Long-term prognostic value of residual pulmonary vascular obstruction at discharge in patients with intermediate- to high-risk pulmonary embolism

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Background
We evaluated prognostic value at 6 months of residual pulmonary vascular obstruction (RPVO) measured before discharge in patients with intermediate- or high-risk pulmonary embolism (PE).

Methods and results
Prospective registry including 416 consecutive patients with intermediate- or high-risk PE who survived the acute phase. Patients with previous cardiopulmonary disease were excluded. Perfusion lung scans were performed within 6–8 days after the onset of treatment. Residual pulmonary vascular obstruction was graded as the proportion of the lung not perfused. Primary objective was a combined endpoint at 6 months, including death, recurrent PE, and appearance of signs of heart failure.

At 6 months, 32 patients (7.7%) had at least one adverse event: 12 deaths (2.9%), 12 recurrent PE (2.9%), and 14 (3.4%) heart failure. Independent predictors of combined endpoint were: cancer [odds ratio (OR) 3.07 (1.22–7.85)]; renal insufficiency at admission [OR: 2.53 (1.17–5.8)]; persistent signs of right ventricular dysfunction at 48 h echography [OR: 3.99 (1.36–11.3)]. The severity of RPVO at discharge was significantly associated with an unfavourable outcome [OR: 2.66 (1.58–3.93)]. The incremental prognostic value of RPVO information was confirmed by significantly improved goodness-of-fit. Threshold RPVO for predicting adverse events was estimated at 35% [area under the curve = 0.76 (0.73–0.82)]. Patients with RPVO greater than threshold at discharge had a significantly higher risk of death at 6 months (P = 0.01).

Conclusions
Residual pulmonary vascular obstruction evaluated before hospital discharge in patients with intermediate- to high-risk PE is a powerful prognostic factor for a 6-month outcome. RPVO ≥35% is associated with an increased risk of adverse events at 6 months.

Keywords
Ventilation–perfusion lung scan • Venous thrombo-embolism • Outcome

Introduction
Previous studies evaluating the prognosis of pulmonary embolism (PE) have mainly focused on identifying predictive factors of early death, namely in-hospital and 30-day mortality, and have led to the development of prognostic risk scores such as the PESI or PREP scores.1–4 The identification of clinical, biological, and echocardiographic markers has also contributed to risk stratification in this setting, defining three levels of risk (low, intermediate, and high) for early death.5–8

Few studies have specifically assessed the long-term prognosis of PE, although it has been established that long-term mortality is mainly influenced by comorbidities, particularly cancer.2,6–8 The persistence of pulmonary artery hypertension (PAH) after acute
PE is also reportedly associated with increased long-term mortality. Persistent PAH usually reflects the presence of residual pulmonary vascular obstruction (RPVO), which, when it exceeds 30% at discharge, is associated with an increased risk of death in the long term in patients with PE treated by thrombolytic therapy. This is all the more important since chronic cor pulmonale has been shown to be more frequent than previously thought.  

Sanchez et al. investigated the prognostic value on a long-term outcome of perfusion defects at 6–12 months after an acute event, and showed that residual obstruction was associated with functional limitation and PAH. However, to date, no study has specifically investigated the prognostic value of RPVO at discharge after hospitalization for intermediate- to high-risk PE for the early identification of patients likely to have an adverse outcome at 6 months. The aim of our study was thus to evaluate the prognostic value on 6-month mortality of RPVO as measured by a ventilation–perfusion lung scan (V–Q scan) before discharge in patients hospitalized for intermediate- or high-risk PE who survived the acute phase.

Methods

Patient selection

The study population was part of a prospective, single-centre registry of patients treated in our centre for acute PE confirmed by a multislice computed tomography (MSCT) scan or V–Q scan. Only patients with intermediate- to high-risk PE who survived the acute phase were included. We excluded patients who were submitted to surgical embolectomy or who died during the in-hospital phase; those with a previous history of heart failure or respiratory failure (in order not to bias interpretation of the V–Q scan images or interfere with the assessment of the primary endpoint) and those with a previous history of thrombo-embolic disease.

