Pulmonary embolism: advances in diagnosis and prognosis
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Chapter 13
Multidetector computed tomography for acute pulmonary embolism: diagnosis and risk stratification in a single test

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Submitted for publication
ABSTRACT

Background
In patients with acute pulmonary embolism right ventricle dysfunction at echocardiography is associated with increased in-hospital mortality.

Methods
The aims of this study in patients with acute pulmonary embolism were: 1) to identify a sensitive and simple criterion for right ventricle dysfunction at multidetector computed tomography (MDCT) using echocardiography as the reference standard and 2) to evaluate its predictive value for in-hospital death and clinical deterioration. Right ventricle dysfunction at MDCT was defined as the right-to-left ventricle dimension ratio.

Results
Right to left ventricle dimension ratio ≥ 0.9 at MDCT had a 92% sensitivity for right ventricle dysfunction (95% confidence interval (CI) 88% to 96%). Overall, 457 patients were included in the in-hospital outcome study: 303 had right ventricle dysfunction at MDCT. In-hospital death or clinical deterioration occurred in 44 patients with and in 8 patients without right ventricle dysfunction at MDCT (14.5% versus 5.2%; p<0.004). The negative predictive value of right ventricle dysfunction for death due to pulmonary embolism was 100% (95% CI 98% to 100%). Right ventricle dysfunction at MDCT was an independent predictor for in-hospital death or clinical deterioration (odds ratio (OR) 2.7; 95% CI 1.2 to 6.4) in the overall population and in hemodynamically stable patients (OR 3.3; 95% CI 1.1 to 10.0).

Conclusions
In patients with acute pulmonary embolism MDCT can be used as a single procedure for diagnosis and risk stratification. Patients without right ventricle dysfunction at MDCT have a very low risk of in-hospital adverse outcome and could therefore candidate for home-treatment.
INTRODUCTION

Patients with acute pulmonary embolism have a wide spectrum of clinical presentation and outcome and require different intensities of care. Therefore, risk stratification for adverse outcome is essential to drive decisions on the optimal management strategies (1). Admission to intensive care unit and treatment with thrombolysis could be necessary in patients with high estimated risk for adverse outcome. Early hospital discharge or even home-treatment could be possible in patients with low estimated risk for adverse outcome. Due to the reduced threshold of clinical suspicion and the increased availability of facilities for diagnosis, the proportion of patients with less severe pulmonary embolism is increasing (2). This makes it essential to identify patients with a relatively good prognosis. Risk stratification in patients with acute pulmonary embolism is mainly based on the clinical presentation and the assessment of right ventricle dysfunction and injury (3). Right ventricle dysfunction is commonly assessed by echocardiography and myocardial injury by serum troponin. Right ventricle dysfunction at echocardiography is associated with an increased risk of in-hospital adverse outcome (4,5). However, echocardiography requires experienced personnel on an around-the-clock basis. Multidetector contrast-enhanced computed tomography (MDCT) is widely used for the diagnosis of pulmonary embolism (1). MDCT allows the visualization and measurement of the heart chambers and thus has the potential to be an alternative to echocardiography to assess right ventricle dysfunction (6-8).

We performed a prospective study in patients with acute pulmonary embolism to identify a sensitive and simple criterion for right ventricle dysfunction at MDCT and to evaluate its prognostic value for in-hospital death and clinical deterioration.

METHODS

Patients

Consecutive patients with symptomatic acute pulmonary embolism confirmed by 4 or 16-detector CT were considered for inclusion in the study, provided that they had transthoracic echocardiography and serum troponin performed before or after 6 hours at maximum from the diagnostic MDCT. Patients with inadequate echocardiography or MDCT due to poor quality images were excluded from the study. Treatment schedule was in charge of the attending physician. The study was approved by local Institutional Review Boards.

Study design

This is a prospective study in patients with acute pulmonary embolism performed in 12 centers in Italy, Poland, Germany and The Netherlands. The objectives of the study were: 1) to evaluate the accuracy of MDCT in the assessment of right ventricle dysfunction, by using echocardiography as the reference standard; 2) to assess the rate of in-hospital death, death
due to pulmonary embolism and clinical deterioration in patients with or without right ventricle dysfunction assessed by MDCT. Clinical deterioration was defined as the occurrence of one or more of the following criteria: shock, need for thrombolysis, endotracheal intubation, catecholamine infusion or cardiopulmonary resuscitation for sustained hypotension or recurrent pulmonary embolism (9). In case of death the cause was reported.

