DOI: 10.1002/pul2.12451

RESEARCH ARTICLE

Pulmonary Circulation Open Access | PVRI | WILEY

Cardiopulmonary exercise testing following acute pulmonary embolism: Systematic review and pooled analysis of global studies

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Abstract

Recent reports have revealed a substantial morbidity burden associated with "post-PE syndrome" (PPES). Cardiopulmonary exercise testing (CPET) has shown promise in better characterizing these patients. In this systematic review and pooled analysis, we aim to use CPET data from PE survivors to understand PPES better. A literature search was conducted in PubMed, EMBASE, and Cochrane for studies reporting CPET results in post-PE patients without known pulmonary hypertension published before August 1, 2023. Studies were independently reviewed by two authors. CPET findings were subcategorized into (1) exercise capacity (percent predicted pVO_2 and pVO_2) and (2) ventilatory efficiency (VE/VCO_2 slope and V_D/V_T). We identified 14 studies ($n = 804$), 9 prospective observational studies, 4 prospective case-control studies, and 1 randomized trial. Pooled analysis demonstrated a weighted mean percent predicted pVO_2 of $76.09 \pm 20.21\%$ ($n = 184$), with no difference between patients tested <6 months ($n = 76$, $81.69 \pm 26.06\%$) compared to ≥6 months post-acute PE ($n = 88$, $82.55 \pm 21.47\%$; $p = 0.817$). No difference was seen in pVO_2 in those tested <6 months ($n = 76$, 1.67 ± 0.51 L/min) compared to ≥6 months post-acute PE occurrence ($n = 144$, 1.75 ± 0.57 L/min; $p = 0.306$). The weighted mean VE/VCO_2 slope was 32.72 ± 6.02 ($n = 244$), with a significant difference noted between those tested

Abbreviations: AT, anaerobic threshold; COPD, chronic obstructive pulmonary disease; CPET, cardiopulmonary exercise testing; CTEPH, chronic thromboembolic pulmonary hypertension; CTPA, computed tomography pulmonary angiogram; DVU, deep venous ultrasound; ECMO, extracorporeal membrane oxygenation; FEV1, forced expiratory volume in the first second; IVC, inferior vena cava; LMWH, low molecular weight heparin; PPES, post-PE syndrome; PR, pulmonary rehabilitation; pVO_2, peak oxygen consumption; RVSP, right ventricular systolic pressure; SD, standard deviation; tPA, tissue plasminogen activator; TTE, transthoracic echocardiogram; USAT, ultrasound-accelerated thrombolysis; V_D/V_T, dead space to tidal volume ratio; VE/VCO_2, ventilatory equivalent for carbon dioxide.

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<6 months ($n = 91$, 36.52 ± 6.64) compared to ≥6 months post-acute PE ($n = 191$, 31.99 ± 5.7; $p < 0.001$). In conclusion, this study, which was limited by small sample sizes and few multicenter studies, found no significant difference in exercise capacity between individuals tested <6 months versus ≥6 months after acute PE. However, ventilatory efficiency was significantly improved in patients undergoing CPET ≥ 6 months compared to those <6 months from the index PE.

KEYWORDS
CPET, post-PE syndrome, pulmonary embolism

INTRODUCTION

Recent data has brought to light a significant morbidity seen in survivors of post-acute pulmonary embolism (PE), establishing the basis of what is known as "post-PE syndrome" (PPES), which is present in up to 50% of patients after acute PE.[1] Currently, PPES encompasses a heterogeneous population ranging from nonspecific symptoms of dyspnea, reduced quality of life, and impaired functional status to the most severe cardiopulmonary dysfunction secondary to chronic thromboembolic pulmonary hypertension (CTEPH).[2] While CTEPH is well understood, it accounts for less than 10% of all PPES patients.[3] The remaining vast majority of PPES patients require further investigation and increased understanding.

Cardiopulmonary exercise testing (CPET) evaluates a patient's exercise capacity and ventilatory efficiency by measuring their oxygen uptake, carbon dioxide output, and ventilation on a breath-by-breath basis. These measures allow the derivation of additional gas exchange parameters that reflect responses to exercise.[4] CPET performance and interpretation are well understood in the assessment of CTEPH, but more recently, CPET is being utilized in the phenotypic characterization of all others with PPES as well.[5,6] Published data reporting CPET findings in PPES patients suggests CPET can provide valuable insights into the cardiopulmonary function, exercise capacity, and overall cardiovascular fitness in such patients.[7–9] Notable findings in patients with acute PE would include an elevated dead space to tidal volume ratio (V_D/V_T) and ventilatory equivalent for carbon dioxide (VE/VCO_2) slope with a decreased peak oxygen consumption (pVO_2) and percent predicted pVO_2.[10–12] This may prove crucial for further risk stratification, prognostication, and tailored care delivery. These studies were primarily single-center, and although well performed, they were limited by their small sample size.

