Transthoracic Echocardiography and Chest Computed Tomography Arteriography in Patients with Acute Pulmonary Embolism: A Two-Year Follow-Up Study

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Key Words
Transthoracic echocardiography · Chest computed tomography arteriography · Pulmonary embolism · Chronic thromboembolic pulmonary hypertension

Abstract

\textbf{Background:} Pulmonary hypertension (PH) is frequently found at the time of diagnosis of pulmonary embolism (PE). An incomplete resolution of PE can lead to chronic thromboembolic pulmonary hypertension (CTPH). Transthoracic echocardiogram (TTE) is the first step to diagnose an abnormality of the pulmonary vasculature. Based on computed tomography (CT), the Qanadli vascular obstruction index has been extensively used to assess acute PE.\textbf{Objectives:} Our aim was to ascertain whether at the time of diagnosis of an acute PE episode TTE variables and a Qanadli CT index score may be associated with CTPH 2 years later. \textbf{Method:} Patients with PE were prospectively enrolled. TTE was performed and the Qanadli CT obstruction index was calculated on admission to the hospital, while only TTE was repeated at the 2-year follow-up. The NYHA (New York Heart Association) functional classification was evaluated. Correlation analyses were performed. \textbf{Results:} Twenty patients (11 males, median age 69.5 years) were considered for the study. There was no significant correlation between TTE parameters and the Qanadli CT obstruction index. A significant distribution ($\chi^2 = 5.69, p = 0.017$) was found in the analysis among patients with CTPH at 24 months and the Qanadli CT index, categorized by a receiver operating characteristic curve cutoff value of 42.5%. Additionally, a significant distribution ($\chi^2 = 4.09, p = 0.043$) was found in the analysis among patients with CTPH at 24 months and right ventricular systolic pressure on admission, categorized as PH (>31 mm Hg). \textbf{Conclusion:} Our study demonstrates that in patients with acute PE there is no relationship between the Qanadli CT obstruction index and TTE parameters on admission to the hospital. However, the occurrence of CTPH at the 24-month follow-up is associated with PH and with a high Qanadli CT obstruction index score.
**Introduction**

Pulmonary hypertension (PH) and right ventricular dysfunction (RVD) are pathophysiological events frequently found at the time of diagnosis of pulmonary embolism (PE). The majority of the patients with PE may experience a regression of PH and RVD within 3 weeks [1]. The occurrence of a chronic thromboembolic pulmonary hypertension (CTPH) is attributed to incomplete resolution of a PE episode and to vascular remodeling, leading to an increased pulmonary vascular resistance [2, 3]. CTPH causes high morbidity worldwide, and its diagnosis and treatment represent a clinical challenge [2, 3].

When CTPH is suspected, transthoracic echocardiography (TTE) is usually used as the first diagnostic tool to assess whether or not an abnormality of the pulmonary vasculature may occur. Relying on the stage of the disease when TTE is performed, a variable degree of right atrial and ventricular dysfunction may be demonstrated [4].

In the assessment of patients with PE or CTPH, the multi-detector computed tomographic (CT) arteriography does not provide essential hemodynamic data, but can be useful for detecting emboli in the main, lobar or segmental arteries [5]. Based on CT scanning, some clot burden scores have been described so far. Among these scores, the Qanadli vascular obstruction index is a simple and easy-to-calculate index, is derived from the amount and location of the thrombi on CT images and was found to be reproducible and highly correlated to the pulmonary angiography index [6]. Although the Qanadli CT index has been extensively used to assess acute PE [7–9], its use in the evaluation of CTPH has given controversial results so far [10, 11].

In this study, we tested the hypothesis whether or not at the time of diagnosis of an acute PE episode, TTE variables and a Qanadli CT index score might be associated with an increased risk for the presence of CTPH 2 years later.

**Methods**

**Subjects**

In this single-center prospective study, we enrolled all consecutive patients referred to the University Hospital of Parma between December 2010 and December 2011 and underwent CT scanning to calculate the Qanadli CT index for the study of pulmonary artery disease. Patients with a first episode of PE diagnosed by CT scanning were included in the study.

