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Exercise induced skeletal muscle metabolic stress is reduced after pulmonary rehabilitation in COPD

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Summary
In COPD, skeletal muscle ATP resynthesis may be insufficient to meet demand during exercise due to excessive anaerobic and reduced oxidative (mitochondrial) energy production, leading to metabolic stress. We investigated the effect of outpatient pulmonary rehabilitation (PR) on the metabolic response (measured by exercise-induced accumulation of plasma ammonia) and determined whether this response predicted functional improvement following PR.

25 subjects with stable COPD [mean (SD) age 67 (8)years and FEV_1 47 (18)% predicted] performed maximal cycling ergometry before and after PR. Plasma ammonia was measured at rest, during exercise and 2 min post-exercise.

Following PR, there were significant increases in peak cycle WR and ISWT performance (Mean (SEM) changes 13.1 (2.0) W and 93 (15) m respectively, $p < 0.001$). Mean (SEM) rise in plasma ammonia was reduced at peak (Pre vs Post-PR: 29.0 (4.5) vs 20.2 (2.5) μmol/l, $p < 0.05$) and isotime (Pre vs Post-PR: 29.0 (4.5) vs 10.6 (1.7) μmol/l, $p < 0.001$) exercise. Improvements in exercise performance after PR were similar among subgroups who did versus those who did not show a rise in ammonia at baseline.

The results suggest that muscle cellular energy production was better matched to the demands of exercise following PR. We conclude that a pragmatic outpatient PR programme involving high intensity walking exercise results in significant adaptation of the skeletal muscle metabolic response with a reduction in exercise-related metabolic stress. However, the outcome of PR could not be predicted from baseline metabolic response.

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Introduction

Peripheral skeletal muscle dysfunction contributes to exercise limitation in patients with COPD.[1] Reduced capacity for oxidative metabolism and excessive anaerobic metabolism occurs during whole body exercise in COPD despite the low absolute workloads these disabled individuals can achieve.[2,3] We have previously demonstrated in COPD patients that this may lead to substantial skeletal muscle adenine nucleotide loss because ATP (adenosine triphosphate) production cannot meet demand.[4] This situation has been termed "metabolic stress" and has been identified as an important cause of fatigue during high intensity exercise in healthy subjects.[5]

Ammonia is released from the skeletal muscles during exercise as a result of the irreversible deamination of AMP to form IMP.[6] Plasma ammonia accumulation is therefore a consequence of adenine nucleotide loss and metabolic stress, and has potential as a biomarker for the skeletal muscle energy response. We recently showed that blood ammonia accumulation occurs during a single bout of high intensity exercise in COPD patients and that this was indicative of muscle adenine nucleotide loss.[7] We have demonstrated that ammonia accumulation occurs in COPD during both walking and cycling exercise.[8] In addition, we have observed a subgroup of patients who did not exhibit a rise in blood ammonia despite performing similar exercise workloads.[7,8] This might be important as the failure to develop metabolic stress during exercise may influence subsequent physiological adaptation to exercise training by moderating the degree of muscle overload.

Pulmonary rehabilitation (PR) is an effective intervention for improving exercise capacity and therefore reducing disability in patients with COPD.[9] Physiological adaptation within the skeletal muscles has been demonstrated in response to PR[3,10] although the gains made depend on the intensity of training.[11] Moreover, the functional benefits that accrue may also be due to behavioural effects such as improving confidence and reducing fear of breathlessness. Whilst this does not diminish the clinical benefits of the intervention, a better understanding of the mechanisms behind the muscle disease and response to PR might allow the components of rehabilitation programmes to be better tailored to individual needs and physiology. For example, pharmacological or nutritional augmentation of rehabilitation would be likely to be more effective in those who demonstrate physiological adaptation.

