

Computed tomography pulmonary embolism residua index (CTPER-index): a simple tool for pulmonary embolism residua description

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ABSTRACT

Objective: Chronic thromboembolic pulmonary hypertension (CTEPH) is a relatively common long-term complication of acute pulmonary embolism (PE) with severely negative impact on the patient's quality of life and prognosis. The aim of our study was to assess morphological changes, with respect to CTEPH development, in the pulmonary artery vascular bed 6 months after diagnosis of acute PE as the first thromboembolic event in the patient's history.

Methods: Our prospective study included a population of 87 consecutive patients with proven PE. Multidetector computer tomography pulmonary arteriography (CTA) was performed 6 months after acute PE to assess residua of thrombi and abnormalities supporting the presence of pulmonary hypertension. To quantify the individual totality of morphological abnormalities, a computer tomography pulmonary embolism residua index (CTPER-index) was constructed and groups of patients with and without CTEPH were compared. The study follow-up was 24 months, with echocardiography performed 6, 12, and 24 months after PE.

Results: Morphological abnormalities corresponding to thrombi residua or pulmonary hypertension on CTA were found in 68% of patients. The CTPER-index reached significantly higher values in patients with CTEPH during a 2-year follow-up. A CTPER-index value ≥ 4 equates to a 12-fold higher risk of CTEPH development ($p=0.013$) with sensitivity 0.80 (95% CI 0.31; 0.989) and specificity 0.79 (95% CI 0.754; 0.799).

Conclusion: Our CTPER-index may provide useful information for a clinician performing CTA for differential diagnosis of dyspnea in a patient with a history of PE. (*Anatol J Cardiol* 2016; 16: 270-5)

Keywords: chronic thromboembolic pulmonary hypertension, CTPER-index, pulmonary embolism residua

Introduction

In the past few years, we have been witnessing an increasing interest in pulmonary circulation diseases. Specific pharmacotherapy and particularly mastery of pulmonary endarterectomy (PEA) offers us the potential also to deal with such a prognostically unfavorable illness as chronic thromboembolic pulmonary hypertension (CTEPH). Importantly, PEA also offers hope for an eventual full recovery (1).

CTEPH is presumed to arise from a single or recurrent thrombotic pulmonary embolism (PE), which is probably the trigger for other functional and structural changes in both obstructed and unobstructed areas of the pulmonary artery vascular bed. The residua of incompletely resolved thromboembolic material leads to increased pulmonary artery pressure, increased wall shear stress, and endothelial dysfunction. Ensuing changes include vascular smooth muscle hypertrophy, intimal thickening and

fibrotization, and plexiform lesion formation (2). A pathophysiological vicious circle is then completed by right ventricle (RV) hypertrophy and dilatation, resulting in secondary tricuspid valve insufficiency and finally RV failure. In addition, in situ thrombosis and pulmonary emboli extension into unobstructed areas may be involved. We also cannot exclude the possibility of embolization of partially organized thrombi, which do not respond either to endogenous or pharmacological fibrinolysis. Moreover, inflammation, infection, and genetic predispositions are thought to be pathophysiological trigger features.

The incidence of symptomatic CTEPH is believed to be approximately 3.8% among patients surviving pulmonary embolism (3); however, the incidence data varies from 0.5% to 9.1% (3-9).

The simplest way to exclude CTEPH is a ventilation-perfusion lung scan. However, in some cases it can fail, with false-positive or intermediate findings (10). The gold standard for CTEPH diagnosis and assessment for operability is an invasive

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pulmonary angiography. However, contemporary multidetector CT seems to have similar diagnostic power.

