Can the CT by-product Time to threshold be a prognostic factor in patients with acute pulmonary embolism?

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Abstract

Introduction: Bolus tracking is applied in computed tomography pulmonary angiography. The time that it takes for contrast to reach a predefined threshold in the pulmonary artery is called time to threshold (TTT). Our purpose was to analyse possible associations between TTT and circulatory state and prognosis in patients with acute pulmonary embolism (PE).

Methods: In a single-centre, retrospective study 138 patients with PE and contrast administration via peripheral venous line were included. Clinical parameters of circulatory state were arterial pH, systolic blood pressure, heart rate, sPESI score, Wells score and GENEVA score. Survival was defined as surviving the following 30 days after the PE diagnosis.

Results: Time to threshold was only weakly correlated with FiO2 (r = 0.26, P = 0.04), pH (r = −0.22, P = 0.009), venous base excess (r = −0.18, P = 0.04) and venous lactate (r = 0.21, P = 0.01). TTT did not correlate with clinical parameters/scores and mortality. There were weak associations between TTT and blood gas analysis parameters. There were no associations with clinically relevant prognosis scores and overall survival.

Conclusion: Therefore, albeit TTT is an easily assessable parameter of CTPA, the potential use in clinical routine is limited for prognosis stratification in patients with PE.

Key words: CT; pulmonary embolism; time to threshold.

Introduction

Acute pulmonary embolism (PE) is a possible life-threatening cardiovascular disease with 30-day mortality rates ranging from 0.5% to over 20% depending on clinical symptoms at presentation.1 However, there are also low-risk clinical courses without severe complications. That is why, an immediate risk stratification of patients with acute PE at time of presentation is crucial for patient care.1,2

Computed tomography pulmonary angiography (CTPA) has been established as diagnostic clinical gold standard in diagnosis of PE. So, sensitivity and specificity were reported in some studies to be up to 100%.3

Some CT signs harbour prognostic information to guide treatment planning and to predict mortality.4 In clinical evaluation, the right ventricle diameter to left ventricle diameter-ratio was identified to be the strongest predictive value and most robust to predict clinical outcomes in patients with acute PE.2

Yet, before the CT scan is obtained, a tracker graph located within the pulmonary trunk is used to time the acquisition of the scan. This is called time to threshold (TTT). This is needed to reach the best contrast media filling of the pulmonary arteries and to visualize the thrombi. It was previously shown that this parameter is associated with pulmonary hypertension and right ventricular dysfunction.5,6 Another study demonstrated that a time-density curve derived from CTPA with a test bolus technique was correlated with mortality.7

Therefore, TTT could be associated with the circulatory state, clinical parameters and ultimately with prognosis in patients with PE. This would be crucial as TTT arises as a by-product in every CTPA examination and a novel biomarker could be easily obtained. In a small single-centre study, several weak associations between TTT and clinical parameters in PE were shown.5

The purpose of the present study was to investigate, whether TTT is associated with clinical parameters in PE.
Methods

This retrospective study was approved by the institutional review board (Nr: 118/19-ck, Ethics Committee, University of Leipzig).

The patient sample was obtained from a study sample, which assessed the associations between CT pulmonary embolism score and clinical features in patients with PE. The CT scans were obtained between 2015 and 2018. There were overall 138 patients (58 females, 42%) with a mean age of 63.4 ± 18.1 years, range 19–100 years.

Imaging technique

Computed tomography pulmonary angiography was performed on a 128-slice CT scanner (Ingenuity 128, Philips, Hamburg, Germany). Intravenous administration of an iodine-based contrast medium (60 mL Imeron 400 MCT, Bracco Imaging Germany GmbH, Konstanz, Germany) was given at a rate of 4.0 mL/s via a peripheral venous line. Automatic bolus tracking was performed in the pulmonary trunk with a trigger of 150 Hounsfield units (HU). The TTT was generated by the CT scanner and displayed as a graph. Typical imaging parameters were as follows: 100 kVp; 125 mAs; slice thickness = 1 mm; and pitch = 0.9. CTPA was performed in every case in deep inspiration level.

Clinical parameters

The following clinical scores were calculated: Wells score, revised Geneva score, and sPESI score. Serologically, D-dimer level (µg/mL), lactate (venous blood, mmol/L), pH (venous blood), troponin (pg/mL) and N-terminal natriuretic peptide (BNP, pg/mL) were acquired for the study. Additionally, a risk stratification of PE was performed according to the American Heart Association (AHA) as follows: low risk PE, submassive PE and massive PE.

Statistical analysis

The statistical analysis and graphics creation were performed using GraphPad Prism (GraphPad Software, La Jolla, CA, USA). Collected data were evaluated by means of descriptive statistics (absolute and relative frequencies). Pearson’s correlation coefficient (r) was used to analyse associations between investigated scores after testing for normality distribution. Group differences were calculated with Mann–Whitney test. In all instances, P-values <0.05 were taken to indicate statistical significance.

Results

Time to threshold ranged from 3 to 40 s with a median of 10 s. There were no correlations with clinical scores (Wells score, GENEVA score, and sPESI), and with mortality (P > 0.05, respectively). There was no correlation with systolic blood pressure and heart frequency. No correlation was identified with Troponin-level, BNP and D-Dimer.

Weak correlations were identified with FiO2 (r = 0.26, P = 0.04) with pH (r = −0.22, P = 0.009), venous base excess (r = −0.18, P = 0.04) and venous Lactate (r = 0.21, P = 0.01), respectively (Fig. 2). Table 1 provides an overview of all correlations.