In this study we aimed to observe prospectively the impact of a pragmatic, semi-supervised walking based outpatient pulmonary rehabilitation programme on the pattern and magnitude of the blood ammonia response to whole body exercise. We hypothesized that rehabilitation would reduce the degree of metabolic stress as measured by blood ammonia accumulation. Our second aim was to determine whether this measure of exercise-induced metabolic stress at baseline predicted the physiological and functional outcome of rehabilitation. We hypothesized that patients not eliciting an ammonia response to exercise would respond less well to pulmonary rehabilitation because of reduced muscle overload in these individuals and therefore adaptation to training would be attenuated.

Methods

Patients referred to the outpatient pulmonary rehabilitation (PR) programme at Glenfield Hospital who met GOLD clinical and spirometric criteria for COPD[12] were consecutively assessed for inclusion in the study. Referral sources were both secondary care specialist respiratory clinics and primary care. Participant's clinical condition and medical therapy were stable prior to commencing PR. Patients were excluded from the programme if considered unsuitable for the exercise component due to musculoskeletal impairment, significant medical conditions such as unstable coronary artery disease or when compliance with PR was not possible. Additional study exclusion criteria were maintenance oral corticosteroids, an established diagnosis of cardiac failure, PR within the last two years or exacerbation requiring hospitalisation within the last 6 weeks. Patients qualifying for home long term oxygen therapy were excluded.

Approval was obtained from the Leicestershire Research Ethics Committee and all participants provided informed written consent.

Study design

This was an observational study of patients participating in the standard 7 week outpatient PR programme at University Hospitals of Leicester NHS Trust.[13] Spirometry was performed to ERS standards (Vitallograph Model R, Buckingham, UK) and predicted values calculated from ERS regression equations.[14] Body mass index (BMI) was calculated from height and weight. Outcome assessments were made prior to commencing, and within 2 weeks of completing PR. Disease specific health status was measured using the Self Reported Chronic Respiratory Diseases Questionnaire (CRQ-SR)[15] (mean clinically important difference for change with PR by 0.5 for each domain). Maximal and sub-maximal field exercise capacity was assessed before and after PR using the incremental (ISWT)[16] and endurance (ESWT) shuttle walk tests respectively.[17] All patients completed a practice ISWT. In the ESWT patients walked at a speed equivalent to 85% of predicted VO_{2max} from ISWT performance.

Pulmonary rehabilitation programme

Patients attended pulmonary rehabilitation at Glenfield-Hospital, University Hospitals of Leicester NHS Trust, twice weekly for a total of 14 sessions over at least 7 weeks. The exercise component consisted of endurance (free walking) and strength training with 1 h supervised exercise in each session. For endurance exercise, patients walked at speed equivalent to 85% peak VO_2 predicted from baseline ISWT performance. Patients were also asked to perform daily home walking exercises. All patients walked at this speed from the first session and walking times were then increased progressively during the course of the programme, with new targets set at each session. Patients also underwent 5 min cycle exercise at each session. Cycle resistance was increased as Borg breathlessness score reduced. Strength training (biceps curls, sit to stand,

pullups and stepups; 3 sets of eight repetitions) was performed at each session. Hand weights started at 1 kg and the weight was increased as perceived exertion fell. Participants were able to rest between the endurance and strength components of the exercise programme. The education component consisted of 1 h each session and covered a range of topics including disease education, medication, diet, energy conservation, breathing control and relaxation.

Laboratory exercise tests

On an initial visit familiarisation tests on a bicycle and treadmill performed. At least 72 h later subjects performed a maximal symptom-limited incremental exercise test on an electrically-braked cycle ergometer. The workload was increased by 10 W every minute using a ramp protocol to determine peak exercise work capacity. Participants cycled at a constant rate of 40–45 rpm and were encouraged to continue cycling at the required rate for as long as possible. Ventilation and gas exchange measurements were made throughout the test using a breath-by-breath computerised system (Zan-680 ErgoTest, Zan Messgeraete GmbH, Germany). Participants were deemed ventilatory limited if ventilation at peak exercise was greater than 90% predicted MVV (calculated as $FEV_1 \times 35$).[18]