Methods

Between July 2007 and March 2010, 163 consecutive patients with PE over the age of 18 years were admitted to our tertiary specialized department (1st department of cardioangiology, University hospital and Medical Faculty of Charles University in Hradec Kralove). Diagnosis of PE was based on multidetector computer tomography pulmonary angiography (CTA) (in 161 patients); perfusion lung scan (one patient with iodine allergy); and on a combination of history, clinical presentation, duplex lower limb sonography, and echocardiography (in one patient). Two patients died early (on the second and fourth hospitalization day). Patients with a previous history of venous thromboembolism were excluded as well as patients with left ventricle, valvular, lung, or systemic connective tissue disease. In addition, non-consenting patients, patients who were apparently non-compliant, or those in the terminal stage of a concomitant illness were excluded from the follow-up. The remaining 120 consecutive patients having none of the abovementioned exclusion criteria signed an informed consent (approved by the local Ethics Committee) for a 2-year follow-up in our prospective study. Unfortunately, there was a decline in the number of patients during follow-up for several reasons: death [stroke (2), oncological disease (8), pneumonia (2), unknown cause but not due to RV failure (1)], immobility, change of residence, non-compliance, and renal impairment. Therefore, a control CTA was performed 6 months after acute PE in 87 patients. The baseline characteristics of our study cohort are listed in Table 1.

All patients were treated according to recent guidelines (11, 12). Thrombolysis (alteplase) was used in 10.8% cases. The remaining 89.2% patients were stable with anticoagulant therapy [unfractionated heparin or low-molecular weight heparin (enoxaparin), followed by a vitamin K antagonist (warfarin)].

Patients with echocardiographic signs of pulmonary hypertension underwent ventilation-perfusion lung scan to verify/exclude ventilation-perfusion mismatch. Symptomatic patients were encouraged to undergo right heart catheterization at our tertiary university hospital or were referred to a centre of excellence for pulmonary hypertension.

Echocardiography [PHILIPS SONOS 5500 (Philips Ultrasound, Massachusetts, U.S.A) or GE Vivid 7 (GE Healthcare, Milwaukee, U.S.A.)] with an emphasis on pulmonary artery systolic pressure, RV diameter, and RV systolic function was performed on admission (or within the first 24 h); before discharge (on average 8 days after an acute phase); and 6, 12, and 24 months after PE. The upper borderline of pulmonary artery systolic pressure (PAsP) normality was 36 mm Hg. Higher values were considered to be possible pulmonary hypertension.

In accordance with the follow-up schedule, a contrast-enhanced multidetector spiral pulmonary CTA was performed

Table 1. Baseline study population characteristics

| | |
|---|------------------------------|
| Number of patients, n | 87 |
| Age, years | 57.2±15.8 |
| Women, n (%) | 41 (47.1) |
| BMI, kg/m ² | 29±5.42 |
| Systemic systolic blood pressure, mm Hg | 135±23.7 |
| Systemic diastolic blood pressure, mm Hg | 80.6±14.1 |
| PE described as extensive, n (%) | 32 (36.8) |
| Smokers, n (%) | 19 (21.2) |
| Steroid hormone therapy, n (%) | 16 (18.4) |
| History of trauma/surgery/ immobilization, n (%) | 10 (11.5)/9 (10.3)/10 (11.5) |
| Concurrent oncological disease, n (%) | 11 (12.6) |
| Thrombophilia (known or newly detected), n (%) | 14 (16.1) |
| NT-proBNP, pmol/L | 201±482 |
| Troponin T, µg/L | 0.027±0.0503 |
| Echocardiographic parameters on admission | |
| Right ventricle diameter, mm | 31.1±4.17 |
| PAsP, mm Hg | 50.5±16.9 |
| TAPSE, mm | 20.6±4.56 |
| Sa _{Tr_l} , cm/s | 12.6±2.63 |
| Data expressed as mean±SD, number, or percentage. BMI, body mass index; NT-proBNP, N-terminal fragment of brain natriuretic peptide; PAsP - pulmonary artery systolic pressure; PE - pulmonary embolism; Sa _{Tr_l} - tissue Doppler velocity of lateral tricuspid annular systolic excursion; TAPSE - tricuspid annular plane systolic excursion | |

during the 6-month visit. Data were acquired with Siemens Somatom Emotion 6 (Siemens AG, Germany) with 6 × 1 mm collimation, pitch 1.8, 130 kV, 110–150 mA, with 0.8 s scanning time. The contrast agent (Iomerone 400, Bracco U.K. Ltd) was injected (Stellant CT Injection Systems, MEDRAD Inc. U.S.A) at a rate of 3 mL/s to a total volume of 60-85 mL into a 20-gauge peripheral venous catheter in the antecubital fossa. Scans were obtained during the patient's suspended inspiration in the caudo-cranial direction involving the space between the diaphragm and a level 2 mm above the aortic arch. Images were viewed at settings for pulmonary vasculature (window width 700, level 80 Hounsfield units) and lung parenchyma (window width 1500, level -500 Hounsfield units).