According to AHA risk stratification groups: 18 patients had massive PE with a mean TTT of 12.6 ± 5.7, 120 patients had a submassive PE with a mean TTT of 11.6 ± 6.1 and 21 patients had a low-risk PE with a TTT of 10.6 ± 4.1. There were no significant differences between the groups (P > 0.05, Fig. 3).

In discrimination analyses, there were no differences in regard of death due to PE (P = 0.9), admission to the ICU (P = 0.21) and intubation (P = 0.4).

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**Fig. 1.** (a) Time dependent graph of the Hounsfield units in a 90-year-old female patient. The TTT was 6 s. The patient was admitted to the intensive care unit. Wells score was 4.5, GENEVA score 4, systolic blood pressure 125 mmHg, Troponin T 17.5 ng/L, BNP 4653 pg/mL. The patient did not die of pulmonary embolism. (b) The axial CT-slide displays the central pulmonary embolism on both sides with full occlusion of both lobar arteries of the lower lobes.
Discussion

The present identified weak associations between TTT and parameters of the blood gas analysis. There were no associations with clinical prognosis scores and overall survival.

In short, TTT as a by-product of CTPA might not be a reliable parameter in patients with PE in clinical routine. TTT can easily be assessed by CTPA as the amount of time the contrast media takes to reach the pulmonary trunk. It is therefore a parameter which should reflect circulatory state. It would be of special interest as a patient with high clinical suspicion, prolongation of the TTT may provide an early hint to the presence of life-threatening PE even before the formal CTPA study is performed.

There were weak associations between TTT with pH, base excess and venous lactate level. According to the literature, serum lactate has been reported as a powerful predictor of short-term PE-related complications and mortality. In another study, it was an independent predictor of mortality with an odds ratio of 0.06. Pathophysiological, the associations between TTT and blood gas parameters should be linked to circulatory state.

TTT is depended on individual factors including anatomical specifications, gender and age specific variables, the size and state of the vascular system, the circulatory state, and pre-existing cardiac disease. Protocol-specific factors include the place where contrast is applied, the viscosity of contrast media, the injection rate, the threshold of the ROI, and the time between ROI scans in phase 2 of the bolus tracking procedure.

In preliminary reports, the clinical benefit of TTT was shown previously. So, Li et al. investigated the time density curves of the region of interest and identified a high area under curve for the upslope time, a parameter very similar to the used TTT, to predict PE-related mortality.

Table 1. Overview of all correlations between Time to threshold with clinical and serologically parameters

| Parameter             | Time to threshold |
|-----------------------|-------------------|
| Overall survival      | \( r = 0.15 \) (\( P = 0.19 \)) |
| Wells Score           | \( r = 0.02 \) (\( P = 0.74 \)) |
| GENEVA                | \( r = -0.08 \) (\( P = 0.32 \)) |
| SPESI                 | \( r = 0.07 \) (\( P = 0.45 \)) |
| Heart frequency       | \( r = -0.10 \) (\( P = 0.25 \)) |
| Systolic blood pressure | \( r = -0.08 \) (\( P = 0.36 \)) |
| Troponine T           | \( r = -0.10 \) (\( P = 0.27 \)) |
| BNP                   | \( r = -0.19 \) (\( P = 0.32 \)) |
| D-Dimer               | \( r = -0.01 \) (\( P = 0.93 \)) |
| venous PH             | \( r = 0.20 \) (\( P = 0.02 \)) |
| venous HCO3-          | \( r = 0.10 \) (\( P = 0.24 \)) |
| venous BE             | \( r = -0.14 \) (\( P = 0.68 \)) |
| venous Lactate        | \( r = 0.21 \) (\( P = 0.01 \)) |

Statistically significant correlations are highlighted in bold.
However, there is to consider that only 5 patients died in this study and that both central and peripheral venous catheters were pooled into the analysis.7

In another study, TTT was weakly correlated with CT parameters of circulatory state, and with mortality.1 Yet, in this mentioned study TTT was only obtained in patients with central venous catheters, which might explain the differences to the present results. This factor should be acknowledged as peripheral venous catheters cause a longer distance for the contrast media.

Another important CT parameter is the quantification of embolus burden.4,12–15 Several scores were proposed. Most commonly Mastora and Qanadli scores are used.12,15 Yet, even these scores were not able to reliably predict mortality and clinical parameters in PE.8 As an important CT parameter is an abnormally increased RV/LV diameter ratio, which is associated with a 2.5-fold risk for all-cause mortality.4 Another interesting parameter could be the differences of muscle attenuation on the ROI images during the contrast media application, which might better reflect circulatory state as the investigated TTT.

There is definite need of larger studies to confirm the present results for a possible translation of TTT as a potential biomarker.

There are several limitations of the present study to address. First, it is a retrospective study with known inherent bias. Second, to harmonize the patient sample, only patients with a peripheral intravenous catheter were included. The present results can therefore not be transferred to patients with central intravenous catheters, which are preferred for patients in acute shock. Third, different flow rates of contrast can have an impact on TTT, which we could not assess for, as it is not routinely recorded in our institution. Moreover, there might be slight differences caused by different contrast media types.

In conclusion, the present study identified weak associations between TTT and blood gas analysis parameters only. There were no associations with clinically relevant prognosis scores and overall survival. Therefore, albeit TTT is an easily assessable parameter of CTPA, the potential use in clinical routine is limited for prognosis stratification in patients with PE.

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