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Cough and exhaled nitric oxide levels: what happens with exercise?

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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 (1). Cough associated with exercise is often considered a symptom of asthma. (2, 3) However, some clinicians have observed that exercise can exacerbate cough in any child with a pre-existing cough, irrespective of diagnosis. Yet, in adult studies on cough sensitivity to fog (which is dependent on minute volume), desensitization of the cough reflex occurs post-exercise (4). Increased cough is usually associated with increased cough reflex sensitivity. (5) Thus, there is controversy on the relationship between cough and exercise and there are currently no published data that have measured cough frequency objectively pre- and post-exercise in children. Indeed there is little published research on cough and exercise in either adults or children (6).

Fractional exhaled nitric oxide (FeNO), is an eosinophilic inflammatory marker measured by a non-invasive test. It is elevated in steroid-naive children with atopy and asthma. Some have advocated its use to diagnose and/or monitor asthma (7). There are no reported studies examining FeNO in children with exercise-associated cough in the absence of exercise-induced broncho-constriction (EIB). Two studies on children with asthma provided conflicting results regarding the relationship between FeNO and EIB. Terada et al. (8) stated that FeNO decreased during EIB, whereas Scollo et al. (9) concluded that FeNO did not change in children with asthma after an exercise challenge.

In the absence of any prospective study relating cough frequency to exercise and FeNO, we recruited 50 children with and without EIB. Our primary aim was to examine whether children with a pre-existing cough have an increase in cough frequency during and post-exercise. We hypothesized that children with any coughing illness will have an increase in cough frequency post-exercise regardless of the presence of exercise-induced broncho-constriction (EIB) or atopy. In addition, we hypothesized that Fractional exhaled nitric oxide (FeNO) levels decreases post-exercise regardless of the presence of EIB or atopy. Of the 50 children recruited (35 with cough, 15 control), 7 had EIB. Children with cough had a significant increase in cough counts (median 7.0, inter-quartile ranges, 0.5, 24.5) compared to controls (2.0, IQR 0, 5.0, p = 0.028) post-exercise. Presence of atopy or EIB did not influence cough frequency. FeNO level was significantly lower post-exercise in both groups but the change was not influenced by atopy or EIB. Cough post-exertion is likely a generic response in children with a current cough. FeNO level decreases post-exercise irrespective of the presence of atopy or EIB. A larger study is necessary confirm or refute our findings.

Keywords: cough, pediatrics, exercise-induced broncho-constriction, atopy, FeNO
MATERIALS AND METHODS

PARTICIPANTS

The inclusion criteria were children aged over 6 years. Coughers had a current chronic (duration >4 weeks) cough at the time of testing. Children with cough were recruited from the outpatient clinics when the clinicians looking after these children were querying if the cough was related to EIB. Controls were children without a current cough and were otherwise well. Controls were recruited from family and friends. We excluded children who were unable to either perform spirometry or run on a treadmill.

The study was approved by the Ethics Committee of the Children’s Health Services, Brisbane. Informed and written consent was obtained from all parents of participants and assent from appropriately aged children. The clinical trial was registered with the Australia New Zealand Clinical Trials Registry (ACTRN12607000511437).

PROTOCOL

Children and their parents were approached when they attended a routine clinic visit at the tertiary hospital. After informed consent was obtained (Figure 1), we recorded the child’s demographics. A series of tests were performed over 2 days. On day 1 all children undertook: pre-baseline measurements (FeNO, spirometry); had a voice recorder fitted (for cough counts) and a skin prick test (SPT). Then the children were randomized to one of two sequences: (1) exercise challenge performed on day 1 with dry powder mannitol (Aridol™) challenge on day 2, or (2) mannitol challenge on day 1 with exercise challenge on day 2. Randomization was undertaken by an independent person off-site using a computer generation sequence list in permuted blocks 2–4. Allocation was fully concealed using opaque covers. Our primary outcome measures were cough frequency pre- and post-exercise challenge, and FeNO levels in children with cough and controls. In this manuscript, we are reporting data relating to the exercise test component of the study.

