Association Among Lung Function, Exhaled Nitric Oxide, and the CAN Questionnaire to Assess Asthma Control in Children

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Summary. Background: The aim of this study was to investigate the association among a validated symptom-based questionnaire for asthma control in children (CAN), forced expiratory volume in 1 sec (FEV1), and fractional exhaled nitric oxide (FENO). Methods: Observational cross-sectional study was performed in a consecutive sample of asthmatic children aged between 7 and 14 years old from December 2007 to February 2008. FENO was measured with a portable electrochemical analyzer and forced spirometry was performed according to American Thoracic Society/European Respiratory Society. The CAN questionnaire was completed by the parents (aged <9 years old) or by the children (≥9 years old). The strength of the association among FEV1, FENO, and CAN questionnaire was studied using Spearman’s rho, and the degree of agreement for asthma control among FEV1, FENO, and CAN questionnaire, with classification of these variables according to values of normality, was studied using Pearson’s χ² test and Cohen’s kappa (KC).

Results: We studied 268 children, mean age 9.7\pm 2.1 years. Significant correlations were found between FENO and CAN (r = 0.2), between FEV1 and CAN (r = -0.3), and between FENO and FEV1 (r = -0.12). On classifying the variables according to values of normality, no agreement was found to establish the degree of asthma control between FENO and CAN (KC = 0.18, χ² = 9.63); between FEV1 and CAN (KC = 0.29, χ² = 38.5); or between FENO and FEV1 (KC = 0.07, χ² = 4.9). Conclusions: The association among the three measurement instruments used to assess asthma control (FEV1, FENO, and CAN) was weak. These are instruments that quantify variables that influence asthma in different ways, in this sense, none can be used instead of another in asthma management although they are complementary.


Key words: asthma control; children; exhaled nitric oxide; lung function; questionnaire.

INTRODUCTION

Asthma is characterized by the presence of symptoms associated with variable airflow obstruction, hyperresponsiveness, and chronic inflammation of the airway. Assessment of asthma control is based on observation of the frequency of symptoms, on the need for rescue bronchodilator therapy, and lung function evaluation.1

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These parameters show wide intra- and intersubject variability, which in itself is one of the essential

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characteristics of asthma. The various studies that have analyzed the association among symptoms, lung function and fractional exhaled nitric oxide (FE\textsubscript{NO}) for asthma management in children have reported contradictory results,\textsuperscript{2–5} sometimes due to the distinct methodology used and/or the heterogeneity of the population studied. Moreover, the measurement parameters reported, probably reflect the distinct physiopathological entities underlying a complex disease such as asthma, which requires the greatest degree of control possible. In this sense, a study performed in asthmatic adults analyzed the association among a questionnaire to assess asthma control in adults (the Asthma Control Test [ACT]), lung function, and FE\textsubscript{NO}, with discouraging results.\textsuperscript{6}

A new questionnaire on symptoms to evaluate asthma control (the “control de asma en niñ\~{o}s” [CAN] questionnaire) has recently been validated in Spanish and in children,\textsuperscript{7} allowing us to perform the present study, whose main aim was to analyze the association among this questionnaire, lung function, and FE\textsubscript{NO}.

**MATERIALS AND METHODS**

A cross-sectional study with prospective data collection was performed in a consecutive sample of girls and boys aged between 7 and 14 years old with a medical diagnosis of asthma according to the Global Initiative for Asthma (GINA),\textsuperscript{8} recruited in the outpatient clinics of two pediatric pneumology units (tertiary and secondary clinics) between December 2007 and February 2008. Patients with associated morbidity, including systemic or degenerative diseases and upper respiratory infections, those who were active smokers, unable to correctly perform the techniques required, or who refused to participate were excluded.

