Novel imaging strategies in venous thromboembolism

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CHAPTER

Computed tomography pulmonary perfusion imaging and 3-months clinical outcomes after acute pulmonary embolism

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INTRODUCTION

In recent years new imaging techniques have been developed for the diagnosis of acute pulmonary embolism (PE). With the introduction of computed tomography pulmonary perfusion (CTPP), functional images of PE can be obtained with the use of perfusion images.[1] Previous studies haves shown that the addition of CTPP to routine computed tomography pulmonary angiography (CTPA), which is the current imaging test of choice for the diagnosis of PE, improves the diagnosis of acute PE and could be of value in initial risk stratification as well.[1,2] Moreover, perfusion imaging may also play a role in the long-term prognosis of acute PE: extensive clot burden and perfusion defects at the moment of a PE diagnosis have been associated with persistent perfusion defects after 6 months of treatment occurring in up to 50% of PE patients despite anticoagulant treatment.[3-6] This poor recanalization of occluded pulmonary arteries may in turn lead to increased dead-space ventilation and/or abnormal cardiopulmonary response to exercise, or in worst case scenario to chronic thromboembolic pulmonary disease (CTEPD) or pulmonary hypertension (CTEPH).[7] Therefore, extensive perfusion defects on the initial CTPA scan at the time of PE diagnosis may correlate with a future diagnosis of CTEPH, CTEPD and/or functional limitations.[6-8] In this study, we aimed to evaluate the predictive value of CTPP-assessed perfusion defects at initial PE diagnosis for persistent symptoms and adverse outcomes at 3-month follow-up.

METHODS

This was an exploratory study in which we studied a convenience cohort of 100 consecutive adult patients (≥18 years old) with hemodynamically stable CTPA-confirmed acute PE in whom CTPP was performed as part of routine clinical practice in the Leiden University Medical Center (LUMC) in Leiden, the Netherlands between July 2017 and October 2019. Patients with clinically suspected acute PE were managed according to the YEARS algorithm, including clinical pre-test probability assessment and D-dimer testing.[9] Anticoagulant treatment was started in patients with CTPA-confirmed acute PE. All patients were followed for three months as part of routine clinical practice. The study protocol was approved by the institutional review board of the LUMC, and informed consent requirement was waived due to its observational nature.

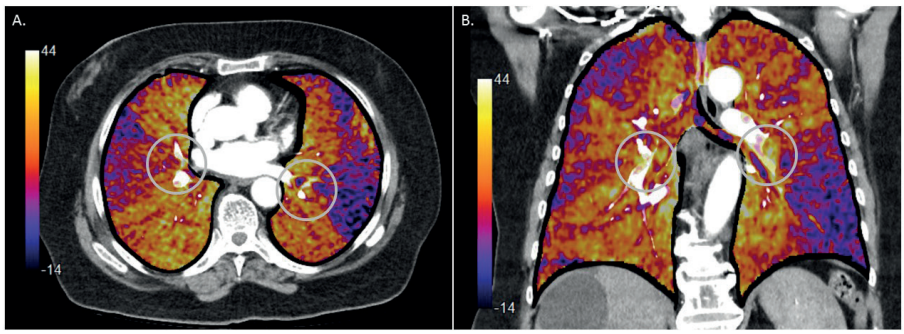
The aim of this analysis was to investigate the predictive value of CTPP-assessed perfusion defects at initial PE diagnosis for persistent symptoms and adverse outcomes at 3-month follow-up. Persistent symptoms included self-reported: 1) dyspnea; 2) chest pain; or 3) post-PE functional impairment. Adverse outcomes included: 1) recurrent venous thromboembolism (VTE); 2) PE-related readmission or; 3) all-cause mortality.

Post-PE functional impairment was defined as new/progressive dyspnea, exercise intolerance and/or diminished functional status following PE adequately treated with anticoagulation for at least 3 months, without an apparent non-PE alternative explanation.[10] PE-related readmission was defined as readmission to hospital due to PE-related complications, such as dyspnea, chest pain, major bleeding or (suspected) recurrent VTE.

