Real Time Risk Stratification of Patients with Acute Pulmonary Embolism
by Grading the Reflux of Contrast into the Inferior Vena Cava on
Computerized Tomographic Pulmonary Angiography

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Received 22 April 2008, accepted 1 July 2008

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Running head: PE risk by contrast reflux on CT Angiography

ABSTRACT

Objective: To investigate whether fast grading of reflux of contrast to the inferior vena cava (IVC) on computerized tomographic pulmonary angiography (CTPA) is a potential biomarker for real-time risk stratification.

Methods: We retrospectively identified 343 patients investigated for possible pulmonary embolism (PE) by CTPA at our medical center between 9/2004-3/2006. A total of 145 consecutive patients with PE (age 67±19 years) and 168 consecutive ones with negative
CTPAs (age 64±20 years) fulfilled entry criteria. CTPAs were evaluated for retrograde reflux of contrast to the IVC by fast visual grading from 1 to 6 using the original axial images. Pulmonary obstruction index, the diameters of right and left ventricles and pulmonary artery, and patient survival data were recorded as well.

**Results:** Twenty-nine (20.0%) patients with positive CTs and in 23 (13.7%) patients with negative CTs had substantial degrees (≥4) of reflux of contrast to the IVC (p=0.14). The Kaplan-Meier 30-day survival curves demonstrated significant reduction in survival in individuals with PE and grade ≥4 reflux of contrast to the IVC compared to lower grades (p=0.008), but not in patients with grade ≥4 and no PE on CTPA (p=0.26). The other cardiovascular parameters showed no significant correlation with survival in patients with and without PE.

**Conclusion:** Substantial grades of reflux of contrast to the IVC during CTPA could predict early mortality in patients with acute PE. Rapid grading of reflux of contrast from the original axial CTPA images can be used for real-time risk stratification in patients with acute PE.

**Key words:** CT, pulmonary embolism, CAT scan pulmonary

**ABBREVIATION LIST**

IVC=inferior vena cava ;
CTPA= computerized tomographic pulmonary angiography;
PE=pulmonary embolism;
RV=right ventricle;
LV=left ventricle;
PA=pulmonary artery
Real-time risk stratification of patients with acute pulmonary embolism (PE) is of clinical relevance [1]. There are multiple lines of evidence of the merits of evaluating acute right-sided heart failure by computerized tomographic pulmonary angiography (CTPA). Right-sided failure can be evaluated by measuring the dimensions of the right (RV) and left (LV) ventricles as well as the main pulmonary artery (PA) [2-12], and by calculating the magnitude of pulmonary arterial obstruction [7-17]. Assessment of these parameters is time consuming and may require multiplanar reformations, while providing controversial results [2-17]. Reflux of the injected contrast medium into the inferior vena cava (IVC) may serve as a dynamic sign of acute right heart failure in patients with acute PE. It can be easily identified and semi-quantitatively graded from the original axial slices, requiring very short time and no special reformations.

The aim of the present study was to investigate whether rapid grading of reflux of contrast into the IVC on CTPA can be used for real-time risk stratification of patients with acute PE. There is little information in the literature regarding the clinical significance of this reflux into the IVC in the context of acute PE. Our results would, therefore, have significant value by showing the utility of a real-time biomarker in order to use CTPA to identify patients who might be at risk for early mortality following the diagnosis of acute PE.

**MATERIALS AND METHODS**

**Study population**

The institutional review board approved this retrospective study with a waiver of informed consent. We studied the records of 343 patients who were investigated for possible PE using CTPA at our center. Recruitment was based on the clinical decision of the referring
physicians and we analyzed in a consecutive way the results all CTPA’s following their performance. Collection of similar numbers of patients with positive and negative CTPAs required different time frames since CTPA studies are more frequently negative. Accordingly, we prospectively evaluated 162 consecutive patients with positive CTPAs who were scanned between September 1, 2004 and March 31 2006, and 181 consecutive patients with negative CTPAs who were scanned between September 1, 2004 and February 22, 2005. For patients with more than one scan, only the results of their first one were entered into the analysis. Thirty patients with incomplete CTPA or survival data were excluded, leaving a final study group of 145 consecutive patients with positive PE findings on CTPA which were compared to 168 consecutive patients with a negative PE on CTPA.

