Original papers

Are clinical parameters and biomarkers predictive of severity of acute pulmonary emboli on CTPA?

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Summary

Background: Previous studies have shown that findings of computed tomography pulmonary angiography (CTPA) relate to outcome in pulmonary embolus (PE). These include clot burden as quantified using an obstruction index and markers of pressure overload such as right ventricle to left ventricle size ratio (RV/LV ratio). Little data exists correlating these findings with clinical presentation and biomarkers.

Aim: To explore the link between clinical presentation and biomarkers with CTPA findings.

Methods: Retrospective case note analysis of consecutive cases presenting to a large teaching hospital. An independent radiologist reviewed CTPAs and clot burden quantified using an obstruction index.

Results: One hundred and seventy cases were identified and notes retrieved in 137 cases. (i) Clinical presentation: correlation was seen between clot burden and systolic blood pressure (BP) ($r = -0.299, P = 0.0006$) and heart rate ($r = 0.240, P = 0.0056$). Median obstruction index was significantly higher in those with a presenting BP <90 mmHg [41.25% (95% CI 30–50) vs. 15% (95% CI 12.5–25), ($P = 0.0004$)]. Clot burden was significantly higher in patients with temperature of >37.5°C [30% (95% CI 25.0–42.5) vs. 15% (95% CI 12.5–28.3), ($P = 0.02$)] and (ii) Biomarkers: significant correlation between clot burden and D-dimer was seen ($r = 0.36, P = 0.0001$). Location of thrombus was associated with significant differences in D-dimer level. A subgroup of patients had cardiac biomarkers measured ($n = 24$). There was a statistically significant correlation between troponin I and clot burden ($r = 0.412, P = 0.048$) and RV/LV ratio ($r = 0.699, P = 0.0013$).

Discussion: These findings suggest that clinical parameters and biomarkers have a role in predicting the radiological severity of PE. These data support the need for further studies of risk stratification in patients presenting with acute PE.

Introduction

Acute pulmonary embolism (PE) is associated with a variable prognosis. Focus has recently shifted towards risk stratification of patients with PE as prognosis depends on the timely delivery of optimal therapeutic strategies.1 There is little doubt that haemodynamic assessment at presentation is a key element to risk stratification, with significantly higher mortality rates reported in those presenting
with circulatory collapse requiring vasopressor therapy, as compared to the haemodynamically stable patients.\textsuperscript{1,2}

Several recent papers have shown that findings on a multi-detector computed tomography (MDCT) can be predictive of outcome especially clot burden [as measured by pulmonary artery obstruction index (PAOI)] and features of right ventricular (RV) dysfunction.\textsuperscript{3–5} The association between haemodynamic parameters at presentation, such as blood pressure (BP) and heart rate (HR), and features of severity on MDCT has, however, not been extensively studied. Although Collomb \textit{et al}.\textsuperscript{6} have demonstrated significantly higher pulmonary artery (PA) clot load in patients with severe PE i.e. requiring thrombolytic or surgical treatment, compared to patients with non-severe PE, little information was provided on the systolic BP of the patients at presentation. Another study demonstrated a correlation between clinical findings such as HR and the extent of perfusion defect on ventilation/perfusion scans (V/Q scans).\textsuperscript{7}

Assessment of patients presenting with PE often includes the measurement of specific biomarkers such as D-dimers and cardiac enzymes. Traditionally the main role of D-dimers has been in the exclusion of PE in patients in whom the diagnosis is suspected.\textsuperscript{8} Increasingly, there is interest in the role of D-dimers as both a marker for prognostic purposes\textsuperscript{9} and also in the evaluation of the extent of embolic disease.\textsuperscript{10} A correlation has been described between D-dimers at presentation and the scintigraphic extent of PE on V/Q scans in patients with acute PE,\textsuperscript{7} while Ghanima and co-workers\textsuperscript{11} reported a correlation between D-dimers and embolic burden and D-dimers and measures of RV dysfunction on computed tomography pulmonary angiography (CTPA). The study population, however, included only outpatients referred to an emergency department with suspected PE.

