Serial imaging after pulmonary embolism and correlation with functional limitation at 12 months: Results of the ELOPE Study

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Abstract
Introduction: Risk factors for exercise limitation after acute pulmonary embolism (PE) are unknown. As a planned sub-study of the prospective, multicenter ELOPE (Evaluation of Long-term Outcomes after PE) Study, we aimed to describe the results of serial imaging by computed tomography pulmonary angiography (CTPA) and perfusion scan during 1 year after a first episode of acute pulmonary embolism, and to assess the association between imaging parameters and exercise limitation at 1 year.

Methods: In a prospective cohort study, 100 patients were recruited between June 2010 and February 2013 at five Canadian university-affiliated hospitals. CT pulmonary angiography was performed at baseline and 12 months, perfusion scan at 6 and 12 months, and cardio-pulmonary exercise testing at 1 and 12 months. Imaging parameters included: on CT pulmonary angiography, CT obstruction index (CTO) (% clot burden in the pulmonary vasculature), and on perfusion scan, pulmonary vascular obstruction (PVO) (% perfusion defect). Abnormal cardio-pulmonary exercise test
Pulmonary embolism (PE) is the most serious form of venous thromboembolism (VTE). Mortality after untreated acute PE has been estimated to be as high as 30%, but with current treatment standards, has decreased to as low as 1.8%. Despite current success in acute PE treatment, up to 4.8% of PE patients continue to develop long-term sequelae such as chronic thromboembolic pulmonary hypertension, or more commonly, exercise limitation. To date, there is a paucity of research aimed at identifying patients at risk to experience persistent long-term functional limitation after PE.

Computed tomography pulmonary angiography (CTPA) and perfusion scan imaging have been shown to have prognostic value following acute PE. In a recent meta-analysis, Meinel et al. reported a correlation between increased right ventricular/left ventricular ratio seen on baseline CTPA and all-cause mortality at 1-6 months after PE (pooled odds ratio [OR], 2.5; 95% confidence interval [CI], 1.8-3.5). However, systematic description of results of serial imaging by CTPA and Q lung scanning in the long term after acute PE and relation to functional outcome is largely lacking. For example, in a retrospective database analysis, Tapson et al. showed that only 20% of patients had repeat CTPA and 6% had repeat ventilation/perfusion following acute PE. Furthermore, to our knowledge, the correlation between findings or change in findings over time on imaging and long-term functional exercise limitation after PE has yet to be evaluated.

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1 | INTRODUCTION

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2 | METHODS

2.1 | Study population

Patients with acute PE were recruited from five university-affiliated centers in Canada between June 2010 and February 2013. Eligibility criteria included aged 18 years or older, first episode of acute PE that was objectively diagnosed within the last 10 days, and planned for
anticoagulation treatment. Patients were excluded if they met the following criteria: inability to perform a cardiopulmonary exercise test (CPET), previous deep vein thrombosis (to avoid including patients with previous PE), life expectancy of less than 1 year, unable to attend the required follow-up visits, or unable or unwilling to provide written informed consent. Detailed exclusion criteria have been previously published, and we now refer the reader to the relevant Chest article for this information.

2.2 | Study visits and procedures

At study entry, demographic and clinical characteristics were recorded on a standardized case report form. Patients attended study visits at baseline, 1, 3, 6, and 12 months. At the 1- and 12-month visits, CPET was performed in the pulmonary function laboratory of the respective hospital (details of CPET protocol were previously described).

2.3 | CTPA

CTPA was performed at baseline and at 12 months in each participating center using the hospital’s standard protocol. Imaging parameters extracted into a standard form included: main pulmonary artery (PA) diameter, presence of contrast reflux in the inferior vena cava, right ventricular/left ventricular ratio, septal shift or bowing, right ventricular wall thickness, and CT obstruction index (CTO index). Presence of pleural or pericardial fluid, acute or chronic pulmonary infarcts, subpleural bands, mosaic attenuation and systemic artery collaterals were also recorded.

CTO index was calculated according to the formula described by Qanadli et al., whereby the arterial tree of each lung was regarded as having 10 segmental pulmonary arteries (3 to upper lobes, 2 to middle lobe or lingula, 5 to lower lobes). Embolus in a segmental PA was given a score of 1 and emboli at the most proximal arterial level are given a value equal to number of segmental PA that arise distally. Each embolus was assigned a weighting factor (0, no defect; 1, partial occlusion; 2, complete occlusion). Subsegmental emboli were considered as partially occluded segmental PA. The maximum clot load score is 40; clot load score is converted to a percent to obtain the CTO index.