**CT Acquisition**

The patients were scanned using a multidetector CT scanner (Mx8000 IDT or Brilliance; Philips Medical Systems, Cleveland, OH, U.S.A.) that acquires 10, 16, 40 or 64 parallel rows of data. Detector collimation was 10X1.5 mm, 16X0.75 mm, or 40 or 64X0.625 mm, respectively. The reconstructed slice thickness was 1.0-2.0 mm with an increment of 0.5-1 mm. The PE protocol included contrast material injections of 100-120 mL of iodinated contrast material at a concentration of 300 mg of iodine per milliliter (Ultravist, Schering, Berlin, Germany) at rates of 3-4 mL/sec. The CT technicians were instructed to determine the patient's injected contrast volume and rate on an individual base, while considering the patient's weight and body habitus. All scans were obtained in a caudo-cranial direction at end of inspiration in a single breath-hold, beginning at the bottom of the posterior costophrenic sulci level and ending at the thoracic inlet.
CT Interpretation

The CT scans were reviewed in consensus by two board-certified radiologists (A.B., G.A.), blinded to the clinical history, the results of other imaging techniques, and to patient outcome. Using a dedicated workstation (MxView; Philips Medical Systems), the reviewers evaluated the scans for the presence or absence of PE, presence or absence of ventricular septal straightening or bowing, measurements of the RV and LV diameters on a four-chamber reformat, measurements of the main PA diameter, and PE clot load score. Grading of reflux of contrast into the IVC was performed separately in order to assess interobserver variation.

Positive findings of a PE were defined as the presence of a discrete low-attenuation filling defect in the pulmonary arterial tree. Ventricular septal bowing was subjectively judged as being present or absent. Four chamber views were reconstructed by using 2-dimensional multiplanar reformats (MPRs) of the original axial source data. RV and LV dimensions were measured by identifying the maximal distance between the ventricular endocardium and the interventricular septum perpendicular to the long axis, and the RV/LV diameter ratio was calculated according to these values. The transverse diameter of the central PA was measured on the axial image 1.5 cm proximal to the main PA bifurcation. The presence and location of arterial clots and the degree of arterial obstruction were scored by using the systems proposed by Qanadli et al. [14]. Since it was proposed for use on twin-slice scanners with a slice thickness of 5 mm and a detector collimation of 2.5 mm, while the present study was performed on 10-64 detector rows with a slice thickness of 1-2 mm and a detector collimation of 0.625-1.5 mm, with significantly better spatial resolution and less partial volume effect, the only minor modification we made was in the determination of "complete" vs. "partial" occlusion: we defined a "complete" occlusion when more than 90% of the vessel’s
cross-sectional area, estimated visually using axial and MPRs, was occupied by a clot, and a "partial" occlusion when it occupied less than 90%.

The severity of reflux of contrast medium into the IVC or hepatic veins was graded from the axial images according to 6 categories based on a previously published scale [18], (Figure 1): 1 = no reflux into IVC, 2 = trace of reflux into IVC only, 3 = reflux into IVC but not hepatic veins, 4 = reflux into IVC and opacifying proximal hepatic veins, 5 = reflux into IVC and opacifying mid-part of hepatic veins, and 6 = reflux into IVC and opacifying distal hepatic veins.

**Clinical Information**

In addition to sex, age and 30-day mortality, the charts were reviewed for 3 comorbid conditions: congestive heart failure, pulmonary disease and chronic PE.

**Statistical analysis**

Data were summarized as mean ± standard deviation (SD) for the continuous variables and as number of individuals (percentage) for categorical variables. The Kappa statistics was calculated in order to evaluate the measure of agreement between the two independent observers (interobserver variation). In order to evaluate the different parameters obtained from the CTPA as distributed among the negative and positive CTPAs and their prognostic values, we divided all continuous variables into tertiles. Comparison of continuous variables between the group with PE on CTPA and the group negative for PE was done using the independent Student’s t-test, while the comparison between frequencies of categorical variables was done using the Chi-square test. The comparison of mortality according to groups was by the log-rank statistics with the Kaplan-Meier estimate. All the above analyses
were considered significant at p value < 0.05 (two tailed). The SPSS statistical package was used for all the statistical evaluations (SSPS Inc., Chicago, IL, USA).

RESULTS

We analyzed the data on 145 PE patients and 168 individuals in whom PE was not found on CTPA. The mean age of these patients was 67±19 years and 64±20 years, respectively (p=0.147). The overall 30-day mortality was 27 (18.6%) and 18 (10.7%), respectively (p=0.047). Table 1 presents the patients’ demographics, mean values of their CTPA findings and 30-day mortality rates. Table 2 presents the 30-day mortality according to each CTPA variable among the patients with a positive CTPA.

