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BMJ Open

Observational cohort study to validate SEARCH, a novel hierarchical algorithm to define long-term outcomes after pulmonary embolism

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ABSTRACT

Background Chronic dyspnoea and exercise impairment are common after acute pulmonary embolism (PE) but are not defined and quantified sufficiently to serve as outcomes in clinical trials. The planned project will clinically validate a novel method to determine discrete, clinically meaningful diagnoses after acute PE. The method uses an algorithm entitled SEARCH, for symptom screen, exercise testing, arterial perfusion, resting echocardiography, confirmatory imaging and haemodynamic measurements. SEARCH is a stepwise algorithm that sorts patients by a hierarchical series of dichotomous tests into discreet categories of long-term outcomes after PE: asymptomatic, post-PE deconditioning, symptoms from other causes, chronic thromboembolism with ventilatory inefficiency, chronic thromboembolism with small stroke volume augmentation, chronic thromboembolic disease and chronic thromboembolic pulmonary hypertension.

Methods The project will test the inter-rater reliability of the SEARCH algorithm by determining whether it will yield concordant post-PE diagnoses when six independent reviewers review the same diagnostic data on 150 patients evaluated at two time points after PE. The project will also determine whether the post-PE diagnoses are stable, according to the SEARCH algorithm, between the first evaluation and the subsequent one 6 months later.

Implications Validation of the SEARCH algorithm would offer clinicians a straightforward method to diagnose post-PE conditions that are rarely distinguished clinically. Their categorisation and definition will allow post-PE conditions to be used as endpoints in clinical trials of acute PE treatment.

Trial registration number NCT05568927.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This study has the novel approach of validating an algorithm to define and categorise the various potential long-term outcomes after acute pulmonary embolism through a logical sequence of complementary diagnostic tests represented by the acronym SEARCH: screening for symptoms, exercise testing, pulmonary arterial perfusion (ventilation:perfusion) scanning, resting echocardiography, confirmatory chest imaging and haemodynamic measurement.

⇒ Multiple independent raters will evaluate identical clinical data from a large series of cases at two defined time points after acute pulmonary embolism according to a prespecified algorithm.

⇒ Inter-rater reliability will be determined using Krippendorff's alpha, a robust technique for comparing multiple raters' decisions regarding multiple possible diagnostic options.

INTRODUCTION

Outcomes after acute pulmonary embolism (PE) occur on a spectrum from complete recovery to chronic thromboembolic pulmonary hypertension (CTEPH). A myriad of diagnostic tests can distinguish each potential outcome (table 1). However, there is wide disagreement about the indications for each test and its proper order in the work-up. This project will validate an algorithm to distinguish among the various potential outcomes through a hierarchical series of tests with the acronym SEARCH (for symptom screen, exercise function, arterial perfusion, resting heart function, confirmatory imaging and haemodynamics).[1] The SEARCH algorithm sorts patients into mutually exclusive and collectively exhaustive diagnostic categories (figure 1).

The study is a prospective, single group observational study to measure the inter-rater agreement regarding diagnostic endpoints determined by the SEARCH algorithm for patients after the acute phase of PE. The study will also determine whether SEARCH-derived clinical outcomes are stable when subjects are reevaluated six additional months later.

METHODS AND ANALYSIS

Study population

The study will enrol patients from the pulmonary embolism clinics within the University of California Alliance on Pulmonary Embolism (UCAPE) network (UC San Diego

Table 1 Potential long-term clinical outcomes after acute pulmonary embolism. The potential outcomes after acute pulmonary embolism and their corresponding expected test results

	Recovery from symptoms	Dyspnoea without cardiopulmonary defects	Alternative diagnoses causing dyspnoea	Chronic thromboembolism with ventilatory inefficiency	Chronic thromboembolism with small stroke volume augmentation	Chronic thromboembolic disease	Chronic thromboembolic pulmonary hypertension
	Post-pulmonary embolism dyspnoea						
	Chronic thromboembolism						
Symptom screen (scripted questions)	Normal	Abnormal	Abnormal	Abnormal	Abnormal	Abnormal	Abnormal
Exercise function (CPET)	–	Normal	Abnormal	High VD/VT	Low SVA	High VD/VT or low SVA	High VD/VT or low SVA
Arterial perfusion (V:Q or SPECT)	–	–	No mismatched defects	Mismatched defects	Mismatched defects	Mismatched defects	Mismatched defects
Resting heart function (echocardiogram)	–	–	–	Normal	Normal	Normal	Typically abnormal
Confirmatory imaging (CTPA or PA)	–	–	–	Typically abnormal	Typically abnormal	Typically abnormal	Typically abnormal
Haemodynamics (PAP/PVR at rest)	–	–	–	Normal	Normal	Normal	Abnormal
Exercise haemodynamics (PA/PVR with exercise)	–	–	–	Normal	Normal	Abnormal	–

