Persistent dyspnea complaints at long-term follow-up after an episode of acute pulmonary embolism: Results of a questionnaire


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Abstract

Background: There is a lack of information on long term complications of patients with pulmonary embolism (PE), including chronic complaints of dyspnea.

Methods: Consecutive patients with a prior diagnosis of acute PE and an age and gender matched control group with no medical history of PE were presented with a questionnaire, designed to establish the presence, severity and possible causes of dyspnea in the clinical course of PE.

Results: The questionnaire was taken in 48 PE-survivors 40±7.4 months after PE; 27 patients (56%) had complaints of dyspnea. Sixteen (35%) were categorized as NYHA class II, 6 (13%) as class III and 5 (10%) as class IV. Overall, 19 patients (70%) had new or worsened complaints after PE. The study included 61 controls. Corrected for gender, age and medical history, the control group was significantly less dyspnoeic compared to the PE survivors (p<0.001). Corrected for gender and age, patients were 4 times more often in NYHA class II (OR 3.6 95%CI 1.4–9.7) and 7-fold more often in NYHA class III or IV (OR 6.5 95%CI 1.7–24), both compared to control subjects.

Conclusion: A large percentage of patients with prior PE have persistent complaints of dyspnea at long term follow-up. The majority of them developed new or worsened dyspnea after the thrombo-embolic event. In comparison to a control population without a medical history of VTE, PE patients were overall significantly more dyspnoeic. An explanation for this phenomenon needs to be studied in further functional work-up of these patients.

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1. Introduction

There is extensive literature on pulmonary embolism (PE) focusing on its incidence, prevention, diagnostic strategies and treatment. Long term prospective studies on the clinical course of PE are however lacking. Patients with a first episode of acute PE end anticoagulant therapy after 3–12 months [1], dependent on the underlying cause of thromboembolism. After this, patients are usually no longer subject to clinical supervision. In spite of frequent clinical impression of persisting dyspnea, no study has systematically evaluated this phenomenon. Most follow-up studies have dealt with different diagnostic strategies, recurrent thrombotic events, major bleeding from anticoagulant therapy and mortality [2–6]. Little studies have follow-up for more than 2 years and describe the natural course of dyspnea complaints [7–9]. Relevance of persisting dyspnea complaints is underscored by Pengo et al [7], describing an incidence of 4% chronic thromboembolic pulmonary hypertension (CTEPH) in patients after a first episode of PE. Chronic thromboembolic pulmonary hypertension is a late complication of PE [10].

One study prospectively followed 136 patients with PE for an average interval of 17.6 months [9]. A total of 65 patients
died immediately or within hours after diagnosis, 6 died during follow-up, 1 was lost due to missing contact specifications and 1 refused informed consent. The total follow up concerned 68 patients; of those 10 (15%) had severe dyspnea and a further 9 (13%) remained moderately dyspnoeic. In two of the patients with severe dyspnea, pulmonary hypertension (PH) with right-ventricular failure was clearly present.

Standardized clinical follow-up, e.g. in the form of a validated questionnaire, could help the physician identifying patients with chronic complaints due to PE. In these latter patients, the cause of chronic symptoms should be further evaluated. Unfortunately, there are no reported studies in which patients with PE were followed up to screen them for long term complaints of dyspnea.

We designed a questionnaire to establish the presence, severity and possible causes of dyspnea in the clinical course of PE and presented it to a group of patients with a history of PE and a control group of random selected persons without a history of PE.

2. Materials and methods

2.1. Questionnaire

This newly developed questionnaire in Dutch, consisting of 25 questions, was based on the clinical work-up of post-PE patients in our clinic of vascular medicine. It was designed to assess complaints of dyspnea by establishing the presence, severity, impact on daily activities and possible causes of dyspnea in patients with a history of PE. Patients were asked for medical history of cardiac or pulmonary disease, anemia, use of medication and smoking behaviour. Ten questions were asked to distinguish the severity of the complaints. Exercise was classified into none (rest), mild (walking short distances and personal hygiene), moderate (normal daily activities, housekeeping) and heavy exercise (swimming, running). Also, a few questions were meant to identify signs of PH and right heart failure (e.g. syncope and angina). When dyspnea was confirmed, three questions were asked to determine the course of the dyspnea; whether the complaints existed before, whether the complaints had worsened and whether patients experienced a period free of complaints after the thrombo-embolic event. A history of cardiopulmonary disease was defined as any current or former visit to a cardiologist or pulmonary physician or current or former use of cardiopulmonary medication.