Main pulmonary artery diameter was measured at the pulmonary artery bifurcation on an axial slice vertical to its long axis. Ventricular measurements were made on axial images perpendicular to the long axis of the heart. Diameters were measured as the maximum distance from the interventricular septum to the endocardial border at the valvular level.

CTPAs were read centrally by a single experienced thoracic radiologist (author CD) kept blind to patient’s clinical data and results on other tests.

2.4 | Nuclear perfusion (Q) lung scan

Perfusion scans were performed at 6 and 12 months at each center using the hospital’s standard protocol. Ventilation scans were not done to minimize expense and radiation exposure. Perfusion scans were obtained with 100-150 MBq of 99Tc-labeled macroaggregated albumin (99Tc-MAA), using a 20% window centered over the 140-keV energy peak. Patients were injected intravenously over 5-10 respiratory cycles in a supine position with a minimum of 200 000 of 99Tc-MAA. Planar images were obtained for 500 000-750 000 counts in at least six views.

Images were read centrally by a single experienced nuclear medicine physician (author CR) kept blind to patients’ clinical data and results of other tests. Percentage of pulmonary vascular obstruction (% PVO) was calculated using a previously validated equation. Each lobe was assigned a weight based on regional blood flow distribution, then a quantitative perfusion score from 0 (no perfusion) to 1 (normal perfusion) was estimated based on gamma count defects seen in each lobe. % PVO was subsequently obtained by the equation % PVO = (1−Σ lobar scores) × 100, whereby the lobar score is the multiple of a lobe’s weight and perfusion score.

2.5 | CPET

The prespecified primary outcome of the study was maximal aerobic capacity defined by peak oxygen uptake (VO2) as a percent of predicted maximal VO2 (VO2 peak) on 1-year CPET, with <80% predicted VO2 peak considered abnormal. CPET tests were interpreted in real time by a respirologist at each center blinded to patient information. Calculations of percent predicted VO2 peak were done centrally, using Wasserman’s equation for predicted VO2: men: (50.72−[0.372 × age]) × weight/1000; women: (22.78−[0.17 × age]) × (43 + weight)/1000.

2.6 | Statistical analysis

Demographic, clinical, and imaging data were summarized. Changes in CTO index (from baseline to 12 months) and in PVO (from 6 to 12 months) over time were presented graphically. We examined the correlation between CTO index on CTPA and PVO on perfusion scan at 1 year using Spearman’s correlation coefficient. We also assessed the association between CTO index at 12 months, PVO at 6 months and 12 months, and ability to achieve normal exercise capacity (percent-predicted VO2 peak >80%) on 12 months CPET. To assess the relationship between baseline abnormalities on CTPA and exercise limitation at 1 year, multiple log-binomial regression modeling was used to estimate relative risks (RR) to identify predictors of abnormal VO2 peak at 1 year. Final model selection was based on the Bayesian Information Criterion BIC.

To assess inter-rater reliability, second raters re-read random samples of 20 CTPA scans (author EP) and 20 perfusion scans (author GA), and concordance correlation coefficients were calculated. Statistical analyses were performed using Stata Statistical Software (StataCorp LP, College Station, TX).
3 | RESULTS

Of the 984 patients screened for participation, 105 were eligible and 100 (67%) consented to participate. A detailed chart of patient flow was previously published. Mean (SD) age was 50 (15) years, 57% were male, and 80% were outpatients. In terms of comorbidity, 13% of patients had preexisting lung disease (COPD or asthma) and none had congestive heart failure or cancer. Most patients were treated with 5-7 days of low molecular weight heparin followed by warfarin. The mean (SD) duration of anticoagulant treatment was 5.7 (2) months. All 100 patients had a CTPA at baseline, and 82 had a follow-up CTPA at 1 year perfusion scan was performed in 84 patients at 6 months and 73 patients at 1 year. CPET was performed in 86 patients at 1 year.

