The Post-Pulmonary Embolism Syndrome: Real or Ruse?

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Pulmonary embolism (PE) occurs in 600,000 to 1 million individuals each year, and has a 15% 1-year mortality, making it the third leading cause of cardiovascular mortality in the United States (1). About one-third of patients who survive acute PE develop persistent symptoms of exercise intolerance and dyspnea, making PE an important cause of disability. However, the presence of dyspnea after PE is poorly understood due to retrospective studies using varying definitions, heterogeneous and incomplete diagnostic testing, and lack of objective symptom assessment before the acute PE. For this reason, some are skeptical that symptoms after a treated PE comprise a clinical entity rather than being attributable to coexisting comorbidities (which may have predisposed to the PE in the first place).

“Post-PE syndrome” has been used to refer to persistent dyspnea, exercise limitation, and impaired quality of life that persist for longer than 3 months after effective anticoagulation for acute PE. Unfortunately, a specific, data-driven definition of the syndrome has not been

established. This syndrome broadly encompasses three groups of patients, which are those with: chronic thromboembolic pulmonary hypertension (CTEPH); chronic thromboembolic disease (CTED); or dyspnea with functional limitations without identifiable pulmonary vascular disease (which we term “post-PE-related dyspnea”). Patients with symptoms predating acute PE, symptoms explained by a non-PE-related alternative diagnosis, and asymptomatic patients with persistent thromboembolic disease by imaging are excluded. Herein, we attempt to better elucidate the clinical spectrum of post-PE syndrome and provide a framework for an approach to patient care.

CTEPH

CTEPH is defined by the presence of a mean pulmonary artery pressure (mPA) of 25 mm Hg or greater with pulmonary artery wedge pressure of 15 mm Hg or less, mismatched perfusion defects on ventilation-perfusion ($\dot{V}/\dot{Q}$) scan, and specific findings by multidetector computed tomography (CT) angiography, magnetic resonance cineangiography, despite at least 3 months of effective anticoagulation (2). CTEPH occurs in approximately 3–4% of patients after a first episode of acute PE, with an annual incidence of 5 per million individuals (2). The severity of symptoms varies from mild exertional dyspnea to severe dyspnea at rest. Screening, diagnosis, and treatment options for CTEPH have been recently reviewed (2, 3). All patients with CTEPH require life-long anticoagulation. Pulmonary thromboendarterectomy (PTE) is potentially curative and is considered first

line treatment for patients who are surgical candidates with amenable disease. Medical therapy and balloon pulmonary angioplasty may improve hemodynamics and symptoms in patients who are not surgical candidates or have persistent pulmonary hypertension (PH) after PTE (4).

CTED

Patients with CTED have imaging findings similar to those of CTEPH and exercise limitation, but resting hemodynamics do not meet criteria for PH (3).

Cardiopulmonary exercise testing (CPET) shows a limitation to exercise consistent with pulmonary vascular disease: reduced exercise capacity (peak oxygen consumption [$\dot{V}O_{2peak}$]), increased dead space ventilation, inefficient ventilation (increased minute ventilation/carbon dioxide production slope), and reduced O_2 pulse (reflecting reduced stroke volume) (5). Patients with CTED generally have more preserved exercise capacity than patients with CTEPH, and patients with CTED do not develop right heart failure (6). Right heart catheterization (RHC) reveals either normal resting hemodynamics or borderline PH (mPA of 20–24 mm Hg with pulmonary vascular resistance of 2–3 Wood units). With exercise, there is an increased mPA/cardiic output slope, exaggerated rise in mPA to over 30–35 mm Hg, and no or inadequate fall in pulmonary vascular resistance (5).

The incidence of CTED is unknown. At Papworth Hospital, only 4% of operable patients had CTED, because either the incidence or detection is less than CTEPH or there is less enthusiasm about operating on patients with CTED (6). Historical data

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suggest that CTED uncommonly transitions to CTEPH, so there is no evidence to guide how to/whether to follow these patients (6). Importantly, there are no studies of medical treatment of these patients. Data from large PTE referral centers suggest that surgery may have benefit in amenable disease, with improved hemodynamics, functional class, and exercise capacity (5, 6). Balloon pulmonary angioplasty has also been used in select patients with improved hemodynamics and functional capacity (7). As with CTEPH, life-long chronic anticoagulation is recommended in all patients with CTED, and exercise training may have a therapeutic role in both CTED and CTEPH (8, 9).

