EUROPEAN RESPIRATORY *journal*

FLAGSHIP SCIENTIFIC JOURNAL OF ERS

Early View

Research letter

The role of cardiopulmonary exercise test in identifying pulmonary veno-occlusive disease

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Please cite this article as: Pérez-Olivares C, Segura de la Cal T, Flox-Camacho Ángela, *et al*. The role of cardiopulmonary exercise test in identifying pulmonary veno-occlusive disease. *Eur Respir J* 2021; in press (https://doi.org/10.1183/13993003.00115-2021).

This manuscript has recently been accepted for publication in the *European Respiratory Journal*. It is published here in its accepted form prior to copyediting and typesetting by our production team. After these production processes are complete and the authors have approved the resulting proofs, the article will move to the latest issue of the ERJ online.

The role of cardiopulmonary exercise test in identifying pulmonary veno-occlusive disease.

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Funding:
This project was founded by project "Bases Genetico Moleculares de la Medicina de Precisión en la Hipertensión Arterial Pulmonar".
Funder: Instituto Carlos III. Ministerio de Economıa y Competitividad.
https://www.isciii.es/Paginas/Inicio.aspx
Award number: PI 18/01233 Grant
Recipient: P E-S The funders had no role in study design, data collection, and analysis, decision to publish, or preparation of the manuscript.

A.C.U. holds a research-training contract “Rio Hortega” (CM20/00164) from the Spanish Ministry of Science and Innovation (Instituto de Salud Carlos III).

J.N. is recipient of a predoctoral grant (Jordi Soler Soler) through CIBERCV

Conflict of interest: The authors declare that there is no conflict of interest regarding the publication of this article.

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To the Editor:

Pulmonary Veno-Occlusive Disease (PVOD) is a rare form of pulmonary hypertension that shares some clinical and haemodynamic features with idiopathic pulmonary arterial hypertension (PAH). However, suspicion of PVOD is crucial, considering that PAH-specific treatment may precipitate life-threatening pulmonary oedema and lung transplant should be considered from diagnosis[1,2].

The absence of pathogenic variants in the *EIF2AK4* gene and the prohibitive risk of performing a lung biopsy in these patients often prevents a definitive diagnosis of PVOD[3-5]. Therefore, PVOD diagnosis frequently relies on the identification of other indicators with a high-associated likelihood of PVOD, namely: decreased diffusing capacity of the lung for carbon monoxide (DLCO) and typical high-resolution computed tomography (HRCT) features[5-7]. However, their sensitivity and specificity are far from perfect and additional diagnostic tools are missing. We hypothesise that cardiopulmonary exercise test (CPET) might reveal characteristic patterns of exercise performance in PVOD patients, strengthening its suspicion and diagnosis.

We studied 23 patients diagnosed with PVOD, referred to a national referral centre for pulmonary hypertension. Among them, 16 patients carried pathogenic biallelic variants in *EIF2AK4*; 2 presented the 3 HRCT typical features; 2 developed pulmonary oedema on PAH-specific treatment; and in the remaining 3, PVOD diagnosis was only possible by histological examination of lung specimens after transplantation. The control group consisted of 52 consecutive PAH patients on regular follow-up (24 idiopathic-PAH and 28 heritable-PAH associated with *BMPR2*).

Patients underwent a symptom-limited incremental CPET on a cycle-ergometer. Exercise variables were measured at rest, ventilatory threshold (VT) and peak exercise. Oxygen saturation was monitored by pulse oximeter. Clinical and hemodynamic data closest to CPET were analysed.

The mean age was 39.8±11.9 years, without differences between PVOD and PAH groups (37.7±11.7 vs. 40.7±12, p=0.28). PVOD patients did not show female sex predominance (43.5 vs. 76.9%, p=0.08). They presented worse functional class (FC) (FC I none PVOD vs. 13 PAH, FC II 11 PVOD vs. 31 PAH, and FC III 12 PVOD vs. 8 PAH, p<0.01) and lower DLCO levels (32.8±7.8 vs. 78.7±13.2%, p<0.01) than PAH patients. Most CPET (85.3%) were performed in patients receiving PAH-specific treatment, including 32% on systemic prostacyclins. Eleven patients were not receiving any PAH-specific medication: 9 (7 PAH and 2 PVOD) who performed CPET at diagnosis and 2 PVOD who did not tolerate it.