CTPA findings at baseline and 1 year are shown in Table 1. On baseline CTPA, mean (median; SD) CTO index was 28.1% (27.5%; 18.3%) and no patients had findings to suggest chronic PE or chronic thromboembolic pulmonary hypertension. At 1 year, mean (median; SD) CTO index at 1 year was 1.2% (0%; 4.3%), and 10 of 82 (12.2%) patients had findings of residual chronic PE, including mural filling defects (4 patients), webs (2 patients), beading (1 patient), and abrupt occlusion with vessel tapering (6 patients) (some patients had more than one finding). Depiction of within-individual change in CTO index from baseline to 12 months is presented in Figure 1. The one patient who had an increase in CTO index from baseline to 12 months had recurrent PE at 12 months, while off anticoagulation.

The presence of contrast reflux into the inferior vena cava, septal shift and pulmonary infarcts diminished from baseline to 1 year. Additional CTPA findings are detailed in Table 1.

To evaluate the association between baseline CTPA variables and percent-predicted VO2 peak abnormality, multivariate modeling adjusted for sex, age, and BMI was done, and showed that baseline CTPA variables abnormal pulmonary artery diameter (≥30 mm; n = 26) (RR = 3.4, [95% CI 1.4, 8.4]; P = .007) and any reflux into inferior vena cava (n = 39) (RR = 1.6, [95% CI 1.04, 2.6]; P = .033) had a significant association with percent-predicted VO2 peak abnormality at 1 year, but obstruction index did not (RR = 0.97, [95% CI 0.95, 1.003]; P = .077).

Perfusion scan findings at 6 and 12 months are presented in Table 2. Mean (median; SD) PVO was 6.0% (0%; 9.6%) at 6 months, and 5.6% (0%; 9.8%) at 1 year. Abnormal perfusion (ie, PVO > 0%) was noted in 39 (46.4%) patients at 6 months (mean [median; SD])

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TABLE 1  CTPA findings at baseline and 12 months

| Variable                          | Baseline N = 100 | 12 months N = 82 |
|-----------------------------------|------------------|------------------|
| CT obstruction index (%)          |                  |                  |
| Mean (median; SD)                 | 28.1 [27.5] (18.3) | 1.2 [0] (4.3)    |
| Abnormal (>0 %)                   | 97 (97)          | 13 (15.9)        |
| Main PA diameter (mm); mean (SD)  | 26.7 (4.7)       | 25.7 (3.8)       |
| Normal (<30 mm)                   | 74 (74)          | 70 (85.4)        |
| Abnormal (≥30 mm)                 | 26 (26)          | 12 (14.6)        |
| Ventricular diameter (mm); mean (SD) |                |                  |
| Left ventricle                    | 44.7 (7.8)       | 47.7 (5.9)       |
| Right ventricle                   | 43.3 (8.2)       | 41.1 (6)         |
| RV/LV ratio                       | 1.01 (0.34)      | 0.87 (0.13)      |
| RV wall thickness (mm); mean (SD) | 1.96 (0.56)      | 2.07 (0.58)      |
| Contrast reflux into IVC          | 39 (39)          | 18 (22)          |
| Septal shift                      | 23 (23)          | 1 (1.2)          |
| Pulmonary infarcts                | 36 (36)          | 1 (1.2)          |
| Any arterial signs of chronic PE  | 0 (0)            | 10 (12.2)        |
| Mural filling defects             | 0 (0)            | 4 (4.9)          |
| Webs                              | 0 (0)            | 2 (2.4)          |
| Beading                           | 0 (0)            | 1 (1.2)          |
| Abrupt occlusion with tapering    | 0 (0)            | 6 (7.3)          |
| Calcification of emboli           | 0 (0)            | 0 (0)            |
| Mosaic attenuation                | 6 (6)            | 8 (9.8)          |
| Sub-pleural bands                 | 0 (0)            | 2 (2.4)          |
| Pulmonary scars                   | 0 (0)            | 17 (20.7)        |
| Pericardial effusion              | 6 (6)            | 0 (0)            |

Values are N (%) unless otherwise specified. CTPA, computed tomography pulmonary angiography; IVC, inferior vena cava; LV, left ventricle; PE, pulmonary embolism; RV, right ventricle; SD, standard deviation.
PVO in these patients was 12.9% (10.7%; 10.4%) and in 30 (41.1%) patients at 1 year (mean (SD) PVO in these patients was 13.7% (11.2%; 11.2%). Among individual patients who had perfusion scans at both 6 and 12 months, 26 of 32 (81.3%) patients with abnormal PVO at 6 months also had abnormal PVO at 12 months. Within individual change in PVO from 6 to 12 months is shown in Figure 2. Five patients had increased PVO from 6 to 12 months, one of whom had recurrent PE and rise in CTO as described above.