Asthma severity was classified according to the GINA,\textsuperscript{8} maintenance therapy according to the British Guideline on the Management of Asthma,\textsuperscript{9} and treatment adherence through the scale proposed by Haynes–Sackett.\textsuperscript{10} Allergic rhinitis was defined on the basis of compatible signs or symptoms and a positive skin prick test to one or more allergens, food allergy on the basis of compatible signs and symptoms, specific IgE in blood (class III or higher), and atopic dermatitis on the basis of compatible signs and symptoms.\textsuperscript{1,8}

In all patients, a medical history was taken and physical examination was performed; the CAN questionnaire\textsuperscript{7} was completed by the parents (in children aged less than 9 years old) or by the children themselves (those aged 9 years old or older). The CAN questionnaire contains nine items (related to symptoms in the previous 4 weeks) with four possible answers (0–4) for each item, and a final score of between 0 and 36 points. The higher score indicates poorer disease control. In all patients, forced spirometry (MasterScreen, v. 4.50 and v. 4.67, Vi\textsubscript{a}si\textsubscript{s}\textsuperscript{R}, Hochberg, Germany) was performed according to the recommendations of the American Thoracic Society (ATS) and the European Respiratory Society (ERS).\textsuperscript{11}

To calculate the percentage of normality, the equations proposed by Zapletal and coworkers\textsuperscript{12,13} were used. In spite of the fact that different variables of forced spirometry could be interesting, in agreement with other authors\textsuperscript{3,6,14} forced expiratory volume in 1 sec (FEV\textsubscript{1}) was used for data analysis.

In all patients, before forced spirometry was performed, single-breath on-line measurement of FE\textsubscript{NO} was carried out with a portable electrochemical analyzer (NIOX-MINO\textsuperscript{R}, Aerocrine, Stockholm Sweden), with an expiration time of 10 sec.\textsuperscript{15,16}

The qualitative variables of sex, asthma severity classification, allergic rhinitis, atopic dermatitis, food allergy, tobacco smoke exposure, current treatment, treatment adherence, treatment step, and the CAN questionnaire were analyzed. Quantitative variables were age, weight, height, age at diagnosis, disease duration, hospital admissions, FEV\textsubscript{1}, and FE\textsubscript{NO}.

For FE\textsubscript{NO} the cut-off for normality was \(<30\) ppb\textsuperscript{17,18} \(\geq 80\%\) for the relative value (% predicted) of FEV\textsubscript{1}, and a CAN score of less than 8 points.\textsuperscript{7}

The statistical methods were chosen as dictated by data distribution. The degree of association among FEV\textsubscript{1}, FE\textsubscript{NO}, and the CAN questionnaire was studied using Spearman’s rho. Given that personal atopy and current treatment with inhaled glucocorticoids can act as confounding factors in the FE\textsubscript{NO} values obtained, the statistical analysis was adjusted by these variables using multiple linear regression. The degree of agreement for asthma control among FEV\textsubscript{1}, FE\textsubscript{NO}, and the CAN questionnaire, with classification of these variables according to values of normality, was studied using Pearson’s \(\chi^2\) test and Cohen’s kappa (KC). The association between atopy and FE\textsubscript{NO} was studied using Student’s \textit{t}-test. For all analyses, the alpha level was set at 5%. The SYSTAT 9.0 statistical package was used.

The sample size was estimated based on the correlation coefficients expected according to published data.\textsuperscript{6,14,19,20} The alpha level was set at 5% and the beta level was set at 20%.

The study was approved by the Ethics and Research Committees of the participating research teams. Informed consent and permission to use the data were obtained from all parents.

**RESULTS**

We studied a cohort of 268 asthmatic children, 170 (63.4\%) from the outpatient clinic of the Pneumology Unit of Hospital Donostia, San Sebastián (tertiary clinic) and 98 (35.6\%) from Hospital Los Arcos, Murcia (secondary clinic), from December 2007 to February 2008. The mean
age was 9.7 ± 2.1 years and there were 167 boys (62.3%) and 101 girls (37.7%). In all patients, forced spirometry and valid FE\textsubscript{NO} determinations were performed. Of the patients included, 206 (76.8%) had allergic rhinitis, 107 (39.9%) atopic dermatitis, and 7 (2.6%) food allergy. Demographic characteristics, treatment and severity are shown in Table 1.