FeNO, SPIROMETRY, AND SKIN PRICK TEST

Fractional exhaled nitric oxide was measured with a chemiluminescence analyzer (Sievers NOA 280i, CO, USA) with children exhaling at 0.05 L/s for >4 s in order to obtain a stable nitric oxide value for >2 s, in accordance with ATS/ERS guidelines (10). Exhalations were repeated until three measurements were within 5% of the mean. Spirometry was performed after FeNO measurements using ATS/ERS criteria and the % predicted calculated based on height, age and sex matched reference values [Eigen (11) and Hibbert (12)].

Allergens used for SPT were alternaria mold, cat hair, cockroach mix, dust mite DPT, couch grass, and grass mix #7 (Hollister-Stier, WA, USA). Negative (diluents) and positive (histamine) controls were also used. Atopy was defined as wheal ≥3 mm larger than that of the histamine control after 15 min.

OBJECTIVE COUGH MONITORING

A digital voice recorder (Sony PCP330F, Japan) recorded continuously for 24 h after being fitted post-randomization. The file (MP3) was downloaded and replayed. The time and number of coughs were manually counted by a person blinded to the child’s other data and recorded in a spreadsheet. Whilst the MP3 file was being listened to, the times of all challenges were recorded, enabling the coughs to be analyzed dependent on challenges. Additionally, the listener recorded the time the child seemed to be sleeping and awake. Wakefulness was defined as when the child could be heard talking or being active.

EXERCISE CHALLENGE

The exercise challenge was undertaken in accordance to on ATS/ERS guidelines (13) using a treadmill (Trackmaster™ TMX425CP, USA). Room temperature and relative humidity were regulated by air conditioning to keep the water content ≤10 mg/mL (14). Children were required to withhold medications that could influence bronchial challenges (Table A1 in Appendix).
Pulse oximetry was monitored during exercise testing. Treadmill slope and speed were adjusted to achieve target heart rates of at least 85% of maximum predicted (220 – age in years) within the first 2–4 min of exercise (15). Children continued exercise to achieve at least 4 min at the target heart rate, or, alternatively, until symptoms of dyspnea or fatigue required the patient to stop. Spirometry was performed post-exercise at 1, 5, 10, and 15 min after the end of exercise. EIB was defined as a decrease in FEV\textsubscript{1} \geq 13% from baseline measurement (16).

STATISTICAL ANALYSES

Descriptive statistics were used to summarize the demographic characteristics of the patients. Data that had a normal distribution were described using means and standard deviations (SD); medians and inter-quartile ranges (IQR) were used otherwise. Chi squared tests were employed for categorical data. Correlations were made using Spearman’s correlation (\(r_s\)). Kruskal–Wallis analyses were used for group comparisons. Two-tailed \(p\) values of <0.05 were considered significant. All analyses were performed using a statistical package, SPSS Version 13.

RESULTS

We recruited 50 children between March 2006 and August 2008, of whom 49 were randomized. One child was not randomized as that parent did not consent to the manitol challenge. One child (aged 6 years) commenced but could not complete the exercise challenge (cried) nor the manitol challenge. Thus, data for cough and exercise were limited to 48 children (Table 1). Although the clinicians’ question was whether the current cough related to EIB, the underlying etiology of children with cough at the point of enrollment were: unknown, i.e., referred for determination of cough (\(n = 11,33.3\%\)), asthma (\(n = 10,30.3\%\)), cystic fibrosis (but referred for exercise test due to suspected EIB) (\(n = 8, 24.3\%\)), suspected tracheomalacia (\(n = 1, 3\%\)), congenital lobar emphysema (\(n = 1, 3\%\)), follicular bronchiolitis (\(n = 1, 3\%\)), and viral upper respiratory tract infection (\(n = 1, 3\%\)). In the 11 children who did not have any diagnosis at the point of referral, the final diagnosis was asthma = 4, non-cystic fibrosis bronchiectasis = 2, and protracted bacterial bronchitis = 5.