**RV Diameter**

There was no significant difference (p = 0.50) between the positive and negative CTPA groups according to tertiles of the RV diameter nor in their mortality rates (p = 0.12 and 0.92, respectively).

**LV Diameter**

There was a significant difference (p=0.044) between the positive and negative CTPA groups according to tertiles of the LV diameters, with a significantly higher percentage of individuals with positive CTPAs in the lower tertile (41% vs. 27%) but no differences in their mortality rates (p=0.61 and 0.18, respectively).
**RV to LV Ratio**

As expected when there is no difference in the RV diameter and smaller LV diameters in the positive CTPA group, the RV to LV ratio was significantly higher ($p=0.009$) in the positive CTPA group. There was no difference in the mortality rates between the 2 groups ($p=0.84$ and 0.96 in the positive and negative CTPAs, respectively).

**PA Diameter**

We found no significant difference ($p=0.07$) between the positive and negative CTPA groups according to tertiles of the PA diameter, nor in their mortality rates ($p=0.95$). There was, however, a significant difference ($p=0.017$) in the negative CTPA patients: there was a higher rate of mortality in the higher PA diameter tertile.

**Ventricular Septal Bowing**

We found a slightly higher percentage of individuals with septal bowing in the positive CTPA group (23.0%) compared to the negative CTPA group (15.7%) ($p=0.15$). We also found no differences in the mortality rates between the 2 groups ($p=0.72$ and 0.71, respectively).
**Grading of Reflux into the IVC**

The degree of contrast reflux was grouped into no reflux (grade 1), minimal (grade 2-3), and substantial (grade 4-6). We found substantial agreement between the independent observers for the division into those three groups (kappa=0.58), that reached even higher agreement (kappa=0.78) when we evaluated division into substantial (grade 4-6) and non-substantial reflux (grades 1-3). There was no significant difference (p=0.064) between the positive and negative CTPA groups according to the degree of reflux, with a trend towards a slightly higher percentage of individuals with reflux grades 2-3 in the positive CTPA group (50% compared to 45%) and a higher percentage of individuals with grade 4-6 reflux (20% compared to 14%). There was no difference in mortality according to reflux grading in the patients with negative CTPAs (p=0.49), in contrast to a significant mortality difference (p=0.029) associated with the various reflux grades in the patients with positive CTPAs. This difference is attributed mainly to the group of individuals with reflux grades ≥4 compared to lower grades. Since the two lower grades demonstrated similar mortality curves, we combined the no reflux (grade 1) with the minimal reflux (grade 2-3) groups and compared them to the group with substantial reflux grades (grade 4-6). The Kaplan-Meier curves are presented in Figure 2 and show a significantly (p=0.008) early mortality in the patients with positive CTPAs and substantial reflux (grades 4-6).

**PE Clot Load Score**

The PE clot load score can be evaluated only for positive CTPA patients. The median (interquartile range) was 8 (3-19), which is equivalent to an obstruction of 20% of the PA
tree. The log-rank statistics showed no significant difference (p=0.32) between the tertiles of clot load scores and mortality among the patients with PE.

Having found a relation between the degree of reflux to the IVC and mortality, we further analyzed a subgroup of patients without any history of congestive heart failure and/or pulmonary disease in order to diminish the probability of reflux to the IVC that is not necessarily attributed to the PE event. This excluded 55 individuals and left 123 and 135 patients with negative and positive CTPA, respectively. The subgroup analysis revealed similar results for all the examined parameters (data not shown) and, again, the only CT parameter with prognostic implications for early (i.e., 30 days) mortality was the degree of reflux to the IVC that reached a level of significance between the three groups (p=0.006), and p=0.001 between the substantial reflux (scores $\geq 4$) and the lower grades of reflux.

**DISCUSSION**

Pathophysiological studies suggest that the outcome from PE is related to both the size of the embolus and the underlying cardiopulmonary reserve [19]. We investigated the prognostic value of various CTPA parameters, including clot extent and cardiovascular measurements. The main finding of the present study is that substantial ($\geq 4$) grades of reflux of contrast material into the IVC on CTPA emerge as predictors of 30-day mortality in patients with acute PE. In addition, the other CT findings (PA, LV, RV diameter, RV/LV diameter ratio) as well as the embolic burden itself were found not to be associated with increased short-term mortality.