Intermediate-risk PE was defined as the presence of myocardial ischaemia with troponin elevation, or the presence of echocardiographic signs of right ventricular (RV) dysfunction, namely the presence of at least one of the following criteria: (i) paradoxical septal motion; (ii) systolic PAH > 30 mmHg; (iii) the end-diastolic RV/left ventricular (LV) diameter ratio > 1. High-risk PE was defined as the presence of cardiogenic shock or arterial hypotension (systolic blood pressure < 90 mmHg or drop in blood pressure > 40 mmHg for > 15 min outside the context of sepsis, hypovolaemia, or arrhythmia).

Management

Standard biological parameters were measured and electrocardiogram (ECG) was performed in all patients. In addition, all patients underwent trans-thoracic echocardiography at admission and at 48 h, and a V–Q scan was performed before discharge (at Day 6 or discharge, whichever occurred first).

Electrocardiogram recordings were systematically scanned for ECG criteria of acute cor pulmonary (STQ3 aspect, negative T-wave in leads V1–V4, right axial deviation, right bundle branch block).

Patients with intermediate-risk PE received anticoagulant therapy with low molecular weight heparin (LMWH) (enoxaparin, at a dose of 1 mg/kg every 12 h, or tinzaparin 175 U/kg o.d.) or with fondaparinux (10 mg if body weight > 100 kg; 5 mg if body weight < 50 kg; otherwise, 7.5 mg, in one s.c. injection). Unfractionated heparin (UFH) (bolus of 80 IU/kg followed by a continuous infusion of 18 IU/kg/h after dose adjustment according to activated partial thromboplastin time (aPTT) to achieve a value of 1.5–2.5 times the control value) was preferred in patients with renal failure (creatinine clearance < 30 mL/min) or with elevated bleeding risk (< 5 days post-operative, haemoglobin < 10 g/dL, thrombocytopenia < 100 000/mm³).

In the absence of contra-indication, patients with high-risk PE were submitted to thrombolytic therapy using alteplase (infused at a dose of 100 mg over 2 h). Intra-venous infusion of UFH was initiated (or resumed) at the end of the alteplase regimen. Infusions were adjusted to maintain an aPTT between 1.5 and 2.5 times the control.

Anti-vitamin K treatment with fluindione was initiated on Day 1 in the case of treatment with UFH, LMWH, or fondaparinux, and on Day 3 in the case of thrombolytic therapy. Target International Normalized Ratio (INR) was between 2 and 3.

Six-month follow-up

Clinical events were recorded at systematic 6-month follow-up consultation. In the case of death, the treating physician was contacted by telephone to identify cause of death.

Primary endpoint

Follow-up data were obtained during hospital readmission, during scheduled patient consultations to the department, or from a standardized questionnaire sent to the attending physician and/or cardiologist. The primary endpoint evaluated at 6 months was a combined endpoint of death, recurrent symptomatic PE, development of clinical signs of congestive heart failure associated with elevated BNP, or change of New York Heart Association functional class to class III or IV. Patients with symptoms suggesting PE and with new filling defects seen on a spiral CT scan or pulmonary angiogram were interpreted as having recurrent PE. Hospital records and death certificates of patients who died during the follow-up period were also reviewed. Events were evaluated by two experienced physicians who were blinded to the patient’s RPVO status at discharge.

Multislice computed tomography and ventilation-perfusion lung scan

Computed tomography was performed using a 16-slice multidetector-row system. The pulmonary arteries were evaluated up to and including the subsegmental vessels. Thrombus burden on MSCT was quantified according to troncular, segmental, or subsegmental PE, as well as uni- or bilateral PE. The V–Q scan was performed before discharge and results were analysed in a double-blind fashion by two independent operators. Residual pulmonary vascular obstruction was evaluated by a semi-quantitative method as previously described. Briefly, a weight is attributed to each lobe based on the distribution of the blood flow in the lungs in the supine position: right lower lobe = 25%, middle lobe = 12%, right upper lobe = 18%, left lower lobe = 20%, left lingual = 12%, and left upper lobe = 13%. Perfusion within each lobe was estimated in the anterior, posterior, and oblique views. A semi-quantitative perfusion score from 0 to 1 (0, 0.25, 0.5, 0.75, or 1) was estimated from the film density by comparing with the photodensity of an apparently normally perfused area. The perfusion score was then calculated for each lobe by multiplying the weight by the perfusion score. The overall score was obtained by summing the six lobar perfusion scores. The percentage of RPVO by a perfusion scan was calculated as: RPVO = (1–overall perfusion score) × 100. The RPVO value retained was the average of the percentages of the two operators. In case of a discrepancy of > 10%, the perfusion images were re-interpreted by the two operators until consensus was reached. The results of discharge V–Q scan were not communicated to the caring physicians in order not to bias patient management.
Statistical analysis

