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## **The aftermath of acute pulmonary embolism: approach to persistent functional limitations**

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## Determinants and management of the post-pulmonary embolism syndrome

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## ABSTRACT

Acute pulmonary embolism is not only a serious and even potentially life-threatening disease in the acute phase, in the past years it has become evident that it may also have a major impact on a patient's daily life in the long run. Persistent dyspnea and/or impaired functional status are common, occurring in up to 50% of PE survivors. Its underlying causes are captured by the Post-PE Syndrome (PPES). Chronic thromboembolic pulmonary hypertension is the most feared long-term complication. When pulmonary hypertension is ruled out, cardiopulmonary exercise testing has a central role in investigating the causes behind persistent symptoms, such as chronic thromboembolic pulmonary disease or other cardiopulmonary conditions. Alternatively, it is important to realize that post-PE cardiac impairment or post-PE functional limitations, including deconditioning, are present in a large proportion of patients. Health-related quality of life is strongly influenced by the PPES, which underlines the seriousness of persistent limitations after an episode of acute PE. In this review, physiological determinants and the diagnostic management of persistent dyspnea are elucidated.

## 1. POST-PE DYSPNEA: LOOKING BEYOND CTEPH

In addition to recurrent venous thromboembolism, arterial cardiovascular disease and anticoagulant-associated bleedings, the clinical course of an adequately treated acute pulmonary embolism (PE) may be complicated by several long-term sequelae.<sup>1,2</sup> Notably, whereas the incidence of chronic thromboembolic pulmonary hypertension (CTEPH) is only 2-4% among PE survivors, up to 50% of PE patients suffer from exertional dyspnea and/or functional limitations despite adequate anticoagulant treatment.<sup>3,4</sup> In recent years, the concept of the Post-PE Syndrome (PPES) was proposed to capture these patients.<sup>5,6</sup> The PPES has a major impact on patient's daily lives and is associated with impaired functional status, reduced health-related quality of life and increased healthcare costs.<sup>7-12</sup> The relevance of recognizing the PPES is shown by the observation that eight years after acute PE, functional impairments are equally present as in patients with coronary heart disease or stroke.<sup>13</sup> The aim of this review is to highlight existing evidence on underlying causes and physiological findings in patients with PPES, and to give guidance on diagnostic work-up in the course after an acute PE.

## 2. PHYSIOLOGICAL DETERMINANTS OF THE POST-PE SYNDROME

The prevalence and determinants of persistent dyspnea months to years after an acute PE has been evaluated in many studies, listed in **Table 1**, of which the most important are discussed below. In a large prospective cohort study, 165 of 607 (27%) PE survivors still reported new-onset or worsened dyspnea at a median of 3.6 (IQR 2.1-5.1) years after the acute episode.<sup>14</sup> This exertional dyspnea could for the most part be explained by pre-existing cardiopulmonary comorbidity - such as COPD, diastolic dysfunction or obesity - in 98% of patients. No association was found between persistent dyspnea and characteristics of the PE, e.g. length of follow-up period, location of PE and VTE history. Several subsequent studies have however shown that impaired functional status after acute PE cannot simply be explained by pre-existing comorbidities. Potential explanatory physiological determinants of persistent dyspnea have been evaluated by performing echocardiography, cardiopulmonary exercise testing (CPET), pulmonary function tests (PFT) and/or ventilation perfusion scans.

### Cardiac recovery

Right ventricular (RV) function after acute PE was evaluated for the first time in two large prospective studies enrolling patients with intermediate-risk PE. Of 109 previously healthy patients with a first PE, echocardiographic evaluation six months after the