For CPET to become routinely utilized in all patients with PPES, we must improve our understanding of its role and interpretation. A unified, comprehensive synthesis of literature examining pooled CPET findings from all studies reporting these results in the post-acute PE patient population can refine our overall understanding of the physiological mechanisms behind PPES and overcome sample size limitations from previously published work.

This systematic review and pooled analysis combines published studies that have reported CPET findings following acute PE. Each of these studies also conducted a pooled analysis of CPET parameters. Systematically assessing CPET parameters across studies makes reporting the range and variability of CPET findings after acute PE possible, providing insights into this population's functional status and cardiovascular adaptations during exercise.

METHODS

Search strategy and selection criteria

PubMed, EMBASE, and Cochrane were searched for studies reporting post-PE CPET results published before August 1, 2023. Keywords used included "cardiopulmonary exercise," "cardiopulmonary exercise testing," "exercise testing," "stress testing," "CPET," "pulmonary embolism," "PE," and "pulmonary thromboembolism." Inclusion criteria for this pooled analysis were (1) Manuscript publication in a peer-reviewed journal (abstracts not followed by a complete manuscript publication were excluded). (2) Studies reporting CPET findings in patients following PE. (3) Reported CPET data included pVO_2, percent predicted pVO_2, or VE/VCO_2 slope data. (4) The patient population studied was ≥18 years old. Exclusion criteria for this pooled analysis were (1) studies published in any language other than English without available

translation; (2) studies conducting CPET only for patients with known pulmonary hypertension (PH); (3) ongoing trials without complete data available; (4) studies conducting CPET only for patients with known, chronic thromboembolic pulmonary disease; (5) retrospective reviews. This analysis was not registered and does not have a published protocol.

Titles, followed by abstracts and complete studies, were independently reviewed by two authors (G.V. and D.W.) and selected based on inclusion and exclusion criteria using Rayyan.[13] Discrepancies at each stage were resolved by consensus or by a third author (V.A.) (Figure 1).

Outcomes

Reported CPET findings were grouped under two broad categories: (1) overall exercise capacity and (2) ventilatory efficiency. Exercise capacity assessment included percent predicted pVO_2 and pVO_2. Ventilatory efficiency outcomes include VE/VCO_2 slope and V_D/V_T. To account for heterogeneity driven by the timing of CPET performed in relation to the index PE, we performed a subgroup/sensitivity analysis by dividing our overall cohort into two subgroups (1. CPET performed <6 m post index PE; 2. CPET performed ≥6 months post index PE).