Blood analysis

Blood was sampled for ammonia and lactate concentration at 1 min and 2 min of exercise, at peak exercise, and at 2 min following the incremental cycle exercise tests. During the post-PR assessments an extra blood sample was taken at the isotime of peak exercise achieved in the pre-PR tests. Timing of blood sampling was based on previous studies investigating the pattern of exercise ammonia accumulation in COPD.[7] Half an hour prior to the exercise test a 12 g retrograde cannula was inserted into a superficial lower forearm vein and placed inside a hand-warmer, warmed to 50–55 °C. The hand-warmer enables arterialised-venous blood to be collected, which is representative of arterial blood and is therefore not contaminated by ammonia generated by the hand and forearm muscles. The method used has been previously validated and used for plasma ammonia measurements.[19,20] Samples were immediately placed on ice. Whole blood lactate concentrations were measured in duplicate immediately following exercise (YSI 1500 sport L-lactate analyser, YSI Inc, USA). Blood for ammonia was centrifuged immediately following the exercise test, plasma stored at −196 °C in liquid nitrogen, and analysed in duplicate by a validated enzyme assay technique (Sigma–Aldrich Co. Ltd, UK) within 24 h as previously described.[7]

Data analysis

Based on data from our previous study[7] we required 22 patients to complete the study to detect a 15 μmol/l within-group reduction in peak exercise blood ammonia with PR (80% power, $\alpha = 0.05$). This difference represents the upper threshold for the lack of ammonia rise during exercise in our previous study[7] and is also 95% confidence interval for the reproducibility of repeat measures of plasma ammonia at rest in healthy subjects recorded in our laboratory (unpublished data). Subjects continued to be recruited to the study until at least 22 had completed. Subgroups were defined *a priori* by exercise-induced ammonia rise during cycling above (group 1) or below (group 2) 15 μmol/l. The response to rehabilitation was assessed using ISWT and ESWT measurements as continuous variables and categorically, defining a positive response to PR as an increase in ISWT performance greater than 48 m. This has been established as the minimum clinically important difference for this outcome measure.[21] Intra- and inter-group differences were compared using the paired and unpaired Students *t*-tests respectively. Correlations between parameters were calculated using Pearson's correlation (SPSS package version 15.0, SPSS Inc Chicago, USA). Statistical significance was assumed at $p < 0.05$.

Results

Patient characteristics

A total of thirty-five patients were recruited and 25 patients (18/7 male/female, Mean (SD) age: 67 (8) years, FEV_1: 47 (18)% predicted, BMI: 28 (6) Kg/m^2, SaO_2 at rest: 96 (2)%) completed the study. As this was an exploration of the physiological adaptation to training, only completers were analysed. The dropout rate is comparable to recent published PR data from our clinical service.[13,22] No differences between subjects who dropped out and completed PR were identified in baseline demographic variables, field or laboratory exercise performance or ammonia and lactate response to exercise.

The response to pulmonary rehabilitation

Laboratory and field exercise performance increased after PR (Table 1). Health status measured by CRQ-SR increased significantly ($p < 0.001$) in all domains; mean (95%CI) changes Dyspnoea 1.19 (0.68–1.70), Fatigue 0.89 (0.36–1.43), Emotion 0.77 (0.10–1.45), Mastery 0.86 (0.18–1.53).

Metabolic response to exercise

In the whole cohort there was a significant exercise-induced rise in plasma ammonia and blood lactate at baseline. The lactate and ammonia response to exercise before and after PR is shown in Table 2 and Fig. 1. Following PR, exercise-induced ammonia accumulation was reduced at all time points including peak exercise despite subjects achieving higher peak exercise work rates. Exercise-induced lactate accumulation was reduced at 1 and 2 min and at isotime but not at peak exercise or 2 min recovery after PR (Fig. 1). There were no differences between patients who did or did not reach the *a priori* definition of ventilatory limitation (during pre-PR exercise) in the ammonia and lactate responses or in the improvement in exercise capacity following PR.

Table 1 Mean (SD) exercise data from maximal cycling test before and after Pulmonary Rehabilitation.