**Table 1:** Studies performed among PE patients focusing on physiological determinants of the PPES

Author, year	PE patients (n)	PE severity	Dyspnea or NYHA II-IV (proportion of patients)	RPVO (proportion of patients)	Imaging modality used	Study design	Time since PE diagnosis	TTE	CPET	PFT	6MWD	RHC	Comments
Lachant 2020 <sup>17</sup>	104	IM/high	55%	48%	V/Q	Prospective cohort	2-4mo	y	-	-	-	-	
Huang 2020 <sup>18</sup>	30	*				Prospective cohort	1 and 6mo	-	y	y	-	-	
Fernandes 2020 <sup>19</sup>	40	*	100%			Retro-spective cohort	5mo	-	y	-	-	-	
Dzikowska 2020 <sup>20</sup>	845	*	65%			Prospective cohort	6mo	y	-	-	-	-	Imaging/CPET/PFT/6MWD only in case of non-explanatory TTE
Danielsbacka 2020 <sup>21</sup>	64	*	67%			Prospective cohort	1yr	-	-	y	y	-	
Barco 2019 <sup>22</sup>	219	IM				Post-hoc analysis	3.1yr	y	-	-	-	-	
Hsu 2019 <sup>23</sup>	253	*	79%			Retro-spective cohort	6-24mo	y	-	-	-	-	Follow-up TTE performed in only those with exertional dyspnea
Keller 2019 <sup>24</sup>	101	*	47%			Prospective cohort	6mo	y	-	-	-	-	
Swietlik 2019 <sup>25</sup>	34	*	70%	100%		Prospective cohort	*	-	y	-	-	-	Routine exercise RHC Technically operable CTEPD cohort, of whom 6 underwent PEA

**Table 1:** Studies performed among PE patients focusing on physiological determinants of the PPES (continued)

Author, year	PE patients (n)	PE severity	Dyspnea or NYHA II-IV (proportion of patients)	RPVO (proportion of patients)	Imaging modality used	Study design	Time since PE diagnosis	TTE	CPET	PFT	6MWD	RHC	Comments
Claeys 2019 <sup>26</sup>	14 (+25 CTEPH, 13 controls)	*	100%	100%		Prospective cohort	*	-	y	-	-	Routine exercise RHC	24/25 CTEPH patients underwent PEA
Guth 2018 <sup>27</sup>	32	*	100%	100%		Prospective cohort	*	-	y	y	y	Routine RHC, partly exercise RHC	All underwent PEA
Albaghdadi 2018 <sup>28</sup>	20	IM/high				Prospective cohort	1 and 6mo	y	y	y	-	-	
Ma 2018 <sup>29</sup>	100	*		41% / 16%	V/Q / CTPA	Prospective cohort	1yr	-	y	-	-	-	
Kahn 2017 <sup>4</sup>	100	*		41% / 16%	V/Q / CTPA	Prospective cohort	1yr	y	y	y	y	-	
Kahn 2017 <sup>30</sup>	100	*				Prospective cohort	1yr	-	y	-	y	-	
Konstantinides 2017 <sup>31</sup>	709	IM/high	30%			RCT	3-2yr	y	-	-	-	-	359 tenecteplase versus 250 placebo
Samaranayake 2017 <sup>32</sup>	87	IM				Retro-spective cohort	8mo	y	-	-	-	-	Follow-up TTE performed in only 42 participants (48%), unclear indication

Table 1: Studies performed among PE patients focusing on physiological determinants of the PPES (continued)

Author, year	PE patients (n)	PE severity	Dyspnea or NYHA II-IV (proportion of patients)	RPVO (proportion of patients)	Imaging modality used	Study design	Time since PE diagnosis	TTE	CPET	PFT	6MWD	RHC	Comments
van Kan 2016 <sup>33</sup>	14	*	100%	100%		Prospective cohort	*	-	Y	Y	-	Routine exercise RHC	All underwent PEA
Held 2016 <sup>34</sup>	10 (+ 31 CTEPH, 41 controls)	*	100%	100%		Retrospective cohort	*	Y	Y	-	-	Routine exercise RHC	All were treatment-naïve
Tavoly 2016 <sup>9</sup>	213	*	46%			Cross-sectional	3.8yr	-	-	-	Y	-	
Chow 2014 <sup>35</sup>	120	*				Prospective cohort	7.7yr	Y	-	Y	Y	-	
Xi 2014 <sup>36</sup>	59 (+ 66 CTEPH, 36 controls)	*		25%	V/Q or CTPA	Case-control	6-12mo	Y	Y	-	-	-	
Taboada 2014 <sup>37</sup>	42	*	100%	100%		Prospective cohort	*	Y	-	Y	Y	Routine RHC	All underwent PEA
McCabe 2013 <sup>38</sup>	15 (+ 15 CTEPH, 10 controls)	*	100%	100%		Prospective cohort	6mo	-	Y	Y	-	Routine RHC	
Dentali 2013 <sup>39</sup>	25 (+ 25 controls)	*		12%	V/Q or CTPA	Case-control	6mo	Y	-	-	-	-	
Yan 2012 <sup>40</sup>	16 (+ 24 controls)	*				Case-control	2wk	Y	Y	-	Y	-	