Statistically significant correlations were found between FE\textsubscript{NO} and CAN scores (r = 0.2) (Fig. 1), between FE\textsubscript{V\textsubscript{1}} and CAN scores (r = −0.3) (Fig. 2), and between FE\textsubscript{NO} and FE\textsubscript{V\textsubscript{1}} (r = −0.12) (Fig. 3). However, when the variables were classified according to normality values, no agreement was found to establish the degree of asthma control between FE\textsubscript{NO} and CAN (KC = 0.18; Pearson’s χ² = 9.63, P < 0.05), although patients with CAN scores of ≥8 had significantly higher FE\textsubscript{NO} values than those with scores of <8 (43.4 ± 49 ppb vs. 27 ± 27.04 ppb) (mean ± SD). Equally, no agreement was found between FE\textsubscript{V\textsubscript{1}} and CAN (KC = 0.29; χ² = 38.5, P < 0.05), although patients with CAN scores of <8 had significantly higher FE\textsubscript{V\textsubscript{1}} values than those with CAN scores of ≥8 (x = 101.9 ± 12.5% vs. 93.8 ± 17.3%) (mean ± SD), or between FE\textsubscript{NO} and FE\textsubscript{V\textsubscript{1}} (KC = 0.07; χ² = 4.9, P < 0.05). A significant association was found between personal atopy and FE\textsubscript{NO} (x = 20 [10–41] ppb vs. 9 [6–14] ppb in non-atopic children; P < 0.05) (median and interquartile range).

**TABLE 1—Descriptive Characteristics of the Study Population**

<table>
<thead>
<tr>
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<th>N</th>
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<tbody>
<tr>
<td>Asthma</td>
<td></td>
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<tr>
<td>Intermittent asthma</td>
<td>75 (28.3%)</td>
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<tr>
<td>Mild persistent asthma</td>
<td>98 (6.7%)</td>
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<tr>
<td>Moderate persistent asthma</td>
<td>91 (34%)</td>
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<tr>
<td>Severe persistent asthma</td>
<td>2 (0.7%)</td>
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<tr>
<td>Personal atopy</td>
<td></td>
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<tr>
<td>Allergic rhinitis</td>
<td>206 (76.8%)</td>
</tr>
<tr>
<td>Atopic dermatitis</td>
<td>107 (39.9%)</td>
</tr>
<tr>
<td>Food allergy</td>
<td>7 (2.6%)</td>
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<tr>
<td>Admissions</td>
<td></td>
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<tr>
<td>Ward</td>
<td>8 (2.9 %)</td>
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<tr>
<td>PICU</td>
<td>1 (0.5 %)</td>
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<tr>
<td>FEV\textsubscript{1} ≥ 80%</td>
<td>254 (93 %)</td>
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<tr>
<td>CAN &lt; 8</td>
<td>213 (79.4%)</td>
</tr>
<tr>
<td>FE\textsubscript{NO} &lt; 30 ppb</td>
<td>170 (63.4%)</td>
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<tr>
<td>Treatment</td>
<td></td>
</tr>
<tr>
<td>IGC monotherapy</td>
<td>125 (46.6%)</td>
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<tr>
<td>ALT monotherapy</td>
<td>19 (7%)</td>
</tr>
<tr>
<td>IGC and long-acting β\textsubscript{2}-adrenergic antagonists</td>
<td>80 (29.8%)</td>
</tr>
<tr>
<td>IGC and ALT</td>
<td>20 (7.5%)</td>
</tr>
<tr>
<td>No treatment</td>
<td>24 (8.9%)</td>
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<tr>
<td>Adherence\textsuperscript{1}</td>
<td></td>
</tr>
<tr>
<td>Excellent</td>
<td>94 (35%)</td>
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<tr>
<td>Good</td>
<td>102 (38%)</td>
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<tr>
<td>Average</td>
<td>24 (8.9%)</td>
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<tr>
<td>Poor</td>
<td>24 (8.9%)</td>
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<tr>
<td>Asthma duration (months)</td>
<td>61.9 ± 35.5</td>
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<tr>
<td>Treatment step\textsuperscript{2}</td>
<td></td>
</tr>
<tr>
<td>Step 1</td>
<td>24 (8.9%)</td>
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<tr>
<td>Step 2</td>
<td>126 (47%)</td>
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<tr>
<td>Step 3</td>
<td>72 (26.8%)</td>
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<tr>
<td>Step 4</td>
<td>41 (15.2%)</td>
</tr>
<tr>
<td>Step 5</td>
<td>5 (1.9%)</td>
</tr>
<tr>
<td>Exposure to tobacco smoke</td>
<td>88 (32.8%)</td>
</tr>
</tbody>
</table>