CPET, cardiopulmonary exercise testing; CTPA, CT pulmonary angiography; PAP, pulmonary artery pressure; PVR, pulmonary vascular resistance; SPECT, single photon emission CT; SVA, stroke volume augmentation; VD/VT, ventilatory dead space ratio; V:Q, ventilation:perfusion scanning.

(UCSD), UC Irvine (UCI), Harbor-UC Los Angeles, UC Los Angeles, UC Riverside (UCR), UC Davis, UC San Francisco and UC San Francisco-Fresno) who underwent the SEARCH algorithm. Inclusion criteria are: objective evidence of acute PE at least 3 months before the clinical assessment; age 18 years or greater; anticipated survival for at least 6 months after the first evaluation; a diagnostic endpoint in the SEARCH algorithm has been reached.

The first SEARCH-based clinical assessment is performed at least 3 months after the onset of acute PE. The second SEARCH-based clinical assessment is performed at least 6 months after the first clinical assessment.

Five pulmonary faculty members from three institutions (UCSD, UCI and UCR) as well as one pulmonary fellow (UCSD) comprise a prespecified rater group. The raters undergo a 1 hour training session to review the SEARCH algorithm (see *Description of SEARCH algorithm*) and the study protocol. Each patient's physician will present to the rater group clinical data relevant to the SEARCH algorithm during the first clinical assessment and after the second clinical assessment. Presentations will not include protected health information or other identifiers.

Ethics and dissemination

The study was approved by the UC San Diego Institutional Review Board and registered with ClinicalTrials.gov (NCT05568927). The study protocol conformed to the Guidelines for Reporting Reliability and Agreement Studies.[2] Results will be published along with the complete data set in a peer-reviewed journal.

Description of SEARCH algorithm

The test results at each step in the algorithm inform the performance of the subsequent steps. The order of the tests is represented by the acronym SEARCH: symptom screen, exercise function, arterial perfusion, resting heart function, confirmatory imaging and haemodynamics (figure 1). Unless otherwise stated, a step is considered positive if at least one of the relevant criteria are met. Management of missing or insufficient data relevant to each step is described in online supplemental appendix 1.

S: symptom screening

Dyspnoea and exercise intolerance are the most frequent problems suffered after PE.[3] About half of patients report some degree of dyspnoea, low exercise capacity or impaired quality of life a year or more after PE.[4] Unfortunately, patient-initiated reports tend to underestimate symptomatic changes during disease.[5] The SEARCH algorithm actively screens patients after PE for dyspnoea using the modified Medical Research Council (mMRC) dyspnoea scale, a clinically validated brief questionnaire that assigns a score from 0 to 4 corresponding to statements about perceived breathlessness associated with specifically recalled events.[6] The minimum clinically important difference[5] of the mMRC is between 0.4 and 1.0 points.[7 8] The symptom screen also allows patients to