First pass reflux to the IVC represents an indirect sign of increased RV pressure with reduced forward flow due to decreased cardiac output or increased pulmonary artery pressures (acute or chronic), tricuspid insufficiency, or obstruction of RV filling due to various
conditions (e.g. constrictive pericarditis, restrictive cardiomyopathy) [20]. It may also be found in patients with conduction abnormalities [21]. Our current results showed that a substantial (grades 4-6) reflux is seen on the CTPAs of patients with and without PE in 20% and 13.7% of the imaging studies, respectively, with no significant difference.

Visualization on CT of reflux of contrast from the right cardiac chambers into the IVC was first described by Collins et al. [22] who reported intense retrograde opacification of the IVC and hepatic veins in all 6 patients who had severe tricuspid regurgitation (TR). Collomb et al. [7] were the first to assess whether reflux of contrast to the IVC on CT indicates the clinical severity of acute PE. They found no relationship between the presence of reflux and the severity of PE in their 81-patient cohort. Ghaye et al. [13] sought to determine whether the presence of reflux to the IVC on CTPA is a predictor of in hospital mortality among 82 patients who were admitted to intensive care facilities with PE-related conditions: the authors reported that this sign was more common in non-survivors. These studies [7, 13], however, examined reflux of contrast to the IVC and hepatic veins qualitatively — as present or absent — and did not differentiate between minimal reflux, which may be associated with a trivial TR and higher grades of reflux that may be clinically relevant. Groves et al. [18] investigated the phenomenon of reflux of contrast on CT by using a semi quantitative method. They correlated between echocardiography and right-heart catheterization in 86 patients with known pulmonary hypertension and found that the presence of reflux at any degree is almost invariably an indicator of TR (100% specificity). Most patients (85%) in that uniform study group, however, did have TR, which was a limitation of their work. In terms of the grading of reflux, they reported moderate agreement between CT and echocardiographic assessment of the severity of TR. Using the same semi-quantitative grading of reflux on CT, our study is apparently the first to investigate the prognostic value of the various degrees of reflux in the context of acute PE.
Among the other CT parameters assessed in the present work, only increased RV/LV ratio, and decreased LV diameter were significantly more common among patients with acute PE. However similar to the study by Araoz et al.[10,11], they were not found to predict mortality, though other authors did find that these parameters are associated with increased mortality [2,5,6,8,12]. Another CT finding previously suggested as a predictor of mortality is the pulmonary arterial obstruction score [8,9,17], which in our series, in accordance with some others [10-12,23] did not show a significant correlation with the mortality. This finding supports the suggested mechanism that in PE the pulmonary vascular resistance is increased not only by the mechanical obstruction (which is reflected by the obstruction score), but also by vasoactive agents, vasoconstriction reflex, and arterial hypoxemia [12,19].

One of the limitations of the present study might be the inability to determine the specific cause of mortality in the patients who had PE. We have used the overall mortality data since a significant portion of the patients had multiple severe co-morbidities such as sepsis and end-stage malignancy. Moreover, most of the deaths occurred in the first week of the 30 days follow up strengthening the assumption that the mortality was related to the event of acute PE. Another limitation is that apart from the reflux grading, interreader agreement was not assessed. Previous studies, however, have shown a good to excellent agreement for both quantitative and qualitative assessment of the CTPA variables [13,14, 23]. All CTPA studies in our series were acquired in caudo-cranial direction, thus the reflux phenomenon when scanning cranio-caudally was not investigated, which is another limitation. In addition, various generations of CT scanners were used during our study, which one may consider as a limitation. However, all scans were acquired on multidetector CT scanners with thin slices of 1-2 mm, covering the pulmonary arterial tree beyond subsegmental levels [24]. Since CT technology is very rapidly developing, collection of data from several CT generations is accepted even in well structured multi-central studies like the PIOPED II [25]. Finally, one
would see the retrospective nature of the study as a limitation. Yet, this might not be a real limitation since our study actually represents a snapshot of the "real life" situation in most medical centers.

In summary, we assessed various CTPA findings including grading of reflux of contrast into the IVC in relations to short term mortality. No relations to mortality were found with any of the variables in patients without PE. In patients with acute PE, only substantial grades of reflux of contrast were shown to be related to increased 30 days mortality. These findings are relevant due to their potential to permit a real time risk assessment in the setting of acute PE.

Acknowledgment

Esther Eshkol is thanked for editorial assistance.

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FIGURE LEGENDS

FIGURE 1. A-F: Axial computerized tomographic pulmonary angiography sections through the liver showing the various degrees of contrast reflux into the inferior vena cava (IVC) and hepatic veins.

