Right ventricular dilation on CT pulmonary angiogram independently predicts mortality in pulmonary embolism

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Summary

Background: The aim of this study was to determine the prognostic significance of right ventricular dilation on CT pulmonary angiogram in acute pulmonary embolism and to distinguish if this feature predicts mortality independently of the Pulmonary Embolism Severity Index, an established admission severity score.

Methods: A retrospective study of patients admitted with pulmonary embolism confirmed by CT pulmonary angiogram to three teaching hospitals in East Scotland between January 2005 and July 2007. Two radiologists judged presence of right ventricular dilation on CT pulmonary angiogram independently. The outcome of interest was 30 day mortality. Multivariable logistic regression was used to compare this outcome in patients with right ventricular dilation compared to those without right ventricular dilation, adjusting for Pulmonary Embolism Severity Index score.

Results: There were 585 patients included and 30.4% had right ventricular dilation on CT pulmonary angiogram. Patients with right ventricular dilation had increased 30 day mortality rates compared to patients without right ventricular dilation (12.4% vs. 5.4%; \( p = 0.006 \)). Survival analysis showed that a significantly greater proportion of deaths in the right ventricular dilation group occurred within the first 48 h after admission compared to the group without right ventricular dilation (45.5% deaths vs. 9.1%; \( p = 0.016 \)). On multivariable analysis, adjusting for Pulmonary Embolism Severity Index score, right ventricular dilation was independently associated with increased 30 day mortality (OR 2.98; 95% CI 1.54–5.75; \( p = 0.001 \)).
Introduction

Severity assessment is an important component of the initial management of patients presenting with acute pulmonary embolism (PE). Recently there has been a trend towards classification of patients into three risk groups. Patients with ‘high risk PE’ are those who develop haemodynamic instability, with high risk of mortality and may benefit from thrombolytic therapy12 while those with ‘low risk PE’ have no haemodynamic instability and are at lower risk of adverse outcome. A separate sub-group of patients exists with ‘intermediate risk PE’ (haemodynamically stable but with evidence of right ventricular (RV) dysfunction). These patients have been shown to have higher rates of mortality in some studies but not in all case series3,4 and the role for thrombolysis in this group is unclear.5,6

Various methods are available to admitting clinicians to assess for presence of RV dysfunction in patients with PE. Clinical examination features (e.g. raised jugular venous pressure, parasternal heave) and electrocardiographic findings (e.g. T wave inversion in right precordial leads, right bundle branch block, S1Q3T3 complex) have some value but are known to be unreliable for accurate detection of RV dysfunction.7,8 More accurate prognostic information can be obtained by use of transthoracic echocardiography which can reliably identify the presence of RV dysfunction.4,9–12 However, in many hospitals, a 24-h echocardiography service is often not available and this modality also suffers from technical difficulties of imaging the right heart, particularly when used by less experienced operators.13 Serum biomarkers, such as troponin and brain-natriuretic peptide have also been shown to correlate with presence of RV injury in PE14,15 but these tests appear to be more useful for their negative predictive value of excluding RV injury rather than for prediction.13

More recently, there has been interest in CT-pulmonary angiographic (CTPA) features of right ventricular dysfunction such as right ventricle/left ventricle (RV/LV) ratio.16–19 Comparative studies have shown that CTPA compares favourably with echocardiography for evaluation of right ventricular dilation in acute PE20–22 and is also predictive of outcome.18,23,24 CTPA may thus be a more convenient method than echocardiography for detecting RV dilation in clinical practice, as the majority of patients with suspected PE will undergo this investigation for diagnostic purposes.

The pulmonary embolism severity index (PESI) is a recently developed tool derived to aid in risk stratification of patients presenting with PE.25,26 However, despite RV dysfunction being associated with adverse outcome, PESI does not incorporate its assessment. Recent guidelines have advocated use of alternative scoring systems that consider presence of RV dysfunction as a predictive factor.1

The aim of this study was to determine the prognostic significance of RV dilation on CTPA in patients presenting with acute PE and to distinguish if this feature predicts mortality independently of PE Severity Index (PESI criteria).

Methods

A retrospective study of patients admitted to the emergency department, with acute PE in three teaching hospitals in East of Scotland between January 2005 and July 2007. We included all patients admitted with acute pulmonary embolism, confirmed by CT pulmonary angiogram. The study was approved by the Lothian Ethics Research Committee.

Exclusion criteria were: Cardiac arrest or cardiogenic shock without confirmed PE diagnosis; A history of a known thrombotic disorder, thrombophilia or haematological malignancy; Ongoing therapeutic anticoagulation at time of admission; Patients not actively treated with anticoagulation (palliative care).

