

Early histological changes of pulmonary arterial hypertension disclosed by invasive cardiopulmonary exercise testing

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Abstract

Early diagnosis of pulmonary artery hypertension (PAH) is diagnostically challenging given the extent of pulmonary vascular remodeling required to bring about clinical signs and symptoms. Exercise testing can be invaluable in this setting, as stressing the cardiopulmonary system may unmask early disease. This report describes a young patient with a positive family history of PAH in whom contemporaneous invasive cardiopulmonary exercise testing and surgical lung biopsy reveal the novel association between exercise pulmonary hypertension (ePH) and early histological changes of PAH. Exercise PH currently carries no pathological correlates which means the hemodynamic effects of early pulmonary vascular remodeling remain unknown. Following the recent proceedings from the World Symposium in Pulmonary Hypertension 2018, which broaden the hemodynamic definition of PAH, this report suggests an important association between ePH and early pulmonary vascular remodeling supporting a role for exercise hemodynamic evaluation in patients at increased familial risk of PAH.

Keywords

cardiopulmonary physiology and pathophysiology, vascular remodeling

Date received: 14 February 2019; accepted: 1 April 2019

Pulmonary Circulation 2019; 9(2) 1–4

DOI: 10.1177/2045894019845615

Case report

A 42-year-old male long-distance runner was referred to our hospital with shortness of breath on very strenuous exercise. On questioning, he volunteered mild Raynaud's and reflux disease, but no "sicca" symptoms. His mother had died from idiopathic pulmonary arterial hypertension (PAH) aged 61 years and his father died from idiopathic pulmonary fibrosis. He took no medicine or recreational drugs. Examination was unremarkable. Laboratory blood tests, which included serum brain natriuretic peptide and an extended connective tissue antibody panel, were normal. Genetic screening for mutations associated with PAH (*FLCN*, *BMPR2*, *CAVI*, *KCNK3*, *SMAD9*, *ACVRL1*, *ENG*, *SMAD4*, *EIF2AK*) were also negative. Spirometry was normal; however, lung transfer capacity for carbon monoxide (TLCO) was 45% of predicted. Six-minute walk test distance was >600 m without arterial oxygen desaturation.

Transthoracic echocardiography and cardiac magnetic resonance imaging (MRI) revealed a structurally normal heart. High-resolution computed tomography (HRCT) was unremarkable with no features of pulmonary veno-occlusive disease or interstitial lung disease. A ventilation perfusion study was within normal limits. The patient underwent cardiopulmonary exercise testing (CPET) which was significant for a peak oxygen consumption (VO_2) of 80% predicted and ventilatory equivalent carbon dioxide (VE/VCO_2) slope of 46, above the suggested cut-off of 30.¹ Given the clinical suspicion of underlying pulmonary vascular disease, he proceeded to invasive CPET (iCPET) (Table

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Table 1. iCPET performed at baseline assessment and six-month follow-up.

	Test 1 (baseline)		Test 2 (six-month follow-up)	
	Peak		Peak	
VO ₂ (mL/kg/min)	27.9		25.6	
VO ₂ predicted	78%		72%	
Work (W)	185		176	
HR (bpm)	165		182	
RR (min ⁻¹)	46		37	
SpO ₂ (%)	88		87	
Minute ventilation (L/min)	112		116	
VE/VCO ₂ slope*	42*		46*	
RER	1.4		1.39	
Vd/Vt (%)	32		51	
	Rest	Peak	Rest	Peak
sPAP (mmHg)	24	48	40	66
dPAP (mmHg)	13	28	16	33
mPAP (mmHg)	18	35	23	47
PAWP	9	9	9	13
CO (L.min ⁻¹)	7.2	14.7	6.5	14.8
CO (% predicted)	–	76	–	76
PVR (WU)	1.2	1.5	3.0	2.9
TPR (WU)	2.5	2.4	3.5	3.2
PVC (mL/mmHg)	7.7	4.4	7.0	2.2

*Defines slope measurement between onset of work and ventilatory threshold.

