Word count: 3512

Abstract word count: 301

Submaximal eccentric cycling in people with COPD: acute whole-body cardiopulmonary and muscle metabolic responses

Thomas J C Ward MBBS[1,2,3], Martin R Lindley PhD[1,4], Richard A Ferguson PhD[1], Despina Constantin PhD[5,6], Sally J Singh PhD[1,2,3,7], Charlotte E Bolton MD[5,6], Rachael A Evans PhD[1,2,3,7], Paul L Greenhaff PhD[1,5,6], Michael C Steiner MD[1,2,3,7]

[1] National Centre for Sport and Exercise Medicine, Loughborough University, UK; [2] Centre for Exercise & Rehabilitation Science, Leicester Biomedical Research Centre-Respiratory, Glenfield Hospital, Leicester, UK; [3] Department of Respiratory Medicine, Glenfield Hospital, University Hospitals of Leicester NHS trust, Leicester, UK. [4] Translational Chemical Biology research group, SSHES, Loughborough University, UK; [5] MRC Versus Arthritis Centre for Musculoskeletal Ageing Research, University of Nottingham, Nottingham UK; [6] NIHR Nottingham Biomedical Research Centre, University of Nottingham, Nottingham, UK; [7] Department of Respiratory Science, University of Leicester, Leicester, UK.

Corresponding author:

Professor Michael Steiner

Respiratory Biomedical Research Centre

Glenfield Hospital

Groby Road

Leicester

LE3 9QP

email: ms346@le.ac.uk

Competing interests: None declared

Prior abstract presentation: These results were previously presented at the European Respiratory Society Conference, 2019: Ward T, Lindley MR, Ferguson RA, Evans RA, Singh SJ, Bolton C, Greenhaff P, Steiner MC. Eccentric cycling for people with COPD: acute cardiorespiratory and metabolic responses. *Eur Respir Soc Conf* Paris: European Respiratory Society; 2019

And at the British Thoracic Society Conference, 2019: Ward T, Lindley MR, Ferguson RA, Evans RA, Singh SJ, Bolton C, Greenhaff P, Steiner MC. The utility of eccentric cycling for people with COPD: acute cardiorespiratory and metabolic responses. *British Thoracic Society Conference;* 2019

ABBREVIATION LIST

ANOVA – Analysis of variance

ATP – Adenosine triphosphate

BMI – Body mass index

CON – Concentric cycling

COPD – Chronic obstructive pulmonary disease

Cr – Creatine

DOMS – Delayed onset muscle soreness

ECC – Eccentric cycling

EMG – Electromyography

HR – Heart rate

PCr – Phosphocreatine

PR – Pulmonary rehabilitation

RER – Respiratory exchange ratio

$\dot{V}CO_2$ – Carbon dioxide production

V_E – Minute ventilation

$\dot{V}O_2$ – Oxygen uptake

$\dot{V}O_{2peak}$ – Oxygen uptake at peak exercise

W_{peak} – Workload at peak exercise

Abstract

Background: Eccentric cycling (ECC) may be an attractive exercise modality in COPD due to both low cardiorespiratory demand and perception of effort compared to conventional concentric cycling (CON) at matched mechanical loads. However, it is unknown whether ECC can be performed by individuals with COPD at an intensity able to cause sufficient metabolic stress to improve aerobic capacity.

Research question: What are the cardiopulmonary and metabolic responses to ECC in people with COPD and healthy volunteers when compared to CON at matched mechanical loads?

Study Design and Methods: 13 individuals with COPD (mean ± SD age 64 ± 9 years, FEV_1 %pred 45 ± 19%, BMI 24 ± 4 $kg.m^{-2}$, $\dot{V}O_{2peak}$ 15 ± 3 $ml.kg^{-1}.min^{-1}$) and 9 age matched controls (FEV_1 %pred 102 ± 13%, BMI 28 ± 5 $kg.m^{-2}$, $\dot{V}O_{2peak}$ 23 ± 5 $ml.kg^{-1}.min^{-1}$), performed up to six 4 min bouts of ECC and CON at matched mechanical loads of increasing intensity. In addition, 12 individuals with COPD underwent quadriceps muscle biopsies before and after 20 min of ECC and CON at 65% peak power.

Results: At matched mechanical loads, oxygen uptake, minute ventilation, heart rate, systolic blood pressure, RER (all $p<0.001$), capillary lactate, perceived breathlessness and leg fatigue ($p<0.05$) were lower in both groups during ECC than CON. Muscle lactate content increased ($p=0.008$), and muscle phosphocreatine decreased ($p=0.012$) during CON in COPD, which was not evident during ECC.

