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Chapter 4

Right ventricular function and thrombus load in patients with pulmonary embolism and diagnostic delay

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Chapter 4

ABSTRACT

Introduction
It has earlier been demonstrated that the time between symptom onset and objective diagnosis of pulmonary embolism (PE) does not influence outcome on re-thrombosis and mortality. This time frame consists of patient’s delay and doctor’s delay. It is unknown whether this patient’s delay is of influence on the thromboembolic burden and right ventricular function. We sought to evaluate this by measuring Qanadli-score and RV/LV-ratio in PE patients with and without patient’s delay.

Methods
Post-hoc analyses of an observational prospective outcome study in 113 consecutive CT proven PE patients. In all patients Qanadli-score and RV/LV ratio were scored and duration from symptom onset until the clinical presentation was requested. Also mortality and hospital readmission in a 6-weeks follow-up period were collected.

Results
Twenty patients with and 93 patients without delay, with identical baseline characteristics and comorbidities, were included. In a linear analysis, Qanadli-scores were not correlated to delay with a R² of 0.021 (p=0.130). RV/LV-ratio had a R² <0.001 (p=0.991). Likewise, longer delay was not associated to 6-week mortality (Odds ratio: 0.65; 95%CI 0.08-5.57) or hospital readmission (Odds ratio: 0.75; 95%CI 0.15-3.65).

Conclusion
In our patient cohort, patient’s delay was not associated with higher thrombus load or right ventricular dysfunction. This could provide a possible explanation for the lack of association between delay in diagnosing PE and clinical outcome as found in earlier studies.
INTRODUCTION

Acute pulmonary embolism (PE) is a frequently diagnosed disease with an incidence of 1-2 per 1000 persons (1). Mortality rates range between 2-30%, depending on the size of the embolism and the cardiopulmonary condition of the patient (2). Especially in the first hours of the acute PE event, patients may die from PE (3). Nonetheless, in 17% of the patients PE is diagnosed more than a week after symptom onset (4). In recent studies no correlation was found between patient’s delay, defined as time between symptom onset and presentation at the hospital, and clinical outcome (5-7). In these studies it is hypothesized that, from symptom onset until presentation, thrombus growth and aggravation of right ventricular function could be negligible in some patients (5-7). However, these studies were unable to confirm or reject this hypothesis.

The aim of present study was to investigate whether elevation of thrombotic burden and aggravated right ventricular function was irrespective of patient’s delay. This was done by measuring Qanadli-scores and RV/LV-ratio in 113 consecutive PE patients presenting with and without delay.

METHODS

Patients

This was a post-hoc analysis of an observational prospective outcome study conducted in an academic and a peripheral teaching-hospital, as described earlier (8-10). In short, during the period September 1st 2005 and December 1st 2008 all consecutive hemodynamically stable in- and outpatients with a clinical suspicion for PE were eligible for inclusion. Patients with a likely clinical decision rule (Wells > 4 points total) and/or an elevated D-dimer blood test (> 500 ng/mL) underwent a computed tomography pulmonary angiography (CTPA; Aquillion 64; Toshiba Medical Systems, Otaware, Japan). In patients with an unlikely clinical decision rule (Wells ≤ 4 points total) and a normal D-dimer blood test (≤ 500 ng/mL) PE was ruled out without further imaging (10). CTPA was considered positive for PE when at least one filling defect in the pulmonary artery tree was present. All patients with a clinical suspicion of PE, regardless of the outcome of the CTPA, were followed for a period of 6 weeks. Patients aged below 18 years, with impossibility to follow-up, hemodynamically unstable at presentation, pregnant, with known allergy to contrast agents, with renal impairment function and patients unable to give informed consent were excluded from this study. The study was approved by the Institutional Review Board of both participating hospitals and all patients provided written informed consent.
Radiological examinations

To quantify the vascular obstruction of the pulmonary arteries caused by PE, the scoring system as proposed by Qanadli et al. was used (12). In this score the left and right lung were regarded having 10 segmental arteries each (3 for the upper lobes, 2 for the middle lobe and to the lingula, and 5 for the lower lobes). Each individual segmental artery is scored 0 points when there is no thrombus present, 1 point for partial occlusion of the artery and 2 points for total occlusion. So, in total the maximal Qanadli-score was 40 per patient. Thrombi in the most proximal artery were scored a value equal to the number of segmental arteries present distally. Subsegmental PE was considered as a partial occlusion and was assigned 1 point.

