Thrombosis Research 148 (2016) 70–75

Contents lists available at ScienceDirect

Thrombosis Research

journal homepage: www.elsevier.com/locate/thromres

Full Length Article

Residual pulmonary vascular obstruction and recurrence after acute pulmonary embolism. A single center cohort study

Benjamin Planquette [a,b,c,*,1], Alexis Ferré [a,b,1], Julien Peron [d,e], Amandine Vial-Dupuy [a,b], Jean Pastre [a,b], Gisèle Mourin [a,b], Joseph Emmerich [a,f], Marie-Anne Collignon [g], Guy Meyer [a,b,h,i], Olivier Sanchez [a,b,c]

[a] Université Paris Descartes, Sorbonne Paris Cité, France
[b] Service de Pneumologie et Soins Intensifs, Service de Pneumologie et Soins Intensifs, Hôpital Européen Georges Pompidou, AP-HP, Paris, France
[c] INSERM UMR-S 1140, Paris, France
[d] Medical Oncology Department, Centre Hospitalier Lyon Sud, Institut de Cancérologie des Hospices Civils de Lyon, Pierre-Bénite, France
[e] CNRS, UMR 5558, Laboratoire de Biométrie et Biologie Evolutive, Equipe Biostatistique-Santé, Université Lyon 1, Villeurbanne, France
[f] Médecine Vasculaire – Cardiologie, Centre de Diagnostic et de Thérapeutique, Hôpital Hôtel Dieu, AP-HP, Paris, France
[g] Service de Médecine Nucléaire, Hôpital Européen Georges Pompidou, AP-HP, Paris, France
[h] INSERM CIC-1418, Paris, France
[i] INSERM UMR-S 970, Paris, France

ARTICLE INFO

Article history:
Received 12 August 2016
Received in revised form 24 October 2016
Accepted 26 October 2016
Available online 29 October 2016

Keywords:
Pulmonary embolism
Management of pulmonary embolism
Thrombosis
Lung scintigraphy
Risk factor
Pulmonary circulation physiopathology

ABSTRACT

Introduction: Up to 50% of patients with pulmonary embolism (PE) present lung perfusion defects after six months of anticoagulant treatment, suggesting residual pulmonary vascular obstruction (RPVO). The risk of recurrence in patients with RPVO remains unknown. The present study aims to assess the risk of recurrent venous thromboembolism (VTE) in patients with RPVO after a first symptomatic episode of PE.
Methods: Consecutive patients who survived a first objectively proven acute PE, treated for at least three months with anticoagulants, were included and followed prospectively. RPVO was defined as a pulmonary vascular obstruction of >10% on ventilation/perfusion lung scan performed at inclusion. Objectively proven VTE recurrences were registered and confirmed by an investigator unaware of the result of the ventilation/perfusion lung scan.
Results: Among the 310 patients (median age: 61 years) included in the study, 60 (19%) had RPVO. During a median follow-up of 51.3 months, 66 patients (21.2%, 95% CI [17.5–26.7]) experienced recurrent VTE. In an adjusted cox proportional hazards analysis, we identified RPVO (HR 1.94; 95% CI [1.11–3.39]; $p = 0.026$) and unprovoked PE (HR 3.56; 95% CI [1.79–7.07]; $p = 0.00051$) as independent risk factors for recurrent VTE whereas extended anticoagulation therapy (HR 0.19; 95% CI [0.07–0.55]; $p = 0.00014$) was associated with a low risk of recurrence.
Conclusion: The results suggest that RPVO is an independent risk factor of recurrent VTE after a first PE.

1. Introduction

A substantial proportion of patients with venous thromboembolism (VTE) experience new events after anticoagulant treatment is withdrawn. This is especially true for patients with unprovoked VTE who carry a risk of recurrent VTE of approximately 10% after one year [1,2]. Even patients with provoked VTE have a substantial risk of recurrent VTE over the long-term, with a recurrence rate of 4.2% per patient-year in patients with transient non-surgical risk factors [3]. Many attempts have been made to identify risk-factors for recurrent VTE [4–7].

