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Eucapnic voluntary hyperventilation test decreases exhaled nitric oxide level in children

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29 Abbreviations:

30 EVH: Eucapnic voluntary hyperventilation test

31 FeNO: Exhaled nitric oxide

32 FEV1: Forced expiratory volume in 1 second

33

34 **Background**

35 Exhaled nitric oxide (FeNO) measurements and eucapnic voluntary hyperventilation (EVH) tests
36 have been used as diagnostic tools for asthma. Data on the impact of hyperventilation on the level
37 of FeNO are limited.

38 **Aim**

39 We aimed to evaluate whether EVH tests affect the level of FeNO in children aged 10–16 years.

40 **Methods**

41 A total of 234 children aged 10–16 years had a 6 min EVH test performed. In total, FeNO values
42 for 153 of 234 children were measured before the test and within 15 minutes after the test.

43 According to a baseline FeNO level of 20 ppb, children were divided into two groups: those with
44 low values ($\text{FeNO} < 20$ ppb) and those with high values ($\text{FeNO} \geq 20$ ppb).

45 **Results**

46 The median age of the children was 13.4 years (interquartile range 12.3–15.3 years); 58% were
47 boys and 42% were girls. Of these children, 51% were sensitized to aeroallergens. In 101 of 153
48 children (66%), the FeNO values decreased after the EVH test. In children with low and high
49 baseline levels, the median level of FeNO decreased after the EVH test: 10.5 ppb before vs 9.5 ppb
50 after ($p < .011$), and 31.0 ppb before vs 28.0 ppb after ($p < .011$), respectively. The decrease in
51 FeNO after EVH test was not associated with induced bronchoconstriction expressed as a change in
52 FEV1 ($R_s = .19$).

53 **Conclusions**

54 The EVH test decreases FeNO levels. Therefore, FeNO should be measured before an EVH test is
55 performed.

56 **Short technical communication**

57 The exhaled nitric oxide (FeNO) measurement is used to assess asthma and asthma-control
58 worldwide. The level of FeNO predicts the response to inhaled corticosteroids in asthma patients
59 (Dweik RA et al., 2011). Monitoring asthma with FeNO reduces exacerbations among children but
60 does not impact day-to-day symptoms (Petsky HL et al., 2016). Studies among children have shown
61 that the level of FeNO decreased after performing the mannitol dry powder challenge and exercise
62 test (Barben J et al., 2013; Petsy HL et al., 2013). The American Thoracic Society recommends that
63 FeNO be performed before a bronchial challenge test (Dweik RA et al., 2011). So far, the effect of a
64 eucapnic voluntary hyperventilation (EVH) test on FeNO among children has not been studied.

65 We examined whether EVH tests affect the FeNO level in children aged 10–16 years. We
66 hypothesized that an EVH test would decrease FeNO level.

67 In the beginning, 234 children (134 patients and 100 controls) aged 10–16 years participated in the
68 study at the paediatrics departments of the university hospitals of Turku and Kuopio, Finland and
69 performed the EVH test between years 2013-2016. The inclusion criteria for the patients in the
70 study were exercise-induced dyspnea symptoms and a referral from a primary or secondary health
71 care provider. The exclusion criteria were physical inactivity, severe comorbidity, chronic
72 autoimmune disease or difficult-to-treat asthma. The Ethics Committee of the Hospital District of
73 Southwest Finland approved the study, and written consent was collected from every patient and
74 their parents upon entrance to the study.

75 SPSS version 22 (IBM Corp, Armonk, NY, USA) was used for the statistical analysis. The FeNO
76 data were not normally distributed (Shapiro-Wilks test, $p < .001$). The data has presented as median
77 and interquartile range. For continuous data, the Wilcoxon Signed-Rank test and the Mann-Whitney
78 U test were used. For categorical data, the chi-square test and Fisher's exact test (when counts < 5)
79 were used. The Spearman correlation test was used for the correlation analysis. In the subgroup

analysis, Bonferroni correction was performed to control for type I error. Statistical significance was established at $p < .05$.

The EVH test was conducted according to European Respiratory Society guidelines for the indirect bronchial challenge test (Hallstrand TS et al., 2018). The spirometry was performed using Jaeger SentrySuite-equipment (version 2.19) before the EVH test and 1, 5 and 10 min after the test. Target minute ventilation was defined as 30 times the patient's baseline forced expiratory volume in 1 second (FEV1), corresponding to 85% of maximal voluntary ventilation (MVV; Hallstrand TS et al., 2018). The feasibility of the EVH test was assessed by the ability of the children to achieve 70% of the target ventilation volume (Hallstrand TS et al., 2018).

FeNO level was measured before and within 15 minutes after the EVH test. The data were analysed using NIOX Vero (Aerocrine, Solna, Sweden) according to international guidelines with a flow rate of 50 ml/s (Dweik RA et al., 2011). Phadiatop tests were performed for 138 of 153 children. Sensitization was defined if sIgE ≥ 0.35 kU/l occurred for at least one of the tested allergens.

Of all children, the FeNO levels of 55 out of 100 controls and 98 out of 134 patients were measured during the visit. Those 153 children were included in the analysis. For 81 children, the FeNO testing was not available due to technical problems.

