

Available online at [www.sciencedirect.com](http://www.sciencedirect.com)

SciVerse ScienceDirect

journal homepage: [www.elsevier.com/locate/rmed](http://www.elsevier.com/locate/rmed)

# Inspiratory airflow limitation after exercise challenge in cold air in asthmatic children

Jean M. Driessen<sup>a,\*</sup>, Job van der Palen<sup>b,c</sup>, Wim M. van Aalderen<sup>d</sup>,  
Frans H. de Jongh<sup>b,d</sup>, Boony J. Thio<sup>a</sup>

<sup>a</sup> Department of Pediatrics Medisch Spectrum Twente, P.O. Box 50 000, 7500 KA Enschede, The Netherlands

<sup>b</sup> Department of Pulmonology, Medisch Spectrum Twente, Enschede, The Netherlands

<sup>c</sup> Department of Research Methodology, Measurement and Data Analysis, University of Twente, Enschede, The Netherlands

<sup>d</sup> Department of Pediatric Respiratory Medicine and Allergy, Emma Children's Hospital, AMC, Amsterdam, The Netherlands

Received 23 March 2012; accepted 25 June 2012

Available online 11 July 2012

## KEYWORDS

Airway  
hyperresponsiveness;  
Asthma in children;  
Extrathoracic airway  
hyperreactivity;  
Exercise induced  
asthma

## Summary

Methacholine and histamine can lead to inspiratory flow limitation in asthmatic children and adults. This has not been analyzed after indirect airway stimuli, such as exercise. The aim of the study was to analyze airflow limitation after exercise in cold, dry air.

72 asthmatic children with mild to moderate asthma (mean age  $13.2 \pm 2.2$  yrs) performed a treadmill exercise challenge. A fall of  $>10\%$  in  $FEV_1$  was the threshold for expiratory flow limitation and a fall of  $>25\%$  of  $MIF_{50}$  was the threshold for inspiratory flow limitation. The occurrence of wheeze, stridor and cough were quantified before and after exercise.

After exercise, the mean fall in  $FEV_1$  was  $17.7 \pm 14.6\%$ , while the mean fall in  $MIF_{50}$  was  $25.4 \pm 15.8\%$ ; no correlation was found between fall in  $FEV_1$  and  $MIF_{50}$  ( $R^2$ : 0.04;  $p = 0.717$ ). 53 of the 72 children showed an inspiratory and/or expiratory airflow limitation. 38% (20/53) of these children showed an isolated expiratory flow limitation, 45% (24/53) showed both expiratory and inspiratory flow limitation and 17% (9/53) showed an isolated inspiratory flow limitation. The fall in  $FEV_1$  peaked 9 min after exercise and correlated to expiratory wheeze. The fall in  $MIF_{50}$  peaked 15 min after exercise and correlated to inspiratory stridor. The time difference in peak fall between  $FEV_1$  and  $MIF_{50}$  was statistically significant (5.9 min;  $p < 0.001$ , 99% CI: 2.3–9.5 min).

**Abbreviations:** EIB, exercise induced bronchoconstriction; VCD, vocal cord dysfunction; RAST, radioallergosorbent test; ACQ, asthma control questionnaire;  $FEV_1$ , forced expiratory volume in the first second;  $MIF_{50}$ , maximal mid inspiratory flow; SD, standard deviation; CI, confidence intervals; FVC, forced vital capacity; ICS, inhaled corticosteroid; LABA, long acting bronchodilating agent; NCS, nasal corticosteroid.

\* Corresponding author. Tel.: +31 053 4872310; fax: +31 053 4872326.

**E-mail addresses:** [jeandriessen@gmail.com](mailto:jeandriessen@gmail.com), [jean.driessen@tjongerschans.nl](mailto:jean.driessen@tjongerschans.nl) (J.M. Driessen), [j.vanderpalen@mst.nl](mailto:j.vanderpalen@mst.nl) (J. van der Palen), [w.m.vanaalderen@amc.uva.nl](mailto:w.m.vanaalderen@amc.uva.nl) (W.M. van Aalderen), [f.h.dejongh@amc.uva.nl](mailto:f.h.dejongh@amc.uva.nl) (F.H. de Jongh), [b.thio@mst.nl](mailto:b.thio@mst.nl) (B.J. Thio).

0954-6111/\$ - see front matter © 2012 Elsevier Ltd. All rights reserved.

<http://dx.doi.org/10.1016/j.rmed.2012.06.017>

In conclusion, this study shows that an exercise challenge in asthmatic children can give rise to inspiratory airflow limitation, which may give rise to asthma like symptoms.