Residual venous obstruction assessed by ultrasound has been identified as an independent predictor of recurrence after deep vein thrombosis (DVT). However, little is known about the role of residual pulmonary vascular obstruction (RPVO) assessed by ventilation/perfusion lung scan (V/Q lung scan) as a risk factor for recurrence after an acute episode of pulmonary embolism (PE) [8,9]. Up to 50% of patients with PE present perfusion defects on V/Q lung scan after anticoagulant treatment, suggesting RPVO [10,11]. RPVO is associated with increased pulmonary artery pressure, a shortened 6 min walking distance, and a higher dyspnea score [12]. However, it is still unclear whether RPVO is associated with the risk of recurrent VTE after an acute episode of PE. The aim of the present study was to assess whether RPVO is associated with an increase in the risk of VTE recurrence.

* Corresponding author at: Service de Pneumologie et de Soins Intensifs Hôpital Européen Georges Pompidou, 20 rue Leblanc, 75015 Paris, France.
E-mail address: benjamin.planquette@aphp.fr (B. Planquette).
[1] These two authors contribute equally to this study.

http://dx.doi.org/10.1016/j.thromres.2016.10.030
0049-3848/

2. Patients and methods

2.1. Study design and setting

This study was a single-center, prospective, observational cohort study conducted in an academic teaching hospital (Hôpital Européen Georges Pompidou, Paris). The study was approved by the local ethics committee. All patients provided written informed consent before enrolment. Patient data were recorded on a database hosted in one computer.

2.2. Patients

Consecutive patients aged over 18 years were included at the intended end of the anticoagulation treatment if they (1) survived a first episode of objectively confirmed symptomatic PE, (2) received at least three months of anticoagulant therapy, and (3) did not present any recurrence during this period. Patients underwent a planar V/Q lung scan at the day of inclusion. Index PE was objectively confirmed by (1) spiral computed tomography (spiral CT) showing at least multiple sub-segmental PE, or (2) high probability V/Q lung scan according to the PIOPED criteria, or (3) proximal lower limb DVT on compression ultrasonography (CUS) in patients with a high clinical probability of PE [13]. The following index PE data were collected at inclusion: demographics, comorbid conditions, risk factors for VTE, initial pulmonary vascular obstruction using validated scores according to the diagnostic procedure [14,15], and initial therapeutic management. The index PE was considered to be provoked if it occurred in the presence of one of the following major risk factors: active cancer, surgery, trauma, or immobilization >3 months. PE occurring in the absence of major risk factors or hormonal therapy, including oral contraceptives and hormonal replacement therapy, was considered to be unprovoked.

2.3. Assessment of residual pulmonary vascular obstruction on V/Q lung scan

Each perfusion scan was compared to ventilation scan to identify mismatched defects and then scored as previously described by an investigator blinded to the occurrence of recurrent VTE. Briefly, (1) each lobe was assigned a weight, based on the regional distribution of pulmonary blood flow: right lower lobe 25%, right middle lobe 12%, right upper lobe 18%, left lower lobe 20%, lingula 12%, and left upper lobe 13%; (2) a semi-quantitative perfusion score (0, 0.25, 0.5, 0.75 or 1) was estimated for each lobe from the film density in the anterior, posterior, and oblique views by comparing them with the photodensity of an apparently normally perfused area; (3) each lobar perfusion score was then calculated by multiplying the weight by the perfusion score; (4) the overall perfusion score was determined by summing the six separate lobar perfusion scores; and (5) the percentage of vascular obstruction was then calculated as (1 − overall perfusion score) × 100 [15]. To consider mismatched defect as a residual pulmonary vascular obstruction, V/Q lung has been compared to the index PE diagnostic test in order to check that the mismatched defect did not concern a new pulmonary vascular segment. A residual perfusion defect was defined as a pulmonary vascular obstruction >10%. This 10% threshold corresponds to an amputation of at least two pulmonary segments and to the minimal obstruction defining a high-probability result on diagnostic V/Q lung scans [12,16].

