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Cardiorespiratory responses between one-legged and two-legged cycling

in patients with idiopathic pulmonary fibrosis.

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INTRODUCTION

International guidelines recommend exercise training within pulmonary rehabilitation (PR) for adults with idiopathic pulmonary fibrosis (IPF) [1]. However, the magnitude of benefits of PR in IPF may be less than in COPD [2] and are not sustained [3]. Partitioned muscle training has been investigated for other chronic diseases where a central limitation to exercise dominates [4-6]. One-legged cycling partitions the targeted exercising muscle thereby reducing the total ventilatory burden for the same muscle specific power. In ventilatory limited patients with COPD, partitioned training increases cardiorespiratory fitness [4, 7] measured by peak oxygen uptake ($\dot{V}O_{2pk}$) greater than that achieved with conventional two-legged cycle training.

We hypothesised that patients with IPF would increase their tolerable exercise time of a leg exercising alone (one-legged cycling) compared to two-legged cycling so that the total work would be doubled (the primary outcome). We also aimed to quantify peripheral muscle aerobic capacity relative to the central capacity by determining the ratio of $\dot{V}O_{2pk}$ achieved during one- versus two-legged cycling.

MATERIALS AND METHODS

Participants

Patients with IPF [1] and an MRC dyspnoea score ≥2 were recruited from a tertiary referral centre between Jan – May 2015. Exclusion criteria included the requirement of supplementary oxygen at rest, significant other lung diseases or co-morbidities contributing to breathlessness and conditions that precluded cycling. The study was approved by Yorkshire and The Humber – South Yorkshire Research and Ethics Committee (14/YH/1152). Written informed consent was obtained from all participants before starting the study.

Study Design

We used a prospective non-randomized crossover design. Participants completed four exercise tests [8], separated by at least 48 hours, on an electrically braked ergometer [9] (modified Corival Recumbent, LODE BV) with 'fixed' wheel thereby preserving a natural cycling pattern when cycling with one leg [5]. The inactive leg rested a safe distance from the free rotating pedal.

Ventilatory parameters were measured breath-by-breath using a calibrated metabolic system (Quark-CPET, COSMED Ltd) connected to a mask (V2 Mask, Hans Rudolph Inc.). Electrocardiography and pulse oximetry were monitored continuously. Leg effort and breathlessness scores were assessed at 2 min intervals using the Borg and modified Borg scales [10], respectively.

Two incremental power tests (IPT) were performed: first, two-legged cycling (2L-IPT) using an individualized ramp protocol aiming for a duration between 8 and 12 minutes; second, one-legged cycling (1L-IPT) using the same ramp used for the 2L-IPT.

Two constant power tests (CPT), that simulated high intensity aerobic training sessions, were performed. The two-legged test (2L-CPT) used 70% of the peak power achieved on the individual's 2L-IPT expecting intolerance would occur between 3 and 15 min. If the 2L-CPT was >15 min, a second 2L-CPT was performed at an appropriately adjusted higher intensity. The 1L-CPT was performed at half the power of the acceptable 2L-CPT. A maximum duration of 1 hr was decided a priori.

Statistical analysis was performed using SPPS v.22. The normality of the data distribution was tested using the Shapiro-Wilk test. To determine whether there was a significant effect between the conditions of two-legged vs. one legged cycling, paired t-tests were used. To demonstrate a large effect (Cohen's d $\geq$1.0) on the work (kJ) achieved (the primary outcome) between the IL-CPT and the 2L-CPT, a sample of 10 was needed with statistical power of 0.80 and alpha 0.05 using a two-tailed paired t-test.

RESULTS

Fifteen patients were enrolled and 12 patients completed the study (11 male, mean [SD] age=61 [6] y, FVC=72 [20] %predicted, TL_{CO}=46 [11] %predicted, resting SpO_2=98 [1] %). The majority had a GAP-IPF severity score of 'Stage II'; two were prescribed pirfenidone (at the time of recruitment pirfenidone had only recently been licensed in the UK and was the only anti-fibrotic agent available) and one oral corticosteroids. Three patients did not complete the protocol for reasons unrelated to the study.

A ventilatory limitation to 2L-IPT was observed in 10 participants. One-legged cycling was well tolerated by all participants. A comparison between the two IPT's is shown in Table 1. Participants achieved 84% of 2L-IPT $\dot{V}O_{2pk}$ during the IL-IPT with similar cardiorespiratory responses but less oxygen desaturation throughout IL-IPT.

Three initial 2L-CPTs were greater than 15 min and repeated at a higher power. A comparison between the 2L-CPT and 1L-CPT is shown in Table 1. For the primary outcome, there was a large effect (Cohen's d = 1.3) as almost twice the total work (difference = 26.7 [5.4 to 48.1] kJ) was performed during the 1L-CPT (53.4 [48.3] kJ) compared to the 2L-CPT (26.7 [20.6] kJ). The increased endurance between the 1L-CPT compared to 2L-CPT (difference = 16.7 [8.3 to 25.0] min) was achieved with evidence of reduced central cardiopulmonary demand (Figure 1) as well as less breathlessness and increased leg effort compared with 2LCPT (Figure 2).