© 2012 Elsevier Ltd. All rights reserved.

## Introduction

Asthma is a common, chronic disease in which indirect stimuli such as exercise may lead to transient narrowing of the lower airways resulting in an expiratory flow limitation (EIB).<sup>1</sup> A direct stimulus such as methacholine may lead to inspiratory as well as expiratory flow limitation in asthmatic children and adults.<sup>2–4</sup> It has been hypothesized that this inspiratory flow limitation is the result of chronic inflammation of the upper airways, a frequent co-morbidity in childhood asthma.<sup>5</sup>

In asthmatic children, exercise may also lead to symptoms mimicking EIB.<sup>6,7</sup> Vocal cord dysfunction (VCD) may lead to many exercise induced symptoms and can easily be mistaken for EIB.<sup>8</sup> In most cases of VCD exercise induced symptoms, such as stridor and acute 'choking' occur during exercise.<sup>9</sup> In field observations however, inspiratory stridor and dyspnoea may be present in asthmatic children well after exercise. We propose that an indirect challenge such as exercise may cause inspiratory airway obstruction like methacholine and histamine, mimicking asthma like symptoms.

The aim of the study was to analyze airflow limitation after exercise in cold, dry air.

## Materials and methods

### Study design

Open, cross sectional design. All exercise challenge tests were performed between January 1st 2005 and April 1st 2008.

### Subjects

Seventy-two children (mean age  $13.2 \pm 2.2$  yrs) with mild to moderate paediatrician diagnosed asthma in accordance with GINA guidelines with exercise induced dyspnoea were selected from the paediatric outpatient clinic of Medisch Spectrum Twente Hospital.<sup>10</sup> Most children used inhaled corticosteroids (79%) and had a history of allergy and 65 completed a radioallergosorbent test (RAST). None of the children were hospitalized for an exacerbation of asthma for at least 6 months prior to testing. Subjects were required to withhold the use of long acting bronchodilators for 24 h and the use of short acting bronchodilators for 8 h prior to the tests. No vigorous exercise was permitted for 4 h prior to the exercise challenge. All testing commenced in the clinical setting and the internal review board (Medisch Ethische Toetsings Commissie of the Medisch Spectrum Twente) filed no complaint to perform the study.

## Exercise challenge

Exercise testing was performed on a treadmill (Reebok®, TR1 premium run, Canton, MA, USA) according to ATS/ERS recommendations.<sup>11</sup> The exercise challenges were performed in the local ice skating rink, to obtain cold air ( $2-5$  °C,  $1-5$  mg l<sup>-1</sup> H<sub>2</sub>O). Children ran, nose clipped, on a treadmill with a 10° slope, for a 4 min period with a heart rate at 90 percent of predicted maximum (210-age) after an acclimatization period of 2 min.<sup>11,12</sup> The total exercise time was 6 min. Heart rate was monitored with a Polar Sport tester (Polar Electro®, Finland). A single observer (JD) quantified respiratory wheeze, inspiratory stridor and cough using auscultation.<sup>13</sup>

The asthma control questionnaire (ACQ) developed by Juniper and colleagues is a reliable and validated instrument to measure asthma control.<sup>14</sup> All children completed the original Dutch version of the ACQ before exercise. Responses were given on a 7-point scale and the overall score is the mean of 6 questions, with the question of the FEV<sub>1</sub> omitted. Well-controlled asthma was defined by an ACQ of less than 0.75 and uncontrolled asthma by an ACQ of more than 1.50; an ACQ between 0.75 and 1.49 was seen as an indifferent control of asthma.<sup>15</sup>

## Pulmonary function measurements

A Masterscope® Jaeger®, (IBM PS 235X; Jaeger, Würzburg, Germany) was used to measure lung volumes and flow-volume loops. This spirometer was calibrated on the morning of each study day. The flow-volume loop was recorded using ATS/ERS guidelines. After exercise flow volume loop measurements were repeated in duplex at 1, 3, 6, 9, 12, 15, 20 and 25 min. Pulmonary function was calculated from the best curve.