Interpretation: Cardiopulmonary and blood lactate responses during submaximal ECC were less compared to CON at equivalent mechanical workloads in health and COPD, and this was confirmed at a muscle level in COPD. Submaximal ECC was well tolerated and allowed greater mechanical work at lower ventilatory cost. However, in people with COPD, a training intervention based on ECC is unlikely to stimulate cardiovascular and metabolic adaptation to the same extent as CON.

Keywords: COPD, exercise, eccentric, oxygen uptake

Exercise training, as part of pulmonary rehabilitation (PR), is an effective treatment for people with COPD, improving quality of life, breathlessness and exercise capacity[1]. However, there is significant variation in the response between individuals[2] and some patients, particularly those with more severe disease[3], are unable to achieve the maximum gain from PR, suggesting the need for novel exercise training modalities targeting these populations. Eccentric exercise (ECC), involving muscle contraction during active lengthening, is one such strategy that might address this need.

Most individuals with moderate or severe COPD stop exercising prematurely due to abnormal ventilatory mechanics[4], thereby limiting exercise intensity and lessening the potential benefits of exercise training. ECC, in comparison to traditional concentric exercise (CON), is known to result in a lower whole-body cardiopulmonary demand at matched mechanical loads[5]. It may therefore be highly appropriate for use in COPD, allowing either higher muscle workloads than CON to be achieved or increased comfort through lower perceived dyspnoea at equivalent muscle workloads[6]. Historically, ECC was avoided due to the propensity to cause delayed onset muscle soreness (DOMS) in unaccustomed muscle, particularly at high exercise workloads[7]. However, it is now apparent that ECC can be safely performed without the occurrence of DOMS, including in disease populations such as those with COPD[8], if the workload is gradually increased over several exercise sessions[9].

Despite the knowledge that ECC is safe for individuals with COPD, the quantification of cardiopulmonary responses during ECC for people with COPD and the implication for aerobic adaptation is unclear. Previous research into the cardiopulmonary responses to ECC in people with COPD has been limited to low mechanical loads[10] such that the responses across a range of workloads and comparison with age matched controls have not been investigated. Furthermore, the muscle level metabolic response to ECC in comparison to CON at an equivalent mechanical load has not been investigated in COPD. This is important because the magnitude of the metabolic stress generated is highly likely to dictate the magnitude of metabolic adaptation if prolonged ECC was used as a training strategy.

We therefore aimed to 1) quantify the relationship between mechanical load and whole-body cardiopulmonary responses during ECC in comparison to CON in individuals with COPD and age matched healthy volunteers and 2) determine the muscle level metabolic response of submaximal ECC in comparison to CON for people with COPD. Finally, as part of the study participants were questioned about their experience of ECC.

Methods

Participants

Full details of recruitment and eligibility criteria can be found in the online supplement (e-Appendix 1). In brief, participants aged over 40 with COPD (FEV1/FVC <0.7), FEV1 ≤ 60% predicted and Medical Research Council (MRC) dyspnoea scale ≥3 and BMI<35 were recruited. In addition, healthy controls aged over 40 free from major illness impairing exercise capacity, without airflow limitation (FEV1/FVC ≥0.7) or significant breathlessness (MRC ≤2) were recruited.

Study design

Participants with COPD and age matched healthy volunteers performed up to six 4 min bouts of ECC and CON at increasing, matched mechanical loads with a 4-minute rest between bouts (Figure 1). The first bout was performed at 15% of peak workload (W_{peak}) obtained from a maximal concentric incremental ramp test at baseline with intensity increasing by 15% W_{peak} for each bout until the participant reached 90% W_{max} or was unable to continue due to volitional exhaustion (e-Figure 1). Expired gas analysis and heart rate (HR) monitoring was performed throughout, blood pressure measured once per stage and capillary lactate measured during the final 10s of each stage.

The same protocol was repeated in ECC at matched mechanical loads during a separate study visit at least one week later. Four-minute bouts were chosen to allow sufficient time for a steady state in physiological parameters to be achieved whilst minimising the effect of fatigue. A subgroup of participants with COPD consented to needle muscle biopsies (vastus lateralis) taken at separate visits before and after 20 min (or until volitional exhaustion) of CON and ECC at matched mechanical load at 65% concentric W_{peak}.

ECC familiarisation was performed on three occasions for 10, 15 and 15 min at increasing relative workloads (10 min at 15% W_{peak} in visit 1, 5 min at 15% W_{peak} and 10 min at 45% W_{peak} in visit 2 and 5 min at 45% W_{peak} and 10 min at 60% W_{peak} in visit 3). These familiarisations were performed at the end of the first three laboratory visits following CON tests. Following completion of the study, participants were asked to complete a questionnaire exploring the perceptual aspects of ECC. This questionnaire was developed during pilot testing and was specific to our study design (e-Appendix 2).