Data collection

Baseline demographics (age, sex), admission vital signs (pulse, blood pressure, respiratory rate, temperature, arterial oxygen saturations on room air) and clinical information (comorbidities and exclusion criteria) were collected on a standardised data collection pro-forma. All parameters recorded were measured within 4 h of admission and the earliest available measurement was used. This information was used to retrospectively calculate PESI class on admission for each patient, as previously described25 (see Appendix 1). Missing data was assumed to be normal in keeping with the methodology in previous studies28 and less than 1% missing data was encountered in this study.

Radiological investigation

All patients had pulmonary embolism confirmed by CTPA. The CT scans were all performed using a 16 slice multi-detector CT scanner. The presence or absence of RV dilation and proximal extension of thrombus, visible on CTPA was judged and recorded independently by two experienced radiologists, with any disagreements resolved by discussion. RV dilation was defined as presence of the following previously described feature: right/left ventricle ratio ≥ 1.16–18 The right/left ventricle ratio was obtained by measuring the ratio between the widths of the right and left ventricular cavities on axial images obtained at plane of maximal distance between the ventricular endocardial free wall and the interventricular septum, perpendicular to the long axis, as previously described.23

Outcomes

The primary outcome of interest was 30-day mortality.
Treatment and follow-up

All patients received standard treatment for acute pulmonary embolism with initial anticoagulation by weight-adjusted low molecular weight heparin while being converted to oral vitamin K antagonist therapy. After completing 5 days of low molecular weight heparin, all patients were continued on dose-adjusted oral vitamin K antagonist therapy (warfarin; target international normalised ratio (INR) of 2.5 (therapeutic range 2.0 – 3.0)). Thrombolytic therapy with recombinant tissue plasminogen activator (rtPA) was administered to patients with PE presenting with cardiogenic shock and/or persistent arterial hypotension, in accordance with current guidelines.1

Survival status was assessed at 30 days for patients who were still an in-patient at this time point or at six week outpatient follow-up, if discharged before day 30. For any patient who did not attend outpatient follow-up, survival status was obtained by reviewing general practitioner records. Survival status was confirmed in 100% of patients included in the study.

Statistical analysis

All data was analysed and processed on SPSS version 13.0 for windows (SPSS Inc., Chicago, IL). Descriptive statistics of demographic and clinical variables are expressed as % of group unless otherwise stated. The Chi squared test was used to compare categorical data between groups. Kaplan Meier analysis was used for comparison of survival between patients with RV dilation and those without RV dilation. The statistical significance was evaluated using the log-rank test. We used multivariable logistic regression to compare 30-day mortality rates between patients with PE with RV dilation, compared to patients with PE and no RV dilation. To the baseline model, we included PE Severity Index (PESI criteria) – non-severe (<3) vs. severe (≥4). All variables were coded as binary data for use in the model. A two-tailed p value <0.05 was considered statistically significant.

Results

There were 585 patients who met the criteria and were included in the study. Baseline characteristics of the study
cohort were similar to previous studies of patients with acute PE (see Table 1). A total of 72% of patients had CT pulmonary angiogram performed within 24 h of admission.

There were 30.4% of patients with evidence of RV dilation on CT pulmonary angiogram. There were 1.2% of patients who received thrombolysis. Baseline characteristics in patients with and without RV dilation are summarised in Table 2. On admission, patients with evidence of RV dilation on CTPA had significantly increased rates of tachycardia (pulse ≥ 110/min), hypotension (systolic blood pressure < 100mmHg), tachypnoea (respiratory rate ≥ 30/min), hypoxia (arterial oxygen saturations on room air < 90%) and confusion, when compared to patients with no RV dilation. A greater proportion of patients with RV dilation were classified as severe according to PESI score (class 4 or 5), compared to patients without RV dilation (32.6% vs. 21.6%; p = 0.007) (see Table 2).

**Right ventricular dilation and correlation with PESI**

Distribution of patients according to PESI criteria was: class 1: 23.4%; class 2: 25.8%; class 3: 25.8%; class 4: 14.2%; class 5: 10.8%. Increasing mortality rates were observed with increasing PESI class for both patients with RV dilation on CTPA and patients with no RV dilation (see Table 3). A trend towards increased mortality rates was observed in patients with RV dilation compared to those with no RV dilation when stratified according to PESI risk class, although no significant differences were observed between the two groups (see Table 3).