CT examinations were performed on a 320-multislice detector row CT scanner (Canon). Perfusion images were obtained with subtraction CT technique in which pre-contrast images are subtracted from contrast-enhanced images. Subsequently, a colour-coded parametric map is produced representing iodine distribution within the lungs, that is fused with the CTPA image. Display settings can be set for normal perfusion: yellow to orange, moderately decreased perfusion: red to purple, severely decreased or absent perfusion: purple to dark blue/black (**Figure 1**). The evaluation of CTPP images was performed by a researcher (L.D.) trained by an expert thoracic radiologist (L.K.) with over 20 years of experience in pulmonary CT reading, and was blinded for symptoms and adverse outcomes. Perfusion defect score (PDS) on CTPP was assessed by using the score proposed by Chae et al. and was expressed as mean PDS in percentages.[2] Additionally, the CTPP images of 24 consecutive patients were independently evaluated by a second reviewer (L.K.) to assess the interobserver agreement for perfusion defect measurement.

Baseline characteristics are described as mean with standard deviation (SD). To assess the correlation between PDS on CTPP and both persistent symptoms and adverse outcomes, differences between mean PDS with corresponding 95% confidence interval (95%CI) in patients with and without persistent symptoms and adverse outcomes were calculated. All statistical analyses were performed in SPSS version 25 (IBM, Armonk, NY, USA).

Figure 1. Colour-coded parametric CT pulmonary perfusion images fused with CT pulmonary angiography images, axial (A) and coronal (B) views of a 68-year-old female patient with an acute pulmonary embolism in the left and right pulmonary arteries (encircled). Several wedge-like dark-coloured areas in both lungs represent hypoperfusion



RESULTS

Of the 100 patients, 7 patients were transferred to another hospital because of logistical reasons. These patients were therefore not taken into account in the following analyses. The mean age of the 93 study patients was 62 years (SD 17), 50 patients (54%) were male, 17 patients (18%) had one or more previous episode(s) of VTE, 25 patients (27%) had an active malignancy and 3 patients (3.2%) had an active infection (urinary tract infection, abdominal infection after complicated pancreaticoduodenectomy and post lumbar laminectomy wound infection) at time of inclusion, 21 patients (23%) had been immobilized for >3 days or had travelled for more than 6 hours by plane or car, and 19 patients (20%) presented with a trauma or surgery in the four weeks before presentation. Mean PDS of the study population was 27% (SD 12). The interobserver agreement of PDS assessment was good with a mean difference in PDS of 4.4% (SD 7.0) between reviewers.

The prevalence of persistent symptoms and adverse outcomes at 3-month follow-up with associated mean PDS are presented in **Table 1**. At 3-months, persistent dyspnea was present in 22 patients (24%), chest pain in 11 (12%) and post-PE functional impairment in 22 patients (24%). None of the patients had been diagnosed with CTEPH at 3-month follow-up. During 3-months of follow-up, 9 patients (9.7%) were readmitted to hospital, of whom 4 patients were readmitted due to pain or dyspnea related to the PE and 5 patients because of major bleeding. Six patients (6.5%) were investigated for suspected recurrent VTE: one patient

(1.1%) was diagnosed with deep vein thrombosis of the leg and recurrent VTE was excluded in the other 5 patients. A total of 6 patients (6.5%) died during the follow-up period, of whom 2 patients as result of the index PE.

PDS was not correlated to persistent dyspnea (mean difference -3.7%; 95%CI -9.7% to 2.3%), chest pain (mean difference -0.70%; 95%CI -8.7% to 7.3%) or post-PE functional impairment (mean difference -4.7%; 95%CI -11% to 1.3%, **Table 1**). Moreover, CTPP-assessed PDS could not predict PE-related readmission (mean difference of 3.3%; 95%CI -5.4% to 12%) or all-cause mortality (mean difference 0.1%; 95%CI -10% to 11%, **Table 1**).