In a first set of patients, the diagnostic performance of MDCT for right ventricle dysfunction was evaluated. Next, the prognostic value of right ventricle dysfunction as assessed by MDCT was evaluated in the overall study population.

**Transthoracic echocardiography**

All patients underwent standard 2-dimension echocardiography. The diagnosis of right ventricle dysfunction required the presence of at least two of the following criteria: right to left ventricle end-diastolic diameter ratio >0.9 in the apical four-chamber view; right to left ventricle end-diastolic diameter ratio >0.7 in the parasternal long axis or sub-costal four-chamber views; paradoxical interventricular septal motion or systolic pulmonary artery pressure over 30 mmHg. All these were to be in the absence of right ventricle hypertrophy. Echocardiography was locally adjudicated by physicians unaware of MDCT results.

**MDCT scan**

Standard contrast-enhanced protocols for the diagnosis of pulmonary embolism were used (image acquisition beginning with a scanning delay of 15–20 seconds after the start of the injection of contrast medium). MDCTs were recorded on CDs and were centrally evaluated by a panel (MD, MCV and CB) which included a radiologist expert in lung CT reading. Disagreement was resolved by consensus. The panel was unaware of the echocardiography results.

Right ventricle dysfunction was assessed by measuring the ratio of the right ventricle to left ventricle short-axis diameters. Ventricular diameters were measured by identifying the maximal distance between the ventricular endocardium and the interventricular septum, perpendicular to the long axis of the heart (5). Measurements were performed at the valvular plane in the 2-dimension axial transverse images, taking into account that the maximum dimension of the right and left ventricles may be found at slightly different levels (Figure 1).

**Statistical analysis**

Data were reported as proportion or as mean ± standard deviation (SD) or median (1st-3rd interquartile range) as appropriate. Continuous data were compared with Student’s t-test. Qualitative variables were compared by χ²-test.

The receiver operating characteristic analysis was used to assess the diagnostic performance of MDCT for right ventricle dysfunction by using echocardiography as the reference standard and to identify a high-sensitivity cut-off for right ventricle dysfunction.
Figure 1. Measurement of right ventricle dysfunction at MDCT. Ventricular diameters were measured by identifying the maximal distance between the ventricular endocardium and the interventricular septum, perpendicular to the long axis of the heart. Measurements were performed at the valvular plane in the 2-dimension axial transverse images. RV= right ventricle, LV= left ventricle.

Agreement among panel members for right to left ventricle ratio at MDCT was assessed by the intra-class correlation coefficient. Logistic regression analysis was used to assess for independent predictors of death and clinical deterioration. All analyses were performed using SPSS 11.0.

We estimated an incidence of death and clinical deterioration of 10% and 2%, respectively, in patients with and without right ventricle dysfunction at MDCT. Given these assumptions, we needed 200 patients per group to detect a difference of this magnitude between groups, with a power of 90% and a type I error rate of 5%. The study was performed without any external financial support.

RESULTS

Overall, 460 patients were evaluated for inclusion in the study. Three patients were excluded due to inadequate images at MDCT (0.7%). Thus, 457 patients were included in the analyses; mean age was 67±16 years, 209 (46%) males. Baseline features of the study population are reported in Table 1. Four-hundred-eleven patients (90%) were hemodynamically stable and 230 (50%) had right ventricle dysfunction at echocardiography at the time of the diagnosis of pulmonary embolism.

Accuracy of MDCT for assessing right ventricle dysfunction

The accuracy analysis was based on the first 260 consecutive patients. Among these patients, 149 (58%) were found to have right ventricle dysfunction at echocardiography. At MDCT evaluation, the median right to left ventricular diameter ratio was 1.07 (interquartile range
Table 1. Main features of study patients