DISCUSSION

Patients with IPF demonstrate significant muscle reserve relative to their central ventilatory capacity evidenced by the high percentage of 2L-IPT $\dot{V}O_{2pk}$ achieved on the 1L-IPT. One-legged cycling was well-tolerated and, at the same muscle-specific power as required during two-legged cycling, enabled patients with IPF to achieve double the work on an exercise test that simulated high intensity aerobic training session. In practice, one would confine exercise to 20 to 30 min (10 to 15 min each leg) by increasing the power thereby optimizing the training stimulus.

Work was increased on a 1L-CPT by reducing the total ventilatory burden imposed by conventional two-legged cycling; patients cycled for almost four times the duration with less desaturation throughout and a slower progression to similar breathlessness at the end of the exercise. Therefore one-legged cycling shows promise to be an effective training strategy for patients with IPF. Our observations in patients with IPF are similar to observations in patients with COPD that led to positive efficacy and effectiveness trials of one legged cycling in that population [4,7,9].

Many patients with IPF stop exercise due to severe oxygen desaturation despite the provision of supplemental oxygen. By limiting aerobic exercise to one-legged cycling, desaturation is lessened by reducing total oxygen extraction and substantially decreasing the pulmonary gas exchange requirements to maintain arterial oxygen. It is reasonable to speculate that less supplemental oxygen would be needed during training.

The results may not be directly extrapolated to patients requiring supplementary oxygen at rest although there is a need to improve the exercise training component of PR offered to this group. We excluded these patients due to technical challenge of accurately measuring $\dot{V}O_2$ inspiring a hyperoxic mixture and chose to perform a 'proof of concept' study supported by physiological measures in all participants. Lastly, we acknowledge the potential for a positive effect of performing three short exercise tests before the IL-CPT but this effect, if any, would likely only contribute a relatively small part to the large effect observed.

In conclusion, one-legged cycling increases muscle specific work without increasing breathlessness in patients with IPF. Our study provides justification for a randomised controlled trial of aerobic exercise training using one- compared to two-legged cycling in patients with IPF with the aim of improving the quality of PR.

CONTRIBUTING STATEMENTS.

Mr Thomas Dolmage and Dr Tom Reilly contributed equally to this manuscript. Dr Rachael Evans designed the study supported by Mr Thomas Dolmage. Dr Tom Reilly, Dr Sally Majd, Dr Bhavesh Popat, Dr Neil Greening, Dr Felix Woodhead, Dr Sanjay Agarwal were all involved in data collection. All co-authors contributed to data interpretation and approved the final manuscript. Mr Thomas Dolmage, Dr Tom Reilly and Dr Rachael Evans jointly drafted the initial manuscript.

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Table 1. Comparison of the peak values achieved on the incremental and constant power tests between one- and two-legged cycling.

	Incremental power tests		**Constant power tests**	
	2L-IPT	1L-IPT	2L-CP	1L-CP
Power, W	93 ± 32	65 ± 26†	69 ± 24	34 ± 12
Duration, min	NA	NA	6.1 ± 3.7	22.7 ± 15.0†
Work, kJ	NA	NA	26.7 ± 20.6	53.4 ± 48.3†
$\dot{V}O_2$, ml/min/kg	16.7 ± 3.3	14.0 ± 3.1†	17.0 ± 3.3	14.2 ± 3.3†
$\dot{V}O_2$, %predicted	74 ± 21	NA	NA	NA
$\dot{V}CO_2$, ml/min	1507 ± 375	1267 ± 400†	1489 ± 389	1139 ± 323†
RER	1.02 ± 0.10	1.03 ± 0.11	1.03 ± 0.11	1.08 ± 0.29
$\dot{V}E$, l/min	68.6 ± 18.1	59.3 ± 18.6†	70.0 ± 23.0	61.6 ± 28.1†
%MMV	92 ± 14	80 ± 17	NA	NA
f_b, breaths/min	49 ± 8	47 ± 10	49 ± 10	51 ± 14
Heart rate, beats/min	119 ± 22	107 ± 23†	118 ± 20	108 ± 20†
End S_pO_2, %	90 ± 6	92 ± 7	87 ± 7	89 ± 6†
Nadir S_pO_2, %	88 ± 7	92 ± 6†	87 ± 7	89 ± 6†
Dyspnoea, 0 – 10*	5 [3 - 7]	4 [4 – 5]	6 [5 - 7]	5 [4 - 7]
LE, 6 – 20*	17 [15 - 18]	14 [13 - 15]	15 [15 - 17]	17 [15 - 19]

Mean ± SD unless *Median [IQR]. N/A: not applicable, $\dot{V}O_2$: oxygen uptake, fb: frequency of breathing, $\dot{V}E$: minute ventilation, $\dot{V}CO_2$: carbon dioxide output, RER: respiratory exchange ratio, HR: heart rate, LE: leg effort, SpO_2: oxygen saturation via pulse oximetry. [†]significant difference between 1- and 2-legged cycling conditions ($p<0.05$).

LEGENDS TO FIGURE

Figure 1: the physiological response to two- (open circles) and one-legged (closed circles) constant power exercise tests. Values are mean and standard error.

Figure 2: the relationship between leg effort and breathlessness during constant power exercise when cycling with two legs (open circles) compared to one leg (closed circles). Insets show leg effort (top left) and breathlessness (bottom right) as a function of time. Values are mean and standard error.