The primary aim of our study was to investigate whether significant association exists between a CT-based scoring system of PA clot load and features of RV dysfunction with the haemodynamic parameters available at the time of a patient’s presentation with an acute PE. We also sought out to assess any association between D-dimer levels at presentation and CTPA features including PA clot load and RV dysfunction in an unselected group of patients, i.e. including not only new patient referrals to the emergency department but also medical and surgical inpatients, irrespective of their underlying comorbidities.

Methods

Study design and patient selection

We performed a retrospective observational study involving a consecutive cohort of patients diagnosed with acute PE at our institution from February 2004 to August 2007. Patients were identified from reviewing archived reports of all CTPAs performed during the 31-month period and included patients presenting to the emergency department as well as those who were either medical or surgical inpatients at the time of diagnosis. Those CTPAs that were reported to show pulmonary emboli were included in the study. An experienced radiologist independently reviewed the positive CTPAs to confirm the diagnosis of PE, apply a CT-based scoring system of clot burden and assess for evidence of right ventricular overload by assessing right ventricle to left ventricle size ratio (RV/LV ratio) and determining presence of interventricular septal (IVS) displacement.

Clinical data acquisition

Clinical data was extracted from each patient’s medical records. A proforma was designed allowing uniform data acquisition of demographic information including risk factors for venous thromboembolism. Charts documenting clinical observations were reviewed for each patient. The following measurements within 48 h of the confirmation of their diagnosis were recorded: maximum HR, maximum temperature and lowest systolic BP. The patients were placed into the following groups: hypotensive (BP < 90 mmHg) and normotensive group (BP > 90 mmHg), tachycardic (HR > 100/min) and non-tachycardic group (HR < 100/min) and febrile (temperature > 37.5°C) and non-febrile groups (temperature < 37.5°C). Patients who had an obvious alternative cause for pyrexia were excluded from the classification into febrile and non-febrile groups. Data on mortality during hospitalization was also recorded from the analysis of the case notes, with deaths being classified as likely PE related and non-PE related.

Biomarkers and laboratory analysis

We chose to collect data on the following biomarkers: D-dimers and cardiac troponin. In our laboratory, D-dimers are assayed via the ELISA-assay. A value of <300 ng/ml has a 98.9% negative predictive value for pulmonary emboli. At our institution troponin assays have a detection limit of >0.01 ng/ml. All levels recorded were taken within
24 h of the confirmation of the diagnosis of PE. Levels higher than 0.01 ng/ml were considered indicative of myocardial injury.

CTPA interpretation

CTPAs were performed using a four detector-row CT scanner during the study period. All CTPAs, that were reported to be positive for pulmonary emboli, were reviewed by an independent radiologist on picture archiving and communication system (PACS). Images with poor contrast enhancement were excluded. CTPAs suggestive of chronic thromboembolism were also excluded. The radiologist was aware that the CTPA had been previously reported to be positive for PE but was blinded to all relevant clinical and biochemical data. PE was diagnosed if a discrete low-attenuation filling defect was visualized in the pulmonary arteries. The most proximal location of the filling defect, i.e. main, lobar, segmental or subsegmental arteries was also recorded. Clot burden was estimated based on the Qanadli index. We used the Qanadli index to score the PA clot load, not only because of its relative simplicity to be applied in clinical practice, but also due to its strong correlation with the Miller index, as derived on pulmonary angiography.

To define the CT obstruction index, the arterial tree of each lung was regarded as having 10 segmental arteries (three to upper lobe, two to middle and lingula and five to lower lobes). The presence of an embolus in a segmental artery scored one point. Emboli in the most proximal arterial level were scored a value equal to the number of segmental arteries arising distally. The value was multiplied by factor 1 if the thrombus was partially obstructive and factor 2 if total occlusion was noted. Isolated subsegmental arterial thrombus was considered a partially occluded segmental artery and assigned a value of one. The maximal score was 40. To obtain the PAOI, the total clot score was divided by the maximal score and the result multiplied by 100.