RV/LV-ratio was calculated by measuring the right and left ventricular dimensions on a post-processing workstation (Vitrea, version 2, Vital Images, Minnetonka, USA). This was done, as described earlier (13), in reconstructed CT-4 chamber view, by identifying the maximal distance between the ventricular endocardium and the interventricular septum, perpendicular to the ventricular long-axis. A RV/LV-ratio greater than 1.0 was considered as right ventricular enlargement.

Patient’s delay

Patient’s delay was defined as the time, expressed as number of days, between onset of symptoms and clinical presentation at the hospital. In case patients presented within 24 hours of symptom onset, delay was scored in hours. Patient’s delay was scored at the day of presentation. In case patients had slowly progressing symptoms, the day the complaints started was scored as the onset of symptoms. If there were complains for a longer period with an acute change in symptoms, the acute moment was scored as the start of onset of symptoms.

Variables and study endpoints

The primary outcome of the study was the Qanadli-score and RV/LV-ratio relative to the duration of symptoms before presentation to the hospital. Secondary endpoints were mortality and hospital readmission 6 weeks after diagnosis of PE compared to patient’s delay for less and more than 7 days, as proposed in previous studies (5-7). In addition, subsegmental PE, a prior history of VTE and active malignancy were scored.

Statistical analysis

Baseline patient characteristics are presented as mean ± standard deviation (SD). Qanadli-score, RV/LV-ratio and patient’s delays are presented as median with an interquartile range (IQR). Nominal data are presented as N, %. Linear analysis was used for the analysis of correlations between delay and Qanadli-score and between delay and RV/LV-ratio. For the correlation between delay and the secondary endpoints mortality and
hospital readmission, odds ratios with 95% confidence intervals (CI) were calculated. Because patients with massive PE are possibly more prone to present at the first or second day after symptom onset, our analyses could be biased. Therefore, all analyses were performed for a second time after excluding patients with a delay less than 2 days. Statistical analysis was performed using SPSS statistics 17.0.2 (SPSS Inc., Chicago, Illinois, The USA). P-values <0.05 were considered statistically significant.

**RESULTS**

PE was confirmed after CTPA in 113 of the 439 patients eligible for inclusion (25.7%). The baseline characteristics are depicted in table 1. Mean age was 56 ± 17 years. There were more male patients (60, 53.1%) than female patients (53, 46.9%; p<0.001), and more outpatients (93, 82.3%) than inpatients (20, 17.7%; p<0.001). The amount of subsegmental PE did not significantly differ in patients with and without PE (p=0.706).

The median time from onset of symptoms to presentation was 2 days, IQR 1-6 days. In patients without PE (data not shown) median time from onset of symptoms to clinical presentation was identical (2 days, IQR 1-7 days). Patient’s delay of more than 7 days was present in 20 patients (17.7%) and 4 patients (3.5%) had a delay of more than a month. Forty-one patients (36.3%) presented within 24 hours of onset of complains of whom 23