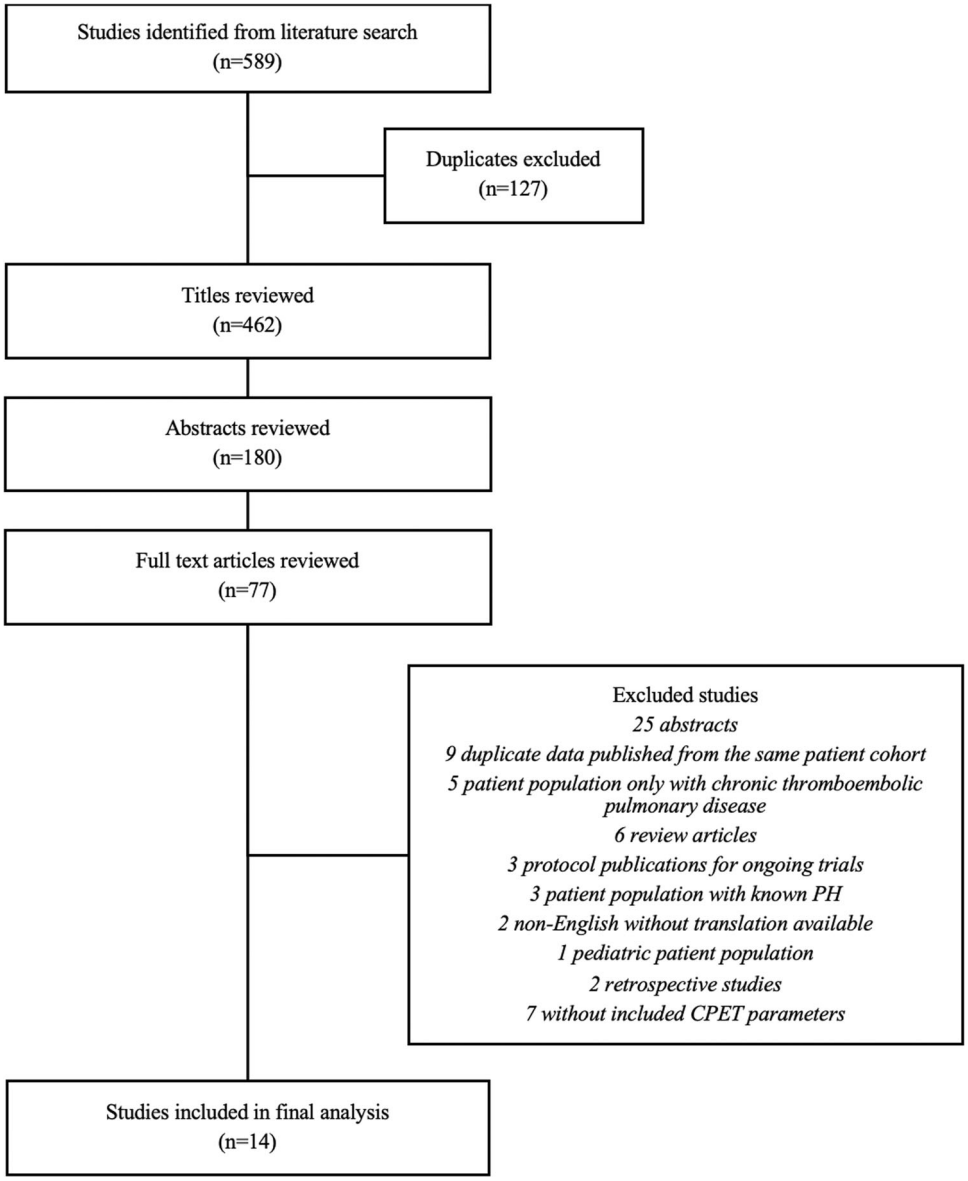

FIGURE 1 Flow chart for inclusion of studies in the review. Of the full-text articles reviewed ($n = 77$), 63 were excluded for only having abstracts without full-text publications,[14–38] duplicate patient data,[6,39–46] patient populations with chronic thromboembolic pulmonary disease,[47–51] review articles,[10,52–56] protocol publications for ongoing trials,[57–59] patients with known PH,[60–62] studies without English translations available,[63,64] pediatric populations,[65] retrospective studies,[66,67] and studies without included CPET parameters.[68–74] CPET, cardiopulmonary exercise testing.

For studies that conducted CPET at multiple time points, the first CPET performed ≥2 weeks post-PE was used for total pooled analysis and analysis of CPET at <6 months from acute PE. For studies that included results for both VE/VCO_2 slope and VE/VCO_2 slope at anaerobic threshold (AT), the results for VE/VCO_2 slope at AT were included in the analysis.

Data extraction

Three authors (G.V., D.W., and D.R.) extracted information on the study design, outcomes assessed, and participant characteristics, and then the other two authors independently reviewed data for accuracy.

Statistical analysis

Excel 2023 was used for statistical analysis. Weighted means and pooled standard deviations were calculated when available for continuous variables. Pooled median and IQR were calculated for studies that reported these values. Student *t*-tests were used for *p*-value calculations. As complete data sets were unavailable for all studies, *p* values for pooled medians are not included.

Ethical considerations

This study conforms to the Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals (ICMJE Recommendations) and the Strengthening The Reporting of Observational Studies in Epidemiology (STROBE) and the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines.[75–77]

RESULTS

Study characteristics

The pooled analysis comprised 14 studies that reported post-PE CPET findings in 804 participants. All included studies used noninvasive CPET, with only two not using a cycle ergometer. Habedank et al. used treadmills for 3- and 6-month CPETs.[78] Kahn et al. did not specify the exercise type used for CPET.[79] All included studies were prospective observational studies, except Guo et al., Yan et al., Milne et al., and Huang et al., which were case-control study designs, and Stavrou et al., a randomized trial. Stavrou et al. recruited patients ($n = 14$; 21.43% female; mean age 50.75 years) ≥6 months following PE who exercised for <100 min/week from an outpatient clinic. These individuals were then randomized into two groups and underwent either supervised or unsupervised pulmonary rehabilitation (PR) for 8 weeks. Cycle ergometer CPET was conducted both before and after PR. For our analyses, only the prepulmonary rehabilitation CPET findings were used. Table 1 summarizes the key characteristics of all included studies.