CT features of RV dysfunction were also recorded, including RV and LV short axes. These were measured in diastole perpendicular to the long axis of the heart. The largest distance between the free wall of the ventricle and inner wall of the IVS were used. RV/LV ratio was then calculated using these measurements. Presence of convex leftward bowing of the IVS (IVS bulge) was also noted.

Statistical analyses

Statistical analyses were performed using a commercially available software programme (Medcalc® version 9.4.2.0). Following the Kolmogorov–Smirnov test, data with normal distribution is expressed as mean ± standard deviations and data with skewed distribution as median with 95% confidence intervals. Spearman’s rank correlation coefficients were used to assess the correlation between continuous variables. The Mann–Whitney U-test was applied to evaluate differences in non-parametric continuous variables between two patient groups. To compare more than two patient groups, the Kruskal–Wallis test was used. For all tests, a P-value of 0.05 was considered to indicate a statistically significant difference.

Results

Patient demographics

From a total of 1062 consecutive CTPAs, 170 were initially reported as consistent with PE. Two CTPAs were found to have poor contrast enhancement on subsequent review by the radiologist and were excluded from the analysis. Data pertaining to clinical presentation were incomplete in 31 patients and they were excluded from the study. Analysis of the mode of presentation of these patients showed that they were representative of the entire cohort. The final study population consisted of 137 patients (57 men and 80 women). The age range was 20–90 years with a mean of 65 years ± 15.

The presence of risk factors for PE was analysed and shown in Table 1. Thirty-eight (27.7%) patients had no identifiable risk factor. Ninety-nine (72.3%) patients had one or more risk factors; 78 (56.9%) had one easily identifiable risk factor, whilst 21 (15.3%) patients had two or more. Forty-one (29.9%) patients were shown to have active malignancy.

Table 1 Risk factors for venous thromboembolism within study population

<table>
<thead>
<tr>
<th>Risk factors</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>None identified</td>
<td>38 (28%)</td>
</tr>
<tr>
<td>Immobility</td>
<td>39 (28%)</td>
</tr>
<tr>
<td>Surgery</td>
<td>26 (19%)</td>
</tr>
<tr>
<td>Malignancy</td>
<td>41 (30%)</td>
</tr>
<tr>
<td>Previous VTE</td>
<td>16 (12%)</td>
</tr>
<tr>
<td>Trauma lower extremities</td>
<td>9 (6%)</td>
</tr>
<tr>
<td>Oestrogen use</td>
<td>2 (1%)</td>
</tr>
</tbody>
</table>
Clinical presentation

One hundred and nineteen (86.8%) patients presented acutely with symptoms consistent with pulmonary embolus and were diagnosed within 48 h of hospital admission. Nine (6.5%) patients were medical inpatients, admitted with another medical diagnosis, when they developed new symptoms of PE. Nine (6.5%) were surgical inpatients within a 14-day post-operative period when the diagnosis was made.

The symptoms described at presentation by the study population are summarized in Table 2. Dyspnoea was the most common presenting symptom present in 99 (71.2%) cases. Among which 29.9% had a systolic BP of < 90 mmHg within 48 h of their diagnosis of PE and 42% of the patients had a temperature of ≥ 37.5°C.

Laboratory parameters

D-dimers were measured in 111 patients. Of these patients, 109 were recorded as positive (> 300 ng/ml). The median value within the study population was 1470 ng/ml (95% CI 1290–2009). CRP was recorded in 126 patients with a median value of 77.5 U (95% CI 58.6–105.1). Troponin I was only measured in 24 patients. Of those measured, 10 were > 0.01 ng/ml (range: 0.1–4.7).

Quantitative CT-based measurements

The distribution of clot burden is demonstrated in Figure 1. The median obstruction index was 25.0 (CI 16.0–33.0). From a total of 137 patients, 47 (34.3%) had an obstruction index of ≥ 40%. Median RV/LV ratio was 0.98 (95% CI 0.95–1.02).