PICU, pediatric intensive care unit; FE\textsubscript{V\textsubscript{1}}, forced expiratory volume in 1 sec; FE\textsubscript{NO}, fractional exhaled nitric oxide; CAN, asthma control in children questionnaire, ppb, parts per billion; IGC, inhaled glucocorticoids; ALT, antileukotrienes.

\textsuperscript{1}Ref. [10].

\textsuperscript{2}Ref. [9].

Fig. 1. Scatterplot showing the correlation between fractional exhaled nitric oxide and CAN questionnaire score. FE\textsubscript{NO}, fractional exhaled nitric oxide; ppb, parts per billion; CAN, asthma control in children questionnaire (expressed in points 0–36); r, Spearman’s correlation coefficient.

Fig. 2. Scatterplot showing the correlation between forced expiratory volume in 1 sec and CAN questionnaire score. CAN, asthma control in children questionnaire (expressed in points 0–36); FE\textsubscript{V\textsubscript{1}}, forced expiratory volume in 1 sec; r, Spearman’s correlation coefficient.
The statistical analysis was adjusted by atopy and current treatment with inhaled glucocorticoids using multiple linear regression and no significant differences were found among the results obtained.

There were 55 (20.5%) asthmatic children who were more symptomatic (CAN > 8) and we did a separate analysis on these patients. Significant correlations were not found between FENO and FEV1 (r = -0.21) or between CAN and FENO (r = 0.13). However, significant correlation was found between FEV1 and CAN (r = -0.38).

There were 93 (34.7%) children with more severe asthma, 91 (34%) with moderate persistent asthma, and 2 (0.7%) with severe persistent asthma. We did a separate analysis on these children. Significant correlations were not found between FENO and FEV1 (r = -0.17) or between CAN and FENO (r = 0.14). On the other hand, significant correlation was found between CAN and FEV1 (r = -0.29), although it was weak.

**DISCUSSION**

The various guidelines and international consensus statements for asthma management recommend evaluation of clinical symptoms and lung function to establish the degree of asthma control, without including evaluation of inflammatory markers. The aim of the present study was to analyze the association among FENO, a surrogate marker of eosinophilic inflammation, obtained through the portable NIOX-MINO analyzer, FEV1, and a questionnaire validated both in Spanish and in the pediatric population to evaluate the degree of asthma control (CAN).

In agreement with other authors, we found a significant association between FENO and FEV1. However, the percentage of variability of FENO explained by changes in lung function was less than 20% (Fig. 3). Other studies have found an association with FEV1/FVC but not with FEV1. Likewise, in studies published by Prasad et al. and Paro-Heitor et al., no association was found between FENO and FEV1. When the variables were classified according to published normal values, in our sample no agreement was found between these two variables to establish the degree of asthma control. Equally, like other authors, we found that although there was a significant association between FEV1 and symptoms (CAN questionnaire), the percentage of variability in FEV1 explained by symptoms was less than 35% (Fig. 2). Moreover, there was no agreement between the two variables to establish the degree of asthma control. However, a significant association was found between personal atopy and FENO and between FENO and CAN score (Fig. 1). In agreement with data published by other authors, the percentage of variability of FENO explained by symptoms was less than 25%. No agreement was found between the two variables to establish the degree of asthma control. The results were analyzed with outliers and without them there were not found statistically significant differences (Figs. 1–3).