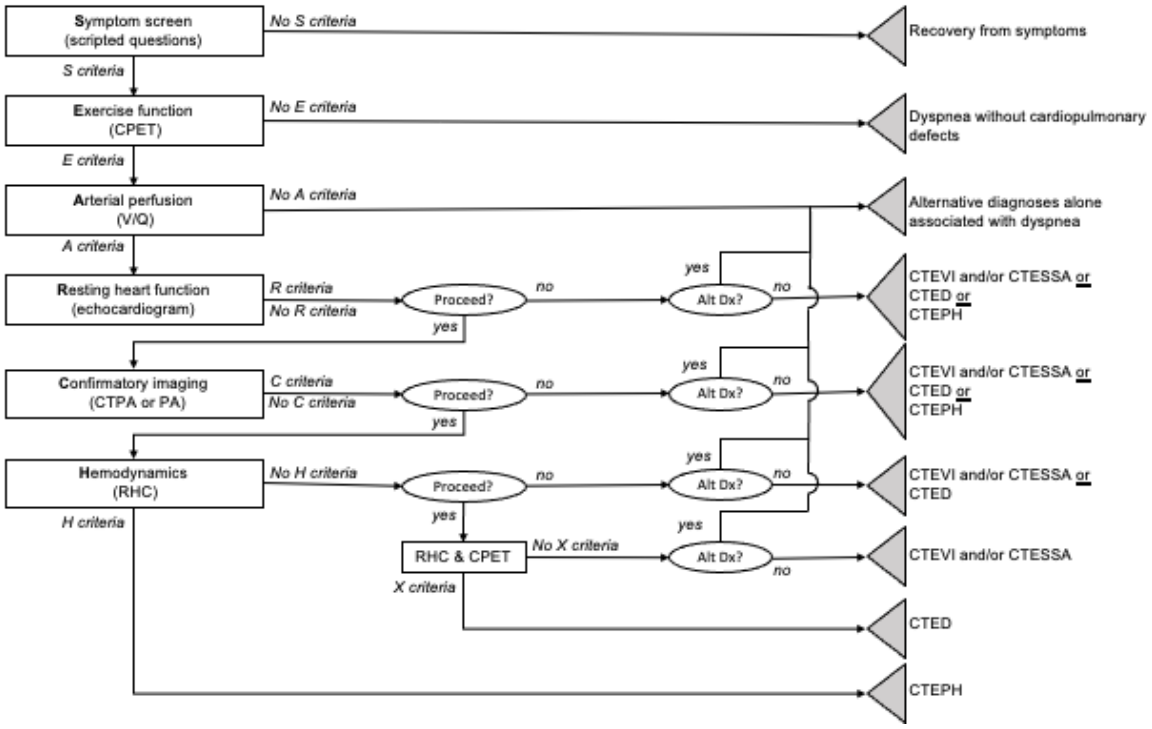

Figure 1 SEARCH algorithm decision tree. Rectangles represent criteria-driven nodes that reflect dichotomous objective test results. The ovals represent subjective clinical decision nodes. The triangles represent endpoint nodes that reflect the specific differential diagnoses warranted from the clinical data. CPET, cardiopulmonary exercise testing; CTED, chronic thromboembolic disease; CTEPH, chronic thromboembolic pulmonary hypertension; CTESSA, chronic thromboembolism with small stroke volume augmentation; CTEVI: chronic thromboembolism with ventilatory inefficiency; CTPA, CT pulmonary angiography; RHC, right heart catheterisation; V:Q, ventilation:perfusion scanning.

identify themselves as not fully recovered clinically, even if the mMRC score returned to the level that existed before the PE. This permits detection of persistent symptoms that are not severe enough to affect the mMRC score but that the patient may appreciate, nevertheless.

'S-criteria'

- The mMRC score during a specific activity in the 2 weeks prior to the interview is one or more points higher than the patient recalls it was during a specific activity in the 2 weeks prior to the PE.
- The patient endorses not feeling fully recovered to the level that existed prior to the PE (eg, reduced tolerance of athletic abilities), regardless of mMRC scores at the time of the interview and before the PE.

If, during the second clinical evaluation, the patient's symptoms are not worse than what was recorded at the first evaluation, the subsequent tests in the SEARCH algorithm may be assumed to be unchanged. Clinicians may use their judgement regarding whether the tests need to be repeated.

E: cardiopulmonary exercise testing

Since some portion of patients with long-term dyspnoea after PE have normal cardiopulmonary function during exercise,[3 4 9 10] we will use cardiopulmonary exercise testing (CPET) in symptomatic patients to identify those with demonstrable physiological defects. While the simpler 6-minute walk distance (6MWD) is suited for intrapatient comparisons to detect differences from baseline, (eg, during therapy for CTEPH[11]), PE patients do not have baseline measurements prior to PE. Interpatient variability of the 6MWD without a baseline to compare to is too high to permit detection of meaningful physiological pathology.[12 13]

'E-criteria'

- The patient did not reach anaerobic threshold (AT).
- Peak oxygen consumption (VO_2) was less than 80% of the predicted peak VO_2.
- Ventilatory dead space ratio (V_D/V_T) at AT is greater than or equal to 0.27.
- Ventilatory dead space (V_D) at AT is greater than or equal to 1.35 mL/lb of ideal body weight.
- In the absence of a V_D/V_T estimate, minute ventilation relative to carbon dioxide production (V_E/VCO_2) at AT is greater than 30.
- Oxygen consumption relative to heart rate $(O_2 \cdot pulse)_{AT}/O_2 \cdot pulse_{rest}$ is less than 2.6.