Exercise capacity

Percent predicted peak oxygen consumption ($pVO_{2\%}$)

The pVO_2% predicted was reported as a mean +/− SD by Guo et al., Huang et al., Knox et al., Samaranayake et al., Boon et al., and Stadlbauer et al.,[7,80–84] and as a median (IQR) by Farmakis et al., Boon et al., Held et al., Knox et al., and Albaghdadi et al.[6,7,9,12,82] The means and medians were pooled and are reported separately. Pooled analysis demonstrated a weighted mean percent predicted pVO_2 of 76.90 ± 20.21 ($n = 184$) and a pooled median percent predicted pVO_2 of 78.53 (28.37) ($n = 785$). In patients undergoing CPET < 6 months from the acute PE occurrence ($n = 76$), the weighted mean percent predicted pVO_2 was 81.69 ± 26.06, which was not significantly different from patients undergoing CPET ≥ 6 months from acute PE occurrence ($n = 88$, 82.55 ± 21.47; $p = 0.817$). In patients undergoing CPET < 6 months from acute PE occurrence, the median percent predicted pVO_2 was 77.15 (28.59) ($n = 405$), compared to 79.99 (28.46) ($n = 333$) in patients who underwent CPET ≥ 6 months following acute PE occurrence.

Peak oxygen consumption (pVO_2, l/min)

Mean (+/− SD) pVO_2 was reported by Milne et al., Kahn et al., Guo et al., Huang et al., Knox et al., Samaranayake et al., and Stavrou et al.[8,79–83,85] while median (IQR) pVO_2 was reported by Knox et al. and Albaghadadi et al.[12,82] Pooled analysis demonstrated a weighted mean pVO_2 of 1.65 ± 0.51 L/min ($n = 240$) and a pooled median peak VO_2 of 2.22 (1.09) L/min ($n = 42$). In patients tested <6 months from acute PE occurrence ($n = 76$), weighted mean pVO_2 was found to be 1.67 ± 0.51 L/min, which was not significantly different compared to patients undergoing CPET ≥ 6 months from acute PE occurrence ($n = 144$, 1.75 ± 0.57 L/min; $p = 0.306$). Table 2 summarizes these parameters from included studies.

TABLE 1 Study characteristics.

	Study design	Study population	Exclusion criteria	Key participant characteristics	Time between PE and CPET	Outcome measures
Albaghadadi et al.,[12] USA (2018)	Single Center Prospective Observational Study	Patients with intermediate or high risks PE who were treated with anticoagulation in addition to catheter-directed therapy ($n = 7$), IV thrombolysis ($n = 4$), or IVC filter ($n = 3$). All participants underwent CPET via cycle ergometer and TTE.	Inability to perform required testing, life expectancy <6 months, electrocardiographic contraindications to CPET.	$N = 20$ Female: 8 (40.00%) Mean age: 57.00 ± 13.00	1 month, 6 months	% Predicted pVO_2, pVO_2
Boon et al.,[7] Netherlands (2021)	Single Center Prospective Observational Study	Patients with imaging-confirmed acute PE who had persistent dyspnea or functional limitations despite ≥3 months of anticoagulation were referred to a PPES clinic where they received a standardized diagnostic workup including CPET.	Those with alternative diagnoses for post-PE limitations, refusal to complete CPET.	$N = 56$ Female: 34 (60.71%)[#] Mean Age: 54.00 ± 14.00[#]	Median: 6.4 months from PE to clinic referral	% Predicted pVO_2, VE/VCO_2 slope, peak V_D/V_T
Farmakis et al.,[6] Germany (2023)	Multicenter Prospective Observational Study	Patients with acute, symptomatic PE without previous CTEPH diagnosis who were enrolled in the FOCUS study.	Incidental PE and previously diagnosed CTEPH	$N = 396$ Female: 172 (43.43%) Median age: 60.00, IQR 48.00–71.00	3 months, 12 months	% Predicted pVO_2, VE/VCO_2 slope
Guo et al.,[80] China (2016)	Single Center Prospective Case-Control Study	Patients with PE with normal CTPA and DVUs following ≥2 weeks of anticoagulation who were referred for evaluation. Patients were stable according to Wells and Geneva scores. Post-PE patients were compared to healthy controls. Only post-PE patients are included in this analysis.	Those with pulmonary veno-occlusive disease, pulmonary hemangiomatosis, pulmonary and cardiac shunt, nerve-skeletal muscle disease, serious metabolic diseases, or COPD.	$N = 50$ Female: 18 (36.00%) Mean age: 55.11 ± 7.61	Not reported	% Predicted pVO_2, pVO_2
Habedank et al.,[78] Germany (2018)	Single Center Prospective Observational Study	Stable patients with low to intermediate risk PE effectively treated with unfractionated heparin or LMWH.	Those with high-risk PE, severe COPD with home-care oxygen or FEV1 < 1000 mL/s, malignancy that limits prognosis, pregnant, <18 years old.	$N = 21$ Female: 14 (66.67%) Mean age: 64.20 ± 18.90	3 months, 6 months	VE/VCO_2 slope