We excluded patients: (1) with a preexisting severe pulmonary or heart disease; (2) with neoplastic disorders; (3) with a previous episode of PE; (4) during pregnancy; (5) at an age of <18 years, and (6) who did not give informed consent. All patients had been treated with long-term oral anticoagulant therapy for at least 6 months [12]. The functional status of the subjects was categorized according to the New York Heart Association (NYHA) functional classification system (classes I–IV) [13].

The ethics review committee of the University Hospital of Parma approved the protocol.

**Transthoracic Echocardiography**

All patients underwent comprehensive two-dimensional TTE examinations at baseline and after 24 months of follow-up [14] by an echocardiography machine (Philips IE33, the Netherlands) equipped with a 2.5- to 3.5-MHz phased-array sector scan probe, coupled with tissue Doppler imaging. Estimated values of pulmonary vascular resistance were obtained through the use of traditional Doppler methods at the level of the tricuspid valve and the outflow tract of the right ventricle or through applications of tissue Doppler at the tricuspid annulus level. Right atrial, pulmonary artery trunk and vena cava dilatation and the reduced inspiratory collapse of the inferior vena cava were measured as indexes of increased pulmonary artery and right ventricle pressures. In the apical four-chamber scan, the percentage reduction in the planimetric area of the right ventricle in systole and the systolic excursion in millimeters of the tricuspid floor [tricuspid annular plane systolic excursion (TAPSE)] was measured with the cursor echo M-mode directed perpendicularly to the lateral portion of the ring.

The echocardiographic parameters considered for this study were: right ventricle end-diastolic volume (RVEDV); right ventricular systolic pressure (RVSP); right atrium area (RAA); right ventricular fractional shortening (RVFS); right atrium volume (RAV); pulmonary flow acceleration time (PFAT) and TAPSE. The RVSP was defined as the difference between the systolic pressure in the pulmonary artery and the mean right atrial pressure, and the RVFS was defined as 100 (systolic pressure in the pulmonary artery – mean right atrial pressure) / RVEDV. The RVFS was considered reduced (<35%) in the presence of PH. The RAA was considered increased (>20 cm²) in the presence of PH. The PFAT was considered reduced (<90 ms) in the presence of PH. The RVSP was considered increased (>30 mm Hg) in the presence of PH.

**CT Scanning and Qanadli CT Index**

All patients underwent a chest CT scan using a 6-slice scanner (Somatom Volume Zoom, Siemens Medical Solutions, Erlangen, Germany) and a 64-slice scanner (Sensation, Siemens Medical Solutions). The scanning parameters for the 6-slice scanner were: 130 kVp, 130 mAs, thickness of scanning section 1.5 mm, and rotation time 0.6 s. The scanning parameters for the 64-slice scanner were: 120 kVp, 100 mAs, thickness of scanning section 0.6 mm, and rotation time 0.5 s.

The Qanadli CT index score [6] is based on the extent of embolism of 10 segmental pulmonary vessels for both left and right sides, and 20 subsegmental vessels; for each segmental pulmonary artery, 0 points were assigned in the absence of embolism, 1 point was given when incomplete embolism was present, and 2 points with complete embolism. If subsegmental vessels were occluded, the involved segmental pulmonary vessel was considered as having incomplete embolism, and 1 point was to be assigned with a total score of no less than 2 points for each segmental pulmonary vessel. When emboli were present in the upper vessels of segmental pulmonary artery, a complete occlusion was to be assigned to segmental vessels, with 2 points assigned in total. After the scores had been summed up, a quantitative analysis was expressed as the percentage of the embolism area.

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Statistical Analysis

The analyses were performed with IBM SPSS Statistics 23.0 (Armonk, New York, N.Y., USA), and a Shapiro-Wilk test has been used to assess the normality of the distribution. Values were reported as medians (1st quartile; 3rd quartile) for continuous variables with non-normal distribution or means ± standard deviation (SD) for those with normal distribution. Number of patients (%) and the presence of CTPH were used as categorical variables. Categorical variables were compared using the χ² test or the Fisher exact test and continuous variables using the t test or the nonparametric Mann-Whitney test.