Association of CTPA findings

Clinical parameters

Median obstruction index in the hypotensive group (BP ≤ 90 mmHg) was 41.25% (95% CI 30.0–50.0). This was significantly higher than the normotensive group (BP > 90 mmHg): median obstruction index 15.0% (95% CI 12.5–25.0; P = 0.0004).

Biomarkers

A weak but statistically significant correlation was noted between the PAOI and D-dimer levels (r = 0.36, P = 0.0001). Correlation was noted between troponin I levels and PAOI (r = 0.412, P = 0.048). There was a trend towards higher PAOI in patients with elevated troponin levels [median 40 (95% CI 11.3–50.0) vs. 10 (95% CI 5.0–41.0), P = 0.07].

There was no significant correlation between RV/LV ratio and D-dimer levels (r = 0.08, P = 0.43). A significant correlation between RV/LV ratio and troponin I levels was noted (r = 0.699, P = 0.0013). RV/LV ratio was significantly higher in patients with elevated troponin I levels (median 1.19; 95% CI 0.92–1.60 vs. median 0.90; 95% CI 0.83–1.01; P = 0.0084).

Similar results were noted in those who were tachycardic at presentation: median obstruction index in the tachycardic group was 36.2% (95% CI 25.0–42.5) when compared to 16.25% (95% CI 12.5–25.9) in the non-tachycardic group (P = 0.012).

Median obstruction index in the febrile group of patients (temperature ≥ 37.5°C) was 30 (95% CI 25.0–42.5) and 15 (95% CI 12.5–28.3) in those with a normal temperature (P = 0.012).

Weak but statistically significant correlation was noted between obstruction index and systolic BP (r = −0.299, P = 0.0006) and between obstruction index and HR (r = 0.240, P = 0.0056).

Median RV/LV ratio was significantly higher in patients with hypotension (median 1.09, 95% CI 0.94–1.30) compared to the normotensive group (median 0.96, 95% CI 0.93–1.00); P = 0.0015. No significant difference was noted in the RV/LV ratio in the tachycardic and non-tachycardic groups of patients median 0.96 (95% CI 0.93–1.09) vs. median 0.98 (95% CI 0.94–1.02); P = 0.35.

Table 2. Clinical presentations of study population

<table>
<thead>
<tr>
<th>Clinical symptoms</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dyspnoea</td>
<td>99 (71.2)</td>
</tr>
<tr>
<td>Chest pain</td>
<td>79 (56.8)</td>
</tr>
<tr>
<td>Haemoptysis</td>
<td>14 (10.1)</td>
</tr>
<tr>
<td>Presyncope</td>
<td>12 (8.6)</td>
</tr>
<tr>
<td>Syncope</td>
<td>12 (8.6)</td>
</tr>
</tbody>
</table>

Figure 1. Frequency of obstruction index on CTPA in study population.
Thirty-eight (27.7%) patients had thrombus within the main pulmonary arteries, 58 (42.3%) had clots most proximally sited within the lobar pulmonary arteries and 41 (30%) had clots localized to segmental pulmonary arteries. Significant differences were seen in median D-dimer levels in patients with a more central location of thrombus (Figure 2).

**Qualitative CT findings**

Eighteen patients were noted to have IVS bulge. This group had a lower median BP of 78 mmHg (95% CI 64.32–95.4 mmHg) than those who did not display this radiological feature: median BP 110 mmHg (95% CI 105–115 mmHg); \( P < 0.0001 \). Median HR in patients with IVS bulge was 130 bpm (95%CI 111.6–146.8 bpm) vs. 95 bpm (95% CI 90–105 bpm) in those without IVS bulge \( (P < 0.0001) \). Troponin I levels were significantly higher in patients with IVS bulge when compared to those without \( [2.97 \text{ U (range: } <0.01–4.72) \text{ vs. } 0.01 \text{ (range: } <0.01–0.01); P=0.019] \). No significant difference was noted in the D-dimer levels in the two groups.