(Continues)

TABLE 1 (Continued)

	Study design	Study population	Exclusion criteria	Key participant characteristics	Time between PE and CPET	Outcome measures
Held et al.,[9] Germany (2023)	Single Center Prospective Observational Study	Patients following acute PE who were positive for dyspnea, dizziness, fainting, syncope, or thoracic pain, assessed via telephone monitoring at 3-, 6-, 12-, and 24-months post PE. Those who tested positive for these symptoms underwent echo and CPET via cycle ergometer.	None specified.	$N = 53$ Female: 33 (62.26%) Mean age: 68.38 ± 14.22	Range: 3 months – 2 years	% Predicted pVO_2, VE/VCO_2 slope
Huang et al.,[81] China (2020)	Single Center Prospective Case-Control Study	Patients treated with ≥4 weeks of anticoagulation and without RV dysfunction (RVSP <45 mmHg while RA end systolic diameter and RV end-diastolic diameter in the normal range) following PE. All patients had an oxygen partial pressure >80 mmHg without oxygen therapy and oxygen saturation >95%. PE was confirmed improved or resolved by imaging. Patients were matched with healthy volunteers.	Those unable to perform normal daily activities without chest pain or shortness of breath, unable to undergo CPET, or with diseases that would impact CPET results.	$N = 30$ Female: 17 (56.67%) Mean age: 57.47 ± 11.33	4 weeks, 6 months	pVO_2, % Predicted pVO_2, VE/VCO_2 slope
Kahn et al.,[79] Canada (2017)	Multicenter Prospective Observational Study	Patients with acute, symptomatic PE diagnosed in the previous 10 days, scheduled to be treated with anticoagulation.	Those unable to perform CPET or 6-min walk distance test, with contraindications to CTPA, with severe comorbidities, previous PE, previous DVT, life expectancy of <1 year, pregnant, lactating, unable to read in English or French, and unable to attend follow-up visits.	$N = 86$ Female: 43 (43.00%) Mean age: 50.00 ± 15.20	12 months	pVO_2, VE/VCO_2 slope
Knox et al.,[82] USA (2019)	Single Center Prospective Observational Study	Patients presenting with acute PE, with symptoms for <14 days with confirmation and determination of right ventricle-to-left ventricle diameter ratio >0.9, who underwent treatment with USAT and tPA. All were hemodynamically stable with	Those who were hemodynamically unstable (systolic BP < 90 mmHg), requiring vasopressor support, with contraindications to anticoagulation or thrombolytic therapy, who declined treatment with tPA or USAT.	$N = 22$ Female: 5 (22.73%) Mean age: 55.50 ± 14.70	90 days	% Predicted pVO_2, pVO_2, peak V_D/V_T

TABLE 1 (Continued)

	Study design	Study population	Exclusion criteria	Key participant characteristics	Time between PE and CPET	Outcome measures
		systolic BP > 90 mmHg, not requiring vasopressor support.				
Milne et al.,[8] Canada (2023)	Single Center Prospective Case-Control Study	Clinically stable patients referred for clinical evaluation for chronic moderate activity-related dyspnea without an alternative diagnosis, with confirmed PPES. Patients were compared with control participants. For this study, only post-PE patients are analyzed.	Those with contraindication to CPET, previous clinical diagnosis of CTEPH, or history of obstructive or restrictive lung disease. Those with evidence of PH.	$N = 14$ Female: 11 (78.57%) Mean age: 59.00 ± 14.70	Median: 16.7 months	pVO_2, VE/VCO_2 slope, peak V_D/V_T
Samaranayake et al.,[83] UK & Australia (2023)	Multicenter Prospective Observational Study	Patients admitted with intermediate or high-risk acute PE treated with ≥3 months of anticoagulation	Those with recurrent PE, unable to receive uninterrupted anticoagulation, unable to perform CPET.	$N = 24$ Female: 14 (58.33%) Median age: 55.00, IQR 22.00	3 months	% Predicted pVO_2, pVO_2, VE/VCO_2 slope, peak V_D/V_T
Stadlbauer et al.,[84] Germany (2021)	Single Center Prospective Observational Study	Patients with acute high-risk PE complicated by cardiogenic shock or cardiac arrest requiring ECMO were recruited.	Those who did not receive ECMO for acute PE.	$N = 54$ Female: 24 (44.44%)[#] Mean Age: 49.00 ± 15.00[#^]	Mean: 53 months	% Predicted pVO_2, VE/VCO_2 slope
Stavrou et al.,[85] Greece (2021)	Single Center Randomized Trial	Patients with a history of PE ≥ 6 months from enrollment with weekly exercise <100 min, recruited from an outpatient PE clinic. Patients underwent CPET testing before pulmonary rehabilitation and following pulmonary rehabilitation. Participants were separated into two groups, receiving either supervised or unsupervised pulmonary rehabilitation. For this analysis, only the CPET results from before pulmonary rehabilitation are included.	Those with contraindications to CPET, or severe comorbidities that may interfere with the results of rehabilitation.	$N = 14$ Female: 3 (21.43%) Mean age: 50.75 ± 15.70	≥6 months	pVO_2
Yan et al.,[86] China (2012)	Single Center Prospective Case-Control Study	Patients with acute PE who received treatment with interventional or IV thrombolysis or anticoagulation	Those with oxygen partial pressure <80 mmHg without oxygen supplementation, or oxygen saturation	$N = 16$ Female: 11 (68.75%)	2 weeks	VE/VCO_2 slope