For the correlation analyses, the Pearson r and the Spearman ρ were used for linearly or normally distributed variables and for not linearly or not normally distributed variables, respectively. Moreover, the receiver operating characteristic (ROC) curve method [15] was used to plot the true positive rate (sensitivity) in function of the false-positive rate (100 – specificity) for different cutoff points of RVSP and of the Qanadli CT index score with respect to the CTPH ml/kg/min as threshold value. A p value <0.05 was considered significant for all analyses.

Results

We consecutively enrolled 25 patients with acute PE. Five out of them did not fall into the inclusion criteria: 2 patients for coexistent ischemic heart disease, 2 patients for the presence of neoplastic disorders, and 1 patient was lost to follow-up. The remaining 20 patients (11 males and 9 females, mean age ± SD 63 ± 16 years) represent our study cohort. There were no deaths due to PE complications.

On admission, in all patients the Qanadli CT index median (1st quartile; 3rd quartile) was 47.5% (25; admis-

<table>
<thead>
<tr>
<th>NYHA class</th>
<th>On admission</th>
<th>At 24 months</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>2 [2; 3]</td>
<td>2 [1; 2]</td>
<td>0.001</td>
</tr>
<tr>
<td>RVEDV, ml</td>
<td>54.1 ± 13.9</td>
<td>47.1 ± 12.9</td>
<td>0.001</td>
</tr>
<tr>
<td>RVSP, mm Hg</td>
<td>39.6 ± 12.9</td>
<td>34.0 ± 10.1</td>
<td>0.018</td>
</tr>
<tr>
<td>RAA, cm²</td>
<td>20.1 ± 3.2</td>
<td>18.0 ± 2.8</td>
<td>0.005</td>
</tr>
<tr>
<td>RVFS, %</td>
<td>22 [20; 24.7]</td>
<td>25 [22; 26.2]</td>
<td>0.007</td>
</tr>
<tr>
<td>RAV, ml</td>
<td>19.2 ± 3.2</td>
<td>18.1 ± 3.2</td>
<td>0.092</td>
</tr>
<tr>
<td>PFAT, ms</td>
<td>121.2 ± 25.2</td>
<td>129.1 ± 29.0</td>
<td>0.213</td>
</tr>
<tr>
<td>TAPSE, mm</td>
<td>21.4 ± 3.9</td>
<td>22.5 ± 3.7</td>
<td>0.191</td>
</tr>
</tbody>
</table>

Data are shown as means ± SD or medians [1st quartile; 3rd quartile].

Table 2. Correlations between the Qanadli CT index score and echocardiographic parameters evaluated on admission

<table>
<thead>
<tr>
<th>Variables</th>
<th>r or ρ</th>
<th>r²</th>
<th>β</th>
<th>95% CI</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>RVEDV (ml)</td>
<td>0.151</td>
<td>0.023</td>
<td>0.347</td>
<td>–0.78 to 1.47</td>
<td>0.525</td>
</tr>
<tr>
<td>RVSP (mm Hg)</td>
<td>0.152</td>
<td>0.023</td>
<td>0.377</td>
<td>–0.83 to 1.59</td>
<td>0.521</td>
</tr>
<tr>
<td>RAA (cm²)</td>
<td>0.038</td>
<td>0.001</td>
<td>0.380</td>
<td>–4.54 to 5.30</td>
<td>0.873</td>
</tr>
<tr>
<td>RVFS (%)</td>
<td>–0.204</td>
<td>0.006</td>
<td>–0.535</td>
<td>–3.94 to 2.87</td>
<td>0.745</td>
</tr>
<tr>
<td>RAV (ml)</td>
<td>0.214</td>
<td>0.046</td>
<td>1.791</td>
<td>–2.25 to 5.84</td>
<td>0.365</td>
</tr>
<tr>
<td>PFAT (ms)</td>
<td>–0.196</td>
<td>0.038</td>
<td>–0.248</td>
<td>–0.86 to 0.367</td>
<td>0.408</td>
</tr>
<tr>
<td>TAPSE (mm)</td>
<td>–0.389</td>
<td>0.152</td>
<td>–3.024</td>
<td>–6.56 to 0.52</td>
<td>0.090</td>
</tr>
</tbody>
</table>

Data are shown as Pearson r and Spearman ρ according to the distribution of variables.