VO₂, oxygen consumption; RR, respiratory rate; VE/VCO₂, minute ventilation (L)/Carbon dioxide production (mL min⁻¹); RER, respiratory exchange ratio; HR, heart rate; sPAP, systolic pulmonary arterial pressure; dPAP, diastolic pulmonary arterial pressure; mPAP, mean pulmonary arterial pressure; PAWP, pulmonary arterial wedge pressure; CO, cardiac output; PVR, peripheral vascular; TPR, total pulmonary resistance; PVC, pulmonary vascular compliance (stroke volume/(sPAP – dPAP); Vd/Vt, dead space/tidal volume.

1, left column). Resting pulmonary hemodynamics were within normal limits; however, there was evidence of exercise ventilatory inefficiency and high exercise pulmonary vascular resistance (PVR). Due to diagnostic uncertainty and concern over early interstitial lung disease (ILD), the patient proceeded to surgical lung biopsy (Fig. 1).

Lung biopsy showed features of an early occlusive microvasculopathy affecting both small arterioles and venules. There was preservation of alveolar architecture, with patchy capillary congestion mild cellular and sclerotic fibrointimal thickening, in places associated with a mild lymphocytic infiltrate. There were no plexiform lesions or thromboemboli, and no evidence of vasculitis, fibrosis, or granulomas.

Following mild progression of symptoms, a further iCPET was performed at a six-month follow-up interval. This again demonstrated no evidence of PAH at rest, but with a higher exercise PVR and mean pulmonary arterial pressure (mPAP) versus cardiac output (CO) slope (>3 mmHg/L/min) confirming development of exercise pulmonary hypertension (ePH) (Fig. 2).^{2,3} Given the patient's

history of Raynaud's phenomenon and swallowing difficulty, signs of ePH, and possibility of early scleroderma-associated pulmonary vasculopathy, the patient was commenced on treatment with mycophenolate mofetil and low-dose prednisolone. The decision to start pulmonary vasodilators was at the time held in reserve due to a lack of benefit in ePH. At an 18-month follow-up assessment, he remains stable with a TLCO > 50% of predicted.

Discussion

Our patient's case is notable for the contemporaneous association between ePH and early histological changes of PAH which, to our knowledge, has not been previously reported. The clinical significance of ePH is still greatly debated, but there has been little progress in defining its pathological correlates. The patient's family history along with the combination of reduced TLCO with normal lung parenchyma on HRCT offered a rare justification to correlate pathology findings of what emerged to be early PAH with serial invasive pulmonary hemodynamics. In this context, a reduced