(Continues)

TABLE 1 (Continued)

Study design	Study population	Exclusion criteria	Key participant characteristics	Time between PE and CPET	Outcome measures
	therapy, who underwent antithrombotic treatment for 2 weeks. All patients had RVSP <45 mmHg while RA end-systolic diameter and RV end-diastolic diameter were in normal range. Patients were compared to healthy controls, who are not included in the present analysis.	<95%, unable to complete daily activities without check pain or shortness of breath, or with conditions that would influence CPET testing.	Mean age: 63.00 ± 10.00		

Note: [#]Data for all participants, or survivors in the case of Stadlbauer et al., is presented. Data for individuals who underwent CPET is not reported separately. [^]Age at the time of PE, not at the time of CPET, is reported.

Abbreviations: CPET, cardiopulmonary exercise testing; CTPA, CT pulmonary angiogram; DVU, deep venous ultrasound; ECMO, extracorporeal membrane oxygenation; FEV1, forced expiratory volume in the first second; IVC, inferior vena cava; LMWH, low molecular weight heparin; RVSP, right ventricular systolic pressure; tPA, tissue plasminogen activator; TTE, transthoracic echocardiogram; USAT, ultrasound-accelerated thrombolysis.

Ventilatory efficiency

VE/VCO_2 slope

The mean VE/VCO_2 slope was reported by Boon et al., Milne et al., Habedank et al., Kahn et al., Huang et al., Samaranayake et al., Stadlbauer et al., and Yan et al.[7,8,78,79,81,83,84,86] The median VE/VCO_2 slope was reported by Farmakis et al., Boon et al., and Held et al.[6,7,9] Pooled analysis demonstrated a weighted mean VE/VCO_2 slope of 32.72 ± 6.02 ($n = 244$). In patients tested <6 months from acute PE occurrence, the weighted mean VE/VCO_2 slope was found to be 36.52 ± 6.64 ($n = 91$), which was significantly higher compared to participants tested ≥6 months after acute PE (31.99 ± 5.71; $n = 191$, $p < 0.001$) as shown in Table 3.

Dead space ventilation (V_D/V_T)

Knox et al., Samaranayake et al., Boon et al., and Milne et al. reported mean VD/VT.[7,8,82,83] Pooled analysis demonstrated a weighted mean V_D/V_T of 0.20 ± 0.08 ($n = 76$), as shown in Supporting Information S1: Table 1.

DISCUSSION

Noteworthy findings from this systematic review include (1) CPET data from patients post-PE are predominately available in smaller single-center observational cohort studies, which makes the currently available data pool for this topic very heterogeneous and limited. (2) Exercise capacity, assessed by peak oxygen consumption, was reduced following acute PE, and contrary to expectations, the reduction in exercise capacity was similar at <6 months and ≥6 months post-acute PE (Figure 2).

In our analysis, overall ventilatory efficiency was reduced in PE survivors. However, ventilatory efficiency was notably poorer in individuals who underwent CPET < 6 months post-acute PE than those who underwent CPET ≥ 6 months post-acute PE. This indicates that ventilatory efficiency may improve over time, but additional studies that collect serial CPET parameters in such patients over time are needed. Interestingly, exercise capacity did not differ amongst those tested <6 months post-PE and ≥6 months post-acute PE. This may suggest a significant contribution from skeletal muscle deconditioning towards lower exercise capacity in such patients; it is also possible that this skeletal muscle deconditioning was present before the index PE event and persisted post-PE. One could hypothesize that an early exercise intervention

TABLE 2 CPET parameters for exercise capacity analyzed by the presence of symptoms and timing of CPET following acute PE.