Finally, the questions were used to classify patients according to the criteria of the New York Heart Association (NYHA) functional classification, although not strictly applicable to a non heart failure population [11]. This classification has been designed for qualifying exertional intolerance in stages of heart failure and has been used to classify patients with PH [12]. Also, NYHA classification was used as instrument of evaluation in long term follow-up after pulmonary embolectomy [13–16].

2.2. Patients and taking the questionnaire

Eighty-eight consecutive patients, as part of a large diagnostic multicenter study [6], with a diagnosis of PE by CT-scan, diagnosed in our hospital between November 2002 and August 2004 were selected for the present study. Our study population comprised of patients with either a first or subsequent episode of venous thromboembolism after a follow-up of at least 2 years. They were treated according to hospital policy, initially with unfractioned heparin aiming at a 1.5 to 2.5 prolongation of the APTT (activated partial thromboplastin time), followed by oral anticoagulant therapy for 6 months. Medical records were searched for contact specifications and documented clinical course.

The questionnaire was taken by telephone in all surviving patients. Possible answers were ‘yes’ and ‘no’. The response rate of the study was 74%. To enable a comparison of patients with a medical history of pulmonary embolism to persons with no such medical history, a control cohort was created by taking the questionnaire in randomly selected persons in a shopping street in the same geographical region during 2 consecutive days. They were asked to answer all questions and their medical history, as previously defined, was noted. Only persons with a history of pulmonary embolism were excluded.

The scoring of the NYHA class was performed by two independent researchers without knowledge of patient or control status. In case of disagreement, a third researcher was consulted. All patients and controls consented to participate in the study and the Medical Ethical Committee of our hospital approved our protocol.

2.3. Statistical analysis

Confidence intervals were calculated by the modified Wald method, the Fisher’s exact test was used to compare discrete variables. Fisher’s analysis of variance (ANOVA) was used to test differences among the study- and control population. Data were considered significant at $p<0.05$.

SPSS (SPSS for windows 12.0.1, Inc. 1989–2003) and GraphPad (GraphPad software, Inc. 2002–2005) software were used for statistical calculations.

3. Results

3.1. Patients’ characteristics

Forty-eight patients completed the questionnaire; they comprised the study population. Their age at time of PE was $53\pm 15$ (24–80) (Table 1). The time between PE and the taken questionnaire was $40\pm 7.4$ (24–51) months. Twenty-three patients (32%) had died before the questionnaire could be taken (Fig. 1). In seventeen of the remaining patients the questionnaire could not be taken due to refused cooperation (3), inaccessibility (11) or absent contact specifications (3). The flowchart of patient selection is displayed in Fig. 1. To
create a control cohort, 90 random selected subjects were presented with the questionnaire. The response rate in the control group was 68%. In most cases, lack of time to complete the questionnaire was indicated as the main reason for refusal. The study included 61 controls; their age was 54±15 (25–88). The control group did not differ from the PE-group in gender, age, history of cardio-pulmonary history and smoking habits (Table 1).

3.2. Outcome questionnaire

Of the 48 study patients, 27 (56%, 95%CI 41–71) reported dyspnea (Table 2). Sixteen of 48 (35%) were categorized as NYHA class II, 6 of 48 (13%) as class III and 5 of 48 (10%) as class IV (Table 2). The period of time between the PE and the questionnaire had no correlation with the severity of complaints. In 19 of the 27 patients reporting dyspnea (70%), the complaints were experienced as new or worsened after PE. The control group comprised of 61 persons, of which 47 (77%) were categorized as NYHA I, 10 (16%) as NYHA II and 4 (6.6%) as NYHA III (Table 2). No controls were classified as NYHA IV. Corrected for gender and age, the control group was significantly less dyspnoeic than the PE survivors (p<0.001). After stratification for medical history, in both groups with (p=0.012) or without (p<0.001) cardio-pulmonary comorbidity, controls were significantly less dyspnoeic. Corrected for gender and age, patients were classified 4-fold more often in NYHA class II (OR 3.6 95%CI 1.4–9.7) and 7-fold more often in NYHA class III or IV (OR 6.5 95%CI 1.7–24), both compared with control subjects.

Twelve of 16 (75%) patients with a prior history of cardiac or pulmonary disease reported dyspnea. Thirty-two patients did not have a cardiac or pulmonary history; in this latter group 15 (47%) had complaints of dyspnea. Significantly more patients with cardio-pulmonary history were dyspnoeic (p=0.02) and they were classified in a higher NYHA-class (p<0.001). In nine of the 27 patients complaining of dyspnea, (pre-) syncope, angina or palpitations as new or worsened symptoms after PE were mentioned. When compared to the cohort without newly developed symptoms of right heart failure, these 9 patients were classified in a higher NYHA-class (p=0.01).

