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RESEARCH LETTER

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The impact of gas transfer on responses to exercise training in patients with pulmonary hypertension

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Abstract

Exercise training is recommended for pulmonary hypertension (PH). Post hoc analysis of the PH and Home-Based (PHAHB) trial stratified patients into two groups based on median diffusing capacity of the lungs for carbon monoxide (DLCO). Patients with higher DLCO had a greater improvement in physical activity performance in response to exercise training, compared to those with lower DLCO. DLCO may be an important consideration in prescribing exercise in PH.

KEYWORDS

DLCO, exercise training program, outcome, pulmonary hypertension

INTRODUCTION

Pulmonary Hypertension (PH) manifests as a chronic and progressive condition characterized by elevated resting mean pulmonary arterial pressure, leading to substantial morbidity and reduced life expectancy. Its classification into five groups is predicated upon distinct pathophysiological mechanisms, clinical features, and treatment responses.[1]

The pathophysiology of pulmonary arterial hypertension (PAH) is multifaceted, encompassing pulmonary vasoconstriction and vascular remodeling characterized by cellular proliferation across the pulmonary artery layers, plexogenic lesions, and in situ thrombosis. These changes elevate pulmonary vascular resistance, increasing right ventricular (RV) afterload, potentially impairing gas exchange, leading to significant exercise limitations, and deteriorating quality of life (QoL).[1]

Diffusion capacity of the lung for carbon monoxide (DLCO) serves as a measure of carbon monoxide conductance from the alveoli, across the alveolar capillary membrane into circulating red blood cells. DLCO is directly proportional to the alveolar surface area and the pulmonary capillary blood volume but inversely proportional to the alveolar capillary membrane thickness.[2,3] In PAH, reduced DLCO often correlates with mortality risk.[4,5] This is purportedly stemming from increased alveolar capillary membrane thickness due to fibroproliferative processes and decreased pulmonary capillary blood volume. As a result this is associated with elevated pulmonary vascular resistance, local thrombosis, and reduced cardiac output.[6]

International guidelines support exercise training for PAH patients to enhance exercise capacity and QoL, as it has been shown to improve peak oxygen consumption and cardiac output.[7] Exercise promotes alveolar recruitment, increasing alveolar surface area, expanding capillary blood volume through capillary distension, and reducing alveolar capillary membrane thickness.[8] Furthermore, regular exercise may also result in physiological hypertrophy and proliferation of skeletal and cardiac muscles, along with angiogenesis and mitochondrial remodeling, augmenting adenosine triphosphate generation for more efficient muscle contraction.[9]

The authors recently demonstrated the safety, feasibility, and efficacy of a remotely-administered PH and Home-Based (PHAHB) exercise program.[10,11] Subsequently, we performed an in-depth post hoc exploratory analysis and evaluated data from the 10-week multicomponent exercise intervention in stable patients with PH. The aim of this study was to compare the changes in physical activity levels and exercise workload in response to the exercise intervention, between those with a high and low baseline DLCO.

We hypothesize that patients with PH who have a higher baseline DLCO will have a greater capacity for physical activity improvement compared to those with a lower DLCO following participation in an exercise training program.

METHODS

The methods of the PHAHB trial have previously been described in detail.[10] Briefly, participants completed a 10-week patient-centered, home-based physical activity intervention. The multicomponent physical activity intervention included three induction sessions, five health coaching sessions and an individualized exercise training program. Eligibility criteria included adults aged ≥ 18 years with a formal diagnosis of PH Groups 1 and 4 by right heart catheterization with mean pulmonary arterial pressure ≥ 25 mmHg and resting pulmonary capillary wedge pressure ≤ 15 mmHg, on optimized conventional PH therapy and clinically stable with no change in medication in the 2 months prior to consent. Outcomes were assessed remotely at baseline and after the 10-week intervention (post-training) and included exercise capacity (6-min walk test [6MWT]), physical activity levels and sedentary behavior (using an ActivPAL3 micro accelerometer), fatigue (fatigue severity scale) and QoL (Emphasis 10).[10] Ethical approval had been obtained from the Mater Misericordiae University Hospital Institutional Review Board REF:1/378/2032 and the study was registered with the ISRCTN registry (ISRCTN83783446).