<table>
<thead>
<tr>
<th></th>
<th>Overall population (457 patients)</th>
<th>Right to left ventricle ratio ≥0.9 at MDCT</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Present (n=303)</td>
</tr>
<tr>
<td>Age, years, mean±SD</td>
<td>67±16</td>
<td>69±15</td>
</tr>
<tr>
<td>Range</td>
<td>18-97</td>
<td>18-97</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>209 (46)</td>
<td>131 (43)</td>
</tr>
<tr>
<td>Cancer, n (%)</td>
<td>91 (20)</td>
<td>62 (21)</td>
</tr>
<tr>
<td>Medical illness, n (%)</td>
<td>178 (39)</td>
<td>122 (40)</td>
</tr>
<tr>
<td>Dyspnea, n (%)</td>
<td>360 (80)</td>
<td>254 (84)</td>
</tr>
<tr>
<td>Chest pain, n (%)</td>
<td>159 (35)</td>
<td>99 (33)</td>
</tr>
<tr>
<td>Tachycardia, n (%)</td>
<td>179 (39)</td>
<td>136 (45)</td>
</tr>
<tr>
<td>Systolic BP ≥ 90mmHg, n (%)</td>
<td>411 (90)</td>
<td>262 (87)</td>
</tr>
<tr>
<td>Echo-RVD, n (%)</td>
<td>230 (50)</td>
<td>207 (68)</td>
</tr>
<tr>
<td>Elevated troponin, n (%)</td>
<td>177 (39)</td>
<td>152 (50)</td>
</tr>
</tbody>
</table>

MDCT, multi-detector computed tomography; SD, standard deviation; BP, blood pressure; RVD, right ventricular dysfunction; NS, not statistically significant (p>0.05).

0.86 to 1.27). Mean right to left ventricle ratio at MDCT was higher in patients with right ventricle dysfunction at echocardiography (1.25±0.27 compared to 0.89±0.19; p <0.001).

The diagnostic accuracy of MDCT for detecting right ventricle dysfunction, by using echocardiography as the reference standard, shown by the area under the curve was 0.86 (95% confidence interval (CI), 0.82 to 0.91) (Figure 2). Sensitivity and specificity for right to left ventricle ratio ≥ 0.9 were 92% (95% CI, 89% to 95%) and 56% (95% CI, 46% to 66%), respectively, with an accuracy of 77% (95% CI, 72% to 82%). Sensitivity and specificity for right to left ventricle ratio ≥ 1 at MDCT were 85% (95% CI, 81% to 89%) and 72% (95% CI, 67% to 77%), respectively, with an accuracy of 79% (95% CI, 74% to 84%). Right to left ventricle ratio ≥ 0.9 was identified as a high-sensitivity cut-off for right ventricle dysfunction at MDCT and used in the clinical outcome analysis.

The intra-class correlation coefficient for right to left ventricle ratio assessment at MDCT among the panel members was 0.91, p<0.001.

Clinical outcome by MDCT assessment

The prognostic value of right ventricle dysfunction as assessed by MDCT was evaluated in the total study population (457 patients). In-hospital death occurred in 25 patients (5.5%). In 14 patients, pulmonary embolism was the cause of death. In-hospital clinical deterioration
occurred in 40 patients (8.8%). Fifty-two patients died or had clinical deterioration while in hospital.

Three-hundred and three patients (66%) had right ventricle dysfunction at MDCT. Baseline characteristics of patients with and without right ventricle dysfunction at MDCT are reported in Table 1. Forty-four of 303 patients (14.5%) with right ventricle dysfunction and eight of 154 patients (5.2%) without right ventricle dysfunction died or had clinical deterioration (odds ratio (OR) 3.1, 95% CI, 1.4 to 6.8; p=0.004) (Table 2). In hospital death was more common in patients with right ventricle dysfunction at MDCT than in patients without (6.9% versus 2.6%, respectively; OR 2.8, 95% CI, 0.9 to 8.3, p= 0.06). In-hospital death due to pulmonary embolism occurred in 4.6% of patients with and in none of the patients without right ventricle dysfunction at MDCT (p<0.001). Thus the negative predictive value of right ventricle dysfunction at MDCT for death due to pulmonary embolism was 100% (95% CI, 98% to 100%).