Table 1. Perfusion defect score (PDS) in 93 acute pulmonary embolism (PE) patients and its correlation with persistent symptoms and adverse outcome at 3-month follow-up

	Prevalence (%)	Mean (SD) PDS in % in patients with:	Mean (SD) PDS in % in patients without:	Mean difference (95% CI)
Persistent symptoms at 3 months				
Dyspnea	22 (24)	24 (11)	28 (13)	-3.7 (-9.7 to 2.3)
Chest pain	11 (12)	26 (11)	27 (13)	-0.70 (-8.7 to 7.3)
Post-PE functional impairment	22 (24)	23 (11)	28 (13)	-4.7 (-11 to 1.3)
Adverse outcomes at 3 months				
Recurrent VTE	1 (1.1)	30 (-)	27 (13)	3 (-)
PE-related readmission	9 (9.7)	31 (12)	27 (12)	3.3 (-5.4 to 12)
All-cause mortality	6 (6.5)	27 (21)	27 (12)	0.1 (-10 to 11)

DISCUSSION

In this analysis, we did not find clinically relevant correlations between PDS at initial PE diagnosis and persistent symptoms nor between PDS and any of the evaluated adverse outcomes at 3-month follow-up.

Multiple studies have shown that incomplete thrombus resolution occurs in around 50% of patients after acute PE episode despite adequate anticoagulant treatment.[3,4,6] At least two studies have demonstrated that pulmonary vascular obstruction (PVO) on initial CTPA and ventilation/perfusion scan (V/Q scan) were

independent predictors of residual PVO assessed by V/Q scan.[3,4] These persistent pulmonary perfusion defects have been associated with functional limitations during long-term follow-up and CTEPH.[3,6] In a study of 647 PE patients, 3.4% of patients with residual PVO after 6 months of the initial PE diagnosis were diagnosed with CTEPH versus none of the patients without residual PVO.[6] We therefore hypothesized that the extend of perfusion defects at initial PE diagnosis could be of value for predicting persistent symptoms and adverse events at 3-month follow-up. However, we had to reject our hypothesis: the extent of perfusion defects on CTPP did not show a trend towards an association with persistent dyspnea or pain. Of note, discrepancy between the extent of perfusion defects and symptoms including dyspnea and pain may exist as the generation of dyspnea and pain involve multiple underlying complex (and not fully understood) mechanisms.[11] Moreover, as the study represents a case mix of patients from the LUMC including patients with a history of VTE and active malignancy, it cannot be ruled out that the predictive value of PDS for persistent symptoms and adverse outcomes is different in other settings or hospitals.

We also assessed whether PDS on CTPP at PE diagnosis could predict recurrent VTE, PE-related readmission and all-cause mortality. In the current literature, there is evidence that the extend of baseline perfusion defects is associated with persistent perfusion defects on V/Q scans, the latter predicting recurrent VTE.[6,12] In the recent PADIS-PE trial, including 371 patients with first unprovoked PE treated with anticoagulants for 6 months, persistent perfusion defects of more than 5% determined by V/Q scan was associated with increased risk for recurrent VTE (hazard ratio of 2.06, 95%CI 1.14-3.72).[12] Since only one recurrent VTE event occurred during 3-month follow-up in our study cohort, we were not able to assess whether the extent of perfusion defects at initial PE diagnosis could predict recurrent VTE.

Our study has limitations. First, the presence of dyspnea and functional limitations was self-reported, which may have introduced bias [8], rather than assessed with a validated instrument such as the Post-VTE Functional Status (PVFS) scale. Further, this was an exploratory study in which we focused on a convenience cohort of 100 patients without a specific sample size calculation and followed patients for 3 months without taking longer follow-up into account. However, since our data did not even show a trend towards an association between perfusion defects and persistent symptoms or adverse outcomes, we expect that a larger sample size would not make a difference and show the same results. Furthermore,

we were not able to assess whether PDS was associated to CTEPH/CTEPD since these conditions are rather rare complications of acute PE [13,14] which can usually only be diagnosed beyond the initial 3-month treatment period with adequate anticoagulation.

In conclusion, in our cohort, CTPP-assessed PDS at initial PE diagnosis was not correlated to persistent symptoms nor with 3-month adverse outcomes in patients diagnosed with acute PE. Large prospective studies with longer follow-up are needed to more definitively determine whether CTPP imaging can be used to predict long-term outcomes after acute PE.

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