There was a statistically significant correlation between CTO index at 1 year and PVO at 1 year (Spearman’s rho = 0.40, \( P = .001 \)).

Mean (median; SD) CTO index at 12 months was similar in patients with percent-predicted VO2 peak <80% vs >80% on 1-year CPET (1.4% [0%; 5.7%] vs 1.0% [0%; 2.4%]; \( P = .70 \)). Similarly, mean (median; SD) PVO at 6 months and at 12 months was similar in patients with percent-predicted VO2 peak <80% vs >80% on 1-year CPET (6 months: 5.9% [0%; 10.4%] vs 6.2% [4.5%; 9.0%]; \( P = .91 \); 12 months: 5.1% [0%; 10.2%] vs 6.0% [0%; 9.7%]; \( P = .71 \)).

Of the 10 patients with evidence of residual chronic PE on CTPA at 12 months, baseline CTO mean (median; SD) was 38.5% (46.3%; 17.2%) vs 27.2% (27.5%; 17.5%) in patients without chronic PE \( (P = .059) \), and 12-month mean CTO was 7.5% (9.3%) vs 0.3% (1.8%), respectively \( (P < .001) \). Similarly, 6-month mean PVO was 17.5% (15.7%; 16.7%) in patients with residual chronic PE at 12 months vs 4.3% (0%; 6.2%) in patients without \( (P < .001) \), and for 12-month PVO was 16.3% (11.2%; 16.0%) vs 3.6% (0%; 5.7%), respectively \( (P < .001) \). However, there was no significant difference in mean % predicted VO2 peak at 1 and 12 months between the presence or absence of chronic residual PE at 12 months (mean % predicted VO2 peak [SD] at 1 month: 81.6% [21.8%] with chronic PE vs 77.5% [24.2%] without; \( P = .617 \); 12 months: 95.7% [19.8%] with chronic PE vs 81.1% [25.2%] without; \( P = .098 \)).

As was previously reported, a the intra-class correlation coefficient for inter-rater concordance on the CTPA obstruction index was 0.96 (95% CI 0.90, 0.98) and for % PVO on Q scan was 0.96 (95% CI 0.89, 0.98), indicating excellent agreement.

### Table 2

|                           | 6 months N = 84 | 12 months N = 73 |
|---------------------------|-----------------|------------------|
| Percentage of vascular obstruction (PVO); Mean % [median] (SD) | 6.0 [0] (9.6) | 5.6 [0] (9.8) |
| Normal (0%); n (%)        | 45 (53.6)       | 43 (58.9)        |
| Abnormal (>0 %); n (%)    | 39 (46.4)       | 30 (41.1)        |
| Mean % (SD)               | 12.9 (10.4)     | 13.7 (11.2)      |

Q scan, perfusion scan; SD, standard deviation.
4 DISCUSSION

To our knowledge, the current study is the first to prospectively describe change in imaging parameters during the first year after PE and to attempt to correlate imaging parameters with long-term functional exercise limitation following acute PE. In our multicenter prospective cohort study of patients with acute PE followed for 12 months, we found that imaging findings after PE did not predict exercise limitation and that residual thrombus does not appear to explain long-term functional limitation after PE. The mean CTO index decreased from 28.1% at baseline to 1.2% at 12 months, and was normal (ie, 0%) in 84.1% of patients at 12 months. On perfusion scan, mean PVO was similar at 6 and 12 months post PE (6.0% and 5.6%, respectively), and was normal (ie, PVO 0%) in 58.9% of patients at 12 months. We did not find any association between CTO index at 12 months or PVO at 6 months or 12 months and abnormal CPET (ie, percent-predicted VO2 peak <80%) at 1 year. We also noted resolution of pulmonary infarcts and signs of right ventricular dysfunction from baseline to the 12-month CTPA, and a relatively low frequency of arterial signs of chronic PE (12.2% of cases).