Percent predicted peak VO_2 (%)													
	Mean ± SD							**Median (IQR)**					
	n	**Total**	***n***	**<6 months since PE**	***n***	**≥6 months since PE**	***p*-Value**	***n***	**Total**	***n***	**<6 months since PE**	***n***	**≥6 months since PE**
Albaghadadi et al.,[12] USA	-	-	-	-	-	-	-	20	68.00 (25.00)	20	68.00 (25.00)	20	73.00 (29.00)
Boon et al.,[7] Netherlands	45	86.44 ± 19.90	-	-	45	86.44 ± 19.90	-	45	89.00 (25.00)	-	-	45	89.00 (25.00)
Farmakis et al.,[6] Germany	-	-	-	-	-	-	-	363	76.00 (29.00)	363	76.00 (29.00)	268	79.00 (29.00)
Guo et al.,[80] China	50	61.17 ± 7.59	-	-	-	-	-	-	-	-	-	-	-
Held et al.,[9] Germany[#]	-	-	-	-	-	-	-	47	80.34 (29.79)	-	-	-	-
Huang et al.,[81] China	30	70.64 ± 29.65	30	70.64 ± 29.65	30	79.43 ± 25.35	0.003*	-	-	-	-	-	-
Knox et al.,[82] USA	22	100.41 ± 21.15	22	100.41 ± 21.15	-	-	-	22	104.50 (25.00)	22	104.50 (25.00)	-	-
Samaranayake et al.,[83] UK & Australia[#]	24	78.35 ± 25.24	24	78.35 ± 25.24	-	-	-	-	-	-	-	-	-
Stadlbauer et al.,[84] Germany	13	76.30 ± 16.10	-	-	13	76.30 ± 16.10	-	-	-	-	-	-	-
Weighted Total	184	76.90 ± 20.21	76	81.69 ± 26.06	88	82.55 ± 21.47	0.817	497	78.53 (28.37)	405	77.15 (28.59)	333	79.99 (28.46)
Peak VO_2 (L/min)													
	Mean ± SD							**Median (IQR)**					
	n	**Total**	***n***	**<6 months since PE**	***n***	**≥6 months since PE**	***p*-Value**	***n***	**Total**	**n**	**<6 months since PE**	***n***	**≥6 months since PE**
Albaghadadi et al.,[12] USA	-	-	-	-	-	-	-	20	1.66 (1.04)	20	1.66 (1.04)	20	1.77 (1.32)
Guo et al.,[80] China	50	1.08 ± 0.11	-	-	-	-	-	-	-	-	-	-	-
Huang et al.,[81] China	30	1.12 ± 0.39	30	1.12 ± 0.39	30	1.25 ± 0.34	0.003*	-	-	-	-	-	-
Kahn et al.,[79] Canada	86	1.97 ± 0.66	-	-	86	1.97 ± 0.66	-	-	-	-	-	-	-
Knox et al.,[82] USA	22	2.55 ± 0.68	22	2.55 ± 0.68	-	-	-	22	2.74 (1.14)	22	2.74 (1.14)	-	-
Milne et al.,[8] Canada	14	1.43 ± 0.33	-	-	14	1.43 ± 0.33	-	-	-	-	-	-	-
Samaranayake et al.,[83] UK & Australia[#]	24	1.56 ± 0.44	24	1.56 ± 0.44	-	-	-	-	-	-	-	-	-
Stavrou et al.,[85] Greece[#]	14	1.75 ± 0.52	-	-	14	1.75 ± 0.52	-	-	-	-	-	-	-
Weighted Total	240	1.65 ± 0.51	76	1.67 ± 0.51	144	1.75 ± 0.57	0.306	42	2.22 (1.09)	-	-	-	-

Note: [#]Weighted median or mean. *Significant at *p*-value ≤0.01.

Abbreviation: CPET, cardiopulmonary exercise testing.

TABLE 3 CPET parameter for ventilatory efficiency, VE/VCO_2 slope, analyzed by the presence of symptoms and timing of CPET following acute PE.