The protocol was approved by the Leicestershire South Regional Ethics Committee (IRAS 214536). All participants gave informed written consent prior to taking part. Separate informed written consent was obtained for biopsy sampling.

All cycling tests were performed on a commercially available upright ergometer able to switch between concentric and eccentric modes (Lode Corival Eccentric, Lode, Netherlands). This is a traditional electrically braked upright ergometer, modified by the addition of a motor which, when engaged during ECC mode, applies constant torque to drive the pedals in reverse. The participant aims to slow down the movement of the pedals, targeting the desired speed. A target of 60 rpm was used for all CON and ECC tests.

Cardiopulmonary exercise testing

Following a 3 min warm up period, participants cycled concentrically at increasingly mechanical load (ramp protocol 5-10 $W.min^{-1}$) until volitional exhaustion. Participants were asked to cycle at 60 rpm, and test end was defined as the point at which the cadence dropped below 50 rpm for 10s. Peak oxygen uptake ($\dot{V}O_{2peak}$) was defined as the peak value of rolling 30s averages of VO_2[11]. Maximal verbal encouragement was given, and all tests were supervised by the same investigator (TW).

Expiratory gas analysis and HR were recorded using a CareFusion metabolic cart (San Diego, United States). The volume and gas analysers were calibrated before each test using a 3-litre syringe and a known concentration of gas (4.99% CO_2, 15.99% O_2). The modified Borg scale[12] was used to measure leg fatigue and breathlessness during exercise.

Capillary blood sampling

Earlobe capillary blood was analysed immediately following sampling for lactate and glucose concentration using an enzymatic assay (Biosen S-line point of care analyser, EKF diagnostics, Germany). Calibration was performed before each use against a standard solution. Where the analyser gave a unrecordable low reading for lactate, the lower limit of detection (0.5 $mmol.l^{-1}$) was included in the analysis.

Muscle biopsies

Individuals with COPD were invited to take part in an optional addition to the study in which vastus lateralis biopsies were performed before and after exercise. Participants performed 20 min bouts of ECC and CON at 65% W_{peak} at separate study visits at least one week apart and biopsies were taken at rest and 60s after exercise cessation from incisions at least 2 cm apart. Biopsies for ECC and CON conditions were obtained from opposite legs. CON bouts were performed first and if 20 min was not achieved (4 out of 12 participants), biopsies were taken at the end of exercise and matched time was performed during ECC. Approximately 100 mg of tissue was removed under local anaesthetic using the modified Bergstrom technique[13]. Tissue was immediately frozen in liquid nitrogen and stored at -80°C until analysis.

Muscle tissue analysis

Samples of approximately 50 mg wet weight were cut, freeze-dried then powdered by hand with removal of visible blood and connective tissue. 4-10 mg of powdered tissue was extracted using 0.5 $mmol.l^{-1}$ perchloric acid containing 0.1 $mmol.l^{-1}$ EDTA. Following mixing and centrifugation, the supernatant was recovered and neutralised with 2.2 $mmol.l^{-1}$ potassium bicarbonate. The sample was again spun down, and the supernatant extracted for analysis. Muscle tissue was analysed for phosphocreatine (PCr), creatine (Cr), adenosine triphosphate (ATP) and lactate using a modification of the spectrophotometric method of Harris et al[14]. For muscle ATP, PCr and Cr, values were normalised against the highest total creatine content (PCr+Cr) for that individual to correct for differences in non-muscle constituents between biopsy samples[15].

Statistical analysis

Full details of statistical analysis methods can be found in e-Appendix 3.

We performed a sample size calculation based on an alpha value of 0.05 and a beta value of 0.2 which identified a required sample size of 6 (full details in e-Appendix 3). Cardiorespiratory and metabolic parameters during CON and ECC tests were compared using linear mixed models. Individual comparisons between CON and ECC at specific time points within groups were performed with Bonferroni corrections for multiple comparisons. For non-parametric data we used the Wilcoxon signed-rank test and the Mann-Whitney U test for repeated and independent data respectively. For all comparisons, a 5% significance level was used ($p<0.05$).

Results

Initially, 15 patients with COPD and 10 healthy volunteers were recruited. One healthy volunteer was excluded due to uncontrolled hypertension and one COPD patient was excluded due to severe exercise induced desaturation. One further COPD patients withdrew after the initial assessment, without giving a reason, therefore 13 COPD patients and 9 healthy volunteers entered the study (e-Figure 2).

From this initial cohort, fewer than expected participants consented to muscle biopsies and therefore six additional individuals with COPD were recruited for an abridged study and had muscle biopsies taken before and after 20 min bouts of CON and ECC but did not perform the repeated 4 min bouts of CON and ECC. Data from these two cohorts is presented separately (Table 1).