PAH patients achieved higher work rates than the PVOD ones. There was a significant reduction in predicted peak oxygen uptake (VO2), oxygen pulse and VO2 levels at VT in PVOD patients compared to PAH. (Table 1)

The main exponents of ventilatory efficiency were increased to a greater extent in PVOD when compared to PAH patients, both VE/VCO2 at VT (EqCO2-VT) and VE/VCO2 slope. Moreover, minimum oxygen saturation was lower in PVOD patients. End-tidal carbon dioxide pressure (PETCO2) at rest was reduced in both groups, although more profoundly decreased in PVOD. (Table 1). After stratifying by FC, these differences observed between PVOD and PAH were maintained in patients in FC II, while a non-significant trend was observed in the group of patients in FC III.

Interestingly, PVOD patients had lower pulmonary vascular resistance (PVR), although similar cardiac output (CO) (Table 1). In fact, the 3 PVOD patients with mildly elevated PVR (between 3 and 4 WU) exhibited profound alterations of CPET parameters: a predicted VO2 below 60%, an EqCO2-VT above 51 and a VE/VCO2 slope exceeding 45.

Most relevant CPET variables were strongly associated with the definitive diagnosis of PVOD, especially when adjusted for PVR. These associations persisted after adjusting for FC. ROC analyses and goodness-of-fit tests were performed to estimate how accurately CPET variables, individually or in combination, identify PVOD patients. As a result, predicted VO2, VE/VCO2 slope, EqCO2-VT and PetCO2 showed the highest areas under the curve (AUC). Their combination with PVR increased AUC for all CPET variables. After selecting those models with adequate goodness-of-fit, predicted VO2 showed the highest AUC (0.89, IC95% 0.81-0.98), closely followed by VE/VCO2 slope (0.85, IC95% 0.76-0.94). The combination of predicted VO2, VE/VCO2 slope and PVR rose the greatest discriminative power (AUC 0.974; CI95% 0.946-1) compared with individual models ($p<0.001$), constituting the final PVOD diagnostic model.

To our knowledge, this is the largest cohort of CPET in confirmed PVOD patients. CPET data in PVOD exhibited characteristic features distinguishable from those in PAH: 1) a significantly greater ventilatory inefficiency demonstrated by higher VE/VCO2 slope and EqCO2-VT values, consistent with data previously published[8]; 2) a more severe functional impairment revealed by lower peak VO2 and earlier VT, 3) CPET parameters may be profoundly altered in PVOD patients with mildly elevated PVR and 4) predicted VO2 and VE/VCO2 slope in combination with PVR showed predictive power for PVOD diagnosis.

The histopathological mechanisms involved in the exercise response of PAH patients have been widely described. The vascular obliteration and the increased PVR in PAH do not allow the alveolar physiological recruitment; hence, ventilation-perfusion mismatch is further aggravated[10]. These changes lead to tissue hypoxaemia, early VT and reduced peak VO2[10].

Despite the worse exercise capacity and prognosis associated with PVOD, various studies did not observe haemodynamic differences between PVOD and PAH[6,9]. Moreover, our research actually shows significantly lower pulmonary pressures in the POVD population. Importantly, previous studies observed an association between CPET parameters and haemodynamic severity in PAH[10,11]. However, in our study, the decrease in VO2 and the degree of ventilatory inefficiency seemed both disproportionate to the haemodynamic severity in PVOD patients, supporting the assumption that additional factors beyond PVR play a critical role in its pathophysiology.

We expose some possible mechanisms: 1) The vascular remodelling occurring in PVOD, which includes venular intimal fibrosis, venular muscular hyperplasia and capillary proliferation, leads to a lower pulmonary capillary blood volume and alveolar membrane diffusion. These alterations are independent of haemodynamic severity and reflected in reduced DLCO values[3,12] 2) The capillary congestion and interstitial oedema decrease gas exchange, further impairing ventilatory efficiency[13] 3) The significant hypoxemia throughout exercise could exacerbate myocardial ischemia and right ventricular failure and may justify the flattening behaviour of oxygen pulse in PVOD, despite a normal CO at rest[14]. 4) The hypoxemia and low CO reduce peripheral oxygen delivery and induce an early onset of lactic acidosis, which results in earlier VT and lower VO2[14].

