High Prevalence of Persistent Breathlessness Following Sub-Massive Pulmonary Embolism in Patients Presenting to a Large Regional Hospital in South Wales

Patrick Flood-Page
Department of Respiratory Medicine, Aneurin Bevan University Health Board, Newport Chest Clinic, Newport, UK

OBJECTIVE: There is a broad literature exploring the investigation, treatment, management and outcomes of patients suffering from pulmonary embolism (PE). Chronic thromboembolic pulmonary hypertension (CTEPH) has been studied but less is known about outcomes for the large majority of individuals surviving PE who do not have persistent thrombus or CTEPH.

MATERIAL AND METHODS: Radiology, hospital and primary care records were reviewed in patients with central pulmonary emboli presenting to a large hospital in South Wales between 2013-16.

RESULTS: 2501 CTPA were reviewed. 380 (15.2%) showed PE and of these 127 (33.4%) involved the main pulmonary arteries or the pulmonary trunk. 4 patients received systemic and 1 catheter directed thrombolysis. 16 (12.6%) patients died of PE during the admission. Excluding patients dying within 3 months, 49 patients (48.5%) were more SOB than before the pulmonary embolus (73.7 % if there was evidence of right heart strain during admission). Of these 6 patients (12.2%) had evidence of persisting PE and/or pulmonary hypertension. In patients with no evidence of persisting clot or pulmonary hypertension where full lung function was performed there was an isolated reduction in gas transfer measurement (mean TLCO 57%).

CONCLUSION: Many patients remain breathless following large volume PE particularly if there is evidence of Right ventricular strain at presentation. The pathophysiology is unclear but lung function testing is consistent with persisting damage to the pulmonary vascular bed. These findings may allow clinicians to better advise patients of expected outcomes following major pulmonary embolus and may avoid unnecessary further investigation.

KEYWORDS: Clinical problems, pulmonary vascular diseases, diagnostic methods

INTRODUCTION

There is a broad literature exploring the investigation, treatment, management, and outcomes of patients suffering from pulmonary embolism (PE) [1-5]. Although chronic thromboembolic pulmonary hypertension (CTEPH) has been widely studied [6-7], there is little published work evaluating clinical outcomes for the large majority of individuals surviving PE who do not have persistent pulmonary artery thrombus or CTEPH. It was our impression that following sub-massive PE, many individuals experience breathlessness.

MATERIAL AND METHODS

Radiology reports of CT pulmonary angiography (CTPA) performed between 2013 and 2016 for the investigation of suspected acute PE in patients presenting to a large regional hospital in South Wales were reviewed. Hospital, primary care records, and CTPA images were reviewed in those patients with radiological evidence of central pulmonary emboli. Central pulmonary emboli were defined as those affecting the right or left main pulmonary arteries or the pulmonary trunk. This group were further subdivided into those with sub-massive embolism and those with the largest radiological clot burden, saddle embolus, clot in the pulmonary trunk, or greater than 50% unilateral or bilateral occlusion of the pulmonary arteries. Patients with sub-massive PE were defined as those with elevated troponin I levels and/or echocardiologic evidence of right heart strain.

Inpatient 3-month and 2-year mortality, thromboembolic risk factors, and the incidence of persistent breathlessness 3 months or more after the index pulmonary embolic event were recorded.
Clinical data was not collected for non-central thrombi but the relative incidence of central, multiple, or solitary segmental and/or lobar pulmonary emboli and sub-segmental pulmonary emboli was determined. Isolated sub-segmental PE are not routinely reported by radiologists within our unit following the recommendation that these are best left untreated if in isolation [5]. When sub-segmental PE has been reported, these are included within the analysis.

Ethical approval for the study was granted by Health Research Association (HRA) and Health and Care Research Wales (HCRW). Informed consent was not required for this study.

Statistical Analysis
The likelihood of persistent breathlessness in those with markers of right ventricular (RV) strain compared with those with no markers of RV strain was analyzed using the $\chi^2$ (chi-squared) technique (Excel, Microsoft Corporation, Redmond, USA).

RESULTS
Totally, 2501 CTPA were examined, 380 (15.2%) of which showed pulmonary emboli and of these 127 (33.4%) involved the main pulmonary arteries or the pulmonary trunk (Figure 1). Of these 127 patients, 19 (14.9%) had a previous history of thromboembolism, 17 (13.4%) recent surgery, 31 (24.4%) known malignancy, and six (4.7%) had cancer identified subsequently (Figure 2). In 53 patients (41.7%), thromboembolism was unprovoked. Four patients received systemic and one catheter directed thrombolysis. Sixteen (12.6%) patients died of PE during the admission, and a further 10 (7.9%) patients within three months of admission. The 3-month and 2-year mortality were 20.5% and 29.5%, respectively.

Three months or more after the pulmonary embolic event, and excluding patients dying within 3 months, 49 patients (48.5%) said that they were more short of breath (SOB) than before the pulmonary embolus (Figure 3). If troponin I level was elevated at admission, this increased to 61.5%. If there was both troponin elevation and echocardiologic evidence of RV strain, 73.7% reported breathlessness after three months (p=0.01) compared with those with no markers for RV strain (Table 1). Conversely, if there were no markers for RV strain, then only 34.5% reported breathlessness.