The best forced expiratory volume in the first second (FEV<sub>1</sub>) value was used for analysis of the expiratory airflow limitation and Zapletal reference values were used to calculate the predicted value of the FEV<sub>1</sub>.<sup>16</sup> A fall of more than 10% in FEV<sub>1</sub> was considered positive for expiratory flow limitation, as recommended by the ATS-ERS guidelines when evaluating EIB in a research setting.<sup>11</sup>

The best maximal mid inspiratory flows (MIF<sub>50</sub>), reaching a plateau and accompanied by a forced inspiratory vital capacity of more than 80% of baseline, were used to evaluate inspiratory flow limitation. A fall of more than 25% of MIF<sub>50</sub> was considered positive for inspiratory flow limitation.<sup>4,5</sup> Tomalek reference values were used to calculate the predicted value of the MIF<sub>50</sub>.<sup>17</sup>

## Statistical analysis

Results were expressed as mean values  $\pm$  standard deviation (SD) for normally distributed data, as median (range)

for non-normal data or as numbers with corresponding percentages if nominal or ordinal. Because of the large number of tests, we chose to set the level of significance at 0.01 (99% confidence intervals (CI)). To identify variables that were associated with inspiratory and expiratory flow limitation, unpaired *t*-tests or Mann–Whitney *U* tests were performed as appropriate. Between-group comparisons of nominal or ordinal variables were performed by Chi-square tests. SPSS® for Windows® version 15 (IBM, Chicago, IL, USA) was used to perform all analyses.

## Results

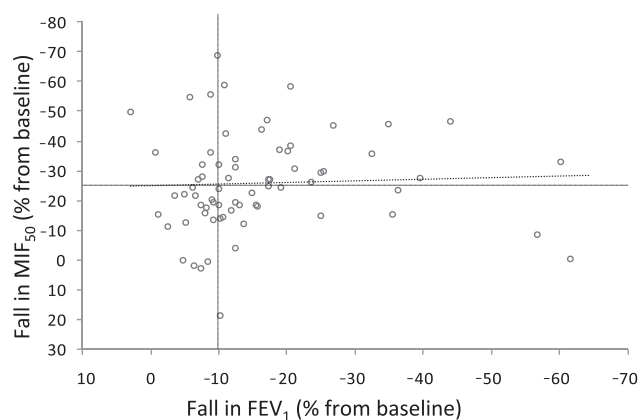
Seventy-two children with mild to moderate asthma performed an exercise challenge test in cold air. Baseline characteristics of the patients are shown in Table 1.

After exercise, the mean fall in FEV<sub>1</sub> was 17.1 ± 14.7%, while the mean fall in MIF<sub>50</sub> was 25.8 ± 16.1%. When plotting the fall in FEV<sub>1</sub> against the fall in MIF<sub>50</sub>, no correlation was found ( $R^2$ : 0.04;  $p$  = 0.717), as can be seen in Fig. 1.

Using the cut-off points as stated before (fall in FEV<sub>1</sub> of more than 10% and fall in MIF<sub>50</sub> of more than 25%) patients were divided into 4 subgroups, after exercise 26% of the patients did not show any flow limitation, while 74% of the patients showed a flow limitation (53/72). Of these, 38% (20/53) showed an isolated expiratory flow limitation, 45% (24/53) an expiratory and inspiratory flow limitation, and 17% (9/53) showed an isolated inspiratory flow limitation. It is remarkable that of the children without a significant fall in FEV<sub>1</sub>, almost half (9/19) showed a significant fall in MIF<sub>50</sub>; additionally, of the children without a significant fall in MIF<sub>50</sub>, almost half (20/39) showed a significant fall in FEV<sub>1</sub>. The mean time to maximum fall in FEV<sub>1</sub> was 9.2 ± 7.6 min after exercise, while the mean time to maximum fall in MIF<sub>50</sub> was 15.1 ± 7.9 min after exercise (Difference 5.9 min;  $p$  < 0.001, 99% CI: 2.3–9.5 min). The

**Table 1** Baseline characteristics. Data are given in mean ± SD or numbers (percentage) FEV<sub>1</sub>: Forced expiratory volume in 1 s. FVC: Forced vital capacity, MIF<sub>50</sub>: Maximal mid inspiratory flow, ICS: Inhaled corticosteroid, LABA: Long acting bronchodilating agent, NCS: Nasal corticosteroid, ACQ: Asthma control questionnaire.

Patient characteristics	Value
Age (years)	13.2 ± 2.2
Male gender	48 (67)
Height (cm)	168 ± 9
FEV <sub>1</sub> (% of predicted)	101.4 ± 9.5
FEV <sub>1</sub> /FVC ratio	83.4 ± 16.5
MIF <sub>50</sub> (% of predicted)	129.7 ± 28.6
ICS	57 (79)
ICS + LABA	44 (61)
NCS	19 (26)
ACQ ≤ 0.75	38 (54)
0.75 < ACQ < 1.50	20 (29)
ACQ ≥ 1.50	12 (17)
House dustmite allergy	43 (60)
Grass - tree pollen allergy	38 (53)
Food allergy	14 (19)



**Figure 1** Expiratory flow limitation plotted against inspiratory flow limitation for each individual patient; no correlation was found ( $R^2$ : 0.04;  $p$  = 0.72). FEV<sub>1</sub>: Forced expiratory volume in 1 s; MIF<sub>50</sub>: Mid inspiratory flow.

inspiratory and expiratory airflow in time for each group can be seen in Fig. 2.

