Impairment of skeletal muscle oxygen extraction and cardiac output are matched in precapillary pulmonary hypertension

To the Editor:

Pulmonary arterial hypertension (PAH) is characterised by pathological pulmonary vascular remodelling and increased resistance leading to right heart failure and death [1]. It is thought that exercise intolerance in PAH arises from an impairment in oxygen transport and delivery, driven by a reduced stroke volume [2].

Compared with healthy controls, skeletal and respiratory muscle in patients with PAH have been shown to have a reduced type I/type II muscle fibre ratio, abnormalities in mitochondrial structure and function, increased oxidative stress and impaired microcirculation [3]. These structural changes are accompanied by functional abnormalities including a reduction in inspiratory muscle strength, forearm muscle strength, quadriceps muscle strength and muscle mass [3]. Patients with mitochondrial and hereditary myopathies are known to have a reduced systemic oxygen extraction ratio (SER), manifesting as raised venous oxygen saturations (S_{vO_2}) [4, 5], lower peak arteriovenous oxygen difference [6] and a smaller increase in deoxygenated haemoglobin and myoglobin during exercise [7]. Given the abnormalities of skeletal muscle in PAH patients, it has been suggested these may cause a similar oxygen extraction impairment to that seen in primary myopathies and be an additional cause of exercise limitation in PAH [8].

In this study we test the hypothesis that there is an impairment of oxygen extraction in the peripheral muscles on exercise, which exceeds the reduction in oxygen delivery.

Prospective data were collected in patients who were referred to a national pulmonary hypertension tertiary referral centre between 2009 and 2013. All patients were pulmonary vasodilator-treatment naïve. Patients were eligible if they were able to give written informed consent, had no musculoskeletal or neurological limitation to exercise, and had resting haemodynamic measurements at right heart catheterisation (RHC) diagnostic of precapillary pulmonary hypertension by established criteria [9].

Cardiopulmonary exercise test (CPET) was undertaken on an upright cycle ergometer 2 days prior to RHC. During RHC, haemodynamic measurements were taken at rest and subjects whose resting measurements were in keeping with a diagnosis of precapillary pulmonary hypertension proceeded with exercise. An electromagnetically braked cycle ergometer was attached to the catheterisation table. Resting haemodynamic measurements were repeated after 5 min rest in this position. Exercise was performed in the supine position at 50% of the work rate achieved during the erect CPET and haemodynamics and mixed venous oxygen saturations were measured after 5 min, whilst at end exercise.

Baseline data are presented as mean±SD unless otherwise stated. Comparison between measurements at rest and exercise was performed using a paired t-test. Correlation for parametric data was performed with Pearson's correlation coefficient. Statistical analysis was performed using GraphPad Prism 9 (GraphPad software, San Diego, CA, USA). A p-value of <0.05 was considered significant.

The SER was calculated as $(S_{aO_2}-S_{vO_2})/S_{aO_2}$ where S_{aO_2} is the arterial oxygen saturation and $S_{aO_2}-S_{vO_2}$ is the arteriovenous oxygen saturation difference. Arterial oxygen content (C_{aO_2}) is calculated as $(Hb \times 0.136) \times (S_{aO_2}/100)+(P_{aO_2} \times 0.023)$ where Hb is haemoglobin concentration ($g \cdot L^{-1}$) and P_{aO_2} is the partial pressure of arterial oxygen (kPa). Oxygen delivery to tissues is calculated as $C_{aO_2} \times CO$ where CO is
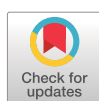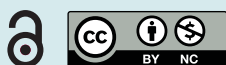
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In precapillary pulmonary hypertension, exercising muscles extract oxygen to a similar level seen in healthy individuals. Exercise limitation is a result of impaired oxygen delivery, which is matched to any impairment in skeletal muscle oxygen extraction. https://bit.ly/3hQUY8m

the cardiac output (L·min^{-1}). Oxygen consumption (V'_{O_2}) is therefore calculated with the Fick equation as $CO \times (C_{aO_2} - C_{vO_2})$ where C_{vO_2} is the venous oxygen content. Pulse oximetry (S_{pO_2}) was used as a surrogate measure of S_{aO_2} in order to minimise the requirement for further invasive procedures.

16 patients were enrolled in the study; nine patients were diagnosed with idiopathic PAH and seven patients with chronic thromboembolic pulmonary hypertension. The mean age was 54 years. Resting and exercise measurements during RHC are presented in table 1. Mean mixed venous saturations (S_{vO_2}) fell from 62±8% at rest to 23±6.8% at peak exercise, with the lowest recorded reading of 16%. The mean SER was 0.75. A low peak exercise S_{vO_2} was strongly correlated with a lower resting S_{vO_2} (r=0.68, p<0.05).