The rates of abnormal CTO index (15.9%) and PVO (41%) at 12 months in our study are within the range of those previously reported.12,13 For instance, Cosmi et al described a prospective cohort study in which 15% (12/80, 95% CI: 8%-25%) of patients had residual PE on CTPA and 28% (26/93, 95% CI: 19%-38%) had residual perfusion defects on perfusion scan at a mean of 9 months after PE.13 The rate of abnormal PVO (52%) about 1 year after acute PE was even higher in the systematic review reported by Nijkeuter et al.,14 although this difference may be explained by differences in patient populations (for example, patients admitted to the intensive care unit were included in some of the studies reviewed) and anticoagulation duration. Of note, the higher rate of abnormal PVO on perfusion scan than CTO on CTPA scan in our study was consistent with our own findings. The reason for this likely relates to the higher sensitivity of ventilation/perfusion scan for the diagnosis of chronic PE. For example, Tunariu et al. showed that a normal or low-probability ventilation/perfusion scan effectively excludes chronic thromboembolic pulmonary hypertension, with a sensitivity of 97.4% and a specificity of 90%, while CTPA had a sensitivity of only about 51% for chronic thromboembolic pulmonary hypertension but a specificity of 99%.15 Indeed, the European Society of Cardiology and Respirology Guidelines support the use of ventilation/perfusion scan as the test of choice to do targeted case-finding for chronic thromboembolic pulmonary hypertension.16

Despite a relatively high incidence of abnormal PVO in our study, we did not find a significant association between PVO at 6 or 12 months and exercise limitation on 12-month CPET. To date, the relationship between PVO and adverse outcomes after PE has not been consistent. Meneveau et al17 have shown that PVO measured prior to hospital discharge was associated with adverse outcomes (including death, recurrent PE and heart failure) at 6 months following acute PE (OR 2.53 [1.17-5.8]). Conversely, Poli et al18 did not find an association between residual perfusion defects on ventilation/perfusion scan after 3 months of anticoagulation and subsequent VTE recurrence during a median of 28 months of follow-up. In the current study, 6-month PVO as opposed to baseline PVO was measured, and by 6 months, mean PVO was only 6%. Our rationale for performing the first perfusion scan at 6 months was to analyze residual clot burden at a time point at which most patients would have stopped anticoagulation. While we thus cannot determine if baseline PVO might have been associated with VO2 peak <80% at 1 year, we previously reported that no significant association was noted for baseline CTO index and VO2 peak <80% at 1 year.5

We also report the lack of association between CTO index at 12 months and CPET at 12 months. In prior studies, baseline CTO index has been associated with adverse PE outcomes such as mortality.6 However, the relation between follow-up CTO after acute PE treatment and long-term adverse events is less certain. For example, in the PROMETHEUS study, den Exter et al19 showed that the presence of residual obstruction on CTPA at 6 months after PE diagnosis was not associated with recurrent VTE after 6 months (adjusted hazard ratio: 0.92; 95% CI: 0.2-4.1). These findings, in correlation with those from the current study, argue against performing repeat imaging after acute PE for prognostic purposes in otherwise asymptomatic patients.

Finally, we found that two baseline CTPA variables, PA diameter and presence of inferior vena cava reflux, were significantly associated on multivariate analysis with percent-predicted VO2 peak <80% at 1 year. Similar to CTO, reflux in the inferior vena cava has been associated with 30-day mortality following acute PE.20 However, pulmonary artery diameter, which has been associated with clot burden, has not demonstrated direct association with adverse PE outcomes.21 To our knowledge, this is the first report associating these two variables to long-term functional limitation, which contrasts with the lack of association between baseline CTO and long-term functional limitation.

Furthermore, those patients with chronic residual PE at 12 months appear to have higher CTO at baseline and 12 months, and higher PVO at 6 and 12 months, but this did not translate into significant differences in percent-predicted VO2 peak at 12 months between those with and without chronic residual PE. Thus, while it is known that patients who develop chronic pulmonary vascular obstruction have significant symptoms,22 our study highlights that exercise limitation may exist even in the absence of chronic imaging abnormalities indicative of vascular compromise. Why baseline imaging parameters, such as abnormal pulmonary artery diameter, appeared to be more prognostic than follow-up imaging parameters is uncertain, although our study patients had normalization of most imaging parameters by 12 months.

There are several limitations to this study that should be acknowledged. First, we excluded patients with severe comorbidity or limited lifespan, and thus it is likely that we selected for a healthier patient population. Second, there was a lack of control group of patients with no PE. Third, this was a modest-sized cohort.
of PE patients (indeed, no patients developed chronic thromboembolic pulmonary hypertension), and there was some missing data during follow-up. Nevertheless, our sample size had adequate power (>84%) to detect a difference of 2.5 units in mean CTO index (range 0-100) at 1 year in those with percent-predicted VO2 peak <80% vs >80% on 1-year CPET. Fourth, we performed only perfusion scan, omitting ventilation scan. Thus, non-embolic pulmonary pathologies could have accounted for the increase in PVO seen in two patients between 6 and 12 months. Fifth, we did not collect data on all parameters required to calculate the PESI score, and had no information on performance status. In addition, the pre-PE exercise status of these patients cannot be known. Low fitness, and sedentary risk factor may be a risk factor for PE, and may contribute to their abnormal exercise capacity 1 year post PE. Finally, although we assessed PVO, pulmonary artery diameter and CTO index as potential markers of poor prognosis after acute PE, validated cut-offs that are indicative of worse prognosis have not been established.