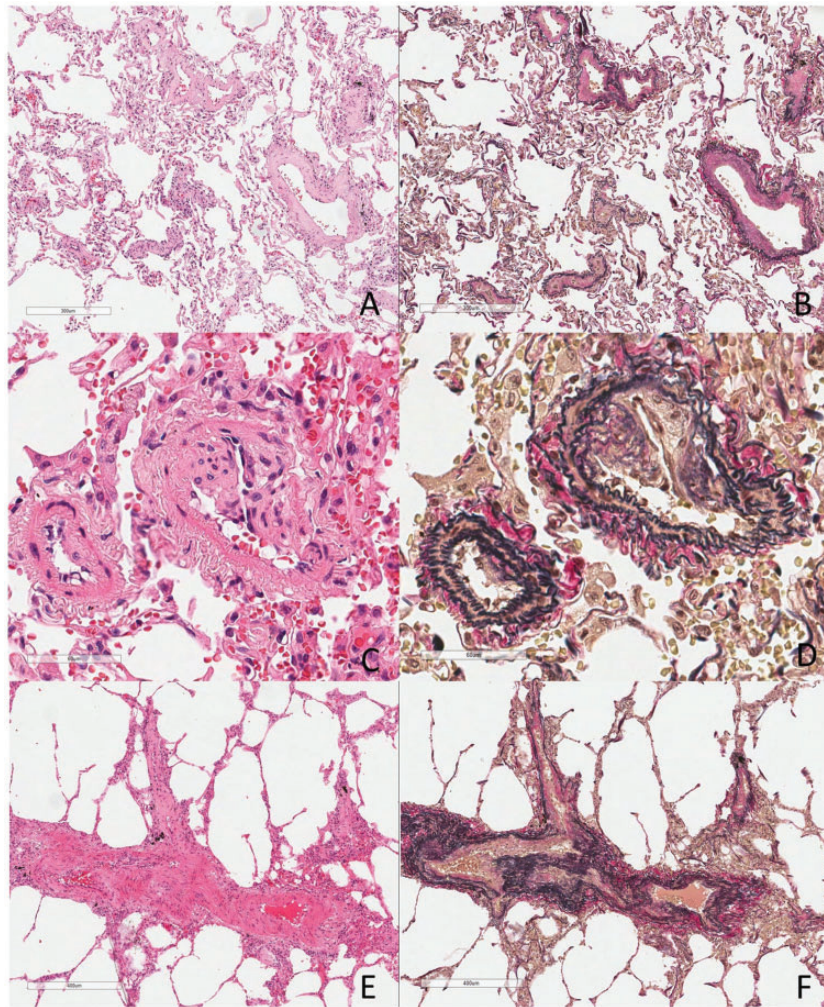


Fig. 1. (a, b) Small parenchymal veins with mild fibrointimal thickening and sclerosis: (a) H&E $\times 100$; (b) EVG $\times 100$. (c, d) Cellular fibrointimal thickening with mild lymphocytic infiltrate in a small arteriole: (a) H&E $\times 400$; (b) EVG $\times 400$). (e, f) Medium-sized vein showing fibrointimal thickening: (a) H&E $\times 100$; (b) EVG $\times 100$. H&E, haematoxylin and eosin; EVG, Elastin van Gieson.

TLCO and peak VO_2 may represent the effects of functional shunting of pulmonary blood away from remodeled vessels. The presence of subtle biopsy changes in both arterioles and venules on lung biopsy were in keeping with the proposed “dual compartment” model of vessel involvement in PAH. However, the “arterialization” of venules in PAH and lack of specific immunohistochemistry make their precise identification difficult.⁴ Nonetheless, there is increasing evidence, especially in inflammatory conditions, of an overlap between arterial and venous remodeling in PAH subtypes.^{5,6}

An abnormal exercise pulmonary vascular response has been described in BMPR2 positive heritable PAH.⁷ However, we identified none of the common PAH-associated mutations in our patient, including the EIF2AK mutation recently identified in patients with idiopathic and heritable PAH who, compared to other PAH patients, were characterized by lower gas transfer and younger age at diagnosis.⁸

As the patient’s mother had died several years earlier, we were also unable to identify inherited mutations. It is possible our patient has early pulmonary veno-occlusive disease and we cannot entirely discount an inflammatory substrate such as scleroderma given the subtle autoimmune clinical features. However, surgical lung biopsy, pursued primarily based on the clinical suspicion of early interstitial lung disease given its known risk in PAH, did not suggest either.

Our case supports proposals from the recent World Symposium in Pulmonary Hypertension 2018 in Nice which include broadening the hemodynamic definition of PAH to include a mPAP of 20–24 mmHg and a PVR ≥ 3 Wood Units, criteria which our patient met at the time of his second iCPET.^{9,10} The close association between ePH, updated hemodynamic criteria of PAH, and early histological changes in PAH support exercise hemodynamic evaluation as an important diagnostic tool in patients harboring increased familial risk of PAH.