	Pre-PR Peak Exercise	Post-PR isotime[a]	Post-PR Peak Exercise
Peak workload (W)	56 (21)	—	69 (22)**
VO_2 (ml/kg/min)	15.9 (4.8)	14.2 (4.8)**	17.2 (5.6)*
V_E (L/min)	34.9 (11.8)	31.2 (8.8)*	38.4 (12.6)**
V_E (% MVV)	86 (19)	78 (17)**	95 (19)**
RER	0.96 (0.05)	0.93 (0.04)	0.96 (0.05)
ISWT (m)	287 (128)	—	380 (141)**
ESWT (s)	176 (53)	—	678 (374)**

WR = Work rate; VO_2 = oxygen uptake; V_E = Exercise ventilation; RER = respiratory exchange ratio; MVV = maximum voluntary ventilation (calculated as $FEV_1 \times 35$).
ISWT = Incremental shuttle walk test; ESWT = endurance shuttle walk test.
Comparison between pre-PR and post-PR values: *$p < 0.05$, **$p < 0.01$.
[a] Time point during post-PR exercise test at which peak exercise was reached in pre-PR test.

Ammonia subgroup analysis

Using our predetermined criteria for a significant ammonia response to exercise at baseline, there were 18 subjects in Group 1 (subjects with a significant exercise-induced ammonia response) and 7 in Group 2 (subjects without a significant exercise-induced ammonia response). There was no statistically significant difference between these subgroups in demographics or disease severity at baseline. Exercise performance at baseline was lower in group 2 but this was not statistically significant (Table 3). There was no significant difference between the groups in oxygen saturation at rest or at peak exercise or in the number of subjects deemed ventilatory limited during the initial incremental exercise test.

There was no significant difference between the subgroups in the change in field or laboratory exercise performance after PR. Measurements of plasma ammonia and blood lactate during exercise at baseline and after PR are shown in Table 4 and Fig. 2. In Group 1 ammonia accumulation was lower after PR at all time points (Fig. 2). In group 2 the lack of ammonia response to exercise was unchanged following PR, although there was a trend towards increased ammonia accumulation at peak exercise post-PR ($p = 0.079$). Lactate accumulation in both groups was attenuated by PR at all time points except when comparing peak exercise lactate concentrations (Fig. 2). Two subjects in group 1 did not subsequently demonstrate an ammonia response following PR whereas one subject in group 2 did subsequently have a significant ammonia rise with exercise after PR.

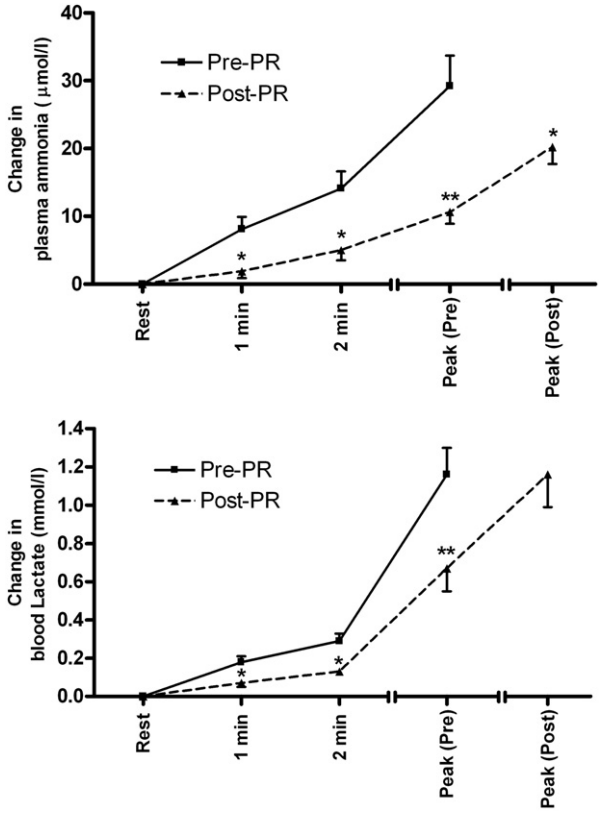

Figure 1 Change in plasma ammonia (upper panel) and blood lactate (lower panel) from resting values during maximal cycling exercise before (solid lines) and after (dashed lines) Pulmonary Rehabilitation (PR). *$p < 0.05$, **$p < 0.001$ between pre-PR and post-PR analysis.