The use of inhaled corticosteroids was not related to the occurrence of EIB (chi-square  $p$  = 0.573) or inspiratory flow limitation (chi-square  $p$  = 0.367). Similarly, the use of nasal corticosteroids was not related to the occurrence of EIB (chi-square  $p$  = 0.528) or inspiratory flow limitation (chi-square  $p$  = 0.457), suggesting that the use of inhaled or nasal corticosteroids did not significantly effect the likelihood for EIB or inspiratory flow limitation in asthmatic children.

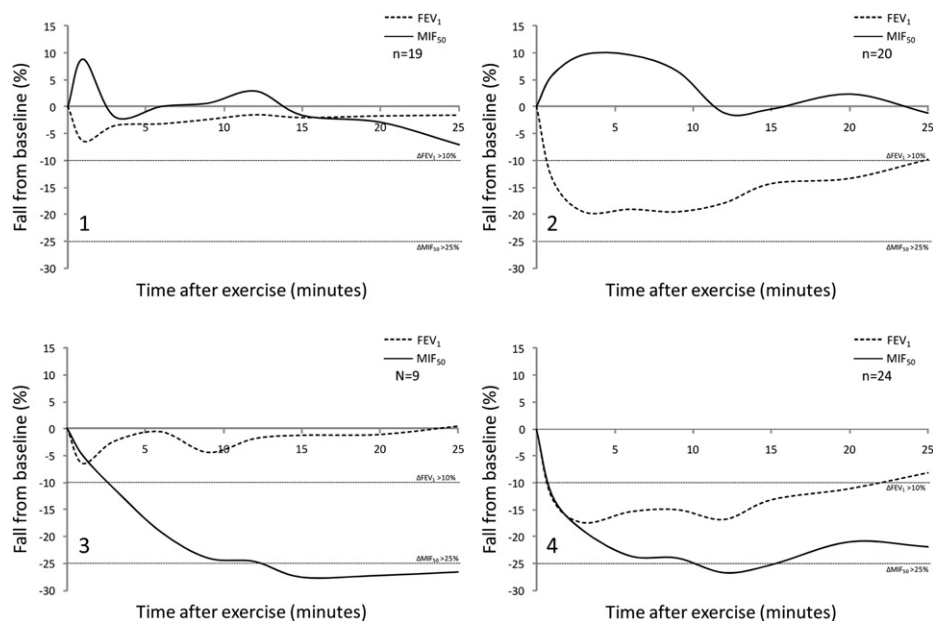
The correlation between the overall ACQ and fall in FEV<sub>1</sub> after exercise was 0.12 ( $p$  = 0.864) and the correlation with the fall in MIF<sub>50</sub> was 0.18 ( $p$  = 0.810). When dividing the patients into groups by the asthma control cut-offs provided by Juniper et al., there was no correlation with fall in FEV<sub>1</sub> ( $p$  = 0.077) nor with fall in MIF<sub>50</sub> ( $p$  = 0.126) as can be seen in Table 2.

The occurrence of expiratory wheeze and cough were linked with a fall in FEV<sub>1</sub>, while the occurrence of inspiratory stridor was linked with a fall in MIF<sub>50</sub>, as can be seen in Table 3. The relation over time between spirometry and wheeze, stridor and cough can be seen in Figs. 3–5 respectively.

## Discussion

This study shows that exercise can induce inspiratory flow limitation as well as expiratory flow limitation in asthmatic children. Inspiratory flow limitation was related to an inspiratory stridor but unrelated to the occurrence or severity of expiratory flow limitation.