Some studies have observed a lack of association between symptom questionnaires and FENO, while others have found a positive, but in general weak association. This is a cross-sectional study with prospective data collection, which was performed in a consecutive sample of asthmatic children. They were included consecutively without taking into account the severity of the disease. There were 55 (20.5%) asthmatic children who were more symptomatic (CAN > 8) and 93 (34.7%) with more severe asthma. We did a separate analysis on these patients and significant correlation were found between CAN and FEV1 (r = -0.38 and r = -0.29, respectively). These findings could be expected. Children with more severe disease or patients with worse asthma control may have further deterioration of lung function.

On the other hand, they were only 2 (0.7%) patients with severe persistent asthma and this could be a limitation of the study. Our results could be different if we looked at a cohort of children with more severe asthma, although we cannot be sure.

Numerous clinical questionnaires are used to try to establish the degree of asthma control according to symptoms. One of the most widely used and validated in English is the ACT, which has recently been validated in the pediatric population; however, to date, no version of this survey has been validated to Spanish. Consequently, we used the CAN questionnaire, which has been validated in Spanish and in the pediatric population and which has a sensitivity and specificity of nearly 70%.
Another limitation of the present study is that it is cross-sectional, since we analyzed the status of a disease that varies over time in a particular moment, performing \( \text{FE}_{\text{NO}} \) determinations at consultation. As pointed out by other authors, serial determinations, even with portable analyzers in primary care or at home, would more accurately reflect airway inflammation and asthma control according to baseline values and those obtained during acute exacerbations. In this sense, other authors have recently published that they found no added value of daily \( \text{FE}_{\text{NO}} \) telemonitoring with portable analyzer (NIOX-MINO\(^{16}\)) for 30 weeks compared with daily symptom monitoring only in the management of childhood asthma. However, they speculate that the frequent tele-monitoring as such could be responsible for the findings, and most likely produced a ceiling effect on treatment compliance.

The portable NIOX-MINO\(^{16}\) device, which has been validated in children,\(^{15}\) analyzes \( \text{FE}_{\text{NO}} \) through an electrochemical reaction and has built-in flow control facilitated by luminous and acoustic feedback. Exhalation time ranges from 6 to 10 sec and pressure during exhalation from 10 to 20 cmH\(_2\)O, which establishes an expiratory flow of between 45 and 55 ml/sec. There are no reference values for \( \text{FE}_{\text{NO}} \) in healthy children with the portable NIOX-MINO\(^{16}\) analyzer. Therefore, we used a cut-off of 30 ppb according to values published by distinct authors.\(^{18,34}\) Nevertheless, on reanalyzing the data and lowering the cut-off to 25 ppb,\(^{17}\) we found no significant differences between the two groups (data not shown). Furthermore, another limitation in pediatrics is that any cut-off point used for the general population represents a bias since, according to data published by several authors,\(^{17,35}\) \( \text{FE}_{\text{NO}} \) is a variable that is modified by age and height.

Given that personal atopy can act as a confounding factor in the \( \text{FE}_{\text{NO}} \) values obtained,\(^{36,37}\) the statistical analysis was adjusted by this variable and, again, no significant differences were found among the results obtained (data not shown).

This is a cross-sectional study that was performed in a consecutive sample of asthmatic children without taking into account of their treatment. There were 244 (91\%) children treated and 225 (83.9\%) of them received inhaled glucocorticoids. Our results could be different if we looked at a cohort of newly diagnosed and untreated children with asthma. In this sense, the analysis was adjusted by this variable and again, no significant differences were found.

In summary, we wish to stress that we found a significant association among the three measurement instruments analyzed to assess the degree of asthma control (the symptom questionnaire, lung function, and exhaled nitric oxide), although this association was weak. This weak association was probably found because different variables that influenced asthma in different ways were measured. This is a cross-sectional study and the status of the disease that varies over time was analyzed in a particular moment. Therefore, in that moment, the three variables analyzed in each patient may not be concordant. The symptom questionnaire, lung function, and exhaled nitric oxide are the instruments that quantify distinct variables that influence asthma in different ways and at different times. In this sense, none can be used instead of another in asthma management in daily clinical practice, although they are complementary.

**REFERENCES**


