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Full Length Article

The impact of post-pulmonary embolism syndrome and its possible determinants

Mazdak Tavoly[a,b,c,*], Hilde S. Wik[d], Per-Anton Sirnes[e], Lars-Petter Jelsness-Jørgensen[a,f], Josef P. Ghanima[a], Frederikus A. Klok[g], Per-Morten Sandset[b,d], Waleed Ghanima[a,h]

[a] Department of Medicine, Østfold Hospital Trust, Sarpsborg, Norway
[b] Institute of Clinical Medicine, University of Oslo, Oslo, Norway
[c] Department of Medicine, Sahlgrenska University Hospital, Gothenburg, Sweden
[d] Department of Haematology, Oslo University Hospital Rikshospitalet, Oslo, Norway
[e] Cardiology Practice, Østlandske Hjertesenter, Moss, Norway
[f] Department of Health Science, Østfold University College, Fredrikstad, Norway
[g] Department of Thrombosis and Hemostasis, Leiden University Medical Center, Leiden, the Netherlands
[h] Department of Haematology, Institute of Clinical Medicine, University of Oslo, Oslo, Norway

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ABSTRACT

Introduction: Recent studies suggest that up to 50% of patients surviving pulmonary embolism (PE) may suffer from post-PE syndrome, which is defined by persistent dyspnea, impaired exercise capacity and/or decreased health-related quality of life (HRQoL). The possible determinants of post-PE syndrome are however not fully established.

Aims: To describe the differences between dyspneic and non-dyspneic PE-patients and to explore determinants of dyspnea, 6-min walking test (6MWT) and HRQoL.

Material and methods: In this cross-sectional study, consecutive patients diagnosed with PE between 2002 and 2011 at Østfold Hospital, Norway were identified from hospital registries. Patients were scheduled for clinical examination and a 6MWT. Dyspnea was assessed by the New York Heart Association (NYHA) classification. HRQoL was assessed with PEmb-QoL questionnaire. PE severity was assessed with PESI score, mean bilateral proximal extent of the clot and right-/left ventricle-ratio (RV/LV-ratio).

Results: 203 patients participated in this study, of which 96 patients reported dyspnea (47%). Median time from diagnosis was 3.6 years (IQR 1.9–6.5). Patients without dyspnea performed better on 6MWT (488 m vs 413 m, $p < 0.005$) and had better HRQoL results ($p < 0.005$). None of the variables we examined, including Charlson comorbidity index, was independently associated with dyspnea. However, higher RV/LV ratio at diagnosis was significantly associated with reduced 6MWT at follow-up. Further, ongoing anticoagulation and unemployment were independently associated with impaired HRQoL.

Conclusions: PE-survivors complaining of dyspnea suffer from impaired HRQoL and reduced exercise capacity. Although PE-severity factors were associated with reduced exercise capacity, none of the examined factors were found to be independent determinants of dyspnea.

Abbreviations: PE, pulmonary embolism; HRQoL, health-related quality of life; 6MWT, 6-min walking test; CTEPH, chronic thromboembolic pulmonary hypertension; CTPA, computed tomography pulmonary angiogram; V/Q-scan, ventilation/perfusion scintigraphy; BMI, body mass index; PESI, pulmonary embolism severity index score; RV/LV-ratio, right ventricle to left ventricle ratio; BNP, brain natriuretic peptide; CCI, Charlson comorbidity index; PEmb-QoL, Pulmonary embolism quality of life questionnaire; NYHA, New York heart association; $Sp0_2$, peripheral oxygen saturation; ADL, activities of daily living; TTE, transthoracic echocardiography; TAPSE, tricuspid annular plane systolic excursion; estPASP, estimated pulmonary artery systolic pressure; pTRV, peak tricuspid regurgitation velocity; RVGLS, the global longitudinal strain of the RV free wall; LVEF, left ventricle ejection fraction; LVGLS, left ventricular global longitudinal strain; LAVI, left atrial volume index; MBPEC, mean bilateral proximal extension of the clot; SD, standard deviation; IQR, interquartile range; VIF, variance inflation factor; SPSS, statistical package for social science; CI, confidence interval

* Corresponding author at: Department of Medicine, Østfold Hospital HF, Postboks 300, 1714 Gralum, Norway.
E-mail address: mazdak.tavoly@vgregion.se (M. Tavoly).

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1. Introduction

Pulmonary embolism (PE) has classically been regarded as a curable disease with the majority of patients expected to fully recover without any sequelae. However, during the last decade several reports have revealed that up to 50% of long term PE survivors suffer from dyspnea, reduced health-related quality of life (HRQoL) and/or impaired exercise capacity, e.g. by 6-min walking test (6MWT) or cardiopulmonary exercise test [1–4]. These observations have led to the proposition of a new syndrome called “post-PE syndrome” [5]. Although a clear definition of post-PE syndrome is still to be fully established, it is considered to be characterized by a combination of the following elements: persistent dyspnea, exercise capacity limitations and/or impaired HRQoL after a PE [5]. Chronic thromboembolic pulmonary hypertension (CTEPH), which also is suggested to fall under the post-PE syndromes umbrella, should be regarded as the most severe presentation of this ‘syndrome’ [6].