The lack of correlation in the current study between imaging findings and long-term exercise limitation may reflect the uncertainty surrounding the exact definition of “post-PE syndrome.” While chronic thromboembolic pulmonary hypertension is widely recognized as the end-stage manifestation of post-PE syndrome, a comprehensive definition of this syndrome has yet to be proposed.23 Studies addressing this issue convey common themes of self-reported dyspnea and/or measured decreased poor physical performance.24 To further complicate the issue, the term “chronic thromboembolic disease” is increasingly used in the medical literature in recent years. While most experts agree that chronic thromboembolic disease is defined as persistent pulmonary vascular occlusion in the absence of pulmonary hypertension, it remains controversial whether actual documented impaired physical performance should also be part of chronic thromboembolic disease.25,26 It might be interesting to hypothesize that post-PE syndrome includes a spectrum of post-PE patients: from those with symptoms and exercise intolerance with no or mild residual imaging abnormalities (as described in this paper), to those with symptoms, residual vascular obstruction, but minimal hemodynamic abnormalities (chronic thromboembolic disease), to full-blown chronic thromboembolic pulmonary hypertension with symptoms, residual vascular obstruction and pulmonary hypertension. What is clear, however, is that post PE symptoms are widespread, and further work is needed to fully define the post-PE syndrome.

A prior study from the ELOPE investigators has attempted to define a post-PE syndrome characterized by persistent dyspnea, exercise limitation, and reduced quality of life at 1 year after PE.4 The current secondary analysis of the ELOPE study provides important information on expected changes in imaging parameters on CTPA and perfusion scan over time after acute PE, and their relation to each other and to functional outcome at 1 year. That both CTO index and PVO lacked association with 1-year CPET results highlights the difficulty in identifying patients who are predisposed to long-term functional limitation after PE, as well as gaps in our understanding of the mechanisms of that limitation. Our findings also suggest that routine serial imaging after PE for prognostic purposes may not be of clinical value in asymptomatic patients, although imaging may still be valuable to establish a new baseline in case of future recurrence and to diagnose chronic thromboembolic pulmonary hypertension in symptomatic patients. Which patient populations would benefit most from post-PE imaging remains to be defined.

RELATIONSHIP DISCLOSURE

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AUTHOR CONTRIBUTIONS

A. M. H takes responsibility for the content of the manuscript, including the data and analysis. K. M., S. R. K., A. A., C. D., C. R., J. T. G., D. A., P. S. W., M. A. R., S. S., M. J. K., L. R., A. S., P. H., S. D. A., E. P., G. A., and A. M. H. made substantial contributions to conception and design, or acquisition of data, or analysis and interpretation of data; drafted the submitted article or revised it critically for important intellectual content; and provided final approval of the version to be published. A. M. H. agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