At univariate analysis, right ventricle dysfunction at echocardiography (OR2.8; 95% CI, 1.5-5.4; p=0.002) as well as elevated serum troponin levels (OR 1.9; 95% CI, 1.1-3.2; p=0.048) were also associated with an increased risk for death or clinical deterioration. At multivariable analysis, right ventricle dysfunction at MDCT was associated with an increased risk of all-cause mortality or clinical deterioration (OR 2.7, 95% CI 1.2 to 6.4) and for death due to pulmonary embolism or clinical deterioration (OR 3.4, 95% CI, 1.3 to 9.0). This association was also found in patients who were hemodynamically stable at time of the diagnosis of pulmonary embolism. Elevated troponin was not an independent predictor of death due to pulmonary embolism or clinical deterioration (OR 1.25, 95% CI, 0.7-2.3).
Table 2. Clinical outcome events according to presence or absence of right ventricle dysfunction at MDCT

<table>
<thead>
<tr>
<th></th>
<th>Present (n=303)</th>
<th>Absent (n=154)</th>
<th>OR (95% CI)</th>
<th>p-value</th>
<th>PPV (95% CI)</th>
<th>NPV (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death or clinical deterioration, n (%)</td>
<td>44 (15)</td>
<td>8 (5.2)</td>
<td>3.1 (1.4-6.8)</td>
<td>0.004</td>
<td>15 (12-18)</td>
<td>95 (93-97)</td>
</tr>
<tr>
<td>Clinical deterioration, n (%)</td>
<td>34 (11)</td>
<td>6 (3.9)</td>
<td>3.1 (1.3-7.6)</td>
<td>0.01</td>
<td>11 (8-14)</td>
<td>96 (94-98)</td>
</tr>
<tr>
<td>Death, n (%)</td>
<td>21 (6.9)</td>
<td>4 (2.6)</td>
<td>2.8 (0.9-8.3)</td>
<td>0.06</td>
<td>7 (5-9)</td>
<td>97 (95-99)</td>
</tr>
<tr>
<td>Death due to PE, n (%)</td>
<td>14 (4.6)</td>
<td>0 (0)</td>
<td>-</td>
<td>&lt;0.001</td>
<td>5 (3-8)</td>
<td>100 (98-100)</td>
</tr>
</tbody>
</table>

MDCT, multi-detector computed tomography; OR, odds ratio; PPV, positive predictive value; NPV, negative predictive value; CI, confidence interval; PE, pulmonary embolism.

Table 3. Multivariable analysis for death or clinical deterioration in the overall study population and in hemodynamically stable patients

<table>
<thead>
<tr>
<th>Death or clinical deterioration in the overall study population</th>
<th>OR</th>
<th>95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>0.97</td>
<td>0.94-0.99</td>
<td>0.01</td>
</tr>
<tr>
<td>RVD at MDCT</td>
<td>2.72</td>
<td>1.16-6.42</td>
<td>0.02</td>
</tr>
<tr>
<td>Female gender</td>
<td>0.84</td>
<td>0.45-1.58</td>
<td>0.59</td>
</tr>
<tr>
<td>Elevated troponin</td>
<td>1.25</td>
<td>0.68-2.32</td>
<td>0.47</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Death or clinical deterioration in hemodynamically stable patients</th>
<th>OR</th>
<th>95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>0.97</td>
<td>0.94-1.00</td>
<td>0.09</td>
</tr>
<tr>
<td>RVD at MDCT</td>
<td>3.28</td>
<td>1.08-9.99</td>
<td>0.04</td>
</tr>
<tr>
<td>Female gender</td>
<td>0.69</td>
<td>0.29-1.59</td>
<td>0.38</td>
</tr>
<tr>
<td>Elevated troponin</td>
<td>0.86</td>
<td>0.38-1.92</td>
<td>0.71</td>
</tr>
</tbody>
</table>

OR, odds ratio; RVD, right ventricle dysfunction; MDCT, multi-detector computed tomography; CI, confidence interval.

DISCUSSION

This study shows that right to left ventricle dimension ratio at MDCT has a good accuracy as compared to echocardiography for the assessment of right ventricle dysfunction in patients.
with acute pulmonary embolism. Right ventricle dysfunction at MDCT is an independent predictor for death or clinical deterioration and can be used for risk stratification for adverse outcome. Thus, MDCT has the potential to provide both diagnosis and prognostic stratification for adverse outcome in patients with acute pulmonary embolism.