For this post hoc analysis, patients were divided into two groups based on the median baseline DLCO of the group which was a value of 61% of predicted. DLCO was measured by the Modified Krogh's single breath method. The predicted DLCO was calculated based on Global Lung Initiative reference values and was corrected for hemoglobin.[12] Anthropometric data such as height, weight, age and gender were inputted into the system before the test and were included in the calculation of predicted DLCO. The primary end points compared were changes in exercise capacity (6MWT), physical activity levels (steps) and resistance exercise workload (total repetitions) between baseline and postintervention measures. Additional end points were also analysis such as 30 s sit to stand test, exercise training load and QoL. Statistical analysis was performed using statistical package for the social sciences v27. Comparisons between two groups of continuous data was made using the *t*-test for parametric and Mann−Whitney *U*- test/Wilcoxon signed rank test for nonparametric data. The Chi-squared test or Fishers exact test (for small numbers) were used to compare categorical variables between the two groups. The significant level was set at α value of $p < 0.05$.

RESULTS

A total of 19 patients (79% female) participated in the 10-week home-based multicomponent exercise intervention. Selected overall baseline characteristics (mean ± SD) were age 48 ± 15 y; body mass index, 29 ± 6 kg/m^2; DLCO, 64 ± 21%; and mean pulmonary arterial pressure, 44 ± 15 mmHg. The intervention was deemed safe as no adverse events were reported. Overall, there was a significant improvement in functional capacity, physical activity, exercise self-efficacy and QoL, between baseline and post-training. Adherence to exercise program was high, as mean self-reported adherence to the individually prescribed/agreed resistance, respiratory and aerobic training was 91%, 94%, and 95%, respectively. There was a significant increase in volume of aerobic and resistance training between block 1 (2−4 weeks) and block 3 (8−10 weeks). Results have been previously published.[11]

Eight patients had DLCO of >61% and eleven had ≤61%. The baseline characteristics of both groups were comparable including 6MWD and are presented (Table 1). Patients with higher DLCO had a significantly greater difference in improvement in 6-min walk distance ($p = 0.001$; 90 vs. 56 m), 30 s sit-to-stand test ($p = 0.001$; 10 vs. 7 reps) daily step count ($p = 0.032$; 3104 vs. 1745 steps) and the cambridge pulmonary

TABLE 1 Baseline characteristics of participants based on median DLCO of 61%.

Characteristic	Below median DLCO ($N = 11$)	Above median DLCO ($N = 8$)	p Value
Age (y)	52.36 ± 16.31	43.13 ± 11.70	0.191
Female (%)	8 (72.8%)	7 (87.5%)	0.603
Height	166.91 ± 12.47	165.65 ± 8.30	0.807
BMI (kg/m^2)	28.59 ± 7.81	28.60 ± 4.54	0.998
Duration of diagnosis (y)	7.18 ± 4.31	5.00 ± 4.50	0.300
Diagnosis (PAH/CTEPH)	9 (81.8%)/ 2 (18.2%)	7 (87.5%)/ 1 (12.5%)	0.315
NYHA functional class			
1	1 (9.1%)	2 (25.0%)	
2	8 (72.7%)	3 (37.5%)	0.371
3	2 (18.2%)	3 (37.5%)	
Comorbidities			
Yes	11 (100%)	7 (87.5%)	0.421
No	0	1 (12.5%)	
PH medication			
None	1 (9.1%)	1 (12.5%)	
Monotherapy	0	2 (25.0%)	0.156
Double combination	6 (54.5%)	1 (12.5%)	
Triple combination	4 (36.4%)	4 (50.0%)	
Blood profile			
Hb (g/dL)	13.63 ± 1.98	14.48 ± 1.82	0.355
BNP (ng/L)	127.09 ± 134.78	154.38 ± 202.46	0.728
eGFR			
>60	8 (72.7%)	5 (62.5%)	0.506
30−60	3 (27.3%)	3 (37.5%)	0.506
6MWD (m)	376.14 ± 65.68	386.13 ± 69.86	0.754
Borg dyspnoea scale[a]	3.36 ± 1.69	2.50 ± 2.07	0.331
Emphasis 10	27.27 ± 12.10	24.88 ± 11.91	0.673
Resting SpO_2	94.70 ± 1.83	96.38 ± 2.26	0.101
Fatigue severity score	46.36 ± 17.97	42.88 ± 18.30	0.684
Resting heart rate (bpm)	76.27 ± 8.61	84.00 ± 17.20	0.213
MAP (mmHg)	88.76 ± 10.54	90.08 ± 6.80	0.760
DLCO (%)	49.55 ± 12.02	83.41 ± 13.59	0.001
RAP (mmHg)	4.63 ± 3.07	5.14 ± 1.86	0.705
mPAP (mmHg)	43.00 ± 12.39	44.38 ± 18.03	0.846
PCWP (mmHg)	9.90 ± 6.64	7.75 ± 3.92	0.431
CO (L/min)	5.35 1.57	4.62 ± 1.14	0.299
PVR (WU)	6.74 ± 3.75	9.43 ± 4.84	0.216

Note: Continuous variables are presented as mean ± standard deviation. Categorical variables are *n* (%).