VE/VCO_2 Slope													
	Mean ± SD							Median (IQR)					
	n	Total	*n*	<6 months since PE	*n*	≥6 months since PE	*p*-Value	*n*	Total	n	<6 months since PE	*n*	≥6 months since PE
Boon et al.,[7] Netherlands	40	33.39 ± 7.75	-	-	40	33.39 ± 7.75	-	40	31.60 (9.88)	-	-	40	31.60 (9.88)
Farmakis et al.,[6] Germany	-	-	-	-	-	-	-	363	28.00 (8.00)	363	28.00 (8.00)	268	27.00 (7.00)
Habedank et al.,[78] Germany	21	36.00 ± 8.80	21	36.00 ± 8.80	21	35.40 ± 8.10	0.819	-	-	-	-	-	-
Held et al.,[9] Germany#	-	-	-	-	-	-	-	38	38.53 (14.33)	-	-	-	-
Huang et al.,[81] China	30	37.19 ± 4.02	30	37.19 ± 4.02	30	37.36 ± 3.80	0.318	-	-	-	-	-	-
Kahn et al.,[79] Canada	86	28.80 ± 4.70	-	-	86	28.80 ± 4.70	-	-	-	-	-	-	-
Milne et al.,[8] Canada	14	34.00 ± 4.00	-	-	14	34.00 ± 4.00	-	-	-	-	-	-	-
Stadlbauer et al.,[84] Germany	13	28.70 ± 4.90	-	-	13	28.70 ± 4.90	-	-	-	-	-	-	-
Samaranayake et al.,[83] UK & Australia#	24	36.83 ± 7.09	24	36.83 ± 7.09	-	-	-	-	-	-	-	-	-
Yan et al.,[86] China	16	35.47 ± 6.66	16	35.47 ± 6.66	-	-	-	-	-	-	-	-	-
Weighted Total	244	32.72 ± 6.02	91	36.52 ± 6.64	191	31.99 ± 5.71	<0.001*	441	29.23 (10.31)	-	-	308	27.60 (9.65)

Note: #Weighted median or mean. *Significant at *p*-value ≤0.01.

Abbreviations: CPET, cardiopulmonary exercise testing; VE/VCO_2, ventilatory equivalent for carbon dioxide.

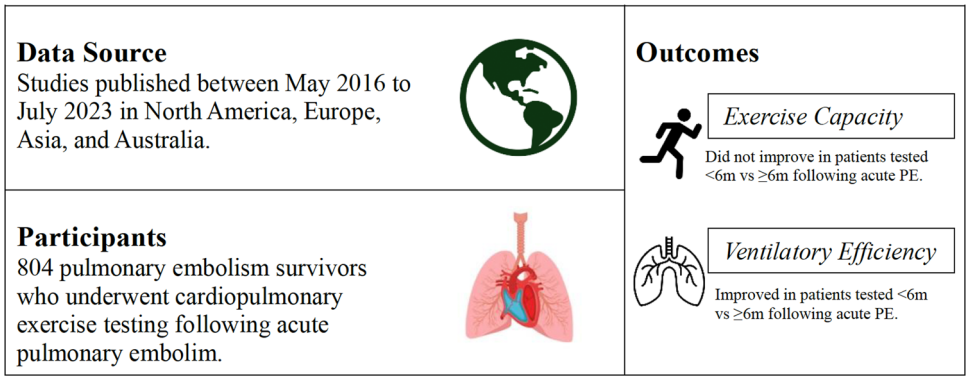

FIGURE 2 Central illustration.

may be beneficial in such patients who will otherwise remain limited over time post-PE, even if there is an improvement in their ventilatory efficiency. In Albaghdadi et al., the investigators demonstrated no significant change in the percent predicted pVO2 at 1- and 6-months post-PE.[12] Additionally, this analysis' results align with findings from the studies by Boon, Knox, and Kahn et al., who reported ventilatory efficiency parameters stratified by those with percent predicted $pVO_2 < 80\%$ or >80%. In these analyses, both V_D/V_T and VE/VCO_2 slope at AT were similar in the $pVO_2 < 80\%$ cohort compared to the >80% cohort.

Limitations of our analysis include (1) The limited number of multicenter studies included in this analysis. (2) Farmakis et al. had the large majority of study participants ($n = 396$), while most included studies had <50 participants to be analyzed. (3) Many of the included studies excluded patients with specific disease states. (4) In this analysis, time to CPET could not be treated as a continuous variable, as individual patient data for each study was unavailable. (5) There was a significant amount of heterogeneity between the studies analyzed.

In conclusion, these results further refine our understanding of the physiological mechanisms behind PPES and suggest a multifactorial explanation for decreased overall exercise capacity in such patients.

AUTHOR CONTRIBUTIONS

Vikas Aggarwal and Gabriella VanAken conceived the study. Gabriella VanAken, Daniel Wieczorek, and Drew Rubick performed data extraction and analysis under the guidance of Vikas Aggarwal. All authors discussed the results and contributed substantially to the interpretation and analysis of data.

ACKNOWLEDGMENTS

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

ETHICS STATEMENT

IRB-Exempt.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: VanAken G, Wieczorek D, Rubick D, Jabri A, Franco- Palacios D, Grafton G, Kelly B, Osinbowale O, Ahsan ST, Awdish R, Aronow HD, Shore S, Aggarwal V. Cardiopulmonary exercise testing following acute pulmonary embolism: systematic review and pooled analysis of global studies. Pulm Circ. 2024;14:e12451. https://doi.org/10.1002/pul2.12451