Currently, HRCT is the key non-invasive test when PVOD is suspected. Two-thirds of PVOD patients have at least two HRTC characteristic signs[6,15]; however, their absence does not

exclude PVOD. Interestingly, HRCT signs are less common at the initial stages of the disease, while we found that CPET exhibits alterations since early phases. Predicted VO2 and VE/VCO2 slope showed high discriminative power which further improved in combination with PVR. In the current scenario, where the identification of PVOD patients remains challenging. We encourage the incorporation of a CPET model that combines predicted VO2, VE/VCO2 slope and PVR to the currently available non-invasive diagnostic tools in suspected PVOD patients. However, larger studies would be needed to validate this model and establish appropriate cut-off points.

In conclusion, PVOD and PAH show different exercise patterns, where the disproportion between haemodynamics and both functional and ventilatory impairment is of particular interest. The combination of predicted VO2, VE/VCO2 slope and PVR showed the highest ability to accurately identify PVOD, positioning CPET as a promising additional tool for the non-invasive diagnosis of PVOD.

Table 1. Haemodynamic and cardiopulmonary exercise characteristics of PVOD and PAH patients.

	All (N75)	PVOD (N 23)	PAH (N 52)	p- value
Haemodynamic characteristics				
Mean PAP, mmHg (SD)	53 (12.7)	46.4 (12.1)	56 (11.9)	0.002
CO, L/min (SD)	4.8 (1.6)	5.1 (1.7)	4.7(1.6)	0.27
CI, L/min/m^2 (SD)	2.74 (0.84)	2.69 (0.64)	2.74 (0.91)	0.75
PVR, UW (SD)	10.3 (5.5)	7.7 (3.5)	11.5 (5.8)	0.006
RAP, mmHg (SD)	7.3 (4.6)	6.3 (3.9)	7.8 (4.8)	0.2
Cardiopulmonary exercise test parameters				
Work rate, w (SD)	67.8(29)	53 (16.7)	73.8 (30.8)	0.005
RER (SD)	1.13 (0.1)	1.15 (0.1)	1.12 (0.1)	0.3
Maximum HR, bpm (SD)	142.4 (18.9)	135.6 (16.8)	145 (19.2)	0.06
Basal oxygen saturation, % (SD)	95.6 (3.9)	91.9 (4.6)	97.1 (2.2)	<0.001
Minimun oxygen saturation, % (SD)	88.7 (11.2)	74.5 (10.8)	94.6 (3.4)	<.0.001
VO2 peak, ml/min/kg (SD)	14.8 (4.9)	11.4(3.5)	16.4 (4.7)	<0.001
VO2 predicted, % (SD)	52.9 (16.9)	37.5 (11.3)	59.4 (14.6)	<0.001
Pulse O2, ml	7.1(2.3)	5.8(1.8)	7.5 (2.3)	0.004
VO2 at VT, ml/min/kg (SD)	10 (3.3)	7.8 (2.1)	10.9 (3.2)	<0.001
PetCO2 VT, mmHg (SD)	27.6(5.2)	23.3(3.9)	29.2 (4.8)	<0.001
EqCo2-VT	40.6 (9.4)	49.3(9.1)	36.9 (6.8)	<0.001
VE/VCO2 Slope	47.4(14.5)	60.5(15.8)	42.5 (10.5)	<0.001

PAP Pulmonary arterial pressure; CO Cardiac output; CI Cardiac index; PVR Pulmonary vascular resistances; RAP Right atrial pressure; RER respiratory exchange ratio; HR Heart rate; VO2 Oxygen uptake; VT ventilatory threshold; EqCO2-VT VE/VCO2 ratio at Ventilatory threshold; PetCO2 End-tidal carbon dioxide pressure.

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