Exercise induced inspiratory stridor and flow limitation is most commonly attributed to VCD. VCD is a heterogeneous entity and as such the inspiratory flow limitation we observed could be attributed to VCD.<sup>8,9</sup> Laryngoscopy during and immediately after exercise and not lung-function is considered to be the gold standard to diagnose VCD.<sup>18,19</sup> However the inspiratory flow limitation we observed peaked well after ceasing exercise and was not accompanied by acute 'choking', both of which are not



**Figure 2** Expiratory flow limitation and inspiratory flow limitation over time for each group of patients: 1) No flow limitation; 2) Isolated expiratory flow limitation; 3) Isolated inspiratory flow limitation and 4) Both expiratory and inspiratory flow limitation. FEV<sub>1</sub>: Forced expiratory volume in 1 s; MIF<sub>50</sub>: Mid inspiratory flow.

compatible with a diagnosis of VCD and suggest another cause.<sup>8,9,18,19</sup>

Methacholine and histamine have also been known to cause inspiratory flow limitation, mimicking asthma like symptoms, in both children<sup>2</sup> and adults.<sup>3,4</sup> Rolla et al. found inflammation of the laryngeal mucosa in patients with methacholine induced inspiratory flow limitation and hypothesized that this was due to chronic mouth breathing as a result of chronic upper airway inflammation.<sup>20</sup> Turktas et al. observed that the responsiveness to methacholine measured with the MIF<sub>50</sub> subsided after appropriate treatment of upper airway co-morbidity.<sup>2</sup> Although the majority of asthmatic children have an upper airway inflammation,<sup>5</sup> we did not find a lower prevalence of inspiratory airflow limitation in children using nasal corticosteroids. We propose this is due to a limited medication adherence.

Several remarks should be made about this study. Analysis of the inspiratory flow limb is difficult, especially in children. The MIF<sub>50</sub> can be used to analyze inspiratory flow limitation in children<sup>17,21</sup> and Tomalak and co-workers have calculated reference values for children.<sup>17</sup> The observed mean pre-exercise MIF<sub>50</sub> was approximately 1 standard deviation above predicted, which indicates that the

children in our study were capable of performing technically acceptable flow volume loops. To accurately analyze the inspiratory limb, three repeated inspiratory limbs are required for analysis.<sup>22</sup> Although feasible before exercise, the time schedule after exercise forced the use of duplex flow volume loops. The number of forced breathing manoeuvres following exercise might have enhanced the observed flow limitation although we did not see the inspiratory flow limitation in all children. Furthermore, the number of forced breathing manoeuvres in the used protocol is similar to the number of forced breathing manoeuvres required for Methacholine testing reducing the likelihood of a significant effect of fatigue.<sup>2,3,11</sup> A reduction of the inspiratory vital capacity could be accompanied by a higher peak and mid inspiratory flow and a reduction of the plateau phase of the curve. To avoid artificially deviant MIF<sub>50</sub> values, and to increase the accuracy of the analysis, the maximal MIF<sub>50</sub> was chosen when accompanied by a forced inspiratory vital capacity of more than 80% of baseline and reaching a plateau phase.<sup>17</sup>

We choose to use the fall in MIF<sub>50</sub> to analyze the inspiratory flow limitation similar to studies using direct challenges. One cannot copy the rate of decline in flow

**Table 2** Subdivision of patients for control of asthma as measured with the ACQ versus fall in FEV<sub>1</sub> and MIF<sub>50</sub>. FEV<sub>1</sub>: Forced expiratory volume in 1 s; MIF<sub>50</sub>: Mid inspiratory Flow. ACQ: Asthma control questionnaire.

	Well-controlled ACQ < 0.75 n = 38	Indifferent ACQ 0.75–1.49 n = 20	Uncontrolled ACQ ≥ 1.50 n = 12
Fall in FEV <sub>1</sub> greater than 10%	14 (37)	5 (25)	8 (67)
Fall in FEV <sub>1</sub> after exercise	17.2 ± 15.8	12.2 ± 5.9	24.4 ± 19.9
Fall in MIF <sub>50</sub> greater than 25%	16 (42)	10 (50)	5 (42)
Fall in MIF <sub>50</sub> after exercise	22.1 ± 17.7	30.9 ± 19.1	28.7 ± 14.5

**Table 3** The occurrence of wheeze, stridor and cough compared to the maximum fall in FEV<sub>1</sub> and MIF<sub>50</sub>.