COUGH COUNTS

The median baseline cough count whilst the child was awake (total number of coughs not during airway challenges/hours awake) was significantly higher in the coughers compared to controls (Table 2). There was no significant difference between cougher and control groups in the number of coughs 30 min pre-exercise. However post-exercise, the median number of coughs was significantly higher in the coughers compared to controls (Figure 2). As the control children had little cough, the difference in cough frequency between 30 min pre and 30 min post-exercise was not significant between groups. None of the controls coughed during the exercise challenge but 13 of 33 children in the coughing group coughed [median number of coughs in these 13 children was 5 (IQR 2, 27)].

There was no significant difference in change of cough frequency in the 30 min post-exercise between children with and without EIB [EIB positive (\(n = 7\)): median 15.0 (IQR 0, 44.3); EIB negative (\(n = 31\)): median 5.0 (IQR 0, 16.0); \(p = 0.63\)]. There was also no difference in cough frequency between children grouped by presence of atopy [atopy present (\(n = 19\)): median 3.5 (IQR 1.7, 7.5); atopy absent (\(n = 29\)): 3.8 (IQR 0.7, 11.9); \(p = 0.91\)]. There was no difference in cough frequency post exercise when grouping by diagnosis in the children with cough (\(p = 0.78\)).

FeNO LEVELS

At baseline measurement of FeNO, there was no significant difference (\(p = 0.089\)) between the coughers and controls (Table 1). In both groups, FeNO levels fell post-exercise at 5 min compared to baseline and there was no significant difference between groups [Coughers: median −2.6 ppb (IQR −0.55, −4.35); controls: −5.9 (IQR −1.0, −7.4), \(p = 0.158\)]. The fall in FeNO was larger in children with EIB [median −7.5 (IQR −3.0, −15.3)] compared to those without EIB (median −2.5, IQR −0.7, −5.98) but the difference did not reach significance (\(p = 0.06\)). There was no significant difference in decrease of FeNO between those with atopy (median −3.65, IQR −7.1, −0.88) and those without atopy (median −2.6, IQR −6.45, −0.75), \(p = 0.822\).

DISCUSSION

To our knowledge, this study is the first to evaluate the effect of exercise on objective cough counts in children with and without a pre-existing cough. Our study found that with exercise, children with a current cough have an increase in cough frequency even in the absence of EIB or atopy. Also, the trend demonstrated a larger decrease in FeNO levels post-exercise in children with EIB, compared to those without EIB. Finally, atopy did not influence the change in FeNO levels post-exercise.

Cough with exercise or post-exercise is not rare and is sometimes used as a marker of asthma in children and adults (2, 3). Delineating whether exercise-associated cough really reflects asthma would be useful in clinical practice, particularly in children. Yet, to date there are no publications that have objectively quantified exercise-associated cough and examined its association with EIB in children. Objective quantification of cough is important in research studies on cough (5). In our cohort, albeit small, we found that post exercise cough objectively quantified was significantly higher in coughers (with and without EIB or atopy).
Table 2 | FeNO and objective cough counts between the groups.

|                          | Coughers (N = 33) | Controls (N = 15) | p Value |
|--------------------------|-------------------|-------------------|---------|
| EIB (≥ 13% fall in FEV₁); n (%) | 7 (20)            | 0                 | 0.06    |
| FeNO at 5 min post exercise (ppb)  | 9.2 (5.3, 28.1)   | 11.4 (7.2, 23.5)  | 0.37    |
| Number of coughs in 30 min pre-exercise  | 2.0 (0, 5.0)     | 0 (0, 2.75)       | 0.11    |
| Number of cough in 30 min post-exercise  | 7.0 (0.5, 24.5)   | 2.0 (0, 5.0)      | 0.03    |
| Difference in cough counts (post 30 min minus pre 30 min)  | 5.5 (0, 18.8)    | 0 (−2.2, 0)       | 0.09    |
| Coughs/hr while awake (time excludes AHR challenges)  | 6.7 (2, 12.2)    | 1.2 (0.4, 2.9)    | 0.001   |

*Median (IQR).