2.4. Anticoagulant treatment, long-term follow, up and recurrence

The duration of treatment was at the discretion of the physician in charge of the patient. Our standard practice was to treat provoked PE for at least three months and unprovoked PE for six months. Extended treatment was defined as anticoagulant therapy given for more than six months. Patients included in the study were trained to quickly detect new symptoms and return to the hospital for diagnostic assessment. Patients lost to follow-up were individually contacted by phone and by post. In the absence of an answer, we contacted their general practitioner and the Civil Register to define if the patient was living or deceased.

2.5. End-point

The primary endpoint was the occurrence of an objectively confirmed symptomatic VTE or death due to PE. A diagnosis of recurrent thromboembolism was confirmed by a new thrombus in a different segmental area than for the initial PE on spiral CT, a new perfusion defect on V/Q lung scan, or detection of proximal lower limb DVT in a new territory by CUS. For the recurrence of ipsilateral DVT, an increase of >4 mm relative to the residual diameter was also considered to be a recurrence for popliteal and femoral veins. Sudden unexplained death was considered to be due to PE. All events were adjudicated by one of the investigators, blinded to the V/Q lung scan results.

2.6. Statistical analysis

Quantitative variables were expressed as median values and 25th–75th percentiles. Categorical variables were expressed as absolute numbers and percentages. Non-parametric Mann–Whitney *U* test or Fisher's exact test were used as appropriate to compare continuous or categorical variables between the two groups with and without recurrence of thromboembolism. Recurrence-free survival was the time from the day of the V/Q lung scan to the date of VTE recurrence or the date of the most recent follow-up visit, if no proven VTE recurrence occurred.

Thromboembolic recurrence-free survival distributions were estimated by the Kaplan-Meier method and compared using the Log-Rank test. The impact of potential prognostic factors (including RPVO) on thromboembolic recurrence-free survival was evaluated by including these factors in univariate cox proportional hazard models. Covariates were modeled as binary or categorical as appropriate. The proportional hazards assumption was assessed using the scaled Schoenfeld residuals. Variables considered to be clinically relevant and yielding p values of <0.1 by univariate analysis were retained for multivariate model analysis. The objective of the multivariate analysis was to assess the independent effect of perfusion defect on thromboembolic recurrence-free survival. The added value of perfusion defect in the multivariate model was evaluated using a likelihood ratio test: likelihood scores of the model evaluated with and without perfusion defect were compared, considering that lower likelihood scores indicate better fitting models. All testing was two-tailed and $p < 0.05$ was considered to be statistically significant. Statistical analysis was performed using R software version 3.2.2.

3. Results

3.1. Population (Fig. 1, Table 1)

From January 1999 to January 2009, 1244 patients with PE were admitted to our institution, of which 868 were for a first episode of PE. Finally, 321 patients were included and had a V/Q lung scan assessment. Eleven patients (3.4%) were lost to follow-up. Thus, we analyzed 310 patients.

The median duration of anticoagulant treatment was 6.5 months (inter-quartile range (IQR) 6.1–9.2). Fifty-one patients (16%) received extended anticoagulant treatment for one or more of the following reasons: atrial fibrillation or other cardiac disease ($n = 17$), cancer ($n = 7$), major thrombophilia ($n = 4$), chronic thromboembolic pulmonary hypertension ($n = 7$), RPVO ($n = 7$), major residual vein obstruction ($n = 1$), clinical trial ($n = 3$), or other ($n = 5$).

3.2. V/Q lung scan results

The median time between initial PE diagnosis and V/Q lung scan was 8.7 months (IQR 7.2–12.4). A residual perfusion defect was observed in