Respiratory Physiology & Neurobiology xxx (xxxx) xxx–xxx

Contents lists available at ScienceDirect

Respiratory Physiology & Neurobiology

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

Cough reflex sensitivity after exercise challenge testing in children with asthma

P. Ferenc[a], J. Fabry[a], T. Zatko[b], P. Kunc[a], J. Sojak[c], M. Grendar[d], R. Pecova[b,*]

[a] Clinic of Paediatric Respiratory Diseases and Tuberculosis, Jessenius Faculty of Medicine in Martin (JFM CU), National Institute of Paediatric Tuberculosis and Respiratory Diseases, Dolny Smokovec, Slovak Republic

[b] Comenius University in Bratislava, Jessenius Faculty of Medicine in Martin (JFM CU), Department of Pathological Physiology JFM CU and Biomedical Center Martin JFM CU, Slovak Republic

[c] Slovak Medical University in Bratislava, Faculty of Medicine, The Clinic of Otorhinolaryngology and Head and Neck Surgery, Central Military Hospital in Ruzomberok, Slovak Republic

[d] Comenius University in Bratislava, Jessenius Faculty of Medicine in Martin (JFM CU), Department of Bioinformatics of Biomedical Center Martin JFM CU, Slovak Republic

ARTICLE INFO

Keywords:
Asthma
Exercise
Cough
Cough sensitivity
Children

ABSTRACT

Bronchial challenge tests are commonly used in clinical medicine and research. The aim of this study was to clarify changes of cough reflex sensitivity before and after exercise challenge testing in asthma children.

42 asthmatic children were submitted to cough reflex sensitivity measurement – capsaicin aerosol in doubling concentrations (from 0.61 to 1250 micromol/l) was inhaled by a single breath method – before and after exercise challenge testing. Concentrations of capsaicin causing two (C2) and five coughs (C5) were reported. Children' (31 boys and 11 girls, mean age 14.05 ± 2.08 yrs) cough reflex sensitivity (median, with the 95% CI) for C2 was before exercise challenge testing 9.77 (6.10–10.99) micromol/l vs. children' C2 after it 7.32 (6.10–14.65) (P = 0.58 for the Wilcoxon two sample paired test). Children' C5 was before exercise challenge testing 19.53 (14.65–80.57) micromol/l vs. C5 after it 39.06 (24.42–58.59) micromol/l (P = 0.09 for the Wilcoxon two sample paired test).

We conclude that cough reflex sensitivity was not significantly changed after exercise challenge testing in children with asthma.

1. Introduction

Cough is one of the most common symptoms presenting to doctors and when present in children, is associated with impaired quality of life and burden to parents (Marchant et al., 2008). Cough associated with exercise is often considered a symptom of asthma (Dryden et al., 2010; Suguikawa et al., 2009). Exercise-induced cough is frequent in asthmatic patients (Boulet and O'Byrne, 2015) or even in athletes developing airway inflammation (Kennedy et al., 2015), suggesting the potential of exercise to trigger cough.

It is now widely accepted that, with rare exceptions, in chronic cough there is hypersensitivity of the vagal afferent nerves or an alteration of the central processing of their input, regardless of the underlying etiology of the cough (Fowles et al., 2017). In hypersensitivity, even trivial stimulation of these sensory nerves leads to the urge to cough. The cause of this hypersensitivity is not fully understood but the concept of cough hypersensitivity syndrome is widely agreed upon in the respiratory community (Morice et al., 2014; Morice et al., 2015).

Increased cough reflex sensitivity was evaluated in patients suffering from allergic rhinitis (Pecova et al., 2005) or atopic dermatitis (Pecova et al., 2003) with no clinical symptoms from lower airways.

Previous studies have shown an unchanged cough reflex sensitivity during exercise in the ovalbumine sensitized and challenged rabbits in contrast with the decrease of cough reflex sensitivity in the control animals (Tiotiu et al., 2017). Cough response to capsaicin is down regulated by exercise both in healthy children and adults (Demoulin-Alexikova et al., 2017).

The main objective of this study was to clarify changes of cough reflex sensitivity in relation to the exercise challenge testing in children with asthma.