Concentric and eccentric 4-minute bouts

In the COPD cohort, five participants were unable to complete the higher load CON bouts due to volitional exhaustion. Completers and non-completers showed no significant differences except in BMI; completers had a higher BMI than non-completers (26 vs 21 $kg.m^{-2}$, $p<0.05$). All participants were able to complete six 4 min bouts of ECC and all healthy volunteers completed six 4 min bouts of CON. Absolute workload performed during bouts is shown in e-Table 2.

$\dot{V}O_2$ (Figure 2, e-Table 1), HR, V_E, capillary lactate concentration (Figure 3), systolic blood pressure, $\dot{V}CO_2$ and RER (e-Figure 3) were all significantly lower during ECC than CON for both COPD and healthy control groups (all $p<0.001$). At higher workloads, perceived leg fatigue was lower during ECC than CON and perceived breathlessness during ECC minimal in both groups ($p<0.01$ from 60% W_{peak} stage onwards, Figure 3). The gradient of the slope of the $\dot{V}O_2$ ($ml.min^{-1}$): Power (Watts) relationship during ECC was 2.8-fold and 3.3-fold lower than CON for the COPD and control groups respectively. There was a significant group by exercise mode by time interaction for $\dot{V}O_2$, $\dot{V}CO_2$, HR, V_E and capillary lactate (all $p<0.003$) therefore, the ratio of these parameters between CON and ECC was different between groups.

Muscle metabolites

Of the 12 participants with COPD consenting to vastus lateralis biopsies before and after 20 min of continuous CON and ECC, three withdrew consent after the CON visit and declined biopsies before and after ECC. A further four participants had unusable tissue samples for the post CON timepoint. There were therefore 12 biopsy samples at rest pre-CON, 8 post CON exercise samples and 9 samples pre and post ECC. Linear mixed model analysis was utilised to allow for missing data.

There was no difference in ATP concentration between timepoints or between modalities ($p=0.51$, Figure 4a). There were significant exercise modality by timepoint interactions for PCr, Cr and lactate ($p=0.001$, $p<0.001$ and $p=0.002$ respectively, Figure 4b-d) indicating a rise in lactate and a conversion from phosphocreatine to creatine after CON but no change from baseline following ECC.

Experience of eccentric cycling

In comparison to the healthy control group, a greater proportion of the COPD group preferred ECC to CON (76% vs. 22%, $p=0.01$, Figure 5h). Greater enjoyment was seen during ECC than CON for the COPD group ($p=0.004$, Figure 5a&b) with no difference seen for healthy controls ($p=0.68$). Both groups found ECC and CON equally challenging ($p=0.1$, Figure 5c). A majority (65% of the COPD group and 56% of the healthy control group) found ECC easy to get used to with no significant difference between groups ($p=0.46$, Figure 5e). When asked whether they would like to do more ECC, there was greater agreement in the COPD than the healthy control group (94% vs 56% $p=0.01$,

Figure 5f). Most participants in both groups thought ECC would improve their fitness with no difference between groups (65% and 89% in COPD and control groups respectively, p=0.71, Figure 5g).

Discussion

This study is the first to describe the physiological responses to ECC across a range of submaximal mechanical workloads in people with COPD in comparison to age matched controls. We have demonstrated that, in direct contrast to CON, there are minimal increases in $\dot{V}O_2$ and V_E during submaximal ECC even at higher relative workloads in both COPD and health, and this is associated with lower perceived breathlessness and leg fatigue at matched mechanical loads compared with CON. Moreover, this was accompanied by the complete lack of muscle lactate accumulation and PCr degradation in the quadriceps during ECC at a fixed submaximal workload in individuals with COPD. Collectively these findings demonstrate that although perception of effort and fatigue were positively influenced by ECC, this exercise modality elicited minimal cardiorespiratory and muscle metabolic stress in healthy volunteers and COPD patients and is therefore less likely to be an effective modality for increasing aerobic capacity in individuals with COPD.

In health, ECC results in lower oxygen demand than CON with the ratio of $\dot{V}O_2$ between CON and ECC at matched mechanical power quoted as between 1.5-5[16,17]. There has been limited previous research on cardiorespiratory parameters during ECC for people with COPD. Rooyackers and colleagues investigated 12 individuals with COPD performing 6 min constant load tests of ECC and CON at 25% and 50% of W_{peak}[10]. They found lower $\dot{V}O_2$, $\dot{V}CO_2$ and V_E during ECC than CON although HR and perception of effort were similar between modalities. However, this study was limited to low mechanical loads and therefore was unable to detect differences evident at higher loads. Lower $\dot{V}O_2$ and V_E has also been demonstrated for individuals with COPD performing downhill walking as compared to level walking[18]. Our study adds to previous research by quantifying several cardiopulmonary parameters across a range of matched workloads in comparison to CON.