The bold font highlights statistical significance.
Another limitation is the heterogenous nature of the children with cough. However, our cohort represented real-life clinical settings where clinicians queried whether the current cough with exercise is a reflective of EIB and hence whether or not the child should receive more asthma medications. In clinical practice, even children with an underlying disorder such as cystic fibrosis may have increased cough with exercise that may or may not be reflective of their underlying respiratory diagnosis.

In spite of our study’s limitations, we have provided novel data relating cough frequency objectively measured with exercise in children with and without cough. Further we examined this relationship with respect to FeNO levels, EIB, and atopy. In conclusion, children with current cough have increased cough frequency post exercise even in the absence of EIB. In the absence of other symptoms, exercise-induced cough is likely a poor marker of asthma but a larger cohort study is required to verify whether children with EIB cough more than those without EIB in response to exercise.

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REFERENCES

1. Marchant JM, Newcombe PA, Juniper EF, Sheffield JK, Stathis SL, Chang AB. What is the burden of chronic cough for families? Chest (2008) 134:630–9. doi:10.1378/chest.07-2236
2. Dryden DM, Swoon CH, Stickland MK, et al. Exercise-Induced Bronchoconstriction and Asthma. Evidence Report/Technology Assessment No. 189 (Prepared by the University of Alberta Evidence-based Practice Center under Contract No. 290-2007-10021-I) AHRQ Publication No. 10-E001. Rockville, MD: Agency for Healthcare Research and Quality (2010).
3. Sugukawa TR, Garcia CA, Martinez EZ, Vianna EO. Cough and dyspnea during bronchoconstriction: comparison of different stimuli. Cough (2009) 5:6. doi:10.1186/1745-9974-5-6
4. Lavorini F, Fontana GA, Chellini E, Magni C, Duranti R, Widicombe J. Desensitization of the cough reflex by exercise and voluntary isocapnic hyperventilation. J Appl Physiol (2010) 108:1061–8. doi:10.1152/japplphysiol.00423.2009
5. Chang AB. Therapy for cough: where does it fall short? Expert Rev Respir Med (2011) 5:503–15. doi:10.1586/ers.11.35
6. Widdicombe J, Fontana G, Gibson P. Workshop – cough: exercise, speech and music. Pulm Pharmacol Ther (2009) 22:143–7. doi:10.1016/j.pupt.2008.12.009
7. Sefer S. Facing the challenges of childhood asthma: what changes are necessary? J Allergy Clin Immunol (2005) 115:685–8. doi:10.1016/j.jaci.2005.01.031
8. Terada A, Fujisawa T, Togashi K, Miyazaki T, Katsumata H, Atsuta J, et al. Exhaled nitric oxide decreases during exercise-induced bronchoconstriction in children with asthma. Am J Respir Crit Care Med (2001) 164:1879–84. doi:10.1164/ajrccm.164.10.2009105
9. Scollo M, Zanconato S, Onaroglu R, Zaramella C, Zacchello F, Baraldi E, et al. Exhaled nitric oxide and exercise-induced bronchoconstriction in asthmatic children. Am J Respir Crit Care Med (1999) 160:1047–50.
10. Sillokk PE, Erurum SC, Lundberg JO, George SC, Marcinz N, Hunt JJ, et al. ATS workshop proceedings: exhaled nitric oxide and nitric oxide oxidative metabolism in exhaled breath condensate. Proc Am Thorac Soc (2006) 3:31–45. doi:10.1513/pats.200406-710ST.
