Thrombosis Research 132 (2013) 659–665

Contents lists available at ScienceDirect

Thrombosis Research

journal homepage: www.elsevier.com/locate/thromres

Regular Article

Inefficient exercise gas exchange identifies pulmonary hypertension in chronic thromboembolic obstruction following pulmonary embolism

Colm McCabe [a], Gael Deboeck [b], Ian Harvey [a], Robert MacKenzie Ross [a], Deepa Gopalan [c], Nicholas Screaton [c], Joanna Pepke-Zaba [a,*,1]

[a] Pulmonary Vascular Disease Unit, Papworth Hospital NHS Trust, Cambridge CB23 3RE, UK
[b] Erasmus University Hospital, Department of Cardiology, Free University of Brussels, Belgium
[c] Department of Radiology, Papworth Hospital NHS Trust, Cambridge CB23 3RE, UK

ARTICLE INFO

Article history:
Received 26 August 2013
Received in revised form 9 September 2013
Accepted 23 September 2013
Available online 27 September 2013

Keywords:
Chronic thromboembolic pulmonary hypertension
Pulmonary embolism
Pulmonary circulation
Cardiopulmonary exercise testing

ABSTRACT

Introduction: Persistent obstruction in the pulmonary artery following acute pulmonary embolism (PE) can give rise to both chronic thromboembolic pulmonary hypertension (CTEPH) and chronic thromboembolic disease without PH (CTED). We hypothesised that cardiopulmonary exercise testing (CPET) may be able to differentiate patients with CTEPH and CTED following unresolved PE which may help guide patient assessment.
Materials and Methods: Fifteen patients with CTEPH and 15 with CTED all diagnosed after PE underwent CT pulmonary angiography, CPET and resting right heart catheterisation. Exercise variables were compared between patients with CTEPH, CTED and 10 sedentary controls and analysed as predictors of a CTEPH diagnosis. Proximal thrombotic burden in CTEPH and CTED was quantified using CT criteria.
Results: Physiological dead space (Vd/Vt) (34.5 ± 11.4 vs 50.8 ± 6.6 %, $p < 0.001$) and alveolar-arterial oxygen gradient (29 ± 16 vs 46 ± 12 mmHg, $p < 0.001$) at peak exercise strongly differentiated CTED and CTEPH groups respectively. Resting ventilatory efficiency also differed from control subjects. In both univariate and multivariate analyses, peak exercise Vd/Vt predicted a diagnosis of CTEPH (ROC AUC > 0.88, 0.67 - 0.97) despite a similar degree of proximal thrombotic obstruction to the CTED group (67.5, 55 - 70% and 72.5, 60 - 80% respectively, $p = 0.08$).
Conclusions: Gas exchange at peak exercise differentiates CTED and CTEPH after PE that can present with no apparent relation to the degree of proximal thrombotic burden. A potential role for CPET exists in guiding further clinical investigations in this setting.

Introduction

Chronic thromboembolic pulmonary hypertension (CTEPH) lies within Group IV of the Dana Point classification of pulmonary hypertension (PH) and may be an uncommon sequela of acute pulmonary embolism (PE) [1–6]. However, up to 75% of patients with CTEPH suffer an antecedent PE with presentation occurring often months after acute thrombotic insult despite a period of therapeutic anticoagulation [7,8]. Patients present with effort dyspnoea predominantly related to incapacity of the right ventricle (RV) to increase cardiac output on exercise. Untreated this condition typically leads to progressive RV dysfunction and death so early detection, ideally using non-invasive methods, prior to physiological decompensation may be advantageous.

CTEPH is haemodynamically defined by a resting mean pulmonary artery pressure (mPAP) > 25 mmHg at right heart catheterisation in the presence of chronic thromboembolic pulmonary vascular obstruction confirmed by radiological criteria [9]. However despite exercise related symptoms, a proportion of patients demonstrate mPAP values < 25 mmHg at rest despite persistent chronic pulmonary thromboembolic obstructions. These patients may be labelled as having chronic thromboembolic disease (CTED) and usually present with preserved resting RV contractility and normal cardiac chamber morphology. Hence, investigations conducted at rest such as echocardiography may lack power to detect changes suggestive of progression to CTEPH. Assessment of potential attenuation in cardiac output on exercise therefore requires an exercise-based assessment method.