To maximise the sensitivity of the E-criteria, we include peak VO_2 (the VO_2 when the patient is performing the highest tolerated level of work during CPET). Peak VO_2 reflects overall exercise performance and predicts survival in severe cardiopulmonary disease. Although it is part of the screening criteria, however, peak VO_2

alone is neither sensitive nor specific for the physiological defects most likely to limit exercise tolerance after PE. Peak VO_2 is influenced by age, sex, body mass index and smoking, such that most PE patients with low peak VO_2 during follow-up CPET have little to no residual pulmonary vascular occlusion.[4] Furthermore, peak VO_2 is similar between post-PE patients with and without right ventricular (RV) dilatation or RV dysfunction.[10]

E-criteria will also include findings more specific for pulmonary vascular disease, such as increased V_D and V_D/V_T during exercise: specifically at AT. Increased V_D/V_T at AT corresponds to scintigraphically measured persistent pulmonary artery obstruction in patients with dyspnoea after acute PE.[14] Increased V_D/V_T may cause exercise intolerance after PE even in the absence of pulmonary hypertension, although V_D/V_T is even more increased among patients with CTEPH and chronic thromboembolic disease (CTED).[15]

A prior limitation of V_D/V_T testing was the need to estimate pulmonary capillary partial pressure of carbon dioxide (PCO_2) by repeated invasive measurements of arterial PCO_2 (P_aCO_2). However, the SEARCH algorithm uses transcutaneous PCO2 ($P_{tc}CO_2$) monitoring for accurate and precise estimation of P_aCO_2 without the need for arterial blood sampling.[16 17] In addition, if neither P_aCO_2 nor $P_{tc}CO_2$ are available with which to estimate V_D/V_T, the E-criteria will include an elevated ratio of the V_E/VCO_2. V_E/VCO_2 greater than 30 at AT has a sensitivity of 94% but a specificity of 48% for a V_D/V_T at AT greater than 30.[18]

Finally, CPET will detect markers of small stroke volume augmentation (SVA) during exercise, which reflects inadequacy of RV reserve among patients with exercise-induced dyspnoea after PE. Normally, ventricular stroke volume (SV) increases by about 40% at the time that AT is reached.[19] Decreased SV response to exercise corresponds to cardiac dysfunction in several clinical conditions including pulmonary hypertension.[20] Among patients with dyspnoea after PE, attenuation of SV response to exercise corresponds to persistent pulmonary artery obstruction after acute PE.[14] SV augmentation between AT and rest is reflected on CPET by the relative increase in VO_2/heart rate (O_2·pulse) between AT and rest ($O_2{\cdot}pulse_{AT}/O_2{\cdot}pulse_{rest}$).[19] $O_2{\cdot}pulse_{AT}/O_2{\cdot}pulse_{rest}$ less than 2.6 corresponds to pathologically decreased SV augmentation at AT (less than 127% of the resting SV).

A: arterial perfusion evaluation by ventilation:perfusion scanning

Dyspnoeic post-PE patients with demonstrable cardiopulmonary dysfunction who meet the A-criteria (below) will be considered to have symptomatic residual pulmonary vascular obstruction (RPVO).[21] We will perform ventilation:perfusion (V:Q) scanning only in symptomatic patients with physiological defects because clinically important V:Q findings among all-comers after PE is low[22] and because residual perfusion defects are not always associated with adverse clinical outcomes after PE.[21 23] RPVO associated with respiratory symptoms, however is associated with at least a 10-fold increase in the incidence of serious adverse outcomes.[21 24]