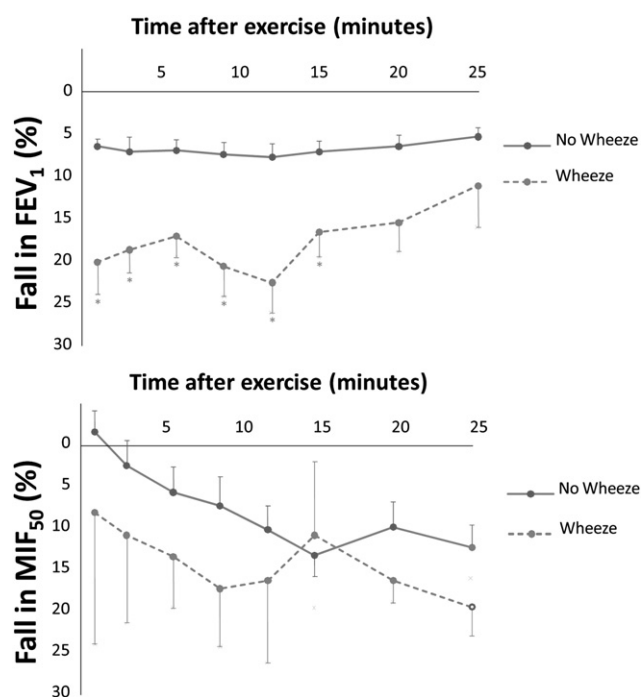
	Fall in FEV <sub>1</sub> (% of baseline)				Fall in MIF <sub>50</sub> (% of baseline)			
	Yes	No	p-value	99% CI	Yes	No	p-value	99% CI
Wheeze	22.6 ± 17.1	11.0 ± 6.0	<0.001	2.8–18.4	26.9 ± 16.6	22.6 ± 15.3	0.080	–6.5–15.0
Stridor	19.4 ± 15.7	13.0 ± 11.7	0.048	–3.0–15.7	28.8 ± 16.2	17.0 ± 12.8	<0.001	1.8–21.8
Cough	19.0 ± 15.8	10.4 ± 4.7	0.001	1.9–15.3	26.2 ± 16.6	20.6 ± 13.5	0.158	–8.0–19.3

limitation used in direct provocation to indirect provocation. As the cut off for expiratory flow limitation used is typically higher in direct challenges than in indirect challenges, we believe using the same cut-offs for inspiratory flow-limitation in indirect challenges is sensible. We did not use the fall in the MIF<sub>50</sub>/MEF<sub>50</sub> ratio, as MEF<sub>50</sub> fell considerably in most children.

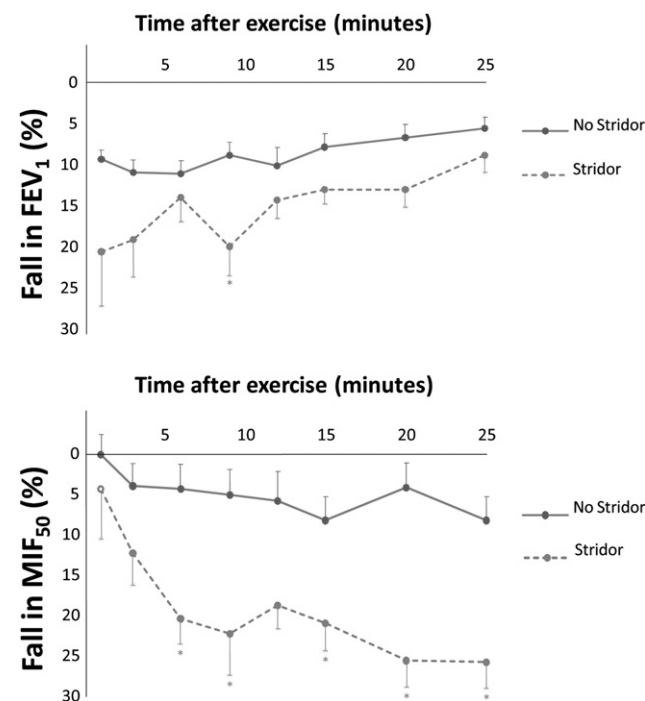
We compared the changes in inspiratory airflow limitation in the different groups with the group of asthmatic children without exercise induced airflow limitation. The pattern of inspiratory airflow limitation is unknown in healthy children. However, in the group in which we did not observe airflow limitation, airway inflammation was apparently well controlled. Allowing comparison between the groups with different flow patterns.

Clinical signs, i.e. cough, wheeze and stridor, were analyzed by a single observer (JD), which might have given rise to observer bias. However the strong association between wheezing and expiratory flow limitation and stridor and inspiratory flow limitation warrants the use of these symptoms for diagnosis.