A simple criterion was used for the assessment of right ventricle dysfunction at MDCT. In previous studies right ventricle dysfunction was measured at MDCT by a quite complex procedure which required reformatted images (6,10-12). In our study, a simple methodology was used for the assessment of right ventricle at MDCT: dysfunction was assessed by using 2-dimension axial transverse images. This measurement does not require multi-planar reconstruction as it is performed in the same images used for the diagnosis of pulmonary embolism. By following our approach, the assessment of right ventricle dysfunction at CT is made easy and rapid, and feasible every-day in the urgent setting. Based on the results of our study, MDCT can replace echocardiography to assess right ventricle dysfunction in patients with acute pulmonary embolism.

The results obtained by this approach are comparable to the results from previous studies. The prevalence of right ventricular dysfunction was 66% in our study, compared to 64% in a study by Schoepf and colleagues (6) (cut-off >9), and 58% and 57% in two studies using a cut-off >1 (7,12), respectively. In these studies, all-cause thirty-day mortality rate in patients with right ventricular dysfunction was 16% (6), while three-month PE-related mortality rate was 10% (7), respectively. The prevalence of in-hospital all-cause mortality and clinical deterioration in patients with right ventricular dysfunction in our study (15%) was comparable to the rate at six weeks follow-up in a study by Klok et al. (12)

Risk stratification could be used to categorize patients with acute pulmonary embolism according to their risk for in-hospital death or clinical deterioration. According to this stratification, patients may candidate to different clinical managements concerning both acute treatment and intensity of care. Because it is generally accepted that patients who are hemodynamically instable should receive thrombolytic treatment (1), in current clinical practice, risk stratification is particularly required in patients who are hemodynamically stable. The current problem is the low positive predictive value of both laboratory biomarkers and echocardiography for adverse outcomes. Although in our study, the presence of right ventricle dysfunction at MDCT increased the risk of mortality in the overall study population and in hemodynamically stable patients, the positive predictive value was only 15%, which does not justify treatment upgrading, for example with thrombolysis. Whether further risk stratification by using additional testing could help to identify those patients with right ventricle dysfunction at MDCT who require intensive monitoring or thrombolysis is unclear. Indeed, in this study serum troponin had no additive prognostic value over right ventricle dysfunction at MDCT at
multivariate analysis, which is in contrast to previous studies (12-15). The reason for this is not clear.

In our study, right ventricle dysfunction at MDCT had a 100% negative predictive value for death due to pulmonary embolism, which is comparable to previous observations (7,12). This high negative predictive value enables the identification of patients at low risk of death due to pulmonary embolism, who may be safely treated at home with anticoagulation. Notably, no less than one third of the patients had a normal right ventricle.

None of the MDCT in this study were ECG-gated, a technique that may allow more accurate evaluation of the heart (16). However, this technique requires longer acquisition time and a higher radiation dose. Moreover, ECG-gated CT is a sophisticated technique that is not routinely used for the evaluation of chest pain or suspected pulmonary embolism in the emergency department. Four- and 16-detector CT were used in this study. More sophisticated CT scanners are currently available in advanced medical centers. Such scanners could allow a further increase in the accuracy of right ventricle evaluation in patients with acute pulmonary embolism.

In our study a good correlation was found between measurements made by an expert radiologist and physicians with experience on pulmonary embolism. This finding supports the reliability of right to left ventricle dimension ratio at MDCT, which is a relatively easy measurement (figure 1).

As a limitation of this large prospective multicenter study, it should be mentioned that the cause of death was adjudicated by the attending physician who was not blinded to the echocardiography assessment. However, right ventricle dysfunction at MDCT was centrally adjudicated by a panel unaware of results at echocardiography and unaware of clinical status and outcome. The rate of inadequate MDCT images was extremely low despite the multicenter nature of the study. Secondly, MDCT is not able to provide functional evaluation of right ventricle (such as hypokinesis, pulmonary artery pressure) easily obtained by echocardiography. However, no specific prognostic value has been associated with these functional assessments and right ventricle dilation is the only predictor of adverse clinical outcome in patients with acute pulmonary embolism.

In conclusion, MDCT can be used as a single test for diagnosis and risk stratification in patients with acute pulmonary embolism. The high negative predictive value enables identification of patients at low risk of death due to pulmonary embolism, who may be safely treated at home with anticoagulation. Whether further risk stratification by using additional testing could help to identify patients with right ventricle dysfunction at MDCT who require intensive monitoring or thrombolysis is needs further investigation.
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