This study demonstrates that in patients with precapillary pulmonary hypertension, mixed venous oxygen saturations fall markedly upon exercise. During RHC, exercise led to a fall in mean mixed venous saturations to 23% and venous partial pressure of oxygen (P_{O_2}) fell to 2.4 kPa. Whilst this study did not have a comparator group, this level of peak exercise mixed venous P_{O_2} is similar to that seen in healthy individuals (2.9 kPa) [10] and lower than that seen in patients with primary myopathy (5.5 kPa) [5]. Furthermore, the mean SER was 0.75 at peak exercise, which is in keeping with results from healthy individuals (0.72), trained individuals (0.78) (as derived from maximal exercise data) [10] and patients with heart failure with reduced ejection fraction (0.74) [8].

These results are in contrast to a retrospective review of CPETs among patients with PAH, heart failure with preserved ejection fraction and heart failure with reduced ejection fraction, which found PAH patients had a reduced SER (0.62) [8]. However, the PAH group was heterogenous in that it included patients with a normal mean pulmonary artery pressure (mPAP) at rest who developed an abnormal mPAP on exercise. Furthermore, it included PAH patients with a raised CO, affecting the linearity of the SER calculated [11].

The data shown in our study would suggest that, although there are structural and functional abnormalities of skeletal muscle in patients with precapillary PH, any resulting impairment of oxygen extraction is matched to the reduction in oxygen delivery caused by impaired cardiac function. As a consequence, the fall seen in S_{vO_2} during exercise is similar to that seen in normal individuals. This concept is well described by WAGNER [12], with peak V'_{O_2} limited by the concentration of inspired oxygen, the convection of oxygen to capillaries and the diffusion of oxygen across to the muscle bed. The oxygen content of blood returning from the muscles depends on the balance of these processes.

One major implication of our results is in the application of exercise training to this patient group. To maximise the benefit of peripheral muscle reconditioning, we would first need to improve oxygen delivery with appropriate disease-targeted therapy so that the balance between the two processes of oxygen delivery and extraction remains matched and optimised.

There are limitations to this study. There was a lack of a within-study comparator group. Inevitably, blood sampled from the pulmonary artery contained blood resulting from exercising and non-exercising muscles.

TABLE 1 Pulmonary haemodynamics at rest and exercise during right heart catheterisation					
	Rest	Exercise	Mean difference	p-value	Median ratio of peak exercise: resting measurements
Pulmonary artery systolic pressure (mmHg)	81±17	126±29	44±20.7	<0.001	1.49
Pulmonary artery diastolic pressure (mmHg)	30±11	42±8	13±7.2	<0.001	1.39
mPAP (mmHg)	50±12	77±13	27±10.4	<0.001	1.58
PAWP (mmHg)	5.8±2	9.3±3	3.1±2.3	0.001	1.5
Cardiac output (L·min^{-1})	3.9±1.1	6.3±2.5	2.4±1.8	<0.001	1.53
PVR (wood units)	11.4±5.5	11.6±4.4	0.55±2.6	0.48	
Heart rate (beats·min^{-1})	79±15	124±17	45±17.9	<0.001	1.63
Stroke volume (mL)	52±19	56±26	2.1±10.1	0.45	1.00
S_{pO_2} (%)	94±3.6	89±8.2	−5.0±7.1	0.03	
S_{vO_2} (%)	62±8	23±6.8	−38.3±6.5	<0.001	
Venous P_{O_2} (kPa)	4.3±0.4	2.4±0.3	−1.9±0.4	<0.001	

Data are presented as mean±SD, unless otherwise stated. mPAP: mean pulmonary artery pressure; PAWP: pulmonary artery wedge pressure; PVR: pulmonary vascular resistance; S_{pO_2}: oxygen saturation measured by pulse oximetry; S_{vO_2}: mixed venous saturations, P_{O_2}: partial pressure of oxygen.

However, this would have caused an underestimate of oxygen extraction. The exercise performed during the RHC used a steady state protocol which may have not reproduced the peak exercise state at end exercise. Again, this would have led to an underestimate of oxygen extraction. Finally, a surrogate marker for S_{aO_2} was used in order to minimise participants' exposure to invasive tests, which may have led to a slight overestimation of S_{aO_2} [13].

This study shows that exercise limitation in pulmonary hypertension is primarily an impairment of oxygen delivery, as a result of a reduced CO. In precapillary pulmonary hypertension, exercising muscles extract oxygen to a similar level seen in healthy individuals, suggesting that any impairment of skeletal muscle oxygen extraction, as inferred from pathological changes in muscle biopsy specimens, is matched to an impaired oxygen delivery.

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