4. Discussion

We studied the natural course of dyspnea complaints in PE-patients by estimating the incidence and severity of persisting dyspnea symptoms using a standardized questionnaire. Our data demonstrates a surprisingly high number of patients with complaints of dyspnea after a mean period of 40 months after PE. The severity of their complaints varied between mild limitations in physical activity to inability to perform almost any activity at all. Importantly, more than two thirds of the patients with dyspnea indicated their complaints to have started or had worsened after the PE.

There are several hypotheses to explain our findings. First, in addition to a considerable contribution of (partly not identified) cardio-pulmonary comorbid conditions, incomplete resolution of pulmonary emboli contributes to the development of dyspnea. A recently published systematic review study [17] suggests persistent perfusion defects in more than 50% of PE patients 6 months after diagnosis, after which resolution of thrombi appears to reach a plateau phase. Clots can be classified in to several categories: central filling defect or complete occlusion, eccentric clot contiguous with the vessel wall, filling defect with central contrast material indicating recanalization and severe arterial luminal narrowing or vessel occlusion of a stenosed artery [17]. Persistent thrombi cause partial or complete obliteration of pulmonary arteries which may result in increased ventilation-perfusion mismatch and dead space ventilation. Indeed, dead space ventilation as determined by V/Q-scans has been shown to correlate with lung perfusion defects in subjects with acute PE [18]. Also, the development of ventilation-perfusion

![Fig. 1. Flowchart of patient selection.](image-url)
inequality has been demonstrated to provide a major contribution to the deranged gas exchange seen following pulmonary embolization [19]. In addition, survivors of PE present signs of ventilation to perfusion mismatch at exertion 3.1 years on average after the thromboembolic event [20]. No study has yet been performed to combine complaints of dyspnea with dead space ventilation measurements and pulmonary perfusion tests after long term follow-up in patients with acute PE.

One other notorious complication of unresolved thrombi after PE is CTEPH [10]. Characteristically, the main symptom of CTEPH is exertional dyspnea and signs of right heart failure [10]. The natural history of CTEPH is not completely known as a result of late presentation in the course of disease [21]. Originally, it was assumed that 0.1%–0.5% of patients surviving PE develop CTEPH [22]. Recent published studies find incidences of 1.0% after one year [23] and 1.0, 3.1 en 3.8% after 6 months, 1 and 2 years [7] subsequent to PE. Notably, both Becattini et al [23] and Pengo et al [7] did not find any new cases of CTEPH after 2 years. This challenges former studies that describe a “honeymoon period” of months to years before symptoms appear [10]. In our study nine patients had reported clinical signs of right heart failure. These patients had significantly more severe dyspnea ($p=0.01$) and more cardiopulmonary comorbidity ($p=0.049$). Importantly, history taking of these patients revealed previous echocardiographic work up in only four of them.

Our study has strengths and limitations. Even with a response rate of 74%, we studied a relatively limited number of patients over a period of time, partly due to a mortality rate of 32%. As result, the confidence limits of our observations are wide. Second, the PE-cohort was questioned by phone whereas the controls were questioned in person. This could have caused a bias. Nonetheless, persons were asked the same questions with only a possible “yes” or “no” answer. Because the results of the questionnaire were interpreted by two independent researchers without knowledge of patient or control status, we do not consider this to have influenced are results. Third, about 33% of the patients had a prior history of cardiac or pulmonary disease. Obviously, this has great influence on patient’s physical condition. After stratification in a history of cardiopulmonary disease, significantly more patients had dyspnea and complaints were overall more serious compared to patients with no history of cardio-pulmonary disease. Although we found a comparable prevalence of prior or concurrent cardiovascular disease in both study groups, it can be reasoned that sampling on the street causes a bias towards more healthy individuals. Finally, because our study-endpoint was the outcome of the questionnaire, we were not capable of determining the causes of the dyspnea.

In conclusion, we found 56% of patients with prior PE to have persistent dyspnea complaints 40 months after the initial event. The majority of them developed new or worsened dyspnea. In comparison to a control population without a medical history of VTE, PE patients were overall significantly more dyspnoeic. Larger, prospective clinical outcome studies using cardiopulmonary exercise testing and echocardiography are however needed to determine the cause of the dyspnea in this patient population.

### References