Of the 127 patients with central PE, 10 (7.9%) had preexisting COPD, 7 (5.9%) asthma, and 11 (8.6%) cardiac conditions, whereas 94 (74.0%) had no prior diagnosis of cardiorespiratory disease. Of the 49 patients with persistent SOB at three months, nine patients (18.4%) had preexisting cardiorespiratory disease. In the analysis, only those patients in whom the increased SOB was not attributable to co-existing disease were included.

When the volume of proximal clot burden was quantified radiologically, whether the clot was >50% occlusive of the pulmonary artery, within the pulmonary trunk, or whether there was evidence of bilateral clot with a saddle embolus did not affect the incidence of breathlessness at follow-up when compared with those with less extensive proximal clot burden.

Of the 49 patients reporting persistent breathlessness, only six (12.2%) had evidence of persisting clot on CTPA and/or pulmonary hypertension at repeat echocardiography.

In patients with no evidence of persisting clot or pulmonary hypertension for whom full lung function was performed, there was an isolated reduction in gas transfer measurement (mean TLCO 57%).

DISCUSSION
This study showed that 3 months or more after developing central PE, 48% of the patients report persistent breathlessness not explained by co-existing cardiorespiratory disease. Those suffering sub-massive PE are more likely to complain of persistent breathlessness than those without echocardiologic or biochemical evidence of hemodynamic compromise at presentation.

Previous Studies
The finding that around 50% of patients suffer persistent breathlessness following PE is broadly consistent with the few studies where long-term outcomes have been reported. In a retrospective study of 217 patients following PE, 36% were found to be breathless after a mean of 3.6 years [8]. In 76% of these patients, the breathlessness was worse than before the PE. In a further study, CPET (cardiopulmonary exercise testing) was performed 1 year after PE in a population without previously known cardiorespiratory disease [9]. Forty of the 86 patients (46%) were found to have a $V_O_{2\text{max}}$ max

**MAIN POINTS**
- Persistent breathlessness is common after large volume pulmonary embolism.
- The incidence of persistent breathlessness is highest in patients with evidence of right ventricular strain at presentation.
- A minority of patients with persistent symptoms have evidence of chronic thromboembolic pulmonary hypertension (CTEPH).
Although this study did not have baseline values for comparison. In a prospective study, 127 patients with no known cardiorespiratory illness were followed up at six months post PE [10]. Forty-five patients (41%) had one or more of RV abnormalities, NYHA breathlessness >2, or 6MWD <330 m². Other similarly small studies have shown comparable findings [11, 12].

This is the only study to date reporting clinical outcomes for large volume PE and the first study showing an association between the degree of hemodynamic compromise at presentation and the likelihood of persistent symptoms after treatment.

Strengths and Weaknesses

In our unit, CTPA is the investigation of choice for PE. VQ (ventilation/perfusion) scanning is not routinely available for the investigation of PE and is only rarely performed and never over the period of this study for the investigation of acute PE unless a CTPA had been done first. The database of all CTPA, therefore, captures practically all acute PE diagnosed in our unit. This avoids the potential bias associated with the use of VQ or perfusion scanning in certain patient subgroups including during pregnancy or in fitter patients where there is less hemodynamic upset at presentation.

This was a retrospective study and, as such, there was no control over the completeness of the clinical record or of investigations. This may affect the precision of the results. For example, investigation for RV strain was not done in all patients with central PE. Although a majority of the surviving patients were followed up after 3 months, in a third of the patients, the clinical record did not indicate whether the patient still experienced breathlessness. The analysis assumed that all these patients were not breathless, and so the value of 48% may be an underestimate of the true value. Conversely, echocardiography and assessment of RV function may have been done less often at presentation in more stable, less symptomatic patients. Had echocardiography been performed for everyone at presentation, some of these more stable patients may have shown signs of RV strain, and thus assuming that these patients remained less symptomatic, the value of 73% for breathlessness in the group with RV strain may be an overestimate.

In addition, clinicians as a part of their routine practice, did not record validated measures of breathlessness and only recorded whether or not the patient was more breathless than before the thromboembolic event. Because of this, for most patients, it was only possible to record breathlessness in a binary fashion-yes or no. Where breathlessness was quanti-

Table 1. The incidence of persistent shortness of breath after central pulmonary embolism with or without markers for right ventricular strain

|                  | Persistent SOB (%) | Comparison with No RV strain (χ²) |
|------------------|---------------------|----------------------------------|
| All              | 49/101 (48.5)       |                                  |
| No RV strain     | 20/58 (34.5)        |                                  |
| Troponin rise    | 24/39 (61.5)        | χ²=0.15                          |
| Troponin rise or | 29/43 (67.4)        | χ²=0.05                          |
| Troponin rise and| 14/19 (73.7)        | χ²=0.01                          |

Echo: echocardiogram; RV: right ventricular; SOB: shortness of breath
fied, this was a descriptive assessment and, in most cases, recorded as ‘mild’ or ‘minor’. In three patients where there was no evidence of residual blood clot or pulmonary hypertension, the persisting breathlessness was recorded as severe and/or disabling. VQ scan in one of these patients was within normal limits and in all the patients, no other disease process was identified as a plausible cause of the breathlessness.