**Table 1:** Studies performed among PE patients focusing on physiological determinants of the PPES (*continued*)

Author, year	PE patients (n)	PE severity	Dyspnea or NYHA II-IV (proportion of patients)	RPVO (proportion of patients)	Imaging modality used	Study design	Time since PE diagnosis	TTE	CPET	PFT	6MWD	RHC	Comments
Fasullo 2011 <sup>41</sup>	72	IM				RCT	6mo	y	-	-	-	-	37 thrombolysis versus 35 heparin treatment
Klok 2010 <sup>14</sup>	607	*	27%			Prospective cohort	3.6yr	y	-	-	-	-	
Golpe 2010 <sup>42</sup>	103	Low/IM		21%	CTPA	Prospective cohort	6mo	y	-	-	-	-	
Sanchez 2010 <sup>43</sup>	254	*	43%	29%	V/Q	Prospective cohort	6-12mo	y	-	y	-	-	
Kjaergaard 2009 <sup>44</sup>	41	Low/IM				Prospective cohort	1yr	y	-	-	-	-	
Kline 2009 <sup>16</sup>	162	IM	34%	28%	V/Q or CTPA	Prospective cohort	6mo	y	-	-	y	-	
Stevinson 2007 <sup>15</sup>	127	IM	17%			Prospective cohort	6mo	y	-	-	y	-	
Ciurzynski 2004 <sup>45</sup>	36 (+ 30 controls)	IM/high				Case-control	3.1yr	y	-	-	y	-	
Ribeiro 1999 <sup>46</sup>	78	*				Prospective cohort	1yr	y	-	-	-	-	

Note: Studies reporting data of echocardiographic or functional outcome measures in the course of an adequately treated acute PE are presented here. Studies reporting outcomes that are limited to quality of life questionnaires, pulmonary hypertension or adverse events are excluded.

\* unspecified.

Abbreviations: NYHA, New York Heart Association classification; RPVO, residual pulmonary vascular obstruction; TTE, transthoracic echocardiography; CPET, cardiopulmonary exercise testing; PFT, pulmonary function test; 6MWD, 6 minute walk distance; RHC, right heart catheterization; IM, intermediate; RCT, randomized controlled trial; V/Q, ventilation/perfusion; CTPA, computed tomography pulmonary angiography; y, yes; PA, pulmonary artery.

diagnosis revealed RV hypokinesis or dilatation in 27 survivors (25%), of whom one-third had functional limitations ("NYHA heart failure score >II or a 6MWD <330 m").<sup>15</sup> The second study with similar inclusion criteria demonstrated the presence of RV hypokinesis in 36 of 179 at PE diagnosis (20%), after 6 months this was 10 of 144 study participants (6.9%). RV dilatation was demonstrated in 70 patients (39%) at baseline, and in 36 (25%) during follow-up.<sup>16</sup>

The suggestion that RV abnormalities can persist or arise after acute PE was further fueled by results of the PEITHO trial, a randomized trial comparing thrombolysis versus placebo in 1005 patients with intermediate/high risk PE. In a follow-up study in 709 PEITHO trial patients, persistent dyspnea was found present in roughly a third of both groups at approximately 3 years (median 3.2, IQR 2.1 to 4.6) after study inclusion.<sup>31</sup> At that time, nearly a third of all study participants underwent echocardiographic follow-up of whom a relevant proportion were found to still have at least one echocardiographic sign of RV dysfunction or pulmonary hypertension: 44% of patients in the tenecteplase group (n=63) and 37% in the placebo group (n=52). CTEPH was diagnosed in 2-3% of patients in each group.<sup>31</sup> In a post-hoc analysis of this trial, incomplete or absent echocardiographic recovery at 6 month assessment was found predictive of developing CTEPH or RV dysfunction with exertional dyspnea corresponding to NYHA class II-IV.<sup>22</sup>