Cardiopulmonary exercise testing (CPET) demonstrates a characteristic profile in pulmonary arterial hypertension (PAH) [10,11]. However patients with chronic thromboembolic obstruction are less well described. Six minute walk distance (6MWD) reflects haemodynamic severity in CTEPH but does not inform on mechanisms of exercise limitation [12].

Abbreviations: AT, Anaerobic threshold; CI, Cardiac Index; Cr, Creatinine Clearance; CPET, Cardiopulmonary exercise testing; CTED, Chronic thromboembolic disease; CTEPH, Chronic thromboembolic pulmonary hypertension; EDP, End diastolic pressure; FEV1, Forced expiratory volume (1 second); FVC, Forced vital capacity; HR, Heart rate; mPAP, Mean pulmonary artery pressure; NT proBNP, N terminal pro brain natriuretic peptide; PCWP, Pulmonary capillary wedge pressure; PE, Pulmonary embolism; RA, Right atrium; RER, Respiratory exchange ratio; RV, Right ventricle; PVR, Pulmonary vascular resistance; SvO_2, Mixed venous oxygen saturations; TPVO Index, Total pulmonary vascular obstruction index.

* Corresponding author. Tel.: +44 480 830541; fax: +44 480 831 315.
E-mail address: joanna.pepkezaba@papworth.nhs.uk (J. Pepke-Zaba).

[1] JPZ is the overall guarantor of the manuscript.

0049-3848/$ – see front matter © 2013 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.thromres.2013.09.032

Therefore, we hypothesised that CPET could be used to differentiate the exercise profiles of patients with CTED and CTEPH compared to sedentary controls. Following this, we aimed to establish which exercise parameters were predictive of a diagnosis of CTEPH and potentially therefore of value in the follow up of patients with unresolved PE who are at risk of deterioration. To account for a potential association between proximal thrombotic burden and pulmonary haemodynamics, we quantified thrombotic obstruction in these groups to evaluate for any effect of greater thrombotic load.

Materials and Methods

Study Protocol

Patients underwent incremental symptom limited CPET and right heart catheterisation (RHC) within 72 hours. Radiological evaluation with CT pulmonary angiogram was carried out prior to RHC in patients with CTED and CTEPH to confirm a radiological pattern consistent with chronic thromboembolic obstruction. Patients with chronic thromboembolic obstruction were grouped by diagnosis following RHC: mPAP > = 25 mmHg (CTEPH), mPAP < 25 mmHg (CTED) and compared with age and sex-matched sedentary controls (Controls). Eligibility for study enrolment was determined following patient referral to our unit with a suspected diagnosis of CTEPH. As a prerequisite, study patients had to be symptomatically limited with evidence of chronic thromboembolic obstruction on CT pulmonary angiogram after PE despite at least 6 months anticoagulation with documented treatment compliance. CT pulmonary angiography was undertaken in either the patient's local institution or our own and in all cases was preceded by at least 6 months anticoagulation. All patients were anticoagulated at study entry.

In total, thirty patients were recruited over thirteen months. 5 patients were not enrolled due to screening failure (see below). One such patient was not enrolled due to lack of thromboembolic disease on CT pulmonary angiography following repeat CT scan at our institution. All patients enrolled completed the CPET and RHC and no patients were withdrawn. Asymptomatic age and sex matched sedentary controls underwent incremental CPET only. The study was approved by the local research ethics committee (Cambridge South Ref 12/EE/0085) and the protocol complied with the amended Declaration of Helsinki. All study participants gave written informed consent prior to study enrolment.