Post-PE-related Dyspnea

Although only a minority of patients who develop acute PE develop CTED or CTEPH, persistent dyspnea and functional limitation after treatment are quite common (10). We have defined “post-PE-related dyspnea” as new or worsening dyspnea, chronic exercise limitation, and impaired quality of life that persist for a minimum of 3 months after effective anticoagulation for acute PE, but without evidence of pulmonary vascular disease (i.e., CTED or CTEPH) on diagnostic testing.

PEITHO (Pulmonary Embolism Thrombolysis Study) was a placebo-controlled, randomized clinical trial of systemic thrombolytics for intermediate risk PE that enrolled 1,006 patients and that included long-term follow-up for a median of 37 months for a subset of 709 patients (11). One-third of patients in each group (thrombolytics vs. anticoagulation alone) had persistent dyspnea; approximately 12% of patients were in New York Heart Association functional class III or IV. More than 35% of patients in each arm had at least one indicator of PH and/or right ventricular (RV) dysfunction on echocardiogram (11), but only 2–3% of patients in each group were diagnosed with CTEPH. The association between dyspnea and RV dysfunction was not assessed. This study suggests that thrombolytic therapy for intermediate-risk acute PE does not reduce the incidence of the post-PE syndrome. CPET, RHC, and imaging studies were not routinely performed to determine if any of these patients had evidence of CTED. Screening for CTEPH included “guideline-based” diagnostic workup only in patients

“whose symptoms and/or echocardiogram indicated PH, so it is possible that more mild CTEPH or CTED was underestimated.

Kahn and colleagues (12) performed serial CPET and imaging in 100 patients after their first episode of PE and showed that nearly half had reduced $\dot{V}O_{2peak}$ at 1 year. Virtually all patients with impaired $\dot{V}O_2$ had exercise limitation consistent with deconditioning; no patients had a circulatory limitation to exercise; 60% of the patients with exercise limitation had normal perfusion scans. Deconditioning without evidence of pulmonary vascular disease was also seen in another smaller cohort of patients after submassive or massive PE, despite half having abnormal RV function on echo (13). Although neither study routinely performed RHC to definitely exclude pulmonary vascular disease, unrevealing CPET makes significant pulmonary vascular disease less likely (5).

Importantly, there was no correlation between residual obstruction on perfusion imaging or echocardiographic parameters of RV dysfunction and reduced exercise capacity in either study, further supporting the notion that persistent pulmonary vascular dysfunction is not the major driver of symptoms. Although residual pulmonary vascular obstruction (RPVO) after acute PE is common (up to 50% of patients) and associated with unprovoked PE, a higher incidence of recurrent PE, and CTEPH (14, 15), RPVO alone is not equivalent to pulmonary vascular disease. The apparent contradiction is explained by the fact that RPVO is typically quantified by $\dot{V}/\dot{Q}$ scan, which is highly sensitive and identifies even small degrees of vascular obstruction that may not be clinically or physiologically relevant. In the study by Kahn and colleagues, at 1 year after acute PE, 46% of patients had an abnormal perfusion scan, but the average vascular obstruction was only 5% in patients with both normal and reduced $\dot{V}O_{2peak}$ (13).

These studies demonstrating persistent dyspnea and chronic RV dysfunction after acute PE in the absence of CTEPH are in line with numerous prior observational studies (10). Therefore, distinguishing CTED from post-PE-related dyspnea is particularly challenging, as both groups of patients may have perfusion defects on $\dot{V}/\dot{Q}$ scan and/or subtle RV abnormalities on echo. The two are often distinguished in clinical studies by pulmonary vascular limitation to exercise on CPET. Further functional studies in patients with post-

PE-related dyspnea, such as exercise cardiac magnetic resonance imaging and/or RHC with exercise, are crucial to understanding if these patients have abnormalities in RV/pulmonary artery coupling or other more subtle metrics of pulmonary vascular disease potentially not detected by CPET.

One criticism of the physiology studies of patients after PE is that they largely exclude patients with significant preexisting cardiopulmonary comorbidity, and perhaps do not reflect comorbidities among “real-world” patients diagnosed with acute PE. Klok and colleagues (16) found at least one preexisting comorbidity in 185 of 189 patients who had dyspnea after acute PE, although 60% of patients did not develop dyspnea until after acute PE, and the authors could not determine if the underlying comorbidity was actually the major driver of dyspnea. It is certainly plausible that the combination of an underlying comorbidity plus deconditioning related to the acute PE led to dyspnea in many of these patients.

There are no established treatments for post-PE-related dyspnea syndrome. Although deconditioning may be a major driver of symptoms, there are no randomized studies evaluating the efficacy of exercise training after acute PE. Studies of pulmonary rehabilitation for patients with dyspnea after acute PE are currently underway (clinical trial ID: NCT03405480).