11. Eigen H, Bieder H, Grant D, Christof K, Terrill D, Heilman DK, et al. Spirometric pulmonary function in healthy preschool children. Am J Respir Crit Care Med (2001) 163:619–23. doi:10.1164/ajrccm.163.3.2002054
12. Hibbert ME, Lannigan A, Landau LI, Phelan PD. Lung function values from a longitudinal study of healthy children and adolescents. Pediatr Pulmonol (1989) 7:101–9. doi:10.1002/ppul.1950072009
13. Crapo RO, Casaburi R, Coates AL, Enright PL, Hankinson JL, Irvin CG, et al. Exhaled nitric oxide and nitric oxide production during exercise. J Appl Physiol (1999) 87:101–9. doi:10.1152/jappl.1999.86.1.99
14. Haby MM, Anderson SD, Prist JK, Mells CM, Twiele BG, Woolcock AL. An exercise challenge protocol for epidemiological studies of asthma in children: comparison with histamine challenge. Eur Respir J (1994) 7:43–9. doi:10.1183/09031936.94.07010043
15. Carlsen KH, Engh G, Mark M. Exercise-induced bronchoconstriction depends on exercise load. Respir Med (2000) 94:750–5. doi:10.1053/rmed.2000.0809
16. Godfrey S, Springer C, Bar-Yishay A. Cut-off points defining normal and asthmatic bronchial reactivity to exercise and inhalation challenges in children and young adults. Eur Respir J (1999) 14:659–68. doi:10.1183/1399-3003.1999.14c28.x
17. Sheppard D, Rizk NW, Boushey HA, Bethel RA. Mechanism of cough and bronchoconstriction induced by distilled water aerosol. Am Rev Respir Dis (1983) 127:691–4.
18. Koskela HO, Kontra KM, Purokivi MK, Randell JT. Interpretation of cough provoked by airway challenges. Chest (2005) 128:329–35. doi:10.1378/chest.128.5.3329
19. Koskela HO, Martens R, Branan JD, Anderson SD, Leppu P, Chan HK. Dissociation in the effect of nedocromil on mannitol-induced cough or bronchoconstriction in asthmatic subjects. Respir Med (2005) 10:442–8. doi:10.1111/j.1440-1644.2005.00724.x
20. Kippelen P, Caillaud C, Robert E, et al. Guidelines for the treatment of chronic cough in children with histamine challenge. Eur Respir J (2002) 21:1280–9. doi:10.1183/09031936.02.00202
21. Persson MG, Wiklund NP, Gustafsson LE. Endogenous nitric oxide in single exhalations and the change during exercise. Am Rev Respir Dis (1995) 152:329–35. doi:10.1183/1399803.1995.152.5.3329
22. Phillips CR, Giraud GD, Holden WE. Exhaled nitric oxide during exercise: site of release and modulation by ventilation and blood flow. J Appl Physiol (1996) 80(6):1865–71.
23. Persson MG, Wilkund NP, Gustafsson LE. Endogenous nitric oxide in single exhalations and the change during exercise. J Appl Physiol (1995) 79:1210–4. doi:10.1152/jappl.1995.79.4.1210
24. Chang AB, Gibson PG, Willis C, Petsky HL, Widdicombe JG, Masters IB, et al. Do sex and atopy influence cough outcome measurements in children? Chest (2011) 140(2):324–30. doi:10.1378/chest.10-2507
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## APPENDIX

### Table A1 | Drugs withheld prior to commencement of protocol.

| Drug                                      | Duration  |
|-------------------------------------------|-----------|
| Long acting beta agonists                 | For 12 h  |
| Beta-2-agonists                           | For 6–8 h |
| Singulair (leukotriene-receptor antagonist)| For 4 days|
| Sodium cromoglicate and nedocromil       | For 8 h   |
| Antihistamines                            | For 72 h  |
| Inhaled corticosteroids                   | For 12 h  |
| Caffeine (cola, chocolate, coffee, tea)   | For 8 h   |
| Strenuous exercise                        | For 6 h   |