<table>
<thead>
<tr>
<th>Variable</th>
<th>All patients (n=113)</th>
<th>Patients without delay (n=93)</th>
<th>Delayed patients (n=20)</th>
<th>Significance (p-value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years ± SD)</td>
<td>56 ± 17</td>
<td>55 ± 17</td>
<td>59 ± 17</td>
<td>0.322</td>
</tr>
<tr>
<td>Male sex (n,%</td>
<td>60 (53.1)</td>
<td>53 (57.0)</td>
<td>7 (35.0)</td>
<td>0.075</td>
</tr>
<tr>
<td>Outpatients (n,%</td>
<td>93 (82.3)</td>
<td>76 (81.7)</td>
<td>17 (85.0)</td>
<td>0.730</td>
</tr>
<tr>
<td>Previous VTE (n,%</td>
<td>25 (22.1)</td>
<td>21 (22.6)</td>
<td>4 (20.0)</td>
<td>0.803</td>
</tr>
<tr>
<td>Malignancy (n,%</td>
<td>24 (21.2)</td>
<td>20 (21.5)</td>
<td>4 (20.0)</td>
<td>0.883</td>
</tr>
<tr>
<td>COPD</td>
<td>7 (6.2)</td>
<td>4 (4.3)</td>
<td>3 (15.0)</td>
<td>0.073</td>
</tr>
<tr>
<td>Heart failure</td>
<td>5 (4.4)</td>
<td>4 (4.3)</td>
<td>1 (5.0)</td>
<td>0.892</td>
</tr>
<tr>
<td>D-dimer (ng/mL ± SD)</td>
<td>2770 ± 1678</td>
<td>2701 ± 1673</td>
<td>3090 ± 1706</td>
<td>0.350</td>
</tr>
<tr>
<td>Delay (days ± SD)</td>
<td>5.7 ± 9.2</td>
<td>2.4 ± 1.8</td>
<td>21.0 ± 13.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Qanadli-score (score ± SD)</td>
<td>12.3 ± 9.3</td>
<td>11.7 ± 9.5</td>
<td>14.6 ± 7.8</td>
<td>0.212</td>
</tr>
<tr>
<td>RV/LV-ratio (ratio ± SD)</td>
<td>1.09 ± 0.33</td>
<td>1.09 ± 0.35</td>
<td>1.09 ± 0.21</td>
<td>0.962</td>
</tr>
<tr>
<td>Subsegmental PE (n,%</td>
<td>14 (12.4)</td>
<td>12 (12.9)</td>
<td>2 (10.0)</td>
<td>0.706</td>
</tr>
<tr>
<td>All-cause mortality (n,%</td>
<td>8 (7.1)</td>
<td>7 (7.5)</td>
<td>1 (5.0)</td>
<td>0.693</td>
</tr>
<tr>
<td>Hospital re-admission (n,%</td>
<td>14 (12.4)</td>
<td>12 (12.9)</td>
<td>2 (10.0)</td>
<td>0.706</td>
</tr>
</tbody>
</table>

SD, Standard Deviation; VTE, Venous Thromboembolic Event; COPD, Chronic Obstructive Pulmonary Disease; PE, Pulmonary Embolism
(20.4%) within the first 12 hours. Twenty-one patients (18.6%) presented on the second day (Figure 1).

The median Qanadli-score was 10 points with an IQR of 4-21 points. The mean Qanadli-score was 11.7 ± 9.5 in patients without delay and 14.6 ± 7.8 in patients with delay (p=0.212). When analyzed in a linear analysis, the Qanadli-score was not correlated to delay after symptom onset (R² 0.021 p=0.130 Figure 2a.). Likewise, in our second analysis after excluding patients presenting at the first 2 days after symptom onset, the Qanadli-score was not associated with delay (R² 0.003, p=0.726 Figure 2b.).

The median RV/LV-ratio was 1.02 with an IQR of 0.92-1.16. Mean RV/LV-ratio was 1.09 ± 0.35 in patients without delay and 1.09 ± 0.21 in patients with delay (p=0.962). In a linear analysis, RV/LV-ratio did not correlate to patient’s delay (R² <0.001 p=0.991 Figure 3a.). After excluding patients presenting at day 1 and 2 similar results were found (R² 0.002 p=0.998 Figure 3b.)

