Respiratory Medicine (2010) **104**, 675–681

available at www.sciencedirect.com

ScienceDirect

journal homepage: www.elsevier.com/locate/rmed

Plasma ammonia response to incremental cycling and walking tests in COPD

L.D. Calvert*, **M.C. Steiner**, **M.D. Morgan**, **S.J. Singh**

Department of Respiratory Medicine, Institute for Lung Health, University Hospitals of Leicester NHS Trust, Glenfield Hospital, Groby Road, Leicester, LE3, UK

Received 2 October 2009; accepted 23 November 2009
Available online 8 December 2009

KEYWORDS
Adenine nucleotide;
Metabolic stress;
Skeletal muscle dysfunction;
Treadmill

Summary
Objective: It is well documented that plasma ammonia accumulates during exercise under conditions of metabolic stress. Metabolic stress (when skeletal muscle ATP supply fails to meet demand) occurs at low work rates during cycling in patients with COPD, but not been described during walking. Walking is an important activity for many patients with COPD and is commonly prescribed in pragmatic outpatient pulmonary rehabilitation programmes. In this study we explored whether metabolic stress occurs during incremental walking at the low work rates these patients achieve.
Methods: Twenty-nine subjects with stable COPD [mean(SD) age 68(7) years, FEV_1 50(19)% predicted] performed maximal cardiopulmonary exercise tests on a cycle ergometer and treadmill. Plasma ammonia concentration was measured at rest, 1 and 2 min of exercise, peak exercise and 2 min recovery.
Results: Subjects achieved mean(SD) cycle work rate of 57(20) W with VO_{2max} 15.5(4.6) ml/min per kg, and treadmill distance 284(175) m with VO_{2peak} 16.8(4.2) ml/min per kg. Plasma ammonia concentration rose significantly ($p < 0.001$) with walking [mean(SEM) change 24.7(3.8) μmol/l] and cycling [mean(SEM) change 35.2(4.3) μmol/l], but peak exercise ammonia was lower in walking ($p < 0.01$). In a subgroup of subjects ($n = 7$) plasma ammonia did not rise during either cycling or walking despite similar lactate rise and peak exercise indices.
Conclusion: Our data indicate that failure of muscle ATP re-synthesis to meet demand and development of metabolic stress can occur during walking in COPD patients at the low work rates these patients achieve. This may therefore be a factor contributing to exercise limitation independent of ventilatory limitation.

* Corresponding author. Department of Respiratory Medicine, Peterborough District Hospital, Thorpe Road, Peterborough, PE3 6DA, UK. Tel.: +44 1733 875065; fax: +44 1733 875287.
E-mail address: lori.calvert@pbh-tr.nhs.uk (L.D. Calvert).

0954-6111/$ - see front matter © 2009 Elsevier Ltd. All rights reserved.
doi:10.1016/j.rmed.2009.11.012

Introduction

Exercise intolerance is a major factor limiting participation in activities of daily living in people with chronic obstructive pulmonary disease (COPD) and patients commonly complain of limited ability to perform walking exercise. Pulmonary rehabilitation programmes aim to improve exercise capacity, and in many centres walking is the most frequent mode of exercise employed.

It is now appreciated that impaired lower limb skeletal muscle function has a significant impact on exercise capacity in patients with COPD.[1] The energy for muscular contraction is provided by the dephosphorylation of adenosine 5-triphosphate (ATP) to ADP. When ATP utilisation during exercise cannot be matched by its re-synthesis, ATP depletion occurs due to irreversible deamination to form IMP and ammonia.[2,3] This is associated with a rise in plasma ammonia. These circumstances have been termed 'metabolic stress' because of the detrimental impact on muscle contraction[4,5] and association with fatigue in healthy subjects.[4,5] The accumulation of ammonia in the blood can be used as an indicator of ATP loss and the development of metabolic stress in exercising skeletal muscle.[2,6,7]

Skeletal muscle ATP depletion[8] and plasma ammonia accumulation[9] has been demonstrated during cycle exercise in COPD patients. Data from the literature suggests that the metabolic and physiological responses to walking and cycling can differ significantly,[10–13] and the degree to which walking exercise imposes skeletal muscle metabolic stress in COPD has not yet been established. However, understanding the magnitude of ATP mismatch and metabolic stress during walking may be important in making decisions on exercise prescription, for example during PR, in these patients.