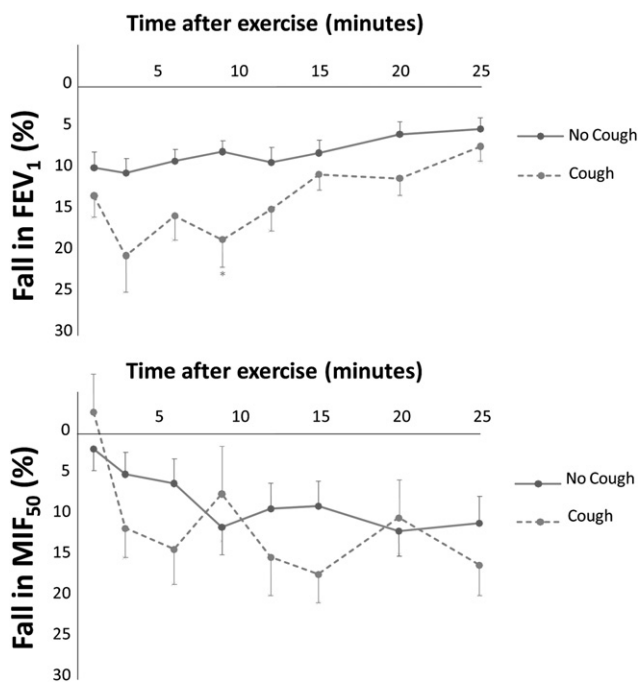
The ACQ can be used to assess control of asthma and exercise induced symptoms (question 3)<sup>14</sup>. We did not find a relation between either expiratory or inspiratory flow limitation after exercise and the outcome of the ACQ. This is in line with previous studies that analyzed the outcome of an exercise challenge of children with exercise induced symptoms.<sup>23</sup> Seear et al. and Abu-Hassan et al. found that persistent exercise induced symptoms can be due to other causes than expiratory flow limitation.<sup>6,7</sup> In these studies a definitive diagnosis for the cause of the exercise induced dyspnoea could not be found in a sizable group (21–63%).<sup>6,7</sup> We speculate that these cases can be due to an inspiratory flow limitation. Inspiratory flow restriction is closely related to overall perceived dyspnea.<sup>24</sup> Furthermore, inspiratory flow limitation can compromise effective inhalation of rescue dry powder beta-2-agonists.<sup>25</sup> The inhalation of dry powder, commonly used by children for EIB in this age group, is dependent on peak inspiratory flow and the ability to sustain inspiratory flow, which are both reduced by inspiratory flow limitation.<sup>26</sup>



**Figure 3** FEV<sub>1</sub> and MIF<sub>50</sub> in % fall over time, for children with and without wheeze. FEV<sub>1</sub>: Forced expiratory volume in 1 s; MIF<sub>50</sub>: Mid inspiratory flow. \* Marks significant differences ( $p \leq 0.01$ ).



**Figure 4** FEV<sub>1</sub> and MIF<sub>50</sub> in % fall in time, for children with and without stridor. FEV<sub>1</sub>: Forced expiratory volume in 1 s; MIF<sub>50</sub>: Mid inspiratory flow. \* Marks significant differences ( $p \leq 0.01$ ) Open marker indicates  $n < 10$ .



**Figure 5** FEV<sub>1</sub> and MIF<sub>50</sub> in % fall in time, for children with and without cough. FEV<sub>1</sub>: Forced expiratory volume in 1 s; MIF<sub>50</sub>: Mid inspiratory flow. \* Marks significant differences ( $p \leq 0.01$ ).

This study shows that an exercise challenge in asthmatic children can give rise to inspiratory as well as expiratory airflow limitation in asthmatic children. Inspiratory airflow limitation is not related to expiratory flow limitation and may give rise to asthma like symptoms after exercise and hamper the effect of inhaled rescue medication. More research should be done to analyze the pathological basis of the observed inspiratory flow limitation.

### Acknowledgements

The authors would like to thank Professor S. Anderson, J. Delong and Euregio<sup>®</sup> kunstijsbaan and its employees for their valuable assistance.

### Funding

This work was supported by an unrestricted grant from the Foundation for pediatric research in Enschede (Stichting Pediatrisch Onderzoek Enschede).

### Conflict of interest statement

All authors have no conflict of interest.

### References

- Godfrey S, Springer C, Novosiki N, Maayan Ch, Avital A. Exercise but not methacholine differentiates asthma from chronic lung disease in children. *Thorax* 1991;46:488–92.