Two experienced radiologists, blinded from the clinical and echocardiographic data, evaluated the scans carefully, searching for residual organized thrombi and patterns suggestive of pulmonary hypertension. The description focused specifically on intraluminal abnormalities (webs, bands, and thrombi wall remnants), stenotic areas, poststenotic dilatations, and obstructions and on findings supporting the presence of pulmonary hypertension (pulmonary artery trunk diameter above 31 mm, dilatation of pulmonary arteries compared to the diameter of concomitant bronchi, and a mosaic perfusion pattern). Abnormalities representing unresolved thrombi were ascribed

two points or one point for findings supporting the presence of pulmonary hypertension, as indicated below. An individual total point count constituted the CTPER-index, thereby allowing abnormality rate quantification. Thus, values could range from 0 to 9.

Data exploration and statistical analysis

Data exploration and statistical analysis were performed using Statistica 10 CZ (StatSoft, Tulsa, USA). Normality was tested by the Shapiro-Wilk test. Continuous data with normal data distribution were assessed by Student’s t-test. Other data were assessed by the Mann-Whitney U test. The significance of hazard ratios was assessed by Fisher’s exact test.

Results

During the follow-up, we saw an expected decrease of PAsP, most remarkable during the hospitalization stay and within the first 6 months (Fig. 1). Through the rest of the follow-up, the decrease of PAsP was not statistically significant. Table 2 draws a comparison between patients with and without CTEPH. CTEPH patients were older and had significantly higher NT-proBNP and estimated PAsP on admission. At the time of discharge, CTEPH patients still had higher NT-proBNP and PAsP and also RV diameter. At the end of follow-up (after 2 years), CTEPH patients had only significantly higher PAsP.

At pulmonary CTA performed 6 months after acute pulmonary embolism, we found abnormalities in more than 2/3rds of our study cohort patients (68%). The most common were webs, bands, and thrombi wall remnants (present in 49% of patients), followed by pulmonary artery dilatation (in 33% cases). The frequencies of all observed findings are listed in Table 3.

In all patients, we aggregated the abnormality points as mentioned above to obtain an individual CTPER-index value. An average CTPER-index throughout our study population was 1.75±1.74

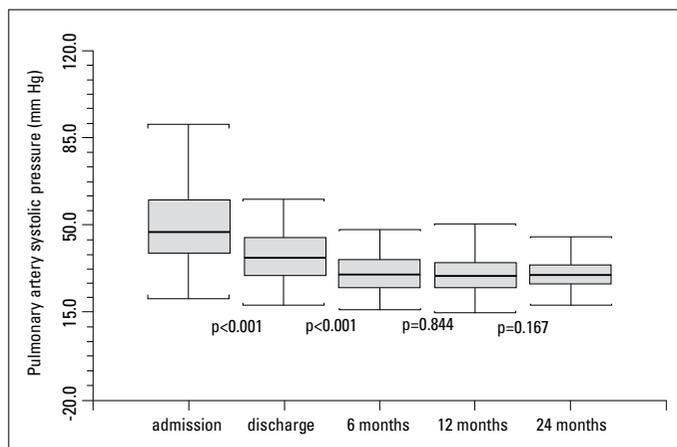


Figure 1. Pulmonary artery systolic pressure during follow-up
Box represents the 1st and 3rd quartile, line in the box represents median, and whiskers represent data variability under the 1st and above the 3rd quartile. P-values represent the significance of pulmonary artery systolic pressure change between visits. Mann-Whitney U test was used

points. We found a statistically significant difference between the group with echocardiographic signs of pulmonary hypertension and the group without pulmonary hypertension at the 6-month visit. This difference was even more remarkable when we divided the patients according to their 12-month echocardiography findings and particularly in patients with diagnosis of CTEPH at the end of follow-up, as shown in Table 4. A CTPER-