Incomplete resolution of mismatched perfusion defects on scintigraphic V:Q scans implicates symptomatic RPVO as a likely cause of dyspnoea[25] and exercise intolerance[21 26–28] after PE. The clinical importance of symptomatic RPVO is supported by its association with hypoxaemia, gas exchange deficits and increased pulmonary artery pressure (PAP).[21] It increases the probability of subsequent pulmonary hypertension and other serious negative outcomes.[21 24–26 29–33]

Planar V:Q and single photon emission CT (SPECT) V:Q studies are useful to evaluate incomplete resolution of mismatched perfusion defects after pulmonary embolism. We will also accept the results of SPECT V:Q, which is at least accurate for the diagnosis of acute PE[34] and produces fewer non-diagnostic test results than planar V:Q.[35–37] SPECT V:Q may be superior to planar V:Q for the quantification of chronic vascular obstruction.[38 39]

'A-criteria'

- Planar V:Q disclosed one or more segmental or larger mismatched perfusion defects.
- Planar Q disclosed one or more segmental or larger perfusion defects not matched by opacities on chest radiograph or chest CT (performed simultaneously or within 30 days).
- SPECT V:Q disclosed one or more segmental or larger mismatched perfusion defects.

SPECT Q disclosed one or more segmental or larger perfusion defects not matched by opacities on chest radiograph or chest CT (performed simultaneously or within 30 days).

R: resting echocardiography

Resting echocardiography is performed only on patients who have met the S-criteria, E-criteria and A-criteria, since its yield in all-comers after PE is quite low.[8 40] Serial echocardiograms typically show near-normalisation of RV function, size and PAP within 2 months.[41 42] However, long-term echocardiographic findings suggestive of pulmonary hypertension and RV dysfunction at rest are more common among patients at risk for long-term complications after PE.[43] Echocardiographic findings of pulmonary hypertension and RV dysfunction at rest after PE are associated with significant increases in mortality and CTEPH.[44]

Pressure overload due to PE may result in RV dilation, wall motion abnormality, systolic dysfunction and haemodynamic compromise. Due to its complex geometry, evaluation of RV function requires a comprehensive assessment of multiple echocardiographic parameters with varying sensitivity and specificity. The R-criteria cited below are adapted from European Respiratory Society, European Society of Cardiology and American Society of Echocardiography guidelines.[45 46] The individual components of the R-criteria characterise RV systolic function, wall motion, right-sided chamber sizes and PAPs. In addition, echocardiography can provide alternate diagnoses

such as post-capillary pulmonary hypertension due to significant valvular disease, congenital heart disease, left ventricular systolic dysfunction and/or diastolic dysfunction.

Even if resting echocardiography demonstrates no evidence of pulmonary hypertension at rest, further work-up may disclose post-PE vascular pathology. Among 71 patients with CTEPH-associated PAPs that were elevated only during exercise, resting echocardiograms disclosed normal RV fractional area change and normal tricuspid annular plane systolic excursion.[47] In addition, some patients with RPVO manifest only defects in gas exchange, without evidence of pulmonary hypertension.[14 21] While echocardiography typically correlates well with right heart catheterisation (RHC) data, its accuracy can be affected by technical challenges and haemodynamic assumptions.[48]

'R-criteria'

- Peak tricuspid regurgitation velocity greater than 2.8 m/s.
- The right:left ratio of ventricular basal diameters greater than 1.0.
- Flattened intraventricular septum or abnormal septal motion.
- Acceleration time of pulmonary ejection greater than 105 ms or there is midsystolic notching.
- Early diastolic pulmonary regurgitation velocity greater than 2.2 m/s.
- Pulmonary artery diameter greater than 25 mm.
- Tricuspid annular plane systolic excursion less than 17 mm.
- Fractional area contraction of RV less than 35% on four-chamber view.