We hypothesized that astmatic children have no change in cough reflex sensitivity after exercise challenge testing.

* Corresponding author at: Department of Pathological Physiology Comenius University in Bratislava Jessenius Faculty of Medicine in Martin Mala Hora 4A 036 01 Martin Slovak Republic.

E-mail address: pecova@jfmed.uniba.sk (R. Pecova).

https://doi.org/10.1016/j.resp.2018.03.008
Received 22 December 2017; Received in revised form 3 March 2018; Accepted 13 March 2018

2. Methods

Children were referred to Clinic of Paediatric Respiratory Diseases and Tuberculosis, Jessenius Faculty of Medicine in Martin (JFM CU), National Institute of Paediatric Tuberculosis and Respiratory Diseases, Dolny Smokovec, Slovak Republic by their pediatric pulmonologist. Asthma was defined by a complaint of wheezing, cough, dyspnea or chest tightness at rest or on exercise and a positive response to exercise challenge. Children had no respiratory symptoms for at least 4 weeks and baseline FEV1 was more than 80%. Bronchodilatator treatment was discontinued 72 h before being examined.

All subjects underwent personal and family history taking, physical examination and initial screening of their basic lung functions measured by spirometry before and after capsaicin challenge (KoKo DigiDoser-Spirometer; nSpire health Inc., Louisville, CO, USA).

This prospective clinical study was approved by the institutional Research Ethics Committee and was performed according to the Declaration of Helsinki. Each parent of the observed child was properly informed about the study, about the cough reflex sensitivity and was asked to sign an informed consent.

CRS was assessed using capsaicin cough challenge, performed in agreement with the ERS guidelines (Morice et al., 2007) with modification for pediatric use (Varechova et al., 2008) (we used a compressed air-driven nebuliser (model 646; DeVilbiss Health Care, Inc., Somerset, PA, USA) controlled by a dosimeter (KoKo DigiDoser-Spirometer; nSpire health Inc., Louisville, CO, USA) with an inspiratory flow regulator valve added (RIFR; nSpire health Inc., Louisville, CO,USA) to assign identical inspiratory flow rate during capsaicin inhalations in all subjects. Each subject inhaled saline randomly interposed among 12 inhalations of incremental capsaicin aerosol concentrations (0.61-1250 micromol/l). Each administration of saline and capsaicin aerosol was performed at 1 min intervals with the inhalation time set at 400 msec. The number of coughs within 30 s after aerosol administration was counted by two independent observers. The endpoint of cough challenge was the inhalation of capsaicin concentration that provoked at least 5 coughs (C5) or when the maximum concentration of capsaicin (1250 micromol/l) was achieved. The concentration of capsaicin causing at least two coughs was assigned as C2 and concentration of capsaicin causing at least 5 coughs was assigned as C5. For children that did not cough at any concentration of capsaicin, CRS value was assigned 1250 micromol/l.

Baseline CRS measurement was realized 2 days before exercise challenge testing. The exercise challenge testing was carried out according to American Thoracic Society Guidelines for methacholine and exercise challenge testing (Crapo et al., 2000). Exercise challenge testing was performed by the same doctor in all patients. The CRS measurement after exercise was realized by the same method within the interval of 60 min after the exercise challenge testing. This interval served to avoid the effect of tachyphylaxis (Morice et al., 2007).

2.1. Statistical analysis

Obtained parameters of CRS were mutually statistically compared and relation between CRS before and after exercise challenge testing was statistically evaluated. The results were evaluated separately for each individual and subsequently for the group as a whole. The results were expressed as median values, the level of statistical significance was determined as $P < 0.05$ and $P < 0.01$. Wilcoxon test (paired for CRS before and after exercise; unpaired for CRS in girls vs boys) with continuity correction was used. Correlation analysis of CRS testing with the spirometric data was used (P value for Spearman correlation coefficient was calculated, the level of statistical significance was determined as $P < 0.05$). Software used: R Core Team (2015), R: A language and environment for statistical computing (R Foundation for Statistical Computing, Vienna, Austria, URL – https://www.R-project.org/, R version 3.2.3, 2015-12-10).