Looking beyond intermediate-risk PE only, several other large cohort studies have also assessed long-term cardiac function after acute PE. An Australian study prospectively followed 120 PE patients for nearly eight years (mean 7.7, SD 1.4). Of 104 patients with repeat echocardiography, persistent RV dysfunction was found in 25 of 104 (24%) and RV dilatation in 7 patients (7%).<sup>35</sup> An increased estimated pulmonary artery pressure (PASP >36 mmHg) was found in 30 of 104 (29%). These echocardiographic abnormalities were associated with shorter 6-minute walk distance (6MWD) many years after their index PE. In another study, 10 year of medical charts of Taiwanese PE patients were reviewed back to ten years. After a median of 6 months (IQR upper range 24) of anticoagulant treatment, 200 of 253 (79%) included patients had persistent dyspnea, in all of whom echocardiography had been performed: RV dilatation was present in 16 of 200 (8%), of whom 8 ultimately developed CTEPH.<sup>23</sup>

The high prevalence of abnormal echocardiograms in PE survivors was confirmed in a meta-analysis comprising 26 studies, and in several MRI studies.<sup>47-49</sup> After a median of 6 months, the pooled prevalence of persistent RV hypokinesis and/or dilatation was prevalent in 18% (95%CI 12-26) with no differences among patients treated with or without thrombolysis.<sup>47</sup> Importantly, different echocardiographic parameters have been used in the above discussed studies. A more comprehensive definition of RV dysfunction has been proposed<sup>50,51</sup> and comprises either a RV basal diameter >4.2 cm, tricuspid annular plane systolic excursion <1.6 cm, elevated right atrial pressure, tricuspid regurgitant velocity  $\geq 2.8$  m/s OR presence of pericardial effusion. When this

definition was used, 25 of 91 (28%) of patients had signs of RV dysfunction 6 months after their acute PE diagnosis in a German study.<sup>24</sup>

Besides RV function, a recent study suggested that left ventricular (LV) dysfunction is also prevalent among PE survivors. In this Polish study, 555 of 845 PE survivors had not recovered completely after at least 6 months (65%), all of whom were referred for echocardiographic assessments.<sup>20</sup> The most likely explanation of the self-reported functional impairment was determined in a multidisciplinary team of experts. Left-sided diastolic dysfunction was by far the most prevalent echocardiographic abnormality that was considered to be the cause of symptoms (34% of patients). CTEPH was established as final diagnosis in 8.4% and CTEPD in only 3.3% of patients. Since imaging tests of the pulmonary artery tree were not routinely performed, the presence of CTEPD may have been underestimated in this study.

### Cardiopulmonary responses to exercise

Performing a symptom-limited cardiopulmonary exercise test (CPET) allows for the differentiation between different mechanisms of unexplained dyspnea, including cardiovascular or ventilatory impairment.<sup>52</sup> Also, during exercise, hypoperfusion of ventilated areas might become evident and can be quantified, which is particularly relevant in patients with PPES.<sup>53</sup> In addition to pulmonary vascular conditions, limitations of cardiovascular or ventilatory origin, or psychogenic components can be quantified or excluded.<sup>54</sup>

Four studies applied CPET in patients with PPES with or without residual vascular occlusions. The first one was the ELOPE study, Canadian study including a total of 100 PE survivors. One year after their acute event, exercise limitations (defined as percentage-predicted peak oxygen uptake (VO<sub>2</sub>) <80% determined by CPET) were objectified in 47 patients (47%).<sup>4</sup> In this study, deconditioning was attributed a marked role for the first time in prospective studies evaluating the etiology of exercise limitation in the long run after PE.