Table 2. Characteristics of CTEPH and non-CTEPH patients

| | CTEPH patients n=4 | Non-CTEPH patients n=83 | P |
|---------------------------------------|-----------------------|----------------------------|--------|
| Age, years | 74.6±1.57 | 56.4±15.8 | 0.011 |
| Gender, women, n (%) | 2 (50) | 39 (47) | |
| Initial NT-proBNP, pmol/L | 1408±1665 | 154±291 | 0.009 |
| Initial PAsP, mm Hg | 73.8±19.2 | 50±16.6 | 0.018 |
| RV diameter on admission, mm | 34±2 | 31±4.23 | 0.689 |
| TAPSE on admission, mm | 16.75±4.5 | 21±4.54 | 0.091 |
| Sa _{Tri} on admission, cm/s | 10.1±1.46 | 12.8±2.63 | 0.027 |
| BMI | 25.4±2.7 | 29.2±5.21 | 0.083 |
| Discharge NT-proBNP, pmol/L | 464±704 | 23.0±58.9 | 0.005 |
| Discharge PAsP, mm Hg | 60.8±20.5 | 36.4±9.22 | 0.011 |
| Discharge RV diameter, mm | 33±1.8 | 29.1±3.7 | 0.017 |
| Discharge TAPSE, mm | 20.5±3.7 | 23.3±3.83 | 0.201 |
| Discharge Sa _{Tri} , cm/s | 12±4.1 | 13±2.22 | 0.628 |
| PAsP after 2 years, mm Hg | 53.5±20 | 29.8±5.69 | <0.001 |
| RV diameter after 2 years, mm | 30±5.7 | 26.7±2.98 | 0.159 |
| TAPSE after 2 years, mm | 21±5.6 | 24.1±3.69 | 0.195 |
| Sa _{Tri} after 2 years, cm/s | 12.9±4.9 | 14±2.40 | 0.958 |

Student’s t-test used for BMI. Mann-Whitney U test used for all others variables. Data expressed as mean±SD or percentage. P-values refer to the comparison of the two subgroups. BMI - body mass index; CTEPH - chronic thromboembolic pulmonary hypertension; NT-proBNP - N-terminal fragment of brain natriuretic peptide; PAsP - pulmonary artery systolic pressure; RV - right ventricle; Sa_{Tri} - tissue Doppler velocity of lateral tricuspid annular systolic excursion; TAPSE - tricuspid annular plane systolic excursion

Table 3. Frequencies of CTA abnormalities 6 months since acute PE and their valuation

| Type of abnormality | Frequency (%) | Value (points) |
|---|---------------|----------------|
| Webs, bands, thrombi wall remnants | 49 | 2 |
| Stenotic arteries | 11 | 2 |
| Sudden artery dilatations | 16 | 2 |
| Obstructions | 2 | 2 |
| Pulmonary artery trunk dilatation | 15 | 1 |
| Pulmonary arteries dilatation compared to concomitant bronchi | 33 | 1 |
| Mosaic perfusion pattern | 17 | 1 |

Frequency expressed as percentage of positive findings; Value express the weight in CTPER-index

Table 4. CTPER-index in patients with and without CTEPH during follow-up

| Months | Patients with CTEPH | | | Patients without CTEPH | | | P |
|--------|---------------------|-----------------------------|-----------------------------|------------------------|-----------------------------|-----------------------------|-------|
| | median | 25 th percentile | 75 th percentile | median | 25 th percentile | 75 th percentile | |
| 6 | 3 | 1 | 5 | 1 | 0 | 3 | 0.017 |
| 12 | 4 | 1 | 5 | 2 | 0 | 3.25 | 0.045 |
| 24 | 5 | 4 | 7 | 2 | 0 | 3 | 0.008 |

Mann-Whitney U test used. P-values refer to the comparison of the two subgroups. CTEPH - chronic thromboembolic pulmonary hypertension

Table 5. Cut-off values of CTPER-index in patients with CTEPH (based on Fisher's exact test)

| CTPER-index | HR (95% CI) | sensitivity (95% CI) | specificity (95% CI) | P |
|-------------|--------------------|----------------------|----------------------|-------|
| ≥3 | 6.0 (0.665; 140) | 0.8 (0.307; 0.989) | 0.627 (0.594; 0.639) | 0.151 |
| ≥4 | 12.0 (1.35; 281) | 0.8 (0.31; 0.989) | 0.787 (0.754; 0.799) | 0.013 |
| ≥5 | 7.73 (1.11; 63.8) | 0.6 (0.177; 0.925) | 0.867 (0.939; 0.888) | 0.028 |
| ≥6 | 5.26 (0.636; 34.8) | 0.4 (0.075; 0.815) | 0.907 (0.885; 0.934) | 0.095 |
| ≥7 | 8.22 (1.01; 48.4) | 0.4 (0.076; 0.797) | 0.947 (0.925; 0.973) | 0.043 |