C: confirmatory chest imaging

CT pulmonary angiography (CTPA) may disclose manifestations of chronic pulmonary vascular scarring that are distinct from the intraluminal filling defects characteristic of acute PE. The CT findings reflect the direct and indirect consequences of incomplete resolution of thromboembolic material via fibrinolysis and subsequent cell-mediated remodelling, of which CTEPH is an extreme example. We categorised the CT findings associated with CTEPH[41 42 47 49] using an acronym similar to the SEARCH algorithm: small vessels; eccentric or web-shaped defects; anastomoses of the bronchial arteries; RV hypertrophy and/or pulmonary artery enlargement; contracted lung regions; and heterogeneous (mosaic) parenchyma. Smaller than normal calibre arteries containing filling defects were observed in 90% of a series of 81 CTEPH patients who received CTPA.[42] Eccentric, wall-adhering defects (with obtuse angles and concave surfaces) were seen centrally in 59% of patients and peripherally in 38%, while web-shaped defects were present within the central arteries in 12% and the peripheral arteries in 51%. Anastomoses via bronchial artery collaterals (resulting in communication between the aorta and pulmonary arterioles in the presence of pulmonary artery obstruction) occurred in 68%. RV enlargement was universal, while the main pulmonary arteries were dilated in 92%. Contracted, radio-opaque lung regions attributed to parenchymal scars were present in 79%.[41] Heterogeneous lung perfusion leading to a mosaic pattern of lung parenchyma was apparent in 91%.

CTPA findings may help guide management strategies, including assessment of candidacy for surgical interventions and evaluation of respiratory defects. For example, CT-detected parenchymal scars were associated with significant restriction on pulmonary function testing in 16% of patients.[41]

CTPA is performed in the current algorithm only after defects in both exercise physiology and lung perfusion defects have been identified, so that abnormal findings will be most likely to represent clinically meaningful disease. Routine repeat CTPA in one trial disclosed complete or partial resolution in 88% of patients after only 3 weeks of anticoagulant therapy.[50] Long-term (average 9-month) follow-up CTPA disclosed chronic vascular findings in only 15% of the patients after PE.[23] Conversely, among a series of patients with long-term vascular findings on CTPA after PE, only 19% had exertional dyspnoea.[51] Furthermore, CTPA findings are not ubiquitous, even among patients with CTEPH.[49] Thus, when patients have arrived at this part of the algorithm and have positive findings on the V:Q scan and echocardiogram, CT imaging is performed but is not typically the last step in the work-up.

'C-criteria'

- Smaller than normal calibre arteries contain filling defects.
- Eccentric filling defects or intravascular bands or webs.
- Anastomoses of bronchial arteries.
- RV enlargement.
- Contracted lung regions.
- Heterogeneous ('mosaic') lung perfusion.

H: haemodynamic measurement by right heart catheterisation and X: exercise RHC

In order to meet the H-criteria for the diagnosis of CTEPH, patients must have evidence of chronic thromboembolism and satisfy all three parts of the definition of pulmonary arterial hypertension: mean pulmonary artery pressure (mPAP) greater than 20 mm Hg; pulmonary capillary wedge pressure less than or equal to 15 mm Hg; and pulmonary vascular resistance (PVR) greater than or equal to 3 Wood units.[52]

If the H-criteria are not met, an RHC with invasive cardiopulmonary exercise testing, as previously described,[53] can further evaluate those who do not have resting pulmonary hypertension. The focus of this test is to determine whether the patient manifests exercise-induced pulmonary hypertension, indicating CTED, or whether exercise tolerance is limited by dead space ventilation, small SV augmentation or an alternative diagnosis.

During RHC and invasive CPET in patients with abnormal perfusion scans, the patient is considered to

have CTED if the mPAP rises excessively as the cardiac output (CO) increases, as determined by the equation: *mPAP/CO slope >3 mm Hg·L−1·min−1*.[52]

The excessive rise in mPAP is due to impaired vessel compliance due to obstruction from chronic thromboembolic material that leads to increased vessel stiffness. As a result of this impaired compliance, a small change in CO cannot be accommodated by the pulmonary vascular bed and results in a large increase in mean PAP. Aside from the mPAP/CO slope, other signs of abnormal pulmonary vascular response to exercise include an increase in PVR[54] and decrease in pulmonary arterial compliance[55] as exertion increases.

'H-criteria'

- MPAP greater than 20 mm Hg with pulmonary arterial wedge pressure less than or equal to 15 mm Hg.
- PVR greater than or equal to 3 Wood units.

'X-criteria'

- During exercise, the mPAP versus CO slope (mPAP/CO slope) greater than 3 mm Hg·L−1·min−1.
- PVR during exercise greater than or equal to PVR at rest.