**Mortality outcome**

Twenty-nine (21%) patients died during the hospitalization. Ten (7.3%) were PE-related deaths and 19 (13.9%) were non-PE related including cancer-related deaths (n=13). Patients who died during hospitalization were more hypotensive than those who survived \([\text{median BP } 81.5 \text{ mmHg (95% CI } 64.7–107.1) \text{ vs. } 110 \text{ mmHg (95% CI } 103.8–112.1), \ P=0.0051]\). Median HR was also noted to be lower in survivors compared to those who died \([\text{median HR } 95/\text{min (95% CI } 90–105) \text{ vs. } 120/\text{min (95% CI } 101–131), \ P=0.0485]\). Interestingly, patients who died because of the PE had significantly higher D-dimer levels than those who did not \([\text{median D-dimer } 3490.0 \text{ ng/ml (95% CI } 1541.1–8953.8) \text{ vs. } 1405.0 \text{ ng/ml (95% CI } 1121.4–1686.3), \ P=0.012]\). In a univariate analysis, no significant association was found between mortality outcome during hospitalization and CT indexes of severity \( (P=0.12 \text{ for PAOI and } P=0.17 \text{ for RV/LV ratio}) \).

**Discussion**

Over the last decade, there has been a considerable increase in the use of CTPAs for the investigation of suspected acute PE. However, in clinical practice, the reporting of CTPAs is frequently focused on the presence or absence of emboli and an approximate estimation of their location. Recent work has been aimed at assessing the radiological severity of PE by using CT-based scoring systems, which allow quantification of PA clot load and RV dysfunction on CT.\(^1\)\(^2\)\(^3\)\(^4\)\(^5\)

A link between the quantification of PA clot load on a CTPA and the outcome of patients with acute PE has been shown. Wu et al.\(^4\) reported a mortality rate of 83% when a PA clot load score exceeded 60% compared to just 2% when the PA clot load was <60%, whilst van der Meer et al.\(^5\) found that patients with a PA clot load of >40% had an 11.2-fold increased risk of death at 3 months.

Other parameters that can be easily measured on MDCT include the presence or absence of RV dysfunction. Most data on RV dysfunction in acute PE to date have been based on echocardiographic findings. However, Contractor et al.\(^15\) and Lim et al.\(^16\) demonstrated that the presence of a RV/LV diameter ratio of more than one and leftward septal bowing (IVS bulge) on MDCT compared to echocardiographic findings of RV dysfunction. The exact cut-off for RV/LA diameter ratio for predicting severity of PE is unclear. A number of investigators have demonstrated that an RV/LV diameter ratio >1.5 indicates severe PE.\(^5\)\(^17\)\(^18\) Quiroz et al.\(^19\) reported a higher mortality rate in patients with an RV/LV diameter ratio >0.9 compared to an RV/LV diameter ratio ≤0.9 calculated on a four-chamber view in 431 patients with PE. Leftward bowing of the IVS on CT has also been related to severe PA obstruction.\(^20\) Collomb et al.\(^18\) and Araoz et al.\(^3\) found this sign to be an indicator of the severity of PE or of subsequent admission to the intensive care unit.

Although the association of CTPA parameters of severity with outcome has been studied, there is little data examining the association of these findings with haemodynamic parameters at presentation.
The importance of haemodynamic assessment in patients presenting with PE was established by the two studies: The International Cooperative Pulmonary Embolism Registry (ICOPER) and Management Strategy and Prognosis of Pulmonary Embolism Registry (MAPPET). These studies showed that circulatory failure and systemic hypotension predicted a poor outcome in patients with PE. In the MAPPET study, overall in-hospital mortality rate ranged from 8.1% in the group of stable patients to 25% in those presenting with cardiogenic shock and to 65% in patients necessitating cardiopulmonary resuscitation. Two studies have suggested a link between clinical haemodynamic parameters and radiological extent of PE. Collomb et al. found that in patients with severe PE (i.e. requiring thrombolytic or surgical treatment), there was a significantly higher PA clot load score (54%±11) when compared to patients with non-severe PE (24%±18), whilst Galle et al. showed that HR at presentation correlated with the extent of perfusion defect on V/Q scans.