Previous evaluation of the muscle metabolic response to ECC has been limited to healthy individuals[19] and this is the first study to our knowledge to study the metabolic response to ECC in people with COPD. In healthy subjects, Bonde-Peterson et al[19] demonstrated no change in muscle ATP, Cr, glycogen and lactate concentration following relatively high intensity ECC, in contrast to CON which induced a decline in muscle PCr and glycogen, and a rise in lactate concentration.

An increase in the muscle lactate and creatine content and a decline in muscle PCr following CON, has previously been demonstrated in COPD[20] and was confirmed in our study indicating that a measurable increase in non-mitochondrial ATP production occurred despite low absolute exercise workloads[21]. The complete absence of such metabolic stress during ECC demonstrates that muscle energy requirement was measurably less than CON and the lower muscle ATP demand could be wholly met by mitochondrial ATP generation[22].

MacMillan and colleagues performed muscle biopsies on patients with COPD after a 10-week progressive ECC cycling training programme and a control group performing CON cycling training at a quarter of the mechanical load[23]. They found an increase in peak strength and muscle mass following ECC training without an increase in fibre cross sectional area. An improvement in oxidative capacity was only seen in the CON group suggesting that the lack of muscle metabolic response seen in our study is likely to result in diminished metabolic adaptation following prolonged ECC training, even at high submaximal mechanical loads. However, the work of Bourbeau and colleagues demonstrates that ECC training results in greater improvements in muscle strength than CON at a matched cardiopulmonary load with similar improvements seen in cycling performance[24] and therefore functional adaptation may occur without improvements in metabolic adaptation . Indeed, the activation of skeletal muscle signalling pathways related to protein synthesis and changes in mRNA expression linked to muscle regeneration/degradation has been observed following repeated bouts of eccentric cycling[25].

ECC resulted in minimal breathlessness in both healthy volunteers and those with COPD, even at higher mechanical loads, unsurprising given the low cardiorespiratory response demonstrated. What is perhaps more surprising, is that ECC elicits lower leg fatigue than CON at matched mechanical loads which could be explained by lower muscle fibre activation during ECC with lower EMG activity for the same force production as CON[26]. Eccentric and concentric cycling were found to be equally challenging although the challenges of eccentric cycling, including the concentration required and the difficulty getting used to the technique, appear different from the exertional challenges of concentric cycling.

The lower effort required for ECC results appears to result in greater popularity of ECC than CON for individuals with COPD suggesting that ECC would be well received in a PR setting and might be useful in improving participation and completion of PR. Patients often cite a belief that exercise is beyond their capabilities as a reason for not attending PR[27] and therefore eccentric cycling could be used as a motivational technique whilst allowing initial muscle remodelling prior to the initiation of traditional aerobic training techniques.

Limitations

This study was limited to a small number of individuals, and variation, particularly within the heterogeneity of COPD, could not be explored. We prescribed mechanical load based on CON peak power and this is likely to have only moderate correlation with peak eccentric strength[28]. Mechanical load was matched to allow direct comparison of ECC and CON modalities, and although CON was performed to exhaustion, participants could have performed significantly higher loads eccentrically. However, we did not feel that an ECC test to exhaustion was ethically justifiable, particularly in an older, relatively frail population as the risk of severe DOMS, muscle damage and functional impairment would have been unacceptably high. Participants were required to attend the laboratory on five separate occasions which may cause a significant burden particularly for individuals with COPD.

ECC training at matched cardiopulmonary load to CON might theoretically allow similar improvements in aerobic capacity but greater improvements in muscle strength. However our study did not include any CON and ECC bouts at matched cardiopulmonary load. Failure of co-ordination during ECC on an upright ergometer, such as the one used in this study, appears to limit the high loads required to elicit a significant metabolic response[29] whereas the same seems not to be true on a recumbent ergometer[23].

For the muscle metabolite analysis, we have only studied one mechanical workload and it may be that higher eccentric loads would demonstrate greater muscle metabolic demand. However, the results of the parameters demonstrated in the repeated 4 min bouts, particularly the absence of a rise in capillary lactate, suggest that this is unlikely. The cohorts consenting for muscle biopsies and performing repeated four-minute bouts of ECC and CON were different and may have had different baseline characteristics.

We have demonstrated that most participants with COPD preferred ECC to CON. However, these were participants who had volunteered for a research study involving a novel exercise modality and therefore may be biased to select the novel exercise as preferable.