Approach to the Patient with Persistent Dyspnea after Acute PE

An assessment for post-PE syndrome should not be undertaken until the patient has completed at least 3 months of effective anticoagulation (1, 3, 17). Patients complaining of dyspnea after 3 months of treatment for PE require further diagnostic evaluation (see Figure 1). We continue therapeutic anticoagulation in all symptomatic patients until an etiology of symptoms is established, regardless of the provoking factor. Current guidelines recommend echocardiography followed by a $\dot{V}/\dot{Q}$ scan and RHC in combination with CT or invasive pulmonary angiogram if the echo is suggestive (2). Importantly, asymptomatic patients *should not* be screened for CTEPH or CTED after acute PE (1–3, 18).

For symptomatic patients, despite 3 months of effective anticoagulation and

Figure 1. Diagnostic algorithm for evaluation of persistent dyspnea after acute pulmonary embolism (PE). Blue boxes indicate diagnostic modalities, whereas orange, green, and red boxes indicate disease-specific diagnostic/treatment pathways. *Suggestive of pulmonary hypertension (PH) refers to intermediate- or high-probability echo criteria per 2015 European Respiratory Society (ERS) guidelines, while low probability PH refers to low probability echo criteria (2); †positive ventilation–perfusion (V/Q) or single-photon emission computed tomography (SPECT)/computed tomography (CT) scan refers to greater than or equal to one segmental or greater than or equal to two subsegmental perfusion defects; ‡PH is defined by 2015 ERS guidelines (2). CPET = cardiopulmonary exercise testing; CTA = computed tomography angiography; CTEPH = chronic thromboembolic pulmonary hypertension; PVD = pulmonary vascular disease; rehab = rehabilitation; RHC = right heart catheterization; TTE = transthoracic echocardiogram.

an echocardiogram with low probability of PH, we exclude other etiologies of dyspnea with pulmonary function testing, exercise oximetry, electrocardiogram, measurement of brain natriuretic peptide and hemoglobin, and review of the echo for left-sided heart disease and the prior CT pulmonary angiogram (from diagnosis of acute PE) for parenchymal lung disease. If comprehensive testing does not reveal an etiology of dyspnea, additional evaluation for pulmonary vascular disease is warranted. A “normal echocardiogram” does not exclude mild CTEPH or CTED, whereas a patient with mild RV dilatation may have no evidence of pulmonary vascular disease upon further testing. For this reason, we then obtain either a $\dot{V}/\dot{Q}$ scan or single-photon emission CT perfusion scan single-photon emission computerized tomography (SPECT)/CT, as a normal perfusion study excludes CTED and CTEPH and usually obviates RHC (see Figure 1). Obtaining a

CPET before a lung perfusion scan is an alternative approach, as this is highly sensitive for the detection of both CTED and CTEPH; however, CPET requires significant expertise for adequate interpretation, and is not readily available to all clinicians (3, 18). Measurement of the arterial partial pressure of carbon dioxide during testing is recommended to accurately measure the change in dead space during the CPET.

A patient with low probability of PH on transthoracic echocardiography, a negative $\dot{V}/\dot{Q}$ scan, and no other etiology of dyspnea is considered to have post-PE-related dyspnea. For those patients with a positive $\dot{V}/\dot{Q}$ scan, we perform CPET, as evidence of pulmonary vascular disease on CPET warrants invasive testing for CTEPH/CTED and/or referral to a PH/CTEPH center. In contrast, those patients with low-probability echo and positive $\dot{V}/\dot{Q}$ scan in whom CPET suggests deconditioning are labeled as having

post-PE-related dyspnea. For patients with a diagnosis of post-PE-related dyspnea, our practice is referral to a cardiopulmonary rehabilitation program versus a self-monitored diet and exercise program, depending on insurance coverage and patient preferences. If symptoms of dyspnea persist despite 3 months of exercise/rehabilitation, and they have not had a CPET, we finish their evaluation with CPET.

Conclusions

Persistent dyspnea and functional limitation after acute PE is a common and increasingly recognized cause of disability. The term “post-PE syndrome” has been used to capture a heterogeneous group of patients, including those with CTEPH, CTED, and a large, but unclassified, group of patients with

dyspnea, many of whom have RV dysfunction, but have no apparent pulmonary vascular disease on diagnostic testing. In reality, we suspect that there is a continuum from severe pulmonary vascular disease to

normal pulmonary vasculature with deconditioning to complete recovery after a PE. The post-PE syndrome remains controversial, in part due to its vague definition and cryptic cause. Further study is needed to better define and

establish treatments for this large and clinically significant population of patients. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

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