A. Grade 1-No opacification of the IVC
B. Grade 2-Trace of contrast in the IVC only
C. Grade 3-Opacification of the IVC but not of the hepatic veins
D. Grade 4-Opacification of the IVC and the proximal hepatic veins
E. Grade 5-Opacification of the IVC and the mid-hepatic veins
F. Grade 6-Opacification of the IVC and the distal hepatic veins

FIGURE 2. Kaplan-Meier curve of cumulative survival in patients diagnosed with pulmonary embolism (PE) according to degree of reflux.
Table 1—Mean (SD) of Continuous Variables and Number (%) of Dichotomous Variables

According to the Group with Negative and Positive Computed Tomographic Pulmonary Angiography (CTPA) Findings

<table>
<thead>
<tr>
<th></th>
<th>Negative CTA</th>
<th>Positive CTA</th>
<th>p Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yr</td>
<td>64 (20)</td>
<td>67 (19)</td>
<td>0.147</td>
</tr>
<tr>
<td>Female gender</td>
<td>105 (62.5)</td>
<td>95 (65.5)</td>
<td>0.579</td>
</tr>
<tr>
<td>RV diameter (mm)</td>
<td>38.9 (6.9)</td>
<td>40.0 (7.4)</td>
<td>0.162</td>
</tr>
<tr>
<td>LV diameter (mm)</td>
<td>42.3 (7.7)</td>
<td>39.7 (7.7)</td>
<td>0.003</td>
</tr>
<tr>
<td>RV to LV ratio</td>
<td>0.94 (0.24)</td>
<td>1.05 (0.32)</td>
<td>0.001</td>
</tr>
<tr>
<td>PA diameter (mm)</td>
<td>28.6 (4.9)</td>
<td>29.3 (5.0)</td>
<td>0.199</td>
</tr>
<tr>
<td>Septum deviation</td>
<td>20 (15.7)</td>
<td>28 (23.0)</td>
<td>0.150</td>
</tr>
<tr>
<td>Substantial reflux (4-6)</td>
<td>23 (13.7)</td>
<td>29 (20.0)</td>
<td>0.135</td>
</tr>
<tr>
<td>30-day mortality</td>
<td>18 (10.7)</td>
<td>27 (18.6)</td>
<td>0.047</td>
</tr>
</tbody>
</table>

RV=right ventricle; LV=left ventricle; PA=pulmonary artery

*Independent Student’s t-test for continuous variables and Chi-square for dichotomous variables.
Table 2—Number (%) of 30-day Mortality According to the tertiles or other divisions of each variable among the Positive Computed Tomographic Pulmonary Angiography (CTPA) Patients

<table>
<thead>
<tr>
<th></th>
<th>Lower Tertile</th>
<th>Middle Tertile</th>
<th>Higher Tertile</th>
<th>p Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>RV diameter</td>
<td>13 (28.9)</td>
<td>7 (14.6)</td>
<td>7 (13.5)</td>
<td>0.12</td>
</tr>
<tr>
<td>LV diameter</td>
<td>13 (22.0)</td>
<td>8 (18.2)</td>
<td>6 (14.3)</td>
<td>0.61</td>
</tr>
<tr>
<td>RV to LV ratio</td>
<td>9 (21.4)</td>
<td>7 (16.3)</td>
<td>11 (18.3)</td>
<td>0.84</td>
</tr>
<tr>
<td>PA diameter</td>
<td>7 (17.9)</td>
<td>9 (18.0)</td>
<td>11 (19.6)</td>
<td>0.95</td>
</tr>
<tr>
<td>PE Clot Load Score</td>
<td>9 (18.0)</td>
<td>11 (23.9)</td>
<td>6 (12.5)</td>
<td>0.32</td>
</tr>
<tr>
<td>Septum deviation</td>
<td>18 (19.1)</td>
<td>6 (21.4)</td>
<td></td>
<td>0.72</td>
</tr>
<tr>
<td>Substantial reflux (4-6)</td>
<td>17 (10.7)</td>
<td>10 (34.5)</td>
<td></td>
<td>0.008</td>
</tr>
<tr>
<td>Reflux degree</td>
<td>7 (16.3)</td>
<td>10 (13.7)</td>
<td>10 (34.5)</td>
<td>0.029</td>
</tr>
</tbody>
</table>

RV=right ventricle; LV=left ventricle; PA=pulmonary artery; PE=pulmonary emboli

* - Kaplan-Meier statistics