**Right ventricular dilation and correlation with proximal extension of thrombus**

Overall, 22.7% patients with PE had main pulmonary artery thrombus, 62.2% had lobar or segmental thrombus and 15.1% had subsegmental thrombus. Right ventricular dilation was present in 77.4% of patients with main pulmonary artery PE, compared to 20.3% of patients with lobar/segmental thrombus and 1.1% of patients with subsegmental thrombus. (p < 0.0001).

**Survival analysis**

A significantly greater proportion of deaths in the RV dilation group occurred within the first 48 h after admission compared to the group without RV dilation (45.5% deaths in RV dilation group vs. 9.1% deaths in group without RV dilation; p = 0.016). Fig. 1 shows Kaplan Meier survival analysis in patients with RV dilation and in those without RV dilation, for 30 days post admission. In patients with RV dilation, mortality occurred earlier, in comparison to those without RV dilation (Comparison of curves: Log rank = 6.4 on 1 degree of freedom; p = 0.011).

**Right ventricular dilation on CTPA as a predictor of 30 day mortality**

**Univariable analysis**

The overall 30-day mortality rate was 7.5%. Patients with RV dilation on CTPA had significantly increased rates of 30 day mortality compared with patients with no RV dilation (12.4% vs. 5.4%; p = 0.006).

**Multivariable analysis**

On multivariable analysis, adjusting for PESI score, RV dilation on CTPA was independently associated with increased 30 day mortality (OR 2.98; 95% CI 1.54–5.75; p = 0.001) (see Table 4).

<table>
<thead>
<tr>
<th>Variable</th>
<th>Adjusted odds ratio</th>
<th>95% Confidence interval</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>RV dilation</td>
<td>2.98</td>
<td>1.54–5.75</td>
<td>0.001</td>
</tr>
<tr>
<td>PESI ≥ 4</td>
<td>3.51</td>
<td>1.68–7.33</td>
<td>0.0008</td>
</tr>
</tbody>
</table>

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**Table 3** Thirty day mortality rates in patients with RV dilation compared to those with no RV dilation, stratified according to PESI risk class. Data presented as % of subgroup.

<table>
<thead>
<tr>
<th>PESI class</th>
<th>RV dilation n</th>
<th>% Mortality</th>
<th>No RV dilation n</th>
<th>% Mortality</th>
<th>p Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>class 1 (n = 137)</td>
<td>29</td>
<td>3.4%</td>
<td>108</td>
<td>0%</td>
<td>0.21</td>
</tr>
<tr>
<td>class 2 (n = 151)</td>
<td>44</td>
<td>4.5%</td>
<td>107</td>
<td>2.8%</td>
<td>0.63</td>
</tr>
<tr>
<td>class 3 (n = 151)</td>
<td>47</td>
<td>10.6%</td>
<td>104</td>
<td>7.7%</td>
<td>0.54</td>
</tr>
<tr>
<td>class 4 (n = 83)</td>
<td>28</td>
<td>14.3%</td>
<td>55</td>
<td>9.1%</td>
<td>0.48</td>
</tr>
<tr>
<td>class 5 (n = 63)</td>
<td>30</td>
<td>33.3%</td>
<td>33</td>
<td>18.2%</td>
<td>0.25</td>
</tr>
</tbody>
</table>

* p Value compares RV dilation vs. no RV dilation groups; **p value compares rates across PESI classes.
Sub-analysis of patients without prior history of chronic lung disease or chronic cardiac failure

As right ventricular dilation may be more frequent in patients with chronic lung disease and chronic cardiac failure, a separate analysis was performed excluding these patients. Overall, 25.8% had a history of chronic lung disease or cardiac failure (or both). Among the remaining population that did not have a history of either chronic lung disease or cardiac failure, the frequency of RV dilation was 28.8%. Thirty-day mortality in this sub-group was also higher in patients with RV dilation compared to those without RV dilation (9.6% vs. 2.9%, \( p = 0.006 \)). On multivariable analysis, in the sub-group without chronic lung disease and/or cardiac failure, RV dilation was independently associated with 30 day mortality (OR 2.59; 95% CI = 1.02–6.54; \( p = 0.04 \)).