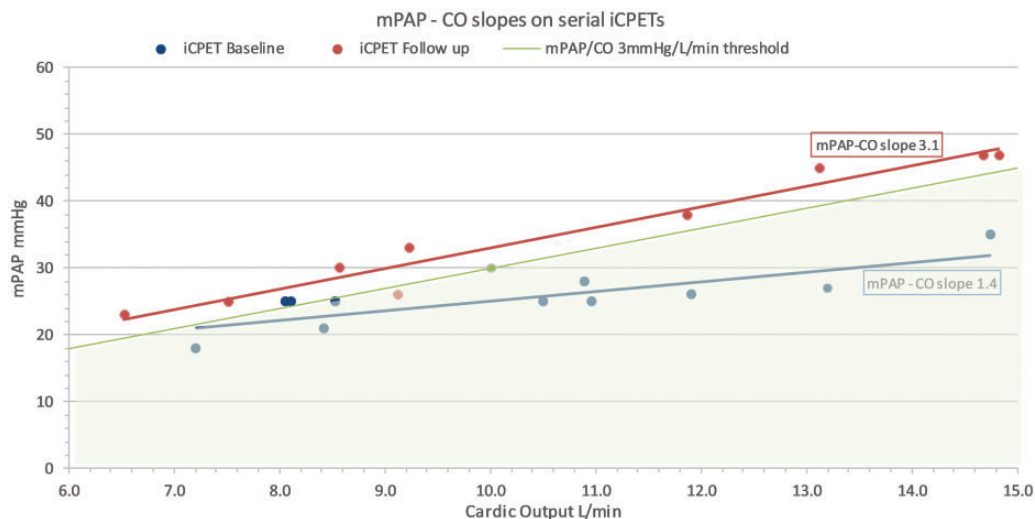


Fig. 2. Mean pulmonary arterial pressure (mPAP) indexed to CO (L/min) measured on invasive cardiopulmonary exercise testing (iCPET) taken at baseline and 6 months. mPAP - CO linear trendlines show progression of gradient from 1.4 mmHg/L/min at baseline to 3.1 mmHg/L/min at follow up. mPAP/CO > 3 mmHg/L/min has been suggested as the threshold for evidence of PH (green shaded area represents normal mPAP/CO < 3 mmHg/L/min). iCPET performed with upright exercise protocol. mPAP measured by Swan-Ganz catheter. CO calculated using Fick method. iCPET trendlines plotted based on linear regression analysis. Threshold line derived from mPAP/CO slope of 3 mmHg/L/min ($y = 3x$).

Conflict of interest

The author(s) declare that there is no conflict of interest.

Funding

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

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References

- Sun X-G, Hansen James E, Oudiz Ronald J, et al. Exercise pathophysiology in patients with primary pulmonary hypertension. *Circulation* 2001; 104: 429–435.
- Oliveira RK, Agarwal M, Tracy JA, et al. Age-related upper limits of normal for maximum upright exercise pulmonary haemodynamics. *Eur Respir J* 2016; 47: 1179–1188.
- Kovacs G, Herve P, Barbera JA, et al. An official European Respiratory Society statement: pulmonary haemodynamics during exercise. *Eur Respir J* 2017; 50: 1700578.
- Tuder RM, Archer SL, Dorfmueller P, et al. Relevant issues in the pathology and pathobiology of pulmonary hypertension. *J Am Coll Cardiol* 2013; 62: D4–12.
- Dorfmueller P, Humbert M, Perros F, et al. Fibrous remodeling of the pulmonary venous system in pulmonary arterial hypertension associated with connective tissue diseases. *Hum Pathol* 2007; 38: 893–902.
- Pietra GG, Edwards WD, Kay JM, et al. Histopathology of primary pulmonary hypertension. A qualitative and quantitative study of pulmonary blood vessels from 58 patients in the National Heart, Lung, and Blood Institute, Primary Pulmonary Hypertension Registry. *Circulation* 1989; 80: 1198–1206.
- Trip P, Vonk-Noordegraaf A and Bogaard HJ. Cardiopulmonary exercise testing reveals onset of disease and response to treatment in a case of heritable pulmonary arterial hypertension. *Pulm Circ* 2012; 2: 387–389.
- Hadinnapola C, Bleda M, Haimel M, et al. Phenotypic characterization of EIF2AK4 mutation carriers in a large cohort of patients diagnosed clinically with pulmonary arterial hypertension. *Circulation* 2017; 136: 2022–2033.
- Simonneau G, Montani D, Celermajer DS, et al. Haemodynamic definitions and updated clinical classification of pulmonary hypertension. *Eur Respir J* 2019; 53: 1801913.
- Humbert M, Guignabert C, Bonnet S, et al. Pathology and pathobiology of pulmonary hypertension: state of the art and research perspectives. *Eur Respir J* 2019; 53: 1801887.