The median age of the children was 13.4 years (interquartile range 12.3–15.3 years); 58% were boys and 51% were sensitized to aeroallergens. Based on the baseline FeNO results, the children were divided into two groups, with either a low (< 20 ppb, $n = 112$) or high (≥ 20 ppb, $n = 41$) level of FeNO. The sensitization to aeroallergens was more frequent among children with high FeNO (80% vs 41%, $p < .001$). There were no significant differences between groups in terms of median age (13.4 vs 14.1 years, $p = .060$), prevalence of asthma (19% vs 23%, $p = .72$), allergic rhinitis (39% vs 54%, $p = .10$) or atopic eczema (24% vs 28%, $p = .61$). In both groups, the majority of

103 children were boys, and both groups performed well on the EVH test; a minimum of 70% of target
 104 ventilation was reached by 150 of 153 children.

105 Among all children, the median level of FeNO decreased significantly after EVH (13.0 ppb before
 106 vs 11.0 ppb after, $p < .011$). FeNO decreased in children with low (10.5 ppb before vs 9.5 ppb after,
 107 $p < .011$) and high (31.0 ppb before vs 28.0 ppb after, $p < .011$) levels compared to the baseline
 108 (Table 1). In children with high FeNO, the absolute change in FeNO was greater compared to
 109 children with low FeNO (-3 ppb vs -1 ppb, $p = .011$). However, expressed as a percentage change
 110 comparing baseline FeNO, the change was similar among children with high and low FeNO (-
 111 11.1% vs -12.0%, $p = .45$). There were no significant differences between boys and girls in the
 112 results (-1 ppb vs -2 ppb, $p = .63$).

113 All other subgroups had significant decreases of FeNO after EVH except for children with a
 114 minimum 10% fall of FEV1 after EVH (Table 1). The decrease in FeNO after EVH was not
 115 correlated with age ($r_s = -.14$), fall of forced expiratory volume in 1 second (FEV1) after EVH ($r_s =$
 116 $.19$) or achieved minute ventilation during the EVH test ($r_s = .02$).

117 The decrease in FeNO was seldom at a clinically relevant level. Fifteen children had a baseline
 118 FeNO > 35 ppb, predicting good responsiveness to corticosteroids (Dweik RA et al., 2011),
 119 whereas after the EVH test, 9 children had FeNO > 35 ppb ($p = .20$). Accordingly, the FeNO cut-
 120 off value of < 20 ppb predicting a less favourable response to corticosteroids (Dweik RA et al.,
 121 2011) was observed in 112 children before the EVH test vs 115 children after the test ($p = .73$). A
 122 minimum decrease of 10 ppb of FeNO was observed for 4 of 153 (2.6%) children.

123 The American Thoracic Society recommends performing FeNO before bronchial challenges (Dweik
 124 RA et al., 2011). In previous studies, the level of FeNO decreased after the exercise test and
 125 mannitol challenge (Barben J et al., 2013; Petsy HL et al., 2013). Our findings with the EVH test

126 are in line with these earlier observations. To our knowledge, this was the first time the effect of the
127 EVH test on FeNO was evaluated.

128 The absolute decrease of FeNO was greater in children with high FeNO. However, the relative
129 change after the EVH test was very similar when compared to children with low and high levels of
130 FeNO. An important finding was that the decrease in FeNO after the EVH test was not associated
131 with induced bronchoconstriction expressed as a change in FEV1. This observation challenges the
132 idea that the mechanism behind the effect could be explained by changes in geometric factors
133 during bronchoconstriction. The reason for this phenomenon remains unknown.

134 The strengths of the study were the large number of children who took part, the prospective study
135 design and usage of the standard measurements for EVH and FeNO. The major limitation is that the
136 results are generalizable only for children. The duration of the phenomenon remains unknown
137 because FeNO was taken only once within 15 minutes after the EVH test.

138 In summary, the EVH test is becoming increasingly popular as an indirect bronchial challenge test
139 in children. Our findings support measuring FeNO level before conducting an EVH test to avoid
140 bias.

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144 Kerttu and Kalle Viik Foundation, Kuopio, Finland.

145 **CONFLICTS OF INTEREST**

146 The authors have no conflict of interest to declare.

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160 **TABLE 1.** Exhaled nitric oxide (FeNO) before and within 15 minutes after a eucapnic voluntary
161 hyperventilation test (EVH)

Group	Baseline FeNO (ppb)	The change of FeNO after EVH (ppb),	Bonferroni corrected P-value
All children N=153	13.0 (9-20)	-2.0 (-4-0)	.011
Patients n=98	13.0 (9-23)	-2.0 (-4-0)	.011
Controls n=55	12.0 (9-18)	-1.0 (-3-0)	.011
Children with FeNO ≥20ppb n=41	31.0 (24.5-39.5)	-3.0 (-8-(-1))	.011
Children with FeNO <20ppb n=112	10.5 (8-13.5)	-1.0 (-2.5-0)	.011
Children with fall in FEV1 ≥10% after EVH n=16	13.0 (10.5-28.5)	-2.5 (-5-0.5)	.242
Children with fall in FEV1 <10% after EVH n=137	13.0 (9-19)	-1.0 (-3-0)	.011
Children with doctor diagnosed atopic eczema n=38	12.5 (9-20)	-2.0 (-4-0)	.011
Children without doctor diagnosed atopic eczema n=109	12.0 (9-19)	-1.0 (-3-0)	.011
Children with sensitization to aeroallergen # n=70	12.5 (9-29)	-1.0 (-4-0)	.011
Children without sensitization to aeroallergen n=68	12.0 (9-16)	-2.0 (-4-0)	.011

162 Data represents the medians and the interquartile range.

163 EVH: eucapnic voluntary hyperventilation test; FeNO: exhaled nitric oxide; FEV1: forced
164 expiratory volume in 1 second. # defined if sIgE ≥0.35kU/l any of eight allergens in the Phadiatop.
165 Calculated using a Wilcoxon Signed Rank Test.

166