Quantitative continuous variables are expressed as mean ± standard deviation, and qualitative variables as number and per cent. Continuous variables were tested for normal distribution with the Kolmogorov–Smirnov test. Between-group comparisons were performed for continuous data using the unpaired t-test and one-way analysis of variance (ANOVA) or the Mann–Whitney and Kruskal–Wallis tests, as appropriate. Qualitative variables were compared using the Chi-square test. Prognostic factors for 6-month outcome were identified using a Cox multivariable model. Variables associated with the primary endpoint with a P-value < 0.10 by univariate analysis were included in the model. A receiver-operating characteristic curve was used to define the threshold of PVO predictive of the primary endpoint at 6 months. To evaluate the additional prognostic value of RPVO, goodness-of-fit of the model was compared with and without the V–Q scan data, according to the different approaches recommended by Cook.14 The contribution of the PVO information was evaluated according to the decrease in the Bayes and Akaike information criteria; and by the variations in calibration (Hosmer–Lemeshow test) and discrimination (C-statistic). Analysis of event-free survival at 6 months was performed by the Kaplan–Meier method and survival at 6 months according to RPVO was compared using the log-rank test. Intra- and inter-observer reproducibility of RPVO measures were assessed using the intra-class correlation coefficient and the concordance correlation coefficient, respectively. All tests were two-sided, and a P-value of 0.05 was considered statistically significant. All analyses were performed using SAS version 9.2 (SAS Institute, Cary, NC, USA).

Results

From January 2005 to May 2010, 505 patients were admitted to our Department for intermediate- to high-risk PE. Diagnosis was confirmed by an MSCT scan in 90% of cases, and by V–Q scan in 10%. Patients with a history of heart failure (n = 24, 4.8%) or chronic obstructive pulmonary disease (n = 30, 6%) were excluded. Patients who died during the acute phase (n = 27, 5.4%) were also excluded. Eight patients (1.6%) were lost to follow-up. The final population consisted of 416 patients, aged 65 ± 14 years on average, and comprising 52% females. Figure 1 shows a flow chart of the study population. Table 1 presents the baseline characteristics of the study population. Average length of stay was 6.4 days (5.8–8.3). Average follow-up was 6.5 ± 1.1 months. Among patients who survived the acute phase, 133 (32%) had high-risk PE, defined as initial haemodynamic instability. At least one transient risk factor for venous thromboembolic disease (oestroprogestative hormone therapy, prolonged...
immobilization, recent surgery, trauma, sepsis, pregnancy) was present in 28% of patients. At least one permanent risk factor for venous thrombo-embolic disease (VTED) including obesity, venous insufficiency, prior VTED, and haemostatic disorders (mutation in the factor V or prothrombin genes, antithrombin deficiency, protein S deficiency, protein C deficiency, increased levels of factor VIII, antiphospholipid syndrome, hyperhomocysteinaemia, or increased titre of anticardiolimin antibodies) was present in 34% of patients. At admission, almost half the population had signs of acute cor pulmonale on ECG, and 81% had signs of RV dysfunction. Initial thrombus burden was evaluated by MSCT in 374 of 416 patients (90%) and did not differ significantly between groups.

During the 6 months of follow-up, 32 patients (7.7%) experienced at least one adverse event, including 12 (2.9%) deaths (five from cancer, one from renal failure, two from bleeding complications (of which one haemorrhagic stroke), two from recurrent PE and two from heart failure). In the two patients with fatal recurrent PE, recurrence was documented in one case, and based on strong clinical suspicion in the other, and, respectively, 59 and 68% of INR values were within therapeutic range in these two patients. Six patients (1.4%) developed heart failure and 6 (1.4%) recurrent PE. Among the six patients who developed heart failure, repeat echocardiography showed an average systolic pulmonary artery pressure (PAP) of 54.7 ± 13.8 mmHg and all six had systolic PAP >45 mmHg.