However, there are several knowledge gaps regarding post-PE syndrome. Firstly, the vast majority of studies reporting on possible long-term effects of PE have mainly focused on clinical outcome measures, e.g. recurrence, residual thrombosis and right ventricular dysfunction, rather than persistent dyspnea, which is the main manifestation of post-PE syndrome [7,8]. This is of particular clinical importance since it is the symptom of persistent dyspnea that mandates further evaluation in such patients [9,10]. Secondly, although associations between dyspnea, reduced exercise capacity and impaired HRQoL have been reported by previous studies, none have primarily aimed to evaluate independent associations between these measures. Thirdly, the pathophysiological basis and possible determinants of post-PE syndrome are still a subject of debate. Whereas some studies argue that the phenomenon is due to residual thrombosis, actual pathological remodeling of the pulmonary vasculature and the right side of the heart [11,12], other studies have suggested that the observed impairment is more likely due to patients' comorbidities and/or physical deconditioning [4,13,14]. From this perspective, there is a need for further research on post-PE recovery in order to better understand the impact, determinants and underlying pathophysiology of the post-PE syndrome.

The main purpose of this study was to characterize the post-PE syndrome. The specific objectives were: 1) To describe the differences in clinical, biochemical and radiological parameters as well as exercise capacity and HRQoL in patients with and without dyspnea; 2) To study whether there were independent associations between persistent dyspnea, reduced exercise capacity and impaired HRQoL; 3) To explore possible determinants of these measures; and 4) To evaluate if echocardiographic parameters were associated with either dyspnea and/or exercise capacity.

2. Materials and methods

2.1. Study design

The details regarding inclusion and exclusion criteria of this cross-sectional study has previously been reported [3]. Briefly, patients who were objectively diagnosed with PE (i.e. by computed tomography pulmonary angiogram (CTPA) or high probability perfusion scintigraphy (V/Q-scan)) at Østfold Hospital Trust, Norway, between January 2002 and December 2011 and who were still alive in March 2012 were eligible for study participation. If patients had multiple separate episodes of PE between 2002 and 2011, the first one occurring during this period was considered as the index episode. Patients were excluded if they were < 18 or > 90 years old or deemed incapable to comply with study procedures, including language barriers, geographical unavailability, known dementia, psychiatric diagnosis, such as any psychotic disorder, or living in nursing homes.

The study was approved by the southeastern Norway Regional Committee for Medical and Health Research Ethics (Approval no 2011/2557b), and written informed consent was obtained for all patients.

2.2. Study procedure

Patients who agreed to participate were invited to a scheduled study visit during which they underwent the following assessments: 1) Clinical examination; 2) Exercise capacity test; 3) Blood tests; 4) Echocardiographic examination; and 5) Assessment of HRQoL. Further, clinical and socio-demographic data were retrieved from the patients' history and medical records and recorded on a standardized case report form by one of the study authors (M.T.).

Prior to the study visit, the HRQoL questionnaire was sent to the patients either by e-mail or post. Patients were asked to complete and return these at their scheduled study visit. In case of missing questionnaire data, patients were asked to complete these during their visit at the hospital.

2.3. Study outcomes

As one of the main components of the post-PE syndrome is persistent dyspnea, the primary objective was to study the differences in clinical, biochemical and radiological variables as well as exercise capacity and HRQoL in patients with and without dyspnea. Based on previous published studies [13,14] and clinical experience following variables were thus recorded for all patients: age, sex, body mass index (BMI; kg/m^2), occupation, smoking, pulmonary embolism severity index (PESI) score [15], right to left ventricle diameter ratio (RV/LV-ratio), mean bilateral proximal extension of the clot [16], disease duration (time in years from PE diagnosis to study visit), recurrence (any PE or deep vein thrombosis prior to study inclusion or after the index episode), blood tests at study visit including hemoglobin (g/L) and brain natriuretic peptide (BNP; ng/L), ongoing anti-coagulation at follow-up, non-age-adjusted Charlson comorbidity index at follow up (fibromyalgia was classified as a connective tissue disease) [17].

The second objective included assessment of possible determinants of dyspnea, 6MWT and Pulmonary Embolism Quality of life questionnaire (PEmb-QoL) sum score. As such, variables mentioned above, were examined for associations with these measures. In addition, we analyzed if there was an independent association between the outcomes of dyspnea, 6MWT and PEmb-QoL sum score. The final objective was to evaluate if right or left ventricular dysfunction had any association with the presence of shortness of breath and/or reduced exercise capacity. In order to do so, echocardiographic parameters were explored for possible independent associations with dyspnea and 6MWT.

In addition, in order to reduce the possible confounding effect of comorbidities, a subgroup analysis was done in patients with no known comorbidities, i.e. Charlson comorbidity index = 0.

2.4. Study measures

2.4.1. Dyspnea

Dyspnea was considered present if the patients experienced any persistent symptom of shortness of breath after their diagnosis of PE. Although not developed for or validated in PE-patients the New York Heart Association (NYHA) classification has been used in several studies evaluating the long-term effects of PE [11,13]. We graded dyspnea with NYHA and persistent dyspnea was scored as NYHA > I.

2.4.2. Exercise capacity

Exercise capacity was assessed with 6MWT according to published guidelines [18]. Based on previous reports we sought to assess the frequency of patients covering 85% of their predicted walking distances [12]. In order to do so, predicted walking distances were derived from the literature for each patient [19]. Moreover, pulse oximetry was used to measure resting peripheral oxygen saturation ($Sp0_2$) as well as $Sp0_2$ during the 6MWT. The mean decrease of $Sp0_2$ was calculated by subtracting resting $Sp0_2$ with the lowest value measured during the 6MWT.