In our study, the median PA clot score was significantly higher in patients with systemic hypotension and tachycardia compared to patients without the latter. A correlation was noted between systolic BP and clot burden and HR and clot burden. Interestingly, patients with a temperature of >37.5°C had a higher burden of thrombus.

We also demonstrated that the median RV/LV diameter on axial CT images was significantly higher in the hypotensive group than in normotensive group. Furthermore, 18 patients were noted to have leftward bowing of the IVS. This group had a lower median BP of 78mmHg than those who did not display this radiological feature: median BP 110mmHg. Patients with IVS bulge were also significantly more tachycardic than those without IVS bulge.

We have, therefore, demonstrated that clinical haemodynamic parameters i.e. systolic BP and tachycardia are strongly related to the anatomical extent of the emboli on CTPA and CT measurements of RV dysfunction. To our knowledge, these findings, although not unexpected, have not been previously systematically reported.

Current guidelines published by expert bodies suggest that the main role of D-dimers lies in the exclusion of PE in patients presenting with appropriate symptoms. However, Aujesky et al. suggested a role of D-dimers as a prognostic marker. Moreover, the level of D-dimers at presentation has been shown to correlate with the scintigraphic extent of PE on V/Q scans, as well as embolic burden and RV/LV ratio measured on axial images on CTPA. The study population, however, in these studies only included outpatients referred to the emergency department. Our study concurs with these observations as we demonstrated a higher embolic burden in patients with higher D-dimer levels. Our study population was unselected, including medical and surgical inpatients as well as those presenting de novo to an emergency department.

In the study by Ghanima et al., higher D-dimer levels were also associated with a more central location of the clots on MDCT. Similar findings were reported by Klok et al. although D-dimers in this study were only performed in patients with a low clinical probability of PE. We have demonstrated in our study that in unselected patients, many with comorbidities, higher levels of D-dimers are associated with a more proximal location of the clot. These findings are interesting and are likely to reflect higher degradation products associated with larger clots. The large confidence interval of the levels, however, would limit the applicability of this concept in practice.

The role of troponin levels in risk stratification has been well studied. A meta-analysis by Becattini et al. included 1985 patients and showed that elevated levels of troponin were associated with a 5-fold increase in mortality in patients with acute PE. We have demonstrated a correlation between clot burden and troponin I levels. Numerous studies have shown that RV dysfunction on echocardiography is more common in patients with elevated troponin levels. In our study, 90% of the patients with elevated troponin levels had a RV/LV ratio of >0.9. Higher troponin levels were also noted in patients with leftward bowing of the IVS. However, only a small number of patients had troponin levels measured; as a result, there has likely been a selection bias. More studies examining the association of troponin levels with features of RV dysfunction on CTPAs may be helpful.

Although our study was not designed to examine the role of CTPA in predicting outcome, we did not find any significant association between in-hospital mortality and CT predictors of PE severity, using the obstruction index or the RV/LV ratio.

There are several limitations to our study. One of them is the retrospective design. Troponin levels were not measured in all patients, leading to significant selection bias. Although studies have shown good inter-reader correlation, the fact that only one radiologist reviewed the CTPAs means we were open to a degree of observer bias. The RV/LV ratios were only measured on axial images. There is evidence to suggest that measurements done on four chamber reconstructed views correlate better with echocardiographic features of RV dysfunction.
In summary, we have demonstrated a link between clinical presentation and biomarkers with both extent of thrombus and signs of RV dysfunction on CTPA. Further prospective studies combining clinical, radiological and biological data, perhaps with the use of scoring systems that incorporate haemodynamic parameters, D-dimers and troponin as well radiological parameters of severity, may allow for the development and validation of a measure of risk stratification for patients with acute PE. This will aid the physician in accurately assessing prognosis and help guide optimal management.

Conflict of interest: None declared.

References