The rate of adverse events at 6 months was significantly higher among patients who presented with cancer, risk factors for thrombo-embolic disease, and renal insufficiency (Table 1). Initial clinical presentation was also more severe in these patients, with a higher proportion of cardiogenic shock and electrocardiographic signs of cor pulmonale. In addition, patients with an unfavourable 6-month outcome more frequently had RV dysfunction at admission. In particular, systolic PAP >30 mmHg and RV dilatation were significantly more frequent in these patients (P = 0.0013 and P = 0.012, respectively) (Table 2). There was no significant difference in BNP levels between those with and without an event at 6 months, although troponin positivity was significantly more
frequent among patients who had an unfavourable outcome ($P = 0.004$). The adequacy of the anticoagulation status during the 6-month follow-up was available only for patients who experienced an adverse event. Among these, 69% of INR values were within the appropriate range (i.e. 2–3). Among the 32 patients with an adverse event, only 4 had ≤55% of INR values in the therapeutic range (51, 52, 53, and 55%, respectively).

### In-hospital course

Bleeding complications and persistent RV dysfunction were more frequently observed during index hospitalization in patients who subsequently had adverse events during the 6-month follow-up ($P = 0.0004$ and $P < 0.0001$, respectively). Residual pulmonary vascular obstruction as evaluated by the V–Q scan at 6 days [average 6.1 days (5.4–7.9)] was more severe in the patients who subsequently developed adverse outcomes during the follow-up (40.8 ± 16.2 vs. 27.6 ± 13.3%, event vs. no event, respectively, $P < 0.0001$ (Table 3)). Intra-class correlation coefficient was 0.976 and concordance correlation coefficient was 0.865 (0.857–0.873). A discrepancy of >10% was observed in 22 patients (5%) requiring reinterpretation of the perfusion images by the two operators until consensus was reached. Residual pulmonary vascular obstruction at discharge was significantly associated with an initial thrombus burden as assessed by MSCT. Residual pulmonary vascular obstruction at discharge was 21.2 ± 10.6% for distal, unilateral thrombi; 24.2 ± 12.1% for proximal, unilateral thrombi; 26.2 ± 13.0% for distal, bilateral thrombi; and 30.7 ± 13.1% for proximal, bilateral thrombi on MSCT at admission ($P = 0.001$, ANOVA).

### Prognostic factors of 6-month clinical outcome

Cox multivariate analysis identified six prognostic factors for clinical outcome at 6 months (Table 4). The extent of RPVO before discharge was significantly associated with unfavourable outcome at 6 months [odds ratio (OR) per decile of vascular obstruction $2.66, 95\%$ CI: 1.58–3.93; Table 4].

The incremental prognostic value of RPVO was confirmed by a decrease in the Akaike Information Criterion (from 221.23 to 210.91) when the V–Q scan information was included, and by the improvement in calibration ($P = 0.25$ by the Hosmer–Lemeshow test without V–Q scan, and $P = 0.58$ with V–Q scan information, $P = 0.007$ for the comparison). Similarly, the C-statistic increased from 0.824 to 0.862 after inclusion of the V–Q data in the model ($P = 0.02$ (Table 4)).