Exclusion Criteria

Patients clinically limited by factors other than chronic thromboembolic obstructions were excluded. This was determined on the basis of the following factors: FEV_1 < 70% predicted, FEV_1/FVC ratio < 70%, suspected intracardiac shunt, BMI > 30 kg/m^2, history of angina, evidence of LV systolic or diastolic dysfunction on echocardiogram. In addition patients unable to perform cycle ergometry were excluded. The enrolment pathway of patients is summarized in Fig. 1.

Exercise Protocol

The exercise protocol consisted of 1) 2 minutes rest 2) 3 minutes of unloaded pedalling 3) a symptom limited incremental exercise protocol using a 5 to 20 W/min work ramp on an electronically braked cycle ergometer. Gas exchange variables were measured breath by breath and averaged over 20 second intervals (Oxycon™ Pro, Carefusion, UK), in accordance with the American Thoracic Society/American College of Chest Physicians Statement on Cardiopulmonary Exercise Testing [13]. Work ramp was estimated from anthropometric data and patients' functional impairment so as to attain an incremental exercise time lasting 8 to 12 minutes. All patients had to maintain a pedaling frequency of 60–65 revolutions per minute. Flowmeter and mouthpiece volumes were calibrated prior to each test (Bi-directional DVT, Carefusion). Participants were continuously monitored by a 12-lead electrocardiogram and pulse oximeter (Radical-7^R, Masimo). Blood pressure was measured at rest, peak exercise and during recovery. Peak aerobic capacity was recorded as the mean value of oxygen uptake during the last 30 seconds of the test. Anaerobic threshold (AT) was determined by the V-slope method, the lowest ventilatory equivalent for oxygen and end tidal oxygen partial pressure. As for peak VO_2, AT was averaged over 30 seconds. Vd/Vt was calculated by the Bohr equation ($Vd/Vt = (P_aCO_2 - P_eCO_2)/P_aCO_2$, where P_aCO_2 is the arterial partial

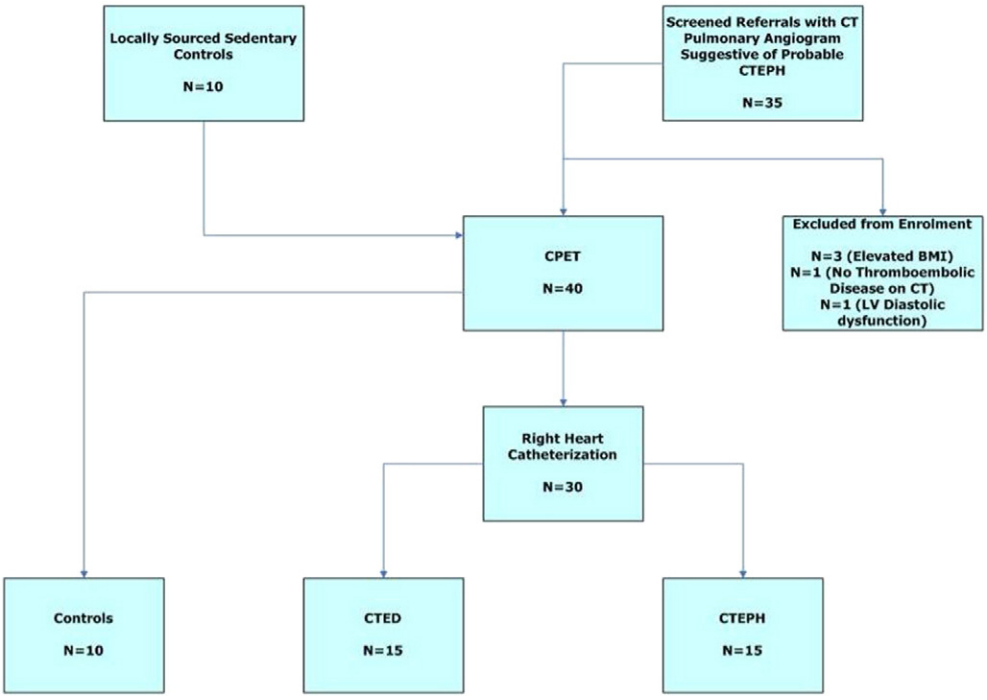

Fig. 1. Enrolment pathway of patients.