Discussion

The results of this study show that, in patients with acute PE, the presence of RV dilation assessed on CTPA is independently associated with increased risk of 30 day mortality, after adjustment for PESI criteria. The PE severity index is a well validated prediction rule that considers 11 clinical and demographic variables and has been proposed as a tool for identifying low risk patients who may be suitable for outpatient therapy.\(^{25,26}\) Despite RV dysfunction being associated with increased mortality risk, prediction rules such as PESI do not consider assessment of RV dysfunction as a predictive factor. Clinicians should consider RV dysfunction along with other markers of severity when risk-stratifying patients with acute PE and our results validate the view that RV dilation on CTPA can be used to identify patients at increased risk of adverse outcomes. Recent guidelines have also recognised the importance of identification of RV dysfunction in PE and have thus advocated use of alternative scoring systems which consider its assessment as a predictive parameter.\(^1\)

In this study, we defined RV dysfunction based on cardiac measurement (right ventricle/left ventricle ratio \( \geq 1 \)). This parameter has been consistently shown to be a reliable marker of acute RV dysfunction in PE.\(^{29}\) Other studies have considered alternative features on CTPA such as clot load scores,\(^{20}\) reflux of contrast into the inferior vena cava,\(^{19,20,31}\) pulmonary artery diameter,\(^{16,24}\) and bowing of the interventricular septum\(^{16,19,24}\) but these parameters are either less accurate or too complex for use in clinical practice.\(^{29}\) RV/LV ratio \( \geq 1 \) is a simple, reliable feature that can be identified by clinicians and general radiologists, without the need for complicated radiological measurements and is thus ideally suited to use in clinical practice. RV/LV ratio \( \geq 1 \) was specifically chosen in this study as it is the cutoff that has been most commonly used to define RV dilation in the literature.\(^{29}\) However, some studies have used slightly different cutoffs such as RV/LV ratio \( \geq 0.9.\)\(^{18}\)

Current guidelines advocate use of echocardiography to identify signs of RV dysfunction\(^1\) as it offers the advantage of allowing a real-time functional assessment of the right ventricle, in contrast to CTPA which only gives information on right ventricular morphology. However, echocardiography has limited availability at many institutions and occasionally the right ventricle may be difficult to image with this modality, particularly when assessed by a less experienced operator.\(^{13}\) In addition, despite having good predictive accuracy for identification of RV dysfunction, echocardiography has poor predictive value for diagnosis of PE.\(^{29}\) Therefore, other modalities are required to confirm presence of PE, if echocardiography is used to identify RV dysfunction. CTPA is a commonly used diagnostic test for suspected PE and is usually more readily available than echocardiography. Our results suggest that, in addition to diagnostic purposes, CTPA could be used to identify patients with PE at increased risk of mortality, by allowing an immediate assessment of the presence or absence of RV dilation, without the need for additional tests.

The increased mortality observed in patients with RV dysfunction, is thought to be caused by pressure overload of the right ventricle secondary to acute pulmonary arterial hypertension caused by PE. This leads to right ventricular dysfunction which then ultimately progresses to RV failure and circulatory collapse.\(^{32}\) This hypothesis is further supported by our finding that patients with RV dilation on CTPA had significantly increased evidence of markers of physiological derangement such as tachycardia, hypotension and hypoxia. Survival analysis of patients with RV dilation in our cohort indicated that a high proportion of deaths in this group occurred early after admission (within 48 h). This reinforces that, in patients with PE, RV dilation on CTPA is a feature that should alert clinicians to a potential need for early aggressive management strategies.

Our results suggest that RV dilation on CTPA may represent an additional marker of severe PE and such patients should be considered as being at increased risk of adverse outcome. This is further confirmed by our finding that patients with RV dilation were more likely to be classified in higher risk groups on the basis of admission severity scoring (PESI criteria). However, RV dilation on CTPA was a marker of poor outcome, independent of severity.

Assessment of the correlation of presence of RV dilation on CTPA with thrombotic load (proximal extension of thrombus) showed that a greater proportion of patients with thrombus in main pulmonary arteries had evidence of RV dilation compared to those with segmental and subsegmental thrombus. The retrospective nature of this study meant that correlation of RV dilation with formal scoring systems of thrombotic burden, such as the Miller score\(^{33}\) could not be evaluated.

This study is limited by its retrospective design. Prospective studies are preferable because of a reduced risk of ascertainment bias. However, as studies of PE require a positive CTPA and we included consecutive patients undergoing CTPA with confirmed PE, no cases of radiologically confirmed PE were missed during the study period. The retrospective nature of our analysis also prevented direct comparison of CTPA determined RV dilation with echocardiographic assessment, as no patients included in the current study had both CTPA and echocardiography performed on admission.

In conclusion, this study shows that RV dilation on CTPA is an independent predictor of increased mortality risk in patients with acute PE. Potentially, CTPA assessment of RV dilation could be used to identify higher-risk patients and guide subsequent management but further studies are required.

Conflict of interest statement

The authors have no conflicts of interest.
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Supplementary material

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.rmed.2010.02.004.

References