- Turktas I, Dalgic N, Botanci I, Cengizlier R. Extrathoracic airway responsiveness in children with asthma like symptoms including chronic persistent cough. *Pediatr Pulmonol* 2002;34:172–80.
- Bucca C, Rolla G, Brussino L, De Rose V, Bugiani M. Are asthma-like symptoms due to bronchial or extra-thoracic airway dysfunction. *Lancet* 1995;346:791–5.
- Kelso JM, Enright PL, Scanlon PD, O’Connell EJ, Sachs MI. Effect of inhaled methacholine on inspiratory flow. *Chest* 1990 Dec;98(6):1426–9.
- Taramarcas P, Gibson PG. Intranasal corticosteroids for asthma control in people with coexisting asthma and rhinitis. *Cochrane Database Syst Rev* 2003;4:CD003570.
- Seear M, Wensley D, West N. How accurate is the diagnosis of exercise induced asthma among Vancouver schoolchildren? *Arch Dis Child* 2005;90:898–902.
- Abu-Hasan M, Tannous B, Weinberger M. Exercise-induced dyspnea in children and adolescents: if not asthma then what? *Ann Allergy Asthma Immunol* 2005;94:366–71.
- Rundell KW, Spiering BA. Inspiratory stridor in elite athletes. *Chest* 2003 Feb;123(2):468–74.
- McFadden Jr ER, Zawadski DK. Vocal cord dysfunction masquerading as exercise-induced asthma. a physiologic cause for “choking” during athletic activities. *Am J Respir Crit Care Med* 1996 Mar;153(3):942–7.
- Bateman ED, Hurd SS, Barnes PJ, et al. Global strategy for asthma management and prevention: GINA executive summary. *Eur Respir J* 2008 Jan;31(1):143–78.
- Crapo RO, Casaburi R, Coates AL, et al. American Thoracic Society. Guidelines for methacholine and exercise challenge testing. 1999. *Am J Respir Crit Care Med* 2000;161:309–29.
- Eggleston PA, Guerrant JL. A standardized method of evaluating exercise-induced asthma. *J Allergy Clin Immunol* 1976; 58:414–25.
- Sprickelman AB, Schouten JP, Lourens MS, Heymans HS, van Aalderen WM. Agreement between spirometry and tracheal auscultation in assessing bronchial responsiveness in asthmatic children. *Respir Med* 1999 Feb;93(2):102–7.
- Juniper EF, O’Byrne PM, Guyatt GH, Ferrie PJ, King DR. Development and validation of a questionnaire to measure asthma control. *Eur Respir J* 1999 Oct;14(4):902–7.
- Juniper EF, Bousquet J, Abetz L, Bateman ED. GOAL Committee. Identifying ‘well-controlled’ and ‘not well-controlled’ asthma using the asthma control questionnaire. *Respir Med* 2006 Apr;100(4):616–21. Epub 2005 Oct 13.
- Zapletal A, Sama M, Paul T. Lung function in children and adolescents. Methods and reference values. In: Herzog H, editor. *Progress in respiratory research*, vol. 22. Basel, Switzerland: S. Karger; 1987. p. 114–218.
- Tomalak W, Radlin J, Pogorzelski A, Doniec Z. Reference values for forced inspiratory flows in children Aged 7–15 Years. *Pediatr Pulmonol* 2004;38:246–9.
- Watson MA, King CS, Holley AB, Greenburg DL, Mikita JA. Clinical and lung-function variables associated with vocal cord dysfunction. *Respir Care* 2009 Apr;54(4):467–73.
- Kenn K, Balkissoon R. Vocal cord dysfunction: what do we know? *Eur Respir J* 2011 Jan;37(1):194–200 [Review].
- Rolla G, Colagrande P, Scappaticci E, et al. Damage of the pharyngeal mucosa and hyperresponsiveness of the airway in sinusitis. *J Allergy Clin Immunol* 1997;100(1):52–7.
- Acres J, Kryger M. Clinical significance of pulmonary function tests: upper airway obstruction. *Chest* 1981;80:207–11.
- Pellegrino R, Viegi G, Brusasco V, et al. Interpretative strategies for lung function tests. *Eur Respir J* 2005;26:948–68.
- Madhuban AA, Driessen JM, Brusse-Keizer MG, van Aalderen WM, de Jongh FH, Thio BJ. Association of the asthma control questionnaire with exercise-induced bronchoconstriction. *J Asthma* 2011 Apr;48(3):275–8. Epub 2011 Feb 25.

24. Lougheed M, Fisher T, O'Donnell D. Dynamic hyperinflation during bronchoconstriction in asthma. *Chest* 2006;**130**: 1072–81.
25. Haidl P, Schmidt F, Wiese C, Koehler D. Peak inspiratory flow rate after methacholine challenge in asthmatic patients and its impact on the effect of formoterol via different inhalers. *J Aerosol Med* 2006 Fall;**19**(3):364–71.
26. Broeders M, Molema J, Vermue N, Folgering H. Peak inspiratory flow rate and slope of the inhalation profiles in dry powder inhalers. *Eur Respir J* 2001;**18**:780–3.