Two small studies confirm the high prevalence of impaired exercise limitation within PE survivors while comparing 1 versus 6 months of anticoagulant treatment after acute PE, which, however, showed inconsistent data on changes over time in exercise capacity as determined by peak VO<sub>2</sub>.<sup>18,28</sup> Besides, the gradual improvement in ventilatory efficiency observed during the 6-month recovery phase still remained below the value of healthy controls.<sup>18</sup>

In a fourth recently published retrospective cohort study, 40 PE patients with persistent exertional dyspnea were subjected to CPET.<sup>19</sup> Increased dead-space ventilation (V<sub>d</sub>/V<sub>t</sub>), decreased stroke volume reserve (oxygen pulse, indicating an insufficient stroke volume for the demand imposed), or both were evident in two-thirds of the study population during incremental exercise.<sup>55</sup>

These responses have repeatedly been found in small case series studying specific patients with chronic thrombi.<sup>25-27,33,34,38</sup> Persistent thrombus load is thought to result in poor adaptation of the vascular bed to increased stroke volume during exercise, which is demonstrated by reduced exercise capacity (as reflected by peak O<sub>2</sub>) and impaired stroke volume (as reflected by reduced oxygen pulse).<sup>33,34</sup> Moreover, limited alveolar ventilation has been observed in these patients, as reflected by increased dead-space ventilation (V<sub>d</sub>/V<sub>t</sub>) and poor ventilatory efficiency (increased minute ventilation/carbon dioxide production slope).<sup>26,27,33,34,38</sup> Clear CPET criteria to differentiate CTEPH from CTEPD have not yet been defined.<sup>26,34,38</sup>

### **Residual pulmonary vascular obstruction**

Incomplete thromboembolic resolution has been reported to be present in 15-60% of PE patients after 6 months of anticoagulant treatment, depending on the imaging modality used and the time between acute episode and radiological re-evaluation.<sup>43,56-64</sup> Impaired recanalization would be expected to negatively affect physical recovery, although available longitudinal data including functional outcomes are contradictory. In a prospective cohort study published in 2010 evaluating pulmonary vascular obstruction (PVO) and its clinical significance, 254 patients underwent repeat V/Q scan 12 months after their PE diagnosis. Persistent perfusion defects were present in 73 patients (29%), which was associated with the presence of dyspnea and a reduced 6MWD.<sup>43</sup> Meanwhile, in the ELOPE study a smaller cohort of 73 patients completed follow-up with a V/Q scan after 12 months, demonstrating residual PVO in 30 (41%).<sup>29</sup> Given an equally present residual PVO in patients with a peak VO<sub>2</sub> <80% of predicted versus those >80% indicated that these imaging findings could not explain long-term functional limitations. Nevertheless, the mean PVO at 12 months was low at 5.6% (SD 9.8), whereas this was 24% (SD 16) in the former study including 254 PE patients. CPET can provide useful information to help understanding the impact of residual thrombi in individuals.

## **3. PRESENTATIONS OF THE POST-PE SYNDROME**

The PPES is defined as the presence of any of the following after a diagnosis of acute PE adequately treated with therapeutic anticoagulation for ≥3 months: 1) CTEPH; 2) CTEPD; 3) post-PE cardiac impairment; or 4) post-PE functional impairment.<sup>65</sup>

### **CTEPH**

CTEPH is considered the most serious long-term complication of acute PE, which is the only curable subcategory among the different groups of pulmonary hypertension.<sup>66</sup>



This rare disease with a 2-4% incidence is characterized by persistent obstruction of pulmonary arteries leading to increased pulmonary vascular resistance that may ultimately result in RV dysfunction and RV failure.<sup>3,67</sup> CTEPH is well-defined and can be diagnosed after  $\geq 3$  months of adequate therapeutic anticoagulation according to the following diagnostic criteria: 1)  $\geq 1$  mismatched segmental perfusion defect demonstrated by ventilation/perfusion scanning; 2) mean pulmonary artery pressure (mPAP)  $\geq 25$  mmHg at rest measured by invasive right heart catheterization; 3) pulmonary capillary wedge pressure  $\leq 15$  mmHg.<sup>68</sup> However, whether the newly proposed PH definition - a cut-off value of a mPAP at rest of 20 mmHg - should also be applied to CTEPH is still under discussion.<sup>27,33,37,69</sup>

Timely treatment initiation consisting of pulmonary endarterectomy, balloon pulmonary angiography and/or PH targeted therapy improves patients' prognosis.<sup>70</sup> However, a major obstacle in early treatment initiation in CTEPH patients is a median diagnostic delay of more than 1 year due to nonspecific symptoms, a long honeymoon period and poor awareness among physicians.<sup>71-73</sup> Further contributing to this delay are inefficient application of diagnostic tests in patients with PPES.<sup>72,74,75</sup> Importantly, it has been shown that longer diagnostic delay is associated with a more advanced disease stage and higher all-cause mortality.<sup>76,77</sup>

