>
<td>18 (12.8)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>Median (range) 45</td>
<td>66 (17–96) 141</td>
</tr>
<tr>
<td>D-dimer (ng/ml)</td>
<td>2644 (369–8047) 25</td>
<td>993 (160–5943) 49</td>
</tr>
<tr>
<td>Prothrombin time (s)</td>
<td>10.0 (8–35) 25</td>
<td>9.75 (3–61) 68</td>
</tr>
<tr>
<td>C reactive protein (mg/l)</td>
<td>74 (7–199) 11</td>
<td>45.5 (2–377) 30</td>
</tr>
<tr>
<td>PaO₂ (kPa)</td>
<td>8.9 (6.5–13.9) 32</td>
<td>9.1 (6.0–14.9) 76</td>
</tr>
<tr>
<td>PaCO₂ (kPa)</td>
<td>4.5 (2.7–6.5) 31</td>
<td>4.7 (2.4–9.5) 74</td>
</tr>
<tr>
<td>( O_{2} ) saturation (%)</td>
<td>95 (80–100) 39</td>
<td>96 (60–100) 100</td>
</tr>
<tr>
<td>( H^+ ) in arterial blood (nmol/l)</td>
<td>35.5 (26.3–45.7) 32</td>
<td>36.3 (15.2–51.3) 71</td>
</tr>
<tr>
<td>RV:LV ratio</td>
<td>0.98 (0.64–2.48) 45</td>
<td>0.92 (0.66–1.95) 141</td>
</tr>
</tbody>
</table>

The first three variables are expressed as \( n \) (%). The lower nine variables are expressed as medians (range), and \( n \) denotes the number of patients for whom data were available—the study was designed to reflect actual clinical practice (i.e. whether variables were measured/recorded was entirely at the discretion of the attending clinical team), hence \( n \) is often less than 45 in the PE group and less than 141 in the non-PE group.

Values from arterial blood gas samples (PaO₂, PaCO₂ and \( H^+ \)) and \( O_{2} \) saturation were only included in analysis if the sample or readings were taken with the patient breathing room air.

In the right hand column \(^*\) \( P < 0.05 \), \(^{**}\) \( P < 0.001 \) when comparing the PE and non-PE groups. Absence of symbol denotes no statistically significant difference.

Figure 2. Co-morbidities described in the PE and ‘non-PE’ groups. No statistically significant differences were observed when comparing the two groups.
MMS and RV:LV ratio (Figure 4). The fitted curve demonstrates convergence towards an approximate linear relationship for MMS scores of 10 or more. In patients with PE neither MMS nor RV:LV ratio were significantly correlated with length of hospital stay.

**Discussion**

Our data suggest that patients with and without PE were similar with regard to co-morbidities, clinical features at presentation and outcome. A retrospective study by Poulsen et al., which relied on

![Figure 4](image-url)  
**Figure 4.** Plot of quadratic fit to smoothed RV:LV data. \( \text{RV:LV} = 0.003 \times \text{MMS}^2 - 0.018 \times \text{MMS} + 0.941 \). \( R^2 = 0.99 \). Data apply only to patients with PE.

**Table 2** Final working diagnoses among the 141 patients in whom PE was excluded at CTPA

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Count</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pneumonia</td>
<td>38</td>
</tr>
<tr>
<td>Exacerbation of COPD</td>
<td>15</td>
</tr>
<tr>
<td>Ischaemic heart disease</td>
<td>9</td>
</tr>
<tr>
<td>Musculoskeletal chest pain</td>
<td>7</td>
</tr>
<tr>
<td>Pleural effusion</td>
<td>6</td>
</tr>
<tr>
<td>Lung cancer</td>
<td>5</td>
</tr>
<tr>
<td>Left ventricular failure</td>
<td>5</td>
</tr>
<tr>
<td>Arrhythmia</td>
<td>3</td>
</tr>
<tr>
<td>Pleurisy of unknown cause</td>
<td>3</td>
</tr>
<tr>
<td>Exacerbation of pulmonary fibrosis</td>
<td>2</td>
</tr>
<tr>
<td>Gastro-oesophageal reflux disease</td>
<td>2</td>
</tr>
<tr>
<td>Sepsis</td>
<td>2</td>
</tr>
<tr>
<td>Trauma</td>
<td>2</td>
</tr>
<tr>
<td>Psychological chest pain/anxiety</td>
<td>2</td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>1</td>
</tr>
<tr>
<td>Lobar/segmental collapse</td>
<td>1</td>
</tr>
<tr>
<td>Exacerbation of asthma</td>
<td>1</td>
</tr>
<tr>
<td>Exacerbation of bronchiectasis</td>
<td>1</td>
</tr>
<tr>
<td>Pneumothorax</td>
<td>1</td>
</tr>
<tr>
<td>Methotrexate pneumonitis</td>
<td>1</td>
</tr>
<tr>
<td>Primary pulmonary hypertension</td>
<td>1</td>
</tr>
<tr>
<td>Dilated cardiomyopathy</td>
<td>1</td>
</tr>
<tr>
<td>Acute pancreatitis</td>
<td>1</td>
</tr>
<tr>
<td>Splenic rupture</td>
<td>1</td>
</tr>
<tr>
<td>Vertebral metastases</td>
<td>1</td>
</tr>
<tr>
<td>Unknown cause</td>
<td>34</td>
</tr>
</tbody>
</table>