Potential implications and future work

These results suggest that ECC training, although allowing exercise at reduced ventilatory cost and improved comfort may not be able to achieve the same gains in cardiorespiratory and metabolic adaptation as CON. However, despite the low cardiometabolic demand of ECC, it may still have a role in the treatment of COPD. A potential mechanism for ECC to increase endurance capacity, which has been showed to be possible in cardiac populations[30–32], may be through dyspnoea desensitisation or improved mechanical efficiency, allowing greater workloads to be performed prior to exercise cessation. We know ECC can improve muscle size and strength, particularly eccentric strength which may be associated with reduced falls risk[33]. Furthermore, the popularity of ECC, might improve participation and completion of pulmonary rehabilitation. The focus of ECC training in clinical populations should perhaps be on enhanced gains in muscle mass and strength with the acceptance that training which overloads the metabolic capacity of the muscle must be performed in addition if the goal is to improve aerobic capacity.

In summary, this study demonstrates that the low cardiopulmonary demand of ECC when compared to CON at matched mechanical loads previously demonstrated in healthy individuals is also seen in individuals with COPD and appears not to be affected by COPD diagnosis. The metabolic demand of ECC on the exercising muscle for people with COPD appears to be minimal with no detectable change in the intramuscular metabolites measured. ECC causes minimal perceived breathlessness and is popular with people with COPD with most preferring it to traditional CON. These findings have implications for the role of ECC in pulmonary rehabilitation and suggest that ECC is unlikely to result in muscle aerobic adaptation but may allow muscle size and strength adaptation whilst improving the comfort of exercise training for people with COPD.

Acknowledgements

Thanks to Katarina Ruettger, Tom Rosser and Nathan Smith for their help with data collection

Author contributions

MS, PG, RE, ML, CB, SS and TW helped to develop the protocol. TW, RF and ML performed data collection. Muscle analysis was performed by TW and DC under the guidance of PG. TW performed the statistical analysis and wrote the first draft of the manuscript. All authors were involved in manuscript preparation and approved the final draft. MS was the study lead and guarantor of the paper.

Funding – this study was funded through the PhD studentship of TW at Loughborough University. Muscle analytical costs were funded by the University of Nottingham. CEB and PG are supported through the NIHR Nottingham Biomedical Research Centre. MS, SS and RE are supported by the NIHR Leicester Biomedical Research Centre. The views expressed are those of the authors and not necessarily those of the NHS, the NIHR or the Department of Health.

References

1. McCarthy B, Casey D, Devane D, Murphy K, Murphy E, Lacasse Y. Pulmonary rehabilitation for chronic obstructive pulmonary disease. *Cochrane Database Syst Rev* 2015;(2):CD003793.
2. Spruit MA, Augustin IML, Vanfleteren LE, et al. Differential response to pulmonary rehabilitation in COPD: Multidimensional profiling. *Eur Respir J* 2015;46(6):1625–1635.
3. Ward T, Jones A, Trethewey R, et al. Change in VO2peak in response to aerobic training in patients with COPD: A meta-analysis. In: European respiratory society conference. Paris: European Respiratory Society; 2018. p. 5197.
4. O'Donnell DE, Revill SM, Webb KA. Dynamic hyperinflation and exercise intolerance in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2001;164(5):770–777.
5. Dufour SP, Lampert E, Doutreleau S, et al. Eccentric cycle exercise: Training application of specific circulatory adjustments. *Med Sci Sports Exerc* 2004;36(11):1900–1906.
6. Ellis R, Shields N, Lim K, Dodd KJ. Eccentric exercise in adults with cardiorespiratory disease: a systematic review. *Clin Rehabil* 2015;29(12):1178–1197.
7. Proske U, Morgan DL. Muscle damage from eccentric exercise: Mechanism, mechanical signs, adaptation and clinical applications. J. Physiol. 2001;537(2):333–345.
8. Rocha Vieira DS, Baril J, Richard R, Perrault H, Bourbeau J, Taivassalo T. Eccentric Cycle Exercise in Severe COPD: Feasibility of Application. *COPD J Chronic Obstr Pulm Dis* 2011;8(4):270–274.
9. Chen TCC, Chen HL, Pearce AJ, Nosaka K. Attenuation of eccentric exercise-induced muscle damage by preconditioning exercises. *Med Sci Sports Exerc* 2012;44(11):2090–2098.
10. Rooyackers JM, Dekhuijzen PN, Herwaarden CL van, Folgering HT. Ventilatory response to positive and negative work in patients with chronic obstructive pulmonary disease. *Respir Med* 1997;91(3):143–9.
11. Robergs R a., Dwyer D, Astorino T. Recommendations for improved data processing from expired gas analysis indirect calorimetry. *Sport Med* 2010;40(2):95–111.
12. Wilson RC, Jones PW. A comparison of the visual analogue scale and modified Borg scale for the measurement of dyspnoea during exercise. *Clin Sci* 1989;76(3):277–282.
13. Bergström J. Percutaneous needle biopsy of skeletal muscle in physiological and clinical

Research. *Scand J Clin Lab Invest* 1975;35(7):609–616.