Chronic thromboembolism with ventilatory inefficiency (CTEVI) is defined as the absence of H-criteria and X-criteria for CTEPH and CTED, respectively, but elevated V_D/V_T, V_D or V_E/VCO_2 on CPET, suggesting that exertional dyspnoea is due to mismatched perfusion defects causing inadequate gas exchange (table 1). Chronic thromboembolism with small stroke volume augmentation (CTESSA) is defined as the absence of H-criteria and X-criteria for CTEPH and CTED, respectively, but pathologically decreased SV augmentation at AT.

The invasive CPET may disclose an alternative diagnosis such as exercise-induced heart failure with preserved ejection fraction which is characterised by an increase in the pulmonary capillary wedge pressure to a value more than 25 mm Hg.

Presentation of data to independent raters

The SEARCH algorithm is the standard of care throughout the UCAPE network, so the research portion of this study is limited to the reporting of the (de-identified) results to the evaluation group and the analyses. Patients who are lost to follow-up or have other reasons for which the SEARCH algorithm is not followed will not be included in the study.

Once the SEARCH algorithm has been completed for the first clinical assessment, the clinician will present a structured summary of the case during a monthly online meeting of the UCAPE clinicians. The presenting clinician will discuss the case in detail, but she/he will not disclose the diagnostic endpoint that was clinically assigned to the patient or any protected health information. Based on their structured evaluation of clinical data generated during long-term follow-up after PE and presented in a de-identified manner, six raters will independently categorise each patient into one of the following nine diagnostic nodes using an online scoring tool (Qualtrics XM V.11–22; Provo, Utah, USA).

1. Recovery from symptoms of dyspnoea and exercise intolerance to the state that pre-existed PE.
2. No cardiopulmonary defect disclosed by CPET (eg, elevated V_D/V_T or decreased SVA) associated with dyspnoea after PE.
3. Alternative diagnoses alone (negative V:Q) associated with dyspnoea after PE.
4. Symptomatic RPVO without echocardiographic evidence of pulmonary hypertension, unspecified among CTESSA, CTEVI, CTED and CTEPH.
5. Symptomatic RPVO without CT evidence of chronic PE, unspecified among CTESSA, CTEVI, CTED and CTEPH.
6. Unspecified between CTESSA, CTEVI and CTED.
7. CTESSA or CTEVI.
8. CTED.
9. CTEPH.

The patient's physician will present the case again to the UCAPE raters with updated information from at least 6 months after the first assessment. The raters will again independently categorise the patient with a diagnostic endpoint node, using the same online scoring tool. In the instance in which a patient dies after the first clinical assessment, the patient's physician will provide clinical details about the death. The raters will then attribute the death either to PE or other pulmonary vascular disease, or to other causes.

Data quality assurance and confidentiality

Study facilitators will review presentations to ensure lack of protected health information. A core group will perform quality assurance reviews of the results of cardiopulmonary exercise tests, V:Q scans, echocardiograms, CTs and RHC test results for completeness, accuracy, uniformity and clarity of (de-identified) data necessary to categorise patients. The study investigators record all patient-related information without patient identifiers. Cases are specified by code numbers only and the investigators do not have access to the patients' protected health information. The investigators will not contact the subjects and will not re-identify the subjects.

Analysis plan and sample size determination

The primary outcome will be the inter-rater agreement regarding the clinical condition during both clinical assessment points (at least 3 months after acute PE and at least 6 months after the first evaluation).

We will use Krippendorff's alpha statistic to measure agreement among the multiple reviewers in Aim 1 and to measure agreement between the first and second evaluations to evaluate stability of disease.[56] Krippendorff's alpha is an accepted method for the comparison of clinical data generated from multiple readers.[57] We will adopt the commonly accepted interpretation criteria for agreement: ≤0.0=poor agreement; 0.01–0.20=slight;

0.21–0.40=fair; 0.41–0.60=moderate; 0.61–0.80=substantial; and 0.81–1.0=almost perfect.