REFERENCES

1. Carson JL, Kelley MA, Duff A, et al. The clinical course of pulmonary embolism. N Engl J Med. 1992;326:1240–5.
2. Jiménez D, de Miguel-Diez J, Guijarro R, et al. Trends in the management and outcomes of acute pulmonary embolism: analysis from the RIETE Registry. J Am Coll Cardiol. 2016;67:162–70.
3. Guérin L, Couturaud F, Parent F, et al. Prevalence of chronic thromboembolic pulmonary hypertension after acute pulmonary embolism. Thromb Haemost. 2014;112:598–605.
4. Kahn SR, Hirsch A, Akaberi A, et al. Functional and exercise limitations after a first episode of pulmonary embolism: results of the ELOPE prospective cohort study. Chest. 2017;151:1058–68.
5. Meinel FG, Nance JW Jr, Schoepf UJ, et al. Predictive value of computed tomography in acute pulmonary embolism: systematic review and meta-analysis. Am J Med. 2015;128:747–59.
6. Tapson VF, Platt DM, Xia F, et al. Monitoring for pulmonary hypertension following pulmonary embolism: the INFORM Study. Am J Med. 2016;129:978–85.
7. Qanadli SD, El Hajjam M, Vieillard-Baron A, et al. New CT index to quantify arterial obstruction in pulmonary embolism: comparison with angiographic index and echocardiography. AJR Am J Roentgenol. 2001;176:1415–20.
8. Truong QA, Massaro JM, Rogers IS, et al. Reference values for normal pulmonary artery dimensions by noncontrast cardiac computed tomography: the Framingham Heart Study. Circ Cardiovasc Imaging. 2012;5:147–54.
9. Araoz PA, Gotway MB, Harrington JR, Harmsen WS, Mandrekar JN. Pulmonary embolism: prognostic CT findings. Radiology. 2007;242:889–97.
10. Azarian R, Wartski M, Collignon MA, et al. Lung perfusion scans and hemodynamics in acute and chronic pulmonary embolism. J Nucl Med. 1997;38:980–3.
11. Schwartz G. Estimating the order of a model. Ann Stat. 1978;2:461–4.
12. Sanchez O, Helley D, Couchon S, et al. Perfusion defects after pulmonary embolism: risk factors and clinical significance. J Thromb Haemost. 2010;8:1248–55.
13. Cosmi B, Nijkeuter M, Valentino M, Huisman MV, Barozzi L, Palareti G. Residual emboli on lung perfusion scan or multidetector computed tomography after a first episode of acute pulmonary embolism. Intern Emerg Med. 2011;6:521–8.
14. Nijkeuter M, Hovens MMC, Davidson BL, Huisman MV, Resolution of thromboemboli in patients with acute pulmonary embolism: a systematic review. Chest. 2006;129:192–7.
15. Tunariu N, Gibbs SJ, Win Z, et al. Ventilation-perfusion scintigraphy is more sensitive than multidetector CTPA in detecting chronic thromboembolic pulmonary disease as a treatable cause of pulmonary hypertension. J Nucl Med. 2007;48:680–4.
16. Gallé N, Humbert M, Vachiery JL, et al. 2015 ESC/ERS guideline for the diagnosis and treatment of pulmonary hypertension. Eur Heart J. 2015;37:67–119.
17. Meneveau N, Ider O, Seronde MF, et al. Longterm prognostic value of residual pulmonary vascular obstruction at discharge in patients with intermediate- to high-risk pulmonary embolism. Eur Heart J. 2013;34:693–701.
18. Poil D, Cenci C, Antonucci E, et al. Risk of recurrence in patients with pulmonary embolism: predictive role of D-dimer and of residual perfusion defects on lung scintigraphy. Thromb Haemost. 2013;109:181.
19. den Exel PL, van Es J, Kroft LJ, et al. Thromboembolic resolution assessed by CT pulmonary angiography after treatment for acute pulmonary embolism. Thromb Haemost. 2015;114:26–34.
20. Aviram G, Rogowski O, Gotler Y, et al. Real-time risk stratification of patients with acute pulmonary embolism by grading the reflux of contrast into the inferior vena cava on computerized tomographic pulmonary angiography. J Thromb Haemost. 2008;6:1488–93.
21. Furlan A, Aghayev A, Chang CCH, et al. Short-term mortality in acute pulmonary embolism: clot burden and signs of right heart dysfunction at CT pulmonary angiography. Radiology. 2012;265:283–93.
22. van Kan C, van der Plas MN, Reesink HJ, et al. Hemodynamic and ventilatory responses during exercise in chronic thromboembolic disease. J Thorac Cardiovasc Surg. 2016;152:763–71.
23. Lang IM, Pesavento R, Banderman D, Yuan JXJ. Risk factors and basic mechanisms of chronic thromboembolic pulmonary hypertension: a current understanding. Eur Respir J. 2013;41:462–8.
24. Klok FA, van der Hulle T, den Exter PL, Lankeit M, Huisman MV, Konstantinides S. The post-PE syndrome: a new concept for chronic complications of pulmonary embolism. Blood Rev. 2014;28:221–6.
25. Taboada D, Pepke-Zaba J, Jenkins DP, et al. Outcome of pulmonary endarterectomy in symptomatic chronic thromboembolic disease. Eur Respir J. 2014;44:1635–45.
26. Held M, Kolb P, Grün M, et al. Functional characterization of patients with chronic thromboembolic disease. Respiration. 2016;91:503–9.

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