Relationships between ammonia and lactate response and the outcome of PR

Complete data for the change in ISWT following PR was available for 24 patients. 15 patients achieved an increase

Table 2 Plasma ammonia and blood lactate concentrations at rest and response to incremental exercise in the whole cohort. Concentrations expressed as mean (SD) and change as mean (SEM).

		Rest	Isotime peak exercise[a]	Peak exercise	2 min recovery	Maximum exercise-induced change[b]
Ammonia conc μmol/l	Pre-PR	53.3 (13.4)	—	82.3 (21.0)	77.3 (25.0)	33.0 (4.7)
	Post-PR	53.1 (12.4)	63.8(11.4)**	73.3 (13.6)*	73.0 (15.3)*	24.0 (2.8)*
Lactate conc mmol/l	Pre-PR	0.74 (0.16)	—	1.90 (0.71)	2.07 (0.82)	1.42 (0.14)
	Post-PR	0.66 (0.13)*	1.33(0.64)**	1.82 (0.88)	2.10 (1.00)	1.46 (0.19)

*$p < 0.05$, **$p < 0.001$ between pre-PR and post-PR.
[a] Time point during post-PR exercise test at which peak exercise was reached in pre-PR test.
[b] Calculated as maximum ammonia concentration (at any time point) minus resting concentration.

Table 3 Baseline characteristics for COPD subjects for subgroup analysis (Group 1: subjects with baseline max exercise-induced change in ammonia > 15 μmol/l; Group 2: subjects with baseline max exercise induced change in ammonia <15 μmol/l). Absolute values expressed as mean (SD). Change expressed as mean (SEM).

	Group 1 (n = 18)		Group 2 (n = 7)	
	Pre-PR	Change with PR	Pre-PR	Change with PR
Age (years)	67 (7)	—	68 (10)	—
FEV_1 (% predicted)	48 (19)	—	46 (15)	—
BMI (kg/m^2)	27.7 (6.4)		27.9 (7.2)	
O_2 saturation at rest (%)	96 (2)	—	96 (1)	—
ISWT distance (m)	309 (128)	97 (19)	203 (113)	82 (23)
ESWT time (s)	118 (57)	531 (89)	158 (46)	417 (143)
Peak workload (W)	61 (22)	14 (3)	43 (14)	11 (3)
VO_2max (ml/kg/min)	16.4 (5.1)	1.36(0.50)	14.2 (3.2)	1.29(0.96)
Peak V_E (L)	37.3 (12.7)	3.9 (4.5)	28.6 (5.7)	2.6 (4.8)
Peak V_E (% MVV)	87 (19)	9.4(8.2)	84 (22)	7.3(14.8)

of >48 m in ISWT performance. There was no statistically significant difference in the ammonia or lactate response at baseline or the change in the ammonia/lactate response resulting from PR between patients who did or did not achieve the threshold of a 48 m improvement in ISWT performance (Table 5).

The exercise ammonia and lactate responses at baseline showed no significant correlation with changes in physical performance (Peak WR, VO_2max or ISWT) when expressed as continuous variables for all COPD patients or for either subgroup of patients. There was a negative correlation between the change in maximum exercise-induced lactate accumulation resulting from PR and the improvement in peak exercise WR ($r = -0.42$, $p = 0.036$). Otherwise there were no other correlations between changes in the ammonia/lactate responses to exercise and changes in physical performance (expressed as continuous variables) after PR.