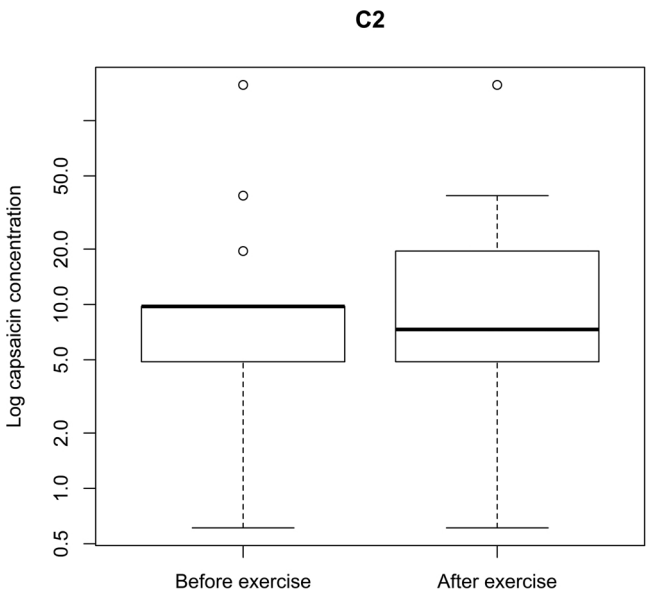

Fig. 1. Cough reflex sensitivity (CRS) – C2 value before and after exercise challenge testing in asthma children. C2: the concentration of capsaicin causing at least two coughs.

3. Results

Forty-two asthmatic children (31 boys and 11 girls, mean age 14.05 ± 2.08 yrs) were prospectively recruited into the study.

Concentrations of capsaicin causing two (C2) and five coughs (C5) were reported. Children' (31 boys and 11 girls, mean age 14.05 ± 2.08 yrs) cough sensitivity (median, with the 95% CI) for C2 was before exercise challenge testing 9.77 (6.10–10.99) micromol/l vs. children' C2 after exercise challenge testing 7.32 (6.10–14.65) ($P = 0.58$ for the Wilcoxon two sample test) (Fig. 1). Children' C5 was before exercise challenge testing 19.53 (14.65–80.57) micromol/l vs. C5 after exercise challenge testing 39.06 (24.42–58.59) micromol/l ($P = 0.09$ for the Wilcoxon two sample test) (Fig. 2).

With regard to the number of girls in the study group, there was a non-significant tendency to changes of the sensitivity of cough reflex in girls and boys (Plevkova et al., 2017).

There was no significant airflow limitation pre-exercise vs post-exercise (Table 1). Correlation analysis of cough reflex sensitivity testing

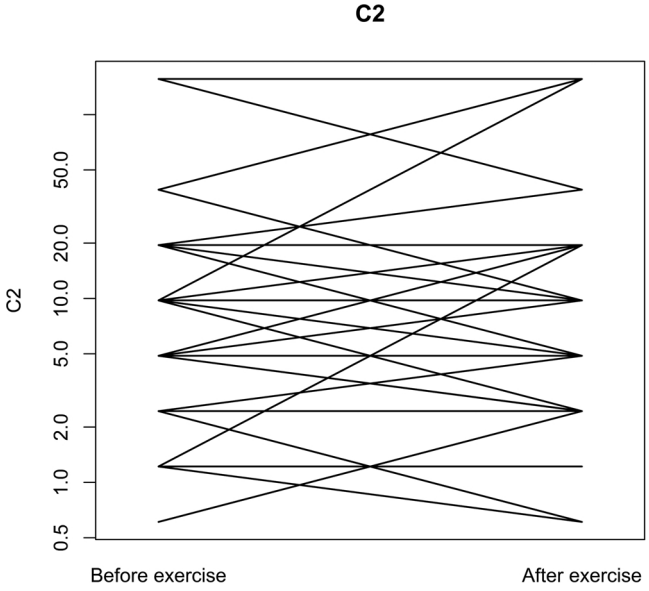

Fig. 2. Individual values of C2 before and after exercise in asthma children.