The threshold RPVO value to predict unfavourable outcome was assessed at 35% using the ROC curve. The area under the curve (AUC) was 0.76 (0.73–0.82) (Figure 2). When integrated...
into the Cox multivariate model as a dichotomous variable (<35 or ≥35%). RPVO at 6 days was associated with a significantly higher risk of an adverse outcome at 6 months (OR: 13.7, 95% CI: 4.7–39.8, P < 0.0001) (Figure 3), with a sensitivity of 78.1% (67.6–88.6%), specificity of 82.1% (71.5–92.7%), positive-predictive value of 24.5% (13.9–35.1%), and negative-predictive value of 97.7% (94.5–100%). One quarter of all patients (n = 102) had RPVO above the threshold at discharge. Residual pulmonary vascular obstruction above the threshold was associated with a significantly higher risk of death, recurrent PE and heart failure at 6 months (Table 5). The risk of an adverse clinical outcome increased with increasing discharge RPVO. The relationship between outcome and quartiles of RPVO is shown in Figure 4. At admission, there was no difference in clinical, echocardiographic, or MSCT characteristics between patients who subsequently had RPVO above the threshold at discharge V–Q scan,
and those who did not. Conversely, at 48 h echocardiography, there was a significantly higher EDRV/EDLV ratio (0.79 ± 0.18 vs. 0.71 ± 0.15, \( P < 0.001 \)) and significantly higher systolic PAP (41.9 ± 13.6 vs. 35.3 ± 12.3 mmHg, \( P < 0.0001 \)) in patients who went on to have RPVO ≥35% at discharge vs. those who did not, respectively.

### Discussion

The aim of our study was to determine the prognostic value of pulmonary vascular obstruction as assessed by V–Q lung scan at discharge in patients with intermediate- to high-risk PE. To the best of our knowledge, this is the first study to investigate the impact and prognostic value of early residual pulmonary thrombus burden on long-term outcome in these patients.

Our data confirm observations from previous studies showing that long-term prognosis after acute PE is influenced by the presence of comorbidities at admission, particularly cancer\(^{2,6–8,15}\) or renal insufficiency.\(^ {16–18}\) Similarly, predisposing factors for venous thrombo-embolic disease have also been shown to be associated with excess mortality at 3 months.\(^ {15}\) The severity of initial clinical, electrocardiographic, or echocardiographic presentation is known to play a major prognostic role beyond the in-hospital phase.\(^ {9,19,20}\) Indeed, our results confirm those observed by Ribeiro et al.\(^ {9}\) who showed that patients with systolic PAP >50 mmHg at admission had a higher risk of persistent PAP at 1 month, as well as an excess of mortality at 5 years. Although troponin and BNP have both been shown to predict mortality from PE in the short term, they do not appear to predict adverse outcomes in the longer term in patients who survive the acute phase,\(^ {21,22}\) and our findings support this.

Our results confirm the prognostic value of certain established variables, but also reveal the prognostic value of RPVO evaluated just before discharge, which we observed to be a powerful

**Figure 2** Receiver-operating characteristic curve identifying the threshold value of residual pulmonary vascular obstruction predictive of unfavourable clinical outcome at 6 months. AUC, area under the curve.

**Figure 3** Kaplan–Meier survival curves at 6 months according to the presence of residual pulmonary vascular obstruction < 35% or ≥ 35% at discharge ventilation-perfusion lung scan.
Table 5  Adverse events at 6 months according to residual pulmonary vascular obstruction above or below the threshold value of 35% at discharge

<table>
<thead>
<tr>
<th></th>
<th>RPVO &lt;35% (n = 314)</th>
<th>≥35% (n = 102)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death (%)</td>
<td>5 (1.6)</td>
<td>7 (6.8)</td>
<td>0.01</td>
</tr>
<tr>
<td>Recurrent PE (%)</td>
<td>6 (1.9)</td>
<td>8 (7.8)</td>
<td>0.003</td>
</tr>
<tr>
<td>HF or worsening dyspnoea (%)</td>
<td>2 (0.6)</td>
<td>10 (9.8)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Combined endpoint (%)</td>
<td>9 (2.8)</td>
<td>23 (22.5)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Figure 4 Combined endpoint at 6 months according to quartiles of residual pulmonary vascular obstruction at discharge.

Data are scarce regarding the natural course of RPVO in the course of PE. Nijkeuter et al.\cite{25} reported that almost 50% of patients still had perfusion defects at 6 months. Similarly, Sanchez et al.\cite{12} reported from a prospective series of 254 PE patients that perfusion defects were observed in 30% of patients at 6–12 months and were associated with increased PAP and dyspnoea. Furthermore, Sanchez et al. observed that age, initial PVO, history of VTE, and the time interval between symptom onset and diagnosis were independent predictors of perfusion defect after treatment of PE. Our results confirm the prognostic value of residual defects, but show that even when evaluated at discharge, this information already carries an important prognostic value. Indeed, in contrast to Sanchez et al., we observed an impact on mortality in the first 6 months after discharge, underlining that the extent of RPVO at discharge must be taken into consideration in the management of PE patients, as there is clearly a benefit to be yielded in terms of mortality and adverse events.