CI - confidence interval; CTEPH - chronic thromboembolic pulmonary hypertension; HR - hazard ratio

Table 6. Characteristics of patients with CTPER-index <4 and ≥4 points

| | CTPER-index <4 n=77 | CTPER-index ≥4 n=10 | P |
|---------------------------------------|------------------------|------------------------|--------|
| Age, years | 56.3±16.1 | 61.7±14.7 | 0.217 |
| Gender, women, n (%) | 37 (48) | 5 (50) | |
| Initial NT-proBNP, pmol/L | 206±525 | 181±212 | 0.236 |
| Initial PAsP, mm Hg | 48.8±15.8 | 58.3±20.3 | 0.071 |
| RV diameter on admission, mm | 30.9±4.46 | 32.5±2.23 | 0.170 |
| TAPSE on admission, mm | 20.7±4.77 | 20.2±3.75 | 0.735 |
| Sa _{Tri} on admission, cm/s | 12.9±2.71 | 11.5±1.96 | 0.076 |
| BMI | 29.1±5.25 | 28.4±4.92 | 0.323 |
| Discharge NT-proBNP, pmol/L | 44.8±187 | 30.6±52.5 | 0.440 |
| Discharge PAsP, mm Hg | 36.2±9.53 | 44.4±15.6 | 0.051 |
| Discharge RV diameter, mm | 28.8±3.68 | 31.5±3.04 | 0.005 |
| Discharge TAPSE, mm | 23.4±3.72 | 20.1±4.37 | 0.291 |
| Discharge Sa _{Tri} , cm/s | 13.3±2.33 | 12.0±2.0 | 0.189 |
| PAsP after 2 years, mm Hg | 29.6±5.06 | 37±15.7 | 0.089 |
| RV diameter after 2 years, mm | 26.5±2.99 | 28.5±3.62 | 0.014 |
| TAPSE after 2 years, mm | 24.9±3.83 | 23.7±3.92 | 0.678 |
| Sa _{Tri} after 2 years, cm/s | 13.9±2.4 | 14.2±3.17 | 0.519 |
| CTPER index, points | 1.11±1.09 | 4.8±0.77 | <0.001 |

Student's t-test used for BMI. Mann-Whitney U test used for all others variables. Data expressed as mean±SD or percentage. P-values refer to the comparison of the two subgroups. BMI - body mass index; CTEPH - chronic thromboembolic pulmonary hypertension; NT-proBNP - N-terminal fragment of brain natriuretic peptide; PAsP - pulmonary artery systolic pressure; RV - right ventricle; Sa_{Tri} - tissue Doppler velocity of lateral tricuspid annular systolic excursion; TAPSE - tricuspid annular plane systolic excursion

index value ≥4 was found to confer a 12-fold higher risk of CTEPH development (p=0.013) with both high sensitivity (0.8) and specificity (0.787) (Table 5).

There was no statistically significant difference in the quantity of thrombi residuals between treatment types (thrombolysis × anticoagulation alone) and between patients with an extensive or non-extensive PE in the acute state, although an extensive PE is one of the CTEPH risk factors.

Table 6 shows the characteristics of patient groups with CTPER-index value <4 and ≥4 points. Patients with CTPER-index value ≥4 had only significantly higher estimated RV diameter at the time of discharge and during the rest of follow-up. Except for this, there are no significant differences between these two groups even in PAsP. The explanation is probably a small number of CTEPH patients in the group with CTPER-index ≥4 and only one CTEPH patient having severe RV dysfunction.

Discussion

In our prospective study population, we have noticed rather high values of on admission PAsP in some patients, resulting in a high average PAsP on admission (Table 1). We cannot exclude that some of these patients had a pre-existing asymptomatic and thus untreated successive PE leading to pulmonary hypertension chronicity. Nevertheless, these patients met our study inclusion criterion of having a first symptomatic thromboembolic event and should receive anticoagulant therapy for at least 3 months before diagnosis of CTEPH is proved. Thus, we will hardly ever be able to exclude all such patients, except those with marked RV hypertrophy on admission.