14. Harris RC, Hultman E, Nordesjö L-O. Glycogen, Glycolytic Intermediates and High-Energy Phosphates Determined in Biopsy Samples of Musculus Quadriceps Femoris of Man at Rest. Methods and Variance of Values. *Scand J Clin Lab Investig* 1974;33(2):109–120.

15. Hultman E, Sjöholm H. Energy metabolism and contraction force of human skeletal muscle in situ during electrical stimulation. *J Physiol* 1983;345(1):525–532.

16. Perrey S, Betik A, Candau R, Rouillon JD, Hughson RL. Comparison of oxygen uptake kinetics during concentric and eccentric cycle exercise. *J Appl Physiol* 2001;91(5):2135–2142.

17. Peñailillo L, Guzmán N, Cangas J, Reyes A, Zbinden-Foncea H. Metabolic demand and muscle damage induced by eccentric cycling of knee extensor and flexor muscles. *Eur J Sport Sci* 2017;17(2):179–187.

18. Camillo CA, Burtin C, Hornikx M, et al. Physiological responses during downhill walking: A new exercise modality for subjects with chronic obstructive pulmonary disease? *Chron Respir Dis* 2015;12(2):155–64.

19. Bonde-Petersen F, Knuttgen HG, Henriksson J, I- J. Muscle metabolism during exercise with concentric and eccentric contractions. *J Appl Physiol* 1972;33(6):792–795.

20. Steiner MC, Evans R, Deacon SJ, et al. Adenine nucleotide loss in the skeletal muscles during exercise in chronic obstructive pulmonary disease. *Thorax* 2005;60(11):932–936.

21. Calvert LD, Singh SJ, Morgan MD, Steiner MC. Exercise induced skeletal muscle metabolic stress is reduced after pulmonary rehabilitation in COPD. *Respir Med* 2011;105(3):363–70.

22. Timmons JA, Poucher SM, Constantin-Teodosiu D, Macdonald IA, Greenhaff PL. Metabolic responses from rest to steady state determine contractile function in ischemic skeletal muscle. *Am J Physiol - Endocrinol Metab* 1997;273(2 36-2).

23. MacMillan NJ, Kapchinsky S, Konokhova Y, et al. Eccentric ergometer training promotes locomotor muscle strength but not mitochondrial adaptation in patients with severe chronic obstructive pulmonary disease. *Front Physiol* 2017;8(MAR):114.

24. Bourbeau J, Sousa Sena R De, Taivassalo T, et al. Eccentric versus conventional cycle training to improve muscle strength in advanced COPD: A randomized clinical trial. *Respir Physiol Neurobiol* 2020;276:103414.

25. Valladares-Ide D, Peñailillo L, Collao N, Marambio H, Deldicque L, Zbinden-Foncea H.

Activation of protein synthesis, regeneration, and MAPK signaling pathways following repeated bouts of eccentric cycling. *Am J Physiol Endocrinol Metab* 2019;317(6):E1131–E1139.

26. Bigland-Ritchie B, Woods JJ. Integrated electromyogram and oxygen uptake during positive and negative work. *J Physiol* 1976;260(2):267–277.

27. Sohanpal R, Steed L, Mars T, Taylor SJC. Understanding patient participation behaviour in studies of COPD support programmes such as pulmonary rehabilitation and self-management: a qualitative synthesis with application of theory. *npj Prim Care Respir Med* 2015;25(1):15054.

28. Wu Y, Li RCT, Maffulli N, Chan KM, Chan JLC. Relationship between isokinetic concentric and eccentric contraction modes in the knee flexor and extensor muscle groups. *J Orthop Sports Phys Ther* 1997;26(3):143–9.

29. Lipski M, Abbiss CR, Nosaka K. Cardio-pulmonary responses to incremental eccentric and concentric cycling tests to task failure. *Eur J Appl Physiol* 2018;118(5):947–957.

30. Gremeaux V. Does eccentric endurance training improve walking capacity in patients with coronary artery disease? A randomized controlled pilot study. *Clin Rehabil* 2010;24:590–599.

31. Besson D, Joussain C, Gremeaux V, et al. Eccentric training in chronic heart failure: Feasibility and functional effects. Results of a comparative study. *Ann Phys Rehabil Med* 2013;56(1):30–40.

32. Casillas JM, Besson D, Hannequin A, et al. Effects of an eccentric training personalized by a low rate of perceived exertion on the maximal capacities in chronic heart failure: A randomized controlled trial. *Eur J Phys Rehabil Med* 2016;52(2):159–168.