Results

Table 3. Comparison of NYHA classes and echocardiographic variables on admission for acute PE between patients with and without CTPH at the 24-month follow-up

<table>
<thead>
<tr>
<th>Variables</th>
<th>Patients with CTPH (n = 9)</th>
<th>Patients without CTPH (n = 11)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CTPA scan score, %</td>
<td>66.7 ± 29.0</td>
<td>40.0 ± 27.1</td>
<td>0.048</td>
</tr>
<tr>
<td>NYHA class</td>
<td>3 [2; 3.5]</td>
<td>2 [2; 2]</td>
<td>0.007</td>
</tr>
<tr>
<td>RVEDV, ml</td>
<td>60.6 ± 15.4</td>
<td>48.0 ± 8.0</td>
<td>0.030</td>
</tr>
<tr>
<td>RVSP, mm Hg</td>
<td>47.1 ± 13.3</td>
<td>33.0 ± 6.8</td>
<td>0.007</td>
</tr>
<tr>
<td>RAA, cm²</td>
<td>21.8 ± 2.5</td>
<td>19.0 ± 3.0</td>
<td>0.040</td>
</tr>
<tr>
<td>RVFS, %</td>
<td>20 [15; 24]</td>
<td>24 [21; 25]</td>
<td>0.085</td>
</tr>
<tr>
<td>RAV, ml</td>
<td>21.7 ± 3.1</td>
<td>18.5 ± 3.6</td>
<td>0.053</td>
</tr>
<tr>
<td>PFAT, ms</td>
<td>111.6 ± 29.2</td>
<td>127.5 ± 16.9</td>
<td>0.143</td>
</tr>
<tr>
<td>TAPSE, mm</td>
<td>20.1 ± 4.5</td>
<td>22.1 ± 3.3</td>
<td>0.272</td>
</tr>
</tbody>
</table>

Data are shown as means ± SD or medians [1st quartile; 3rd quartile].

pared to admission. By contrast, no differences in RAV, PFAT and TAPSE were found. NYHA classes and the echocardiographic parameters evaluated on admission and at the 24-month follow-up are reported in table 1.

The correlations between the Qanadli CT index score and echocardiographic parameters evaluated on admission are listed in table 2. No significant correlations between the Qanadli CT index score and TTE were found.

The number of patients with RVD on admission was 16 (80%). Nine out of these (45%) had a CTPH with a significant increase (>30 mm Hg) in RVSP at the 24-month follow-up. Patients with CTPH significantly differed in NYHA class, in RVEDV, RVSP and RAA and in the Qanadli CT index on admission, as compared to the patients without CTPH (table 3). According to the
ROC curve analysis, the plot of the true-positive rate in function of the false-positive rate for different cutoff points of RVSP on admission with respect to CTPH showed an AUC value of 0.828 (p = 0.014). The RVSP on admission that maximized sensitivity and specificity was 42.5 mm Hg (0.67 sensitivity and 1.0 specificity). According to the ROC curve analysis, the plot of the true-positive rate in function of the false-positive rate for different cutoff points of the Qanadli CT index with respect to CTPH showed an AUC value of 0.763 (p = 0.048). The Qanadli CT index score on admission that maximized sensitivity and specificity was 42.5% (0.89 sensitivity and 0.64 specificity).

In addition, a significant distribution ($\chi^2 = 5.69$, $p = 0.017$) was found in the analysis of patients with CTPH at 24 months and the Qanadli CT index, categorized by the ROC curve cutoff value of 42.5% (fig. 1). Another significant distribution ($\chi^2 = 4.09$, $p = 0.043$) was found in the analysis of patients with CTPH at 24 months and RVSP on admission, categorized as PH (>30 mm Hg) (fig. 1).