Discussion

We have described the effects of a pragmatic, semi-supervised outpatient pulmonary rehabilitation programme on the skeletal muscle metabolic response to exercise. Our data suggest a reduction in exercise-induced metabolic stress following PR despite higher peak work rates achieved, as evidenced by reduced blood ammonia and lactate accumulation. However, contrary to our initial hypothesis, the subgroup of patients without an exercise-induced ammonia response showed similar improvements in exercise capacity following PR, and the functional outcome of PR could not be predicted from the baseline exercise ammonia response.

Improving physical performance is an important therapeutic goal in COPD and impaired skeletal muscle metabolic function is a modifiable factor contributing to exercise intolerance in this population. The current study is the first to report the effects of PR on metabolic stress (as measured by plasma ammonia levels) during exercise in COPD. Previous studies in healthy subjects have suggested a similar effect of aerobic training on the ammonia response.[23,24] The reduction in plasma ammonia accumulation in COPD patients following PR suggests a reduction in adenine nucleotide loss due to better cellular ATP delivery in response to the demands of exercise. The precise mechanisms for these observations cannot be determined directly as we did not obtain muscle biopsies during exercise in this study. However, the concomitant reduction in lactate accumulation suggests that this is mediated through

Table 4 Mean values for ammonia and lactate with isotime and peak exercise-induced changes in COPD subgroups (Group 1: subjects with baseline max exercise-induced change in ammonia > 15 μmol/l; Group 2: subjects with baseline max exercise-induced change in ammonia <15 μmol/l). Figures in parenthesis refer to SD for absolute values at rest and SEM for exercise-induced changes.

		Group 1 (n = 18)			Group 2 (n = 7)		
		Rest	Isotime change[a]	Peak exercise change[b]	Rest	Isotime change[a]	Peak exercise change[b]
Plasma ammonia	Pre-PR	51.4 (12.7)	—	39.7 (3.9)	58.2 (14.9)	—	1.5 (1.4)**
(μmol/l)	Post-PR	51.5 (10.2)	12.7 (2.0)	24.1 (2.6)	57.2 (17.0)	5.3 (2.5)*	10.2 (4.0) **
Blood lactate	Pre-PR	0.76 (0.15)	—	1.26 (0.18)	0.68 (0.18)	—	0.91 (0.17)
(mmol/l)	Post-PR	0.65 (0.13)	0.73 (0.15)	1.30 (0.21)	0.68 (0.14)	0.51 (0.16)	0.80 (0.22)

*$p < 0.05$, **$p < 0.01$. Between group comparison; group 1 vs group 2.
[a] Change over resting values at the same time point during post-PR exercise test at which peak exercise was reached in pre-PR test.
[b] Change over resting values at peak exercise.