Death after 6 weeks of follow-up occurred in 8 patients (7.1%) in which 7 out of 93 without delay (7.5%) and 1 of 20 patients with delay (5.0%) died (Odds ratio: 0.65; 95% CI 0.08 – 5.6). A total of 14 out of 113 patients (12%) were readmitted to the hospital. In the group of patients with delay, 12 of 93 (13%) were readmitted and 2 of 20 patients (10%) with delay were readmitted to the hospital (Odds ratio: 0.75; 95% CI 0.15 – 3.6). Excluding the patients who presented within 48 hours of onset of symptoms or those with subsegmental PE did not change these findings.
DISCUSSION

Our results show that the thromboembolic burden (assessed by the Qanadli-score) and right ventricular function (measured by the RV/LV-ratio on CT-scan) in patients diagnosed with acute symptomatic PE were not adversely affected in patients with a delay. Also, the 6-weeks survival and hospital readmission rates are identical in patients with and without patient’s delay. The latter findings correlate with earlier studies. One study showed that 3-month survival and recurrence VTE rates were not adversely affected by patient’s delay in 397 symptomatic PE patients presenting at the emergency ward. Seventy-two of these patients had patient’s delay of more than 7 days (18%). Deaths were identical in both groups (OR 0.9; 95% CI 0.4-2.0) (5). These results were confirmed by a second study,
in which 375 patients, admitted with the diagnosis of PE, were included. Patient’s delay of more than 7 days was present in 186 patients (50%). The primary outcome, mortality, was identical in patients with and without delay (6). A third retrospective study in 454 consecutive PE patients, in which 113 patients (28%) were delayed more than a week, found that mortality was identical in patients with and without delay (7). However, none of these studies provided a pathophysiological explanation for these findings and all suggested further studying this observation. Our study strengthens the hypothesis by showing that, besides outcome on mortality and hospital readmission, also thrombo-embolic burden was identical in patients with and without patient’s delay.

In an earlier study of our group, the predictive value of RVD and Qanadli-score on outcome during 3-months follow-up of patients with PE was evaluated (12). In that study, the RV/LV ratio and fatal PE related with a regression coefficient of 1.55 (p=0.04). PE
patients with an obstruction index of 40%, 16 points or more which is the cut-off value as proposed by Qanadli (11), had an 11-fold risk of PE-related mortality than patients with an index smaller than 40% (13). Since our present study showed identical RV/LV ratios and Qanadli-scores in patients with and without patient’s delay, we assume that our data strengthens the hypothesis that patient’s delay does not influence outcome in patients presenting with PE. A previous study suggested that the lack of effect of delay on outcome might affect the guidelines that advise initial anticoagulant treatment before radiological examinations are performed (5). Although our data showed identical results regarding outcome on mortality and morbidity, only the effect of patients delay, time between symptom onset and presentation at the emergency ward, was studied. Withholding anticoagulant treatment before radiological examinations is doctors delay and has not been studied. Therefore we do not believe the results should affect current guidelines.

Nonetheless, our thrombus loads are identical to those found in earlier studies using the Qanadli and/or Miller-index (11;14). An explanation could be the actual duration of the delay in our study, which was defined by reported time between the moment of symptom onset up to the moment of diagnosis. Notably, it is unknown whether the subjectively reported initial symptoms were actually caused by a PE. Another limitation to our study is that we only included hemodynamically stable patients who survived the first hours to undergo evaluation at the emergency ward. All these patients underwent a CT-scan based on an elevated Wells clinical decision rule and/or elevated D-dimer levels causing a selection bias in which only patients with multiple complains or patients with a certain degree of pulmonary artery obstruction were included. Therefore, the complaints and thromboembolic burden in patients with and without delay could be identical at the day of presentation in the hospital. However, there was a big interval in D-dimer levels indicating that our study population included both larger and smaller PE. It could also be debated that patients with patient’s delay had smaller PE at onset of symptoms and presented at the emergency ward after exacerbated symptoms due to thrombus growth. Still, the amount of subsegmental PE did not significantly differ between patients with and without patient’s delay. Finally, differences in patient characteristics or VTE risk factors between patients with and without delay could also act as a confounder. However, the presence of active malignancy, COPD, congestive heart failure or a prior history of VTE was not different between the 2 study groups.

We conclude that both RV/LV ratio, and the arterial pulmonary obstruction assessed by the Qanadli-score, was identical in hemodynamic stable patients with and without patient’s delay. This strengthens the findings that PE-related mortality after a 6-week follow-up period was not related with patient’s delay.
REFERENCES