However, our results also confirm our previous work showing that RPVO ≥35% after thrombolysis is a predictor of long-term mortality.\cite{22} This 30% threshold has often been evaluated empirically.\cite{23} However, the 35% RPVO threshold identified in our study can be considered as a robust criterion, since it is associated with an increased risk of death, recurrent PE, and heart failure at 6 months. In more general terms, the additional prognostic value is confirmed by the increased AUC, and the improvement in the model discrimination and goodness-of-fit criteria when compared with the multivariable model that did not include the V–Q scan information. These findings argue in favour of a systematic evaluation of RPVO before discharge in patients with intermediate-to high-risk PE. Residual pulmonary vascular obstruction at discharge ≥35% could identify patients at risk of adverse outcome, whereas those with RPVO <35% likely have a favourable long-term prognosis, with a high negative-predictive value. With the increasing domination of MSCT as a first-line imaging test to diagnose PE, our results suggest that the V–Q scan still remains useful for prognostic purposes. Further, larger studies are warranted to investigate whether tailored follow-up for patients identified at discharge to be at a high risk of events could yield a clinical benefit.

Study strengths and limitations

In our study, the selection of the population aimed to minimize possible bias in the interpretation of the results. Indeed, we excluded from this analysis all patients with previous diseases likely to interfere with V–Q scan analysis.

This study suffers from certain limitations. First, it is a single-centre study with a relatively small sample size. Secondly, external validation in a larger population is necessary. Thirdly, we used a combined endpoint, in which only recurrent symptomatic PE were taken into account, and events were not independently adjudicated. Fourthly, while our data make it possible to identify patients at risk of an adverse outcome, the exact mechanisms by which RPVO influences an outcome at 6 months remain unclear, with the result that no specific management strategy can be proposed for this clinical situation at present. Initial evaluation of thrombus distribution and burden by MSCT as opposed to follow-up by lung scan is a further limitation of the study, since we cannot accurately determine to what extent initial thrombi resolved upon early anticoagulation. Nonetheless, it should be noted that the severity and distribution of PE, as evaluated by MSCT, was identical in both groups at admission. Thus, the likelihood that initial pulmonary vascular obstruction differed between groups at baseline is low.

In our study, the anticoagulation status was only known for patients who experienced an event. We therefore cannot rule out the possibility that the time in therapeutic range may have been greater in patients without any event at 6 months, and this could explain the difference observed between groups. However, outside the context of randomized trials, TTR is generally reported to be in the range of 50%.\cite{25,26} Among the patients with adverse events in our study, 69% of INR values were in the

\begin{table}[!h]
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\begin{tabular}{|l|c|c|c|}
\hline
\textbf{Combined endpoint (%)} & \textbf{9 (2.8)} & \textbf{23 (22.5)} & \textbf{<0.0001} \\
\hline
\end{tabular}
\caption{Adverse events at 6 months according to residual pulmonary vascular obstruction above or below the threshold value of 35% at discharge.}
\end{table}
appropriate range, which suggests that they were treated appropriately. The likelihood that the patients without any event were treated better is relatively low.

Conclusion

Our results suggest that RPVO as evaluated by V–Q scan at discharge in patients with intermediate- to high-risk PE is a powerful prognostic factor for outcome at 6 months. In particular, one quarter of the patients in our study had RPVO ≥35%, and this was associated with an increased risk of death, recurrent PE, or heart failure at 6 months. Conversely, RPVO of <35% at discharge may identify patients with high likelihood of favourable outcome. These results warrant confirmation in a larger-scale study, and plead in favour of a strategy of systematic V–Q scan at discharge in this population to identify patients at the greatest risk of adverse outcome.

Authors’ contribution

Conception and design of the study: N.M., Y.B., F.S., S.D. Acquisition of data: all authors. Analysis and interpretation of data: N.M., F.S. Drafting and critical revision of the article for important intellectual content: All authors. Final approval of the version to be published: All authors.

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Conflict of interest: none declared.

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