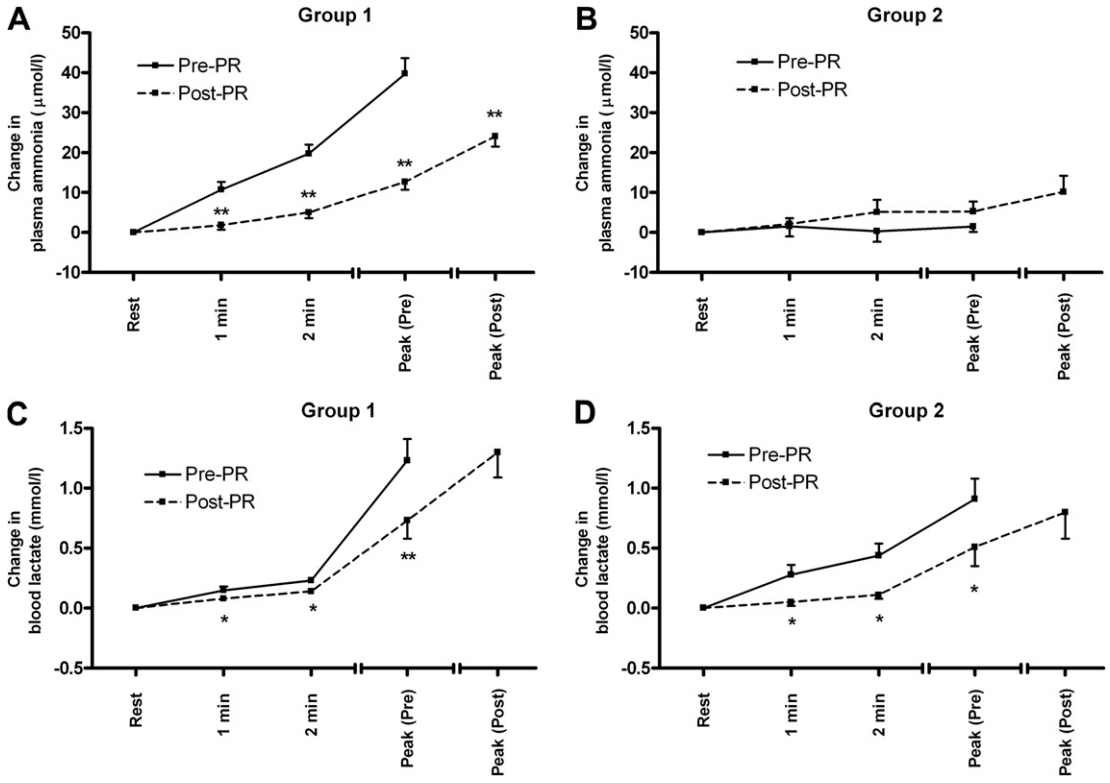

Figure 2 A—D: Subgroup comparison of COPD subjects with and without an ammonia rise on pre-PR cycling exercise. Change in plasma ammonia and blood lactate from resting values during maximal cycling exercise in group 1 ($n = 18$) (A and C) and group 2 ($n = 7$) (B and D). Pre-PR data is depicted in solid lines and post-PR data in dashed lines. Group 1: subjects with baseline max exercise-induced change in ammonia >15 μmol/l; Group 2: subjects with baseline max exercise-induced change in ammonia <15 μmol/l $^{**}p < 0.001$, $^{*}p < 0.05$ between pre-PR and post-PR analysis.

a reduction in anaerobic energy delivery resulting from an increase in mitochondrial (oxidative) capacity. This is in keeping with previous studies which have demonstrated increases in mitochondrial oxidative enzyme concentrations from muscle biopsies,[10] reduced blood lactate accumulation[11] and improved rates of phosphocreatine resynthesis following aerobic training in COPD.[3] Alternative explanations could be a shift in the relative sizes of type I and II fibres towards a greater proportion of type I fibres following PR or an improvement in oxygen delivery to the ambulatory muscles through central cardiopulmonary adaptations to physical training.

We had hypothesized that the functional response to rehabilitation would be reduced in Group 2 (no exercise-induced ammonia rise) because of insufficient muscle overload during training, but in fact we found that improvements in field and laboratory exercise capacity were of similar magnitude to Group 1 and there was no correlation between the ammonia or lactate response to exercise at baseline and the functional outcome of PR. One

Table 5 Mean (SEM) changes in the ammonia and lactate responses to maximal cycling exercise before and after PR in patients with and without a clinically significant increase in ISWT performance (defined as a change of 48 m (see Ref.[20])).

	ΔISWT >48 m ($n = 15$)	ΔISWT <48 m ($n = 9$)
Change in ammonia at peak exercise pre-PR (μmol/l)	33.5 (6.4)	24.8 (5.7)
Maximum exercise induced change in ammonia Pre PR (μmol/l)[b]	37.4 (6.6)	29.3 (26.2)
Change in lactate at peak exercise pre-PR (mmol/l)	1.26 (0.21)	0.98 (0.16)
Maximum exercise-induced change in lactate Pre PR (mmol/l)[b]	1.52 (0.80)	1.26 (0.19)
Change in ammonia response at isotime after PR (Pre—Post-PR) (μmol/l)[a]	20.8 (5.94)	16.9 (4.39)
Change in Maximum exercise-induced ammonia rise after PR (Pre—Post) (μmol/l)[b]	7.3 (5.9)	13.1 (5.5)
Change in lactate response at isotime after PR (Pre—Post) (mmol/l)[a]	0.46 (0.12)	0.51 (0.13)
Change in maximum exercise-induced lactate rise after PR (Pre—Post PR) (mmol/l)[b]	−0.24 (0.23)	0.21 (0.11)