We estimated the sample size using the open-source programme RStudio, Build 372 (RStudio, PBC) and the kappaSize V.1.2 package.[58] The number of raters (n) to review and score each case will be 6. There are nine possible nodes from the outcome decision tree represented in figure 1. Based on clinical experience within the UCAPE PE clinics, we expected prevalences of:

- Node 1, 50%: assuming half of patients are asymptomatic on follow-up.
- Node 2, 12%: assuming 1/5 of symptomatic patients manifest no physiological defects during CPET.
- Node 3, 7%: assuming that alternative diagnoses are responsible for 1/4 of patients with abnormal CPET.
- Node 4, 7%: assuming that 1/4 patients with abnormal V:Q will not proceed in the work-up further than echocardiography.
- Node 5, 7%: assuming that 1/4 patients with abnormal V:Q will not proceed in the work-up further than CT.
- Node 6, 7%: assuming that 1/4 patients with abnormal V:Q and normal resting RHC will not proceed to exercise RHC.
- Node 7, 4%: assuming that 4% of the study population will be diagnosed with symptomatic RPVO.
- Node 8, 2%: assuming that 2% of the study population will be diagnosed with CTED.
- Node 9, 4%: assuming that 4% of the study population will be diagnosed with CTEPH.

We grouped the nodes into five clinically-related groups that we expect to have the following probabilities of occurrence (px) in our population:

- p1=nodes 1 and 2 (symptomatic recovery or dyspnoea without CPET defect)=62%.
- p2=node 3 (dyspnoea not due to RPVO)=7%.
- p3=nodes 4 and 5 (indeterminate among CTEVI, CTESSA, CTED and CTEPH)=14%.
- p4=nodes 6, 7 and 8 (CTED or indeterminate among CTEVI, CTESSA and CTED)=13%.
- p5=node 9 (CTEPH)=4%.

These categories will be treated as nominal rather than ordinal. The expected agreement among raters is at least 0.75, based on clinical experience with the algorithm. A validation sample of n=150 will be enrolled, and up to 10% loss to follow-up is expected at the second evaluation. Two evaluation visits will be combined with an assumption of high (0.7–0.8) dependence between first and second evaluation visits of the same patient. With these assumptions, computer-based simulation models estimate 80% power at alpha level of 0.05 to distinguish an observed Krippendorff's alpha of 0.75 from a value of 0.66 or lower.

A secondary analysis will consider all nine diagnostic nodes as separate groups. Krippendorff's alpha statistic will measure agreement among the multiple reviewers regarding patients' assignment into the nine groups.

Another secondary outcome will be the stability between first evaluation point and second evaluation point, defined as the proportion of patients whose consensus diagnostic category is the same at both points. The mode of the combined reviewers' diagnostic category scores at a particular time point will be accepted as the consensus diagnostic category.

Patient and public involvement

Patients and the public were not involved in the design of the project nor in the plans for its conduct, reporting or dissemination.

Data statement

Data set will be published with the manuscript as a online supplemental file.

DISCUSSION

Our study will validate the inter-rater reliability of the SEARCH algorithm as a structured approach to diagnostic testing that will distinguish among the variety of outcomes that are possible after acute PE.[1] Although a battery of advanced diagnostic tests can identify each outcome, the yield of individual tests is low enough that routine testing of all PE patients is not typically performed.[22] Our study will determine whether the SEARCH protocol is a reliable way to navigate these tests in a logical, stepwise fashion. Each individual test used in the algorithm has been clinically validated in pulmonary embolism patients, including the CPET technique that the investigators developed and validated.[14]

Recovery after PE depends on many clinical factors including the severity of the initial presentation, the effectiveness of initial treatment, subsequent anticoagulation and a variety of patient-specific characteristics.[59] This manuscript focuses on an unequivocal method for evaluating and categorising recovery. We are optimistic that our study will facilitate future research to determine how various clinical factors and, more importantly, how specific treatment options might influence clinical recovery as described by the SEARCH protocol.

PE sequelae can chronically limit mobility, self-care, activity and well-being even in the absence of recurrence.[60–62] Over half of patients suffer chronic problems after PE,[63] which can be as life-altering as the effects of myocardial infarction.[61] Exertional dyspnoea is the most common symptom,[4 64 65] which may persist for months[9] or years.[4] Validation of the SEARCH algorithm would offer clinicians a straightforward method to diagnose post-PE conditions that are rarely distinguished clinically. Distinct conditions defined by the algorithm (table 1) would require different strategies for follow-up, monitoring and treatment. A structured diagnostic approach would allow timely identification of the various post-PE conditions while avoiding unnecessary testing. Unequivocal categorisation of the chronic conditions will allow them to be used as endpoints in randomised clinical trials of acute PE treatment.

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