In this study, plasma ammonia was used as a marker of skeletal muscle ATP depletion and metabolic stress. We hypothesised that metabolic stress would develop during walking despite the low work rates these patients achieve. In a cohort of COPD patients with significant exercise limitation, we examined firstly whether plasma ammonia accumulated during an incremental walking test, and secondly whether walking provoked a similar peak response to cycling.

In our previous work we observed, in a post hoc analysis, a subgroup of patients who did not demonstrate a significant rise in blood ammonia during cycling exercise despite showing a rise in blood lactate. We hypothesised that there would therefore be a subgroup of patients that would not develop plasma ammonia accumulation with either walking or cycling exercise tests.

Methods

Study population

Stable patients ($n = 29$) who met GOLD criteria for COPD[14] were recruited from the pulmonary rehabilitation waiting list at Glenfield Hospital. Patients were excluded if taking maintenance oral corticosteroids, had significant cardiac dysfunction, or had undergone pulmonary rehabilitation within the last 2 years. Full approval was obtained from the Leicestershire Research Ethics Committee and all participants provided informed written consent.

Study design

Subjects attended an initial visit for baseline measurements [spirometry performed to ERS standards (Vitallograph Model R, Buckingham, UK);[15] body mass index] and familiarisation tests on the cycle and treadmill. On a second visit at least 72 h later, subjects performed a maximal symptom-limited incremental exercise test on an electrically-braked cycle ergometer (Ergometric Er900; Ergoline GmbH, Bitz, Germany) with increments of 10 W/min, using a ramp protocol. Subjects re-attended after a further 72 h or more to perform a maximal symptom-limited treadmill exercise test (RAM 770CE Treadmill; RAM Medical and Industrial Instruments & Supplies, Padova, Italy). The incremental walking protocol mirrored the ISWT (initial speed 1.8 km/h, increasing every minute by 0.6 km/h, gradient 0°) because this field test is commonly used in clinical practice for assessment of exercise ability and as an outcome measure in pulmonary rehabilitation. Ventilation and gas exchange measurements were made throughout the exercise tests using a breath-by-breath computerised system (Zan-680 ErgoTest, Zan Messgeraete GmbH, Germany). End-exercise Borg breathlessness score and reason for termination were recorded.

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 throughout exercise, warmed to 50–55 °C. Blood was sampled for ammonia and lactate concentration during cycle and treadmill exercise tests at rest, at 1 min and 2 min of exercise, at peak exercise, and at 2 min after exercise cessation (recovery). Timing for blood tests was determined from our previous studies examining pattern of ammonia rise in COPD patients.[9] 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, 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.[9]

Data analysis

Using data from our previous study[9] we required 22 patients with an ammonia response to detect a 15 μmol/l within-group difference in peak exercise blood ammonia between the 2 exercise tests (80% power, $p = 0.05$). Normality of data was confirmed and significance was assumed at $p < 0.05$. Paired t-tests were used to evaluate differences between cycle and treadmill. Correlations between parameters were calculated with Pearson's correlation tests (SPSS package version 15.0, SPSS Inc, Chicago, USA). Subgroups were defined a priori by exercise-induced ammonia rise with cycling above (group 1) or below (group 2) 15 μmol/l. This was based on the 95% limit of agreement for resting variability of repeat measures of plasma ammonia (unpublished data in healthy subjects) and on our previous post hoc analyses in cycle exercise demonstrating