33. LaStayo PC, Ewy GA, Pierotti DD, Johns RK, Lindstedt S. The Positive Effects of Negative Work: Increased Muscle Strength and Decreased Fall Risk in a Frail Elderly Population. *Journals Gerontol Ser A Biol Sci Med Sci* 2003;58(5):M419–M424.

Footnotes

Table 1 – MRC: medical research council dyspnoea scale, BMI: body mass index, $\dot{V}O_{2peak}$: oxygen uptake at peak concentric exercise, W_{peak}: peak concentric workload. Mean ± SD or Median (IQR). *Difference from healthy control group $p<0.05$

Figure legends

Figure 1 – Study diagram. Healthy volunteers and some participants with COPD performed the full study without muscle biopsies but data for these participants from visits 3 and 5 are not presented. Fewer participants than expected consented for muscle biopsies and therefore further COPD patients were recruited for an abridged study and performed only visits 1, 3 and 5. CON: concentric cycling, ECC: eccentric cycling.

Figure 2 – Oxygen uptake ($\dot{V}O_2$) during concentric and eccentric cycling, CON: concentric cycling, ECC: eccentric cycling, W_{peak}: peak concentric workload. Absolute workload performed during bouts is shown in e-Table 2. Mean ± SEM *$p<0.001$ COPD CON vs ECC, ǂ$p<0.001$ Healthy controls CON vs ECC. ¶$p<0.05$ between groups.

Figure 3 – Cardiorespiratory parameters during 4 min bouts of concentric and eccentric cycling at matched mechanical load in individuals with COPD and age matched healthy controls. a) minute ventilation (V_E), b) tidal volume (V_T), c) respiratory rate, d) capillary lactate concentration, e) heart rate, f) perceived breathlessness, g) perceived leg fatigue. CON: concentric cycling, ECC: eccentric cycling, W_{peak}: peak concentric workload. Absolute workload performed during bouts is shown in e-Table 2. Mean ± SEM or Median ± IQR. *$p<0.05$ COPD CON vs ECC, ǂ$p<0.05$ Healthy controls CON vs ECC, ¶$p<0.05$ between groups.

Figure 4 – Metabolite concentration in vastus lateralis biopsies from COPD patients before and after continuous bouts of concentric (CON) and eccentric (ECC) cycling at matched mechanical load of 65% peak power. a) adenosine triphosphate (ATP), b) phosphocreatine, c) creatine, d) lactate. Mean ± SEM, *$p<0.05$.

Figure 5 – Experience of eccentric cycling for individuals with COPD and healthy controls (HC) – results from qualitative questionnaire at end of study, CON: concentric cycling, ECC: eccentric cycling.

Table 1 – participant demographics

		Participants performing repeated 4 min bouts		Participants consenting to muscle biopsies
		COPD (n=13)	Healthy controls (n=9)	COPD (n=12)
Age (years)		64 ± 9.4	64 ± 8.8	67 ± 10
Gender (M:F)		8:5	6:3	7:5
Current smoker (%)		15	11	17
Smoking history (pack years)		55 ± 38*	10 ± 15	62 ± 38
MRC dyspnoea score		3 (3-4)*	1 (1-1)	3 (3-3)
Height (cm)		167 ± 10	171 ± 7	168 ± 9
Weight (kg)		68 ± 15	81 ± 16	75 ± 14
BMI ($kg.m^{-2}$)		24.2 ± 4.5	27.7 ± 4.8	26.7 ± 4.5
FEV_1 (L)		1.12 ± 0.6*	2.88 ± 0.4	1.2 ± 0.4
FEV_1 (% pred)		45 ± 19*	102 ± 13	48 ± 19
FVC (L)		2.7 ± 1*	3.9 ± 0.6	2.6 ± 0.7
FVC (% pred)		81 ± 23*	110 ± 14	81 ± 22
FEV_1/FVC		0.44 ± 0.13*	0.74 ± 0.04	0.47 ± 0.14
$\dot{V}O_{2peak}$ ($ml.min^{-1}$)		1019 ± 343*	1867 ± 394	1158 ± 333
$\dot{V}O_{2peak}$ ($ml.kg^{-1}.min^{-1}$)		15.0 ± 3.2*	23.3 ± 4.6	15.4 ± 2.9
Peak workload (W)		69 ± 35*	147 ± 24	80 ± 30
Peak heart rate (bpm)		124 ± 17*	150 ± 22	118 ± 23
Reason for stopping exercise	Breathlessness	67%*	22%	67%
	Leg fatigue	17%	67%	17%
	Breathlessness and leg fatigue	17%	11%	17%