[a] Time point during post-PR exercise test at which peak exercise was reached in pre-PR test.
[b] Peak change is calculated as peak ammonia/lactate concentration (measured at any time point) minus resting concentration.

possibility is that patients in this subgroup were too disabled to exercise intensively enough to provoke metabolic stress because of ventilatory limitation. There was no difference between the groups in maximum exercise ventilation and no difference in the metabolic response to exercise between patients with and without ventilatory limitation, although we acknowledge we have not measured exercise-related dynamic hyperinflation. Patients in group 2 showed a significant rise in blood lactate in the absence of an ammonia response suggesting that the intensity of exercise was substantial, although we recognise that we do not have detailed session to session data on training workloads. We speculate that in these individuals, despite the mobilisation of non-oxidative sources of energy, ATP resynthesis was sufficient to meet the demands of muscular work (presumably because of better preservation of mitochondrial sources of ATP). The reasons for this cannot be determined from this study but could reside in the fibre characteristics of the lower limb muscles in this group. Previous studies have suggested a shift in fibre composition towards a greater proportion of Type II fibres in COPD.[25] Type II fibres are more susceptible to adenine nucleotide loss and ammonia production[26] and therefore Group 2 patients could represent those with better preservation of Type I fibre numbers and/or size.

We acknowledge a number of limitations to the interpretation of the data in this study. Blood measurements may not always reflect intramuscular events. However, previous studies have confirmed the relationship between blood ammonia accumulation and adenine nucleotide loss in healthy subjects[6,27] and we have done so ourselves previously in COPD patients.[7] Our threshold for a significant rise in ammonia is inevitably arbitrary but was determined rationally from the variation of repeated measurements of ammonia in our laboratory and our previous studies which showed clear separation of the groups at this level.[7,8] The numbers in each subgroup were relatively small and therefore statistical comparisons may be subject to type II error. We acknowledge that our observations have been restricted to maximal cycling exercise and would need to be confirmed for other exercise modes or platforms such as constant load exercise or walking performance. Similarly, we recognise our data may not be generalisable to the wider COPD population, for example those with milder disease.

The clinical benefits of pulmonary rehabilitation are well established and the intervention is enshrined in national and international guidelines for the management of COPD.[9,28,29] Previous studies in controlled laboratory settings have indicated that skeletal muscle adaptations occur in response to aerobic training.[10,11] In the current study, we have confirmed that substantial improvements in skeletal muscle ATP delivery can be brought about by a pragmatic semi-supervised outpatient rehabilitation programme incorporating high intensity walking exercise. Our observation that the clinical outcome of rehabilitation could not be predicted from these adaptations or the baseline physiological response highlights the complex, mixed mechanisms underpinning the benefits of PR, including behavioural factors such as motivation and mood. For example many patients may be able to utilise more of their pre-existing physical capacity after rehabilitation through improvements in confidence and self-efficacy rather than through physiological adaptation. Predicting the outcome of PR from baseline disease, demographic and physiological variables has proved difficult and as a result inclusion criteria for PR remain broad.[9] The current study highlights this issue and also suggests that physiological adaptation during training itself may not identify those with a favourable clinical response. However, further understanding of the mechanisms underpinning metabolic adaptation to PR is essential if we are to individualise and augment therapy in the future.

In summary, we have demonstrated that a pragmatic outpatient PR programme results in significant adaptation to the metabolic response to exercise. However, the clinical response to rehabilitation could not be predicted from the baseline exercise response highlighting the heterogeneous mechanisms that underpin clinical outcomes in pulmonary rehabilitation.

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Conflict of interest

We confirm that we have no conflicts of interest relevant to this manuscript.

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