There was an expected decrease in PAsP during follow-up, being statistically significant during the first 6 months.

Significantly higher RV diameter in the CTEPH group was observed only during hospitalization stay. As mentioned above, some of these patients could have previous untreated asymptomatic pulmonary thromboembolic events and worse on admission parameters fading away during anticoagulant treatment.

There was no difference in RV function between these two groups on admission and at the time of discharge, which does not support a suspicion of pre-existing severe CTEPH.

Our data are indicating a rather high number of abnormal findings, which is probably due to better image quality using multidetector CT in contrast to the abovementioned studies. However, in comparison with a recent study (13) related to this topic and using 64-row multidetector CT, the number is unexpectedly high. This contrast can be explained by the relatively small study cohorts that can be markedly different, particularly in initial PE risk categorization which is not mentioned. Our study involved only patients considered for hospital admission; no PE patients treated in the outpatient setting were involved. This issue is not discussed in any of the relevant papers.

Thromboembolic masses in the pulmonary vascular bed are generally resolved early [in experiments within 4-6 weeks (14, 15)] by the endogenous fibrinolytic system or become organized if unresolved. Residual findings in the pulmonary vascular bed after PE have been described in several studies based on perfusion lung scanning (16-19) or CTA (Table 7) (13, 20).

Persisting vascular obstruction and secondary vessel wall changes cause CTEPH in approximately 4% of patients surviving PE. The diagnosis should be made as soon as possible to prevent progression of RV overload and dysfunction and to improve prognosis and the patient's quality of life. Most importantly, the possibility of CTEPH must be taken into diagnostic consideration because it is an often under-diagnosed disease (21). Every tool helping us to reveal CTEPH in the early disease stages is welcome because we are still not able to identify patients who develop CTEPH after PE for effective follow-up.

The differential diagnostic program for dyspnea of course generally does not start with CT or CTA, but if performed, whether in an elective or acute regimen, attention should be paid also to less common and less noticeable changes. We should also be aware that the first clinical presentation of CTEPH can mimic PE, as published recently (22). We chose CTA also because it represents a noninvasive tool not only for the diagnosis of CTEPH but also may be helpful for the estimation of suitability for pulmonary endarterectomy too.

Table 7. Studies with systematic lung perfusion or CTA scanning after PE

| | Method | Time (months) | Abnormal findings (%) | n |
|-------------------------|-------------------------------|---------------|-----------------------|-------|
| UPET trial (16) | Perfusion lung scan | 3 | 16 | 105 |
| Wartski et al. (17) | Perfusion lung scan | 3 | 66 | 157 |
| Sanchez et al. (18) | Perfusion lung scan | 12 | 29 | 254 |
| Cosmi et al. (19) | Perfusion lung scan/ MDCTA | 9 | 28/15 | 93/80 |
| Remy-Jardin et al. (20) | CTA (single slice) | 11 | 52 | 62 |
| Pesavento et al. (13) | CTA (64-row) | 6 | 15 | 113 |

CTA - computer tomography angiography; MDCTA - multidetector computer tomography angiography; PE - pulmonary embolism; UPET - The urokinase pulmonary embolism trial

Study limitations

A possible limitation of our study is the relatively small cohort of patients and the study monocentricity. More accurate conclusions could be reached if more pulmonary hypertension-related changes at CTA could be assessed [e.g., RV dilatation and hypertrophy, bronchopulmonary collateral circulation, interventricular septum curvature measurement etc.]. Newer techniques such as dual-energy CT could be used to obtain more detailed and complex information, even about pulmonary hemodynamics.

Conclusion

We of course do not suggest routine CTA scanning during follow-up of patients with PE history. However, it is highly important to exclude not only an acute thromboembolic event but also previous PE residua when CTA is performed in a patient with PE history during differential diagnosis of dyspnea. In those (not rare) cases, our CTPER-index, as described above, can become a useful tool for directing further diagnostic and therapeutic efforts. Another larger study would be welcome for the external validation of our results.

Conflict of interest: None declared.

Peer-review: Externally peer-reviewed.

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