## CTEPD

Even in the absence of abnormal pulmonary hypertension at rest, significant chronic occlusions of the pulmonary arteries may lead to abnormal pulmonary vascular responses to exercise (**Table 2**). In this group of patients, pulmonary vascular resistance (used as a parameter of RV afterload) was observed higher and RV contractile reserve was reduced compared to those without residual thrombosis.<sup>26,27,33</sup> These hemodynamic parameters improved after PEA, just like dead-space ventilation, ventilatory inefficiency and exercise capacity.<sup>27,33</sup> For establishing a diagnosis of chronic thromboembolic pulmonary disease (CTEPD), pulmonary hypertension should be excluded<sup>37,66,78</sup> Most experts agree that its definition should not be limited to hemodynamic and imaging abnormalities, but rather includes presence of exertional dyspnea, and dead-space ventilation and/or pulmonary hypertension during exercise. PEA has resulted in favorable outcomes in small case series of CTEPD patients with mostly high thrombotic burden.<sup>37,78,79</sup> Also, a few small studies have suggested that balloon pulmonary angioplasty may be a safe and effective treatment of CTEPD too.<sup>80,81</sup> More evidence is however needed to identify those with amenable disease who are likely to benefit from surgical or interventional treatment. Furthermore, the question whether CTEPD is an early stage of CTEPH and indefinite anticoagulation should be considered in these patients has yet to be answered.<sup>6,82</sup> Importantly, according to current international guidelines, persistent perfusion defects

**Table 2:** Diagnostic test results compared between CTEPH and CTEPD patients (not limited to diagnostic criteria)

Common disease characteristics	CTEPH	CTEPD
Symptoms	Exertional dyspnea	Comparable to CTEPH, mostly at a lower intensity
Hemodynamics	PH at rest	No PH at rest, possibly exercise-induced PH
CTPA scan	Signs of chronic thrombi, e.g. intravascular webs, PA retraction or dilatation, and bronchial artery dilatation, RV hypertrophy, interventricular septum flattening	Signs of chronic thrombi
V/Q scan	Mismatch ventilation/perfusion defect(s)	Comparable to CTEPH
Angiography	Abnormal vessel morphology	Comparable to CTEPH
CPET	Peak VO <sub>2</sub> decreased Ventilatory inefficiency (VE/VCO <sub>2</sub> increased, PetCO <sub>2</sub> decreased) RV dysfunction (O <sub>2</sub> pulse decreased)	Comparable to CTEPH, except for RV dysfunction
Echocardiography	Signs of RV dysfunction and/or increased PA pressure	

only are not among the criteria for long-term anticoagulant therapy.<sup>83-85</sup> Because of that, performing routine follow-up imaging in all PE patients is not recommended.

### Post-PE cardiac impairment

Incomplete RV recovery following an adequately treated acute PE is defined as the presence of intermediate/high echocardiographic probability of PH according to ESC criteria, RV hypokinesis or RV dilatation, and exertional dyspnea corresponding to NYHA class II-IV.<sup>65</sup> In addition to CTEPD, based on animal models, RV dysfunction in this context has been suggested to be caused by myocardial fibrosis, although this hypothesis remains to be studied and proven.<sup>78,86</sup>

### Post-PE functional impairment

Impaired functional status describes the composite of new or progressive dyspnea, exercise intolerance and/or functional limitations following an acute PE.<sup>87</sup> General deconditioning, pain and anxiety are known factors that contribute to post-PE functional impairment in addition to CTEPH and CTEPD.<sup>10,88,89</sup>

In the ELOPE study, it was suggested for the first time that deconditioning occurring after acute PE appeared to be the most likely explanation of exercise limitations rather than circulatory or ventilatory impairment.<sup>4</sup> This phenomenon of relative unfitness was confirmed in an intermediate/high-risk PE cohort: no meaningful associations between RV function or pulmonary function and patient-reported symptoms or objective exercise

capacity were found.<sup>28</sup> Few studies have shown clinical improvements after exercise training, which further emphasizes deconditioning to be an important contributor to the PPES.<sup>90-93</sup>

VTE-related mental health problems are also an important contributor to post-PE functional impairment, and may include post-thrombotic panic syndrome or depression.<sup>7,10,94-96</sup> Anxiety and pain could in turn lead to less physical activity, with deconditioning and a downward spiral as result.