The pathophysiology of the persistent symptoms is unclear. Persisting perfusion defects were found in 73 of 254 patients one year after PE [13]. This is consistent with our observation that in the five patients for whom full lung function tests were performed, transfer factor was reduced. However, neither this study nor ours had baseline examinations to compare, although in our study there was no known preexisting lung disease. One author suggested that persisting breathlessness might be explained by a lack of fitness following a period of inactivity post PE [9]. The persistence of breathlessness several years after the index event would argue against this theory [8].

A high proportion of patients remain short of breath after PE. This study suggests that in patients with large volume PE, breathlessness may be even more common, particularly in those with massive or sub-massive PE. The pathophysiology of the breathlessness is unclear, but our observations and those from previous studies are consistent with persisting damage to the pulmonary vascular bed.

The persistence of breathlessness after PE is not widely recognized by healthcare professionals. It is not mentioned in common undergraduate textbooks [14-16] and does not feature in patient information literature produced by prominent lung and PE organizations and charities (British Lung Foundation, Thrombosis UK, NHS helpline, National Heart, Lung and Blood Institute, American Thoracic Society). Although the breathlessness is minor in some, it is disabling. For only a small minority where there is evidence of pulmonary hypertension or persistent clot are treatments available. Wider recognition of this problem is needed both to avoid unnecessary investigation and also to better advise patients of expected outcomes following a PE.

**REFERENCES**

1. Sanchez O, Trinquet L, Colombet I, et al. Prognostic value of right ventricular dysfunction in patients with hemodynamically stable pulmonary embolism: a systematic review. Eur Heart J 2008;29:1569-77. [Crossref]
2. Meyer G, Planquette B, Sanchez O. Long-term outcome of pulmonary embolism. Curr Opin Hematol 2008;15:499-503. [Crossref]
3. Donato AA, Khoche S, Santora J, et al. Clinical outcomes in patients with isolated sub-segmental pulmonary emboli diagnosed by multidetector CT pulmonary angiography. Thromb Res 2010;126:e266-70. [Crossref]
4. Stein PD, Goodman LR, Hull RD, et al. Diagnosis and management of isolated subsegmental pulmonary embolism: review and assessment of the options. Clin Appl Thromb Hemost 2012;18:20-6. [Crossref]
5. Kearon C, Akl EA, Ornelas J, et al. Antithrombotic Therapy for VTE Disease: CHEST Guideline. Chest 2016. doi: 10.1016/j.chest.2015.11.026. [Crossref]
6. Pengo V, Lensing AWA, Prins MH, et al. Incidence of chronic thromboembolic pulmonary hypertension after pulmonary embolism. N Engl J Med 2004;350:2257-64. [Crossref]
7. Becattini C, Agnelli G, Pesavento R, et al. Incidence of chronic thromboembolic pulmonary hypertension after a first episode of pulmonary embolism. Chest 2006;130:172-5. [Crossref]
8. Klok FA, Tijmsen JE, Haeck ML. Persistent dyspnea complaints at long-term follow-up after an episode of acute pulmonary embolism: results of a questionnaire. Eur J Intern Med 2008;19:625-9. [Crossref]
9. Kahn SR, Hirsch AM, 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. [Crossref]
10. Stevinson BG, Hernandez-Nino J, Rose G, et al. Echocardiographic and functional cardiopulmonary problems 6 months after first-time pulmonary embolism in previously healthy patients. Eur Heart J 2007;28:2517-24. [Crossref]
11. Ciurzynski M, Kurzyna M, Bochowicz A, et al. Long-term effects of acute pulmonary embolism on echocardiographic Doppler indices and functional capacity. Clin Cardiol 2004;27:693. [Crossref]
12. Kline JA, Steuerwald MT, Marchick MR, et al. Prospective evaluation of right ventricular function and functional status 6 months after acute submassive pulmonary embolism: frequency of persistent or subsequent elevation in estimated pulmonary artery pressure. Chest 2009;136:1202-10. [Crossref]
13. 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. [Crossref]
14. Kumar P, Clark M, editors. Clinical Medicine. Elsevier Saunders; 2005.
15. Longmore M, Wilkinson IB, Baldwin A, Wallin E, editors. Oxford Handbook of Clinical Medicine. Oxford University Press; 2014. [Crossref]
16. Walker BR, Colledge NR, Ralston SH, Penman I, editors. Davidson’s Principles and Practice of Medicine. 22nd ed. Churchill Livingstone; 2014.

**Ethics Committee Approval:** Ethics Committee Approval for the study was obtained from the Health Research Association (HRA) and Health and Care Research Wales (HCRW).

**Informed Consent:** N/A.

**Peer-review:** Externally peer-reviewed.

**Conflict of Interest:** The author has no conflicts of interest to declare.

**Financial Disclosure:** The author declared that this study has received no financial support.