Numbers exceed 141 because some patients were given more than one simultaneous working diagnosis to explain presentation.

![Figure 3](image-url)  
**Figure 3.** Extravascular radiological features detected at CTPA. \(^*P < 0.01\) when comparing the two groups.
scintigraphy for the diagnosis of PE, found similar trends. The clinical implication is that patients presenting with clinical features compatible with acute PE have a relatively poor prognosis irrespective of whether PE is detected.

Considering the group without PE specifically, our data suggest an all-cause mortality rate of 13% at 1 year with a trend towards this group having a worse prognosis than patients with PE. This can be compared with an estimated all-cause 1 year mortality in 65-year-olds in Scotland of 2.5% (personal communication, Ms. Marie Climson, General Register Office for Scotland). This trend supports data from a separate retrospective study performed by our group showing that patients with an indeterminate lung scintigraphy scan had significantly worse prognosis than patients with PE. This can be derived with regard to extravascular pathology.17 We found a high rate of consolidation at CTPA, this being significantly more common in patients with PE. Secondary consolidation has been recognized as a frequent accompaniment to PE before.26–28

The similar clinical and radiological features of patients with and without PE confirm and emphasize the notorious difficulties in making the clinical diagnosis. In recent years pre-test prediction models have made significant advances in identifying patients who are at very low risk of PE, do not require invasive imaging and have a relatively good prognosis.15,29–32 Identification of positive clinical predictors of acute PE would also be helpful. However, we only found elevated D-dimer concentrations to be significantly associated with PE. While these data must be interpreted with caution given the small numbers of patients for whom data were available, D-dimer concentrations have found clinical utility as a negative predictor for PE,29,32,33 and high concentrations have been associated with larger thrombi.34

The PE group in our study was also found to have a higher RV:LV ratio, which is a well recognized consequence of acute pulmonary arterial obstruction. The ratio correlated closely with thrombus load, the relationship appearing to be particularly strong above a MMS of 10. This observation is in keeping with the concept that there is a break point below which the right ventricle copes with increased pulmonary vascular resistance, but above which acute dilatation proceeds. Right ventricular dilatation, increasing thrombus load and interventricular septal bowing have been identified as adverse prognostic factors in acute PE.35–37 Measurements of RV diastolic dimensions on axial multislice CT scan have been found to correlate with outcome,38 and CT dimensions have been shown to correlate with findings using transthoracic echocardiography.39,40

We acknowledge several limitations of our study. In particular, the study is relatively small. Other limitations relate to the decision to make the study design entirely observational and ‘non-interventional’, i.e. investigators were not permitted to influence investigations or management in the expectation that the study would reflect ‘real life’ clinical practice (thereby having greater general applicability). In addition, data were not complete for each variable studied, as the decision whether to perform an investigation (e.g. D-dimer) was entirely dependent on attending physicians. Furthermore, we cannot determine how many patients clinically suspected of having possible PE were not submitted
for CTPA on the grounds of a low probability clinical prediction score. Therefore our data should only be interpreted in the setting of patients in whom clinical suspicion was sufficient to warrant a CTPA. Similarly, detection of mortality out of hospital was reliant on hospital-recorded demographics matching those held by the Registrar General for Scotland (responsible for collating all deaths in Scotland). The main confounding factor for this system would arise if a patient died outside Scotland (e.g. a visitor to Scotland who died on returning home, or a Scottish resident who died whilst visiting another country). We have no data to suggest either eventuality arose. Whilst recognizing the relevance of all these limitations we have no reason to believe that biases should be specifically over-represented in either group of patients studied.

In summary, patients with clinically suspected PE have a poor prognosis regardless of whether PE is confirmed on definitive imaging and comprise a group deserving of further study and careful medical follow-up.

Conflict of interest: None declared.

Acknowledgements

We are grateful to Mr Ian Brown and Ms. Marie Climson, General Register Office for Scotland, for providing help with mortality data, and to staff in the medical units and CT Department of the Royal Infirmary of Edinburgh.

References