Abbreviations: BMI, body mass index; BNP, brain natriuretic peptide; CO, cardiac output; CTEPH, chronic thromboembolic pulmonary; DLCO, diffusing capacity of the lung for carbon monoxide; eGFR, estimated glomerular filtration Rate; Hb, Hemoglobin; MAP, mean arterial pressure; mPAP, mean pulmonary arterial pressure; NYHA FC, New York Heart Association Functional Classification; PAH, pulmonary arterial hypertension; PCWP, pulmonary capillary wedge pressure; PH, pulmonary hypertension; PVR, pulmonary vascular resistance; RAP, right arterial pressure; Spo2, peripheral oxygen saturation; 6MWD, 6 min Walk Distance.

[a]After 6 min walk test.

hypertension outcome review (CAMPHOR) symptoms score ($p = 0.031$; −6 vs. −2). Patients with higher DLCO had a greater resistance training workload, which was the number of total repetitions completed in block 1 compared to block 3 of the intervention, ($p = 0.009$; 56 vs. 28 reps) than patients with lower DLCO following the exercise intervention. Further post hoc analysis of the PHAHB results stratified by DLCO and presented as the change difference from baseline to postintervention are presented in Table 2 (Supporting Information File).

DISCUSSION

This post hoc analysis explores the potential of DLCO as a predictive metric, for assessing the response to exercise training, in patients with PH. Our findings highlight that exercise training potential may differ depending on baseline DLCO. Specifically, participants with a higher DLCO at baseline had a greater increase in exercise capacity, intensity and daily physical activity levels compared to those with lower DLCO following the PHAHB exercise intervention.

All participants achieved significant improvements in outcomes, irrespective of their baseline DLCO levels, which is a positive finding given that it is recognized that patients with low DLCO have poorer survival.[13,14] However, we found that participants with a higher DLCO at baseline obtained a greater training response and achieved a higher workload over the same period of time compared to those with a lower baseline DLCO. The

observed magnitude of difference in improvement in exercise outcomes among PH patients based on baseline DLCO may in part be explained by a multifaceted consideration of underlying physiological factors.

Individuals with the higher baseline DLCO are likely to possess a more structurally normal alveolar-capillary membrane and a higher pulmonary capillary blood volume, thereby facilitating enhanced oxygen transfer during physical exertion. Insights from previous studies by Ehlken et al.[7] and Spruit et al.[15] highlight potential mechanisms associated with exercise-induced improvements in pulmonary hemodynamic, cardiac output, skeletal muscle oxidative capacity, and indeed capillary density in PH patients. The interplay of these factors may differ based on the baseline DLCO, contributing to the observed variations in exercise response.

Recognizing the potential impact of baseline DLCO could be of clinical relevance in assisting clinicians and exercise professionals in the personalization of exercise prescriptions. Tailoring exercise programs based on an individual's DLCO level may assit in designing interventions that are better aligned with the specific physiological characteristics of each patient in order to optimize the improvements in exercise capacity.

Baseline DLCO may serve as a useful marker for risk stratification in individuals with PH undergoing exercise training. Patients with lower DLCO may benefit from a more gradual progression in exercise intensity to ensure enjoyment and long-term adherence. In contrast, patients with higher baseline DLCO may tolerate and benefit from higher exercise intensities. Adjusting intensity and session frequency based on DLCO could contribute to achieving optimal training effects, promote exercise adherence and long-term benefits. Integrating DLCO assessment into program design aligns with precision medicine, enhancing treatment efficacy and improving functional capacity and QoL for PH patients.

The small sample size along with the post-hoc approach may limit the confirmatory power of the findings. Future research should aim to confirm these results across different settings and exercise program designs. Nevertheless, baseline DLCO may be used to more effectively design a exercise training programs for patients with PH. This approach aligns with the broader paradigm of personalized medicine, ensuring that interventions are tailored to individual patient characteristics for optimal outcomes.

AUTHOR CONTRIBUTIONS

Ciara McCormack and Syed Rehan Quadery conceived the idea for the study. Ciara McCormack and Syed Rehan Quadery completed the study design. Ciara McCormack acquired the data. Ciara McCormack and Syed Rehan Quadery analyzed the data. All authors interpreted the data. Ciara McCormack and Syed Rehan Quadery drafted the manuscript. All authors read and revised the content critically, approved the final manuscript, and are accountable for its content.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

ETHICS STATEMENT

Ethical approval for this study was granted by Mater Misericordiae University Hospital Institutional Review Board Ref 1/378/2032.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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