## 4. OPTIMAL DIAGNOSTIC APPROACH OF PERSISTENT DYSPNEA AFTER ACUTE PE

The first priority in the management of patients with persistent dyspnea or functional limitations after PE is diagnosing CTEPH early given the impact of diagnostic delay on survival.<sup>72,77</sup> The target population requiring diagnostic work-up of CTEPH comprises three groups: 1) PE patients with new/progressive exertional dyspnea, edema, palpitations, syncope or chest pain; 2) those with a high pre-test probability for CTEPH<sup>97,98</sup>; and 3) patients with signs of chronic thrombi or RV overload at the initial CTPA scan at the moment of acute PE diagnosis.<sup>17,99,100</sup> Functional status should be quantified by using a standardized assessment tool, such as the Medical Research Council Scale, the World Health Organization Functional Class or the recently developed Post-VTE Functional Status (PVFS) Scale (**Table 3**).<sup>101,102</sup> In the 2019 European Society of Cardiology Guidelines on PE, echocardiography is recommended as initial step to rule out CTEPH in those patients with risk factors or predisposing conditions for CTEPH.<sup>103</sup> Besides risk factors for CTEPH, the 2019 Canadian Thoracic Society Guideline on CTEPH have also selected the following groups warranting closer follow-up after acute PE:

**Table 3:** Post-VTE Functional Status (PVFS) Scale

PVFS scale grade	Description
0 No functional limitations	No symptoms, pain, or anxiety.
1 Negligible functional limitations	All usual duties/activities at home or at work can be carried out at the same level of intensity, despite some symptoms, pain, or anxiety.
2 Slight functional limitations	Usual duties/activities at home or at work are carried out at a lower level of intensity or are occasionally avoided due to symptoms, pain, or anxiety.
3 Moderate functional limitations	Usual duties/activities at home or at work have been structurally modified (reduced) due to symptoms, pain, or anxiety.
4 Severe functional limitations	Assistance needed in activities of daily living due to symptoms, pain, or anxiety: nursing care and attention are required.
D Death	-

patients with clues to the presence of CTEPH at the moment of acute PE diagnosis or those with unexplained dyspnea despite adequate anticoagulant treatment.<sup>104</sup> Notably, a preserved RV function might give rise to a false-negative echocardiography result, particularly in patients with mild CTEPH.<sup>79</sup>

If the echocardiography does not show signs of PH, CPET is the next test of choice to objectivate exercise limitations and differentiate between different underlying mechanisms, followed by pulmonary perfusion imaging and/or pulmonary function tests dependent on its results. Patients with suspected CTEPD or CTEPH should be referred to expertise centers for dedicated imaging tests and right heart catheterization.

Non-PE related causes of dyspnea need to be evaluated as well, e.g. anemia, cancer and interstitial or obstructive lung disease, with targeted treatment where appropriate.<sup>70</sup> Screening instruments for depression and anxiety are indicated in selected patients. In case no underlying condition is diagnosed, it is worth considering to refer patients for cardiopulmonary rehabilitation.<sup>90-93</sup> This might be especially relevant in those patients with deconditioning.

## 5. CONCLUSION

The Post-PE Syndrome describes a heterogenous group of patients with persistent functional limitations and/or decreased quality of life in the course of an acute PE. A wide range of abnormalities in cardiac and pulmonary function have been described in patients with the PPES, but available studies have used diverse definitions and heterogenous diagnostic tests making it difficult to come to an all-explaining pathophysiological mechanism. CTEPH needs to be ruled out in all patients with the PPES. Even in the absence of pulmonary hypertension, persistent perfusion defects have been shown to cause exertional dyspnea. Both patients with CTEPH and CTEPD need to be referred to expertise centers for dedicated imaging tests and right heart catheterization. The remaining patients and especially those with no treatable pulmonary, cardiovascular and/or mental health conditions may benefit from cardiopulmonary rehabilitation.



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