**Discussion**

The main finding of the present study is that in patients with PE, the occurrence of CTEPH at the 24-month follow-up is associated with PH (RVSP >30 mm Hg) and with a high Qanadli CT index score, both of them recorded at baseline. In addition, we found that the scan score and parameters of transthoracic echocardiography were not related, when both of them are recorded at the time of the diagnosis of the PE episode.

Following a thromboembolic event, after a period of clinical stability, symptoms of CTPH may occur. This phenomenon may be related to progression of PH with progressive and poorly reversible remodeling of the arterial pulmonary branches to be clogged, due to the increased blood flow [16]. Some worsening of PH may occur even in the absence of further embolic episodes [17]. The progression of CTPH may be slow and insidious, and in patients who had suffered from acute PE this condition can be diagnosed even after more than 1 year [18]. The capability of the right ventricle to cope with a progressive increase in pulmonary arterial pressure is the main determining factor for the functional capacity and survival of these patients [3]. Therefore, the morphological and functional evaluation of the right ventricle is crucial in the diagnosis and follow-up of this disorder.

Findings consistent with PH at TTE usually are the first steps that lead cardiologists to diagnose CTPH [3]. In patients at high risk of developing CTPH, the TTE routine assessment may be helpful to detect a long-term persistency of PH after an acute episode of PE [18]. Venous thromboembolism, older age and the extension of pulmonary vascular obstruction during the episode of PE are considered as risk factors of CTPH [18]. In addition, CTPH may be due to a complex interaction between thrombotic/thrombolytic processes and angiogenic cellular remodeling of organized thrombi. Notably, Morris [19] showed that fibrin from patients with CTPH was more resistant to plasmin-mediated fibrinolysis than fibrin from healthy control subjects.

In the present study, we found that 45% of patients had a CTPH with a significant increase (>30 mm Hg) in RVSP...
at the 24-month follow-up. Patients with CTPH were 9 years older (68 ± 13 vs. 59 ± 17 years) than patients without CTPH, even if this difference did not reach statistical significance. In addition, patients with CTPH significantly differed in NYHA class, in echocardiography parameters and in Qanadli CT index on admission, as compared to the patients without CTPH. In other words, the clinical picture as well as the echocardiographic features of the RVD and the extension of pulmonary vascular obstruction of an acute episode of PE were associated with the long-term occurrence of CPTPH. Our results are in line with a previous study, which reported that patients with persistent PH at the 1-year follow-up were 44% of the entire sample of patients, were older and presented with a higher level of pulmonary artery systolic pressure than those who recovered PH [20]. It is of note that according to the ROC curve analysis, in our study we additionally provided a cutoff value for baseline RVSP and for the Qanadli CT index score, which are associated with a high likelihood with the CTPH.

In this study, we did not find any relationship between the Qanadli CT obstruction index and the parameters of echocardiography, as recorded at the time of the diagnosis of the PE episode. This finding suggests a complementary role of the two diagnostic tools in the assessment of PE. Interestingly, in patients with CTPH, Liu et al. [10] showed that the pulmonary artery obstruction, as assessed by the Qanadli CT index, was not related to pulmonary vascular resistance measured by means of right heart catheterization.

A limitation of this study is the small number of patients recruited and therefore, our findings must be considered with prudence. In addition, although it is indeed an excellent screening method with high sensitivity and specificity in patients with suspected PH [20], TTE is not the gold standard diagnostic tool in these patients. Lastly, we lack information about CTPA at follow-up. However, previous findings do not support the routine use of follow-up CTPA imaging in patients treated for acute PE [11].

In conclusion, our study demonstrates that in patients with acute PE, there is a lack of relationship between the Qanadli CT obstruction index and TTE parameters on admission to the hospital. However, the occurrence of CTEPH at the 24-month follow-up is associated with PH and with a high Qanadli CT obstruction index score.

Financial Disclosure and Conflicts of Interest

The authors declare that they have no conflict of interest to declare.

References


