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Nitric oxide in children with persistent asthma

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Chronic inflammation characterized by the presence of lymphocytes, eosinophils and mast cells is considered to be the hallmark of asthma, yet airway inflammation is not measured directly and routinely in clinical practice.[1] Probably this is one of the factors that makes management of asthma difficult, because it is based only on indirect measurements, such as symptoms and lung function. There is now evidence that inflammation may precede the onset of asthma, suggesting that asymptomatic children may already suffer from chronic airway inflammation.[2] Current evidence suggests that early detection of this might have an important therapeutic impact.[3]

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Airway inflammation can be detected by several methods, such as bronchial biopsy and bronchoalveolar lavage. However, because all of the above are invasive tests with a very low practical applicability, these methods are not suitable for routine use in children. Today we rely on clinical symptoms and lung function measurements, but these do not directly reflect airway inflammation. Subjective measures of asthma control include patient-derived parameters, such as number of wheezing episodes, nocturnal symptoms, exercise-induced symptoms, short-acting beta-agonist use, steroid bursts, emergency department visits, and hospitalizations. Asthma-related quality of life is related to asthma morbidity, and patients with better baseline quality of life have improved outcomes. Asthma-related costs include direct costs, mostly comprised of hospitalizations and emergency room visits, and indirect costs, including school absenteeism. Symptoms may not reflect the extent of the underlying inflammation due to differences in perception, and lung function may have little role especially in pediatric mild persistent or intermittent asthma.[4] None of these parameters are able to distinguish the effect of different doses of inhaled corticosteroids (IC).

Although nitric oxide (NO) was first identified 200 years ago, its physiological importance was not recognized until the early 1980s. Many studies have established the role of NO as an essential messenger molecule in body systems. NO is present in the exhaled breath of humans and other mammalian species. It is generated in the lower airways by enzymes of the nitric oxide synthase (NOS) family, although nonenzymatic synthesis and consumptive processes may also influence levels of NO in exhaled breath. The biological properties of NO in the airways are multiple, complex, and bidirectional. Under physiological conditions, NO appears to play a homeostatic bronchoprotective role. However, its proinflammatory properties may also potentially cause tissue injury and contribute to airway dysfunction in disease states such as asthma and chronic obstructive pulmonary disease (COPD). In addition, studies have demonstrated a significant relationship between changes

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in exhaled NO levels and other markers of airway inflammation. Over the past decade, there has been increasing interest in the potential role of measurements of exhaled NO as an indicator of airway inflammation in different lung diseases. Exhaled NO is a noninvasive, sensitive, objective, easy, reproducible, reliable and suitable marker of some types of airway inflammation, such as eosinophilic asthma, and varies in different diseases. Exhaled NO concentration may be increased also in COPD, bronchiectasis, cystic fibrosis and some connective tissue diseases. An increased NO production from alveolar source has been shown to be involved in oxygenation impairment in patients with liver disease, particularly in cases of hepatopulmonary syndrome.[5] Measurements can be performed online, with direct exhalation into the NO analyzer, or offline. Standardized measurements provide a completely noninvasive means of monitoring airway inflammation. Exhaled NO levels have been studied in a high number of healthy children. They increase with worsening asthma control and correlate with markers of inflammation within the lungs. Adult and pediatric subjects with asthma have higher fractional exhaled NO concentration as a group than controls without asthma. It is elevated in asthma, during acute asthma attacks, and also in late asthmatic responses to inhaled allergens; moreover, its levels fall after treatment with oral and inhaled corticosteroids, with a significant positive correlation with eosinophils in sputum[4,5].

In this issue of Jornal de Pediatria, Jentzsch et al., from Dr. Camargo's group, wanted to evaluate the difference in exhaled NO levels in patients with atopic and nonatopic asthma treated with anti-inflammatory drugs. They compared exhaled NO measurements with lung function tests.[6] The aim of the study was to determine the clinical and functional profile and exhaled NO levels in atopic and nonatopic children and adolescents with persistent asthma. Their cross-sectional study reported the exhaled NO in 45 consecutively selected children with asthma. The frequency of eczema and exhaled NO levels were higher among atopic patients. Their results suggest that clinical and functional stability of asthma among atopic patients does not necessarily reflect an efficient control over the inflammatory process, nor does it reflect a higher probability for recurrence after IC discontinuation. This study is a natural follow-up to other previous studies[7,8] that convincingly demonstrated that exhaled NO is a useful marker of airway inflammation. It seems, however, that exhaled NO did not reflect asthma control, nor did it reflect asthma severity. Compared with values for the control group, exhaled NO was more elevated in patients with moderate to severe atopic asthma apparently adequately treated with IC.

Jentzsch et al. established asthma diagnosis according to GINA criteria, but the severity of airway inflammation is often not established before children start long-term IC treatment. Unfortunately, one of the main advantages of serial exhaled NO measurements has not been fully explored in the present study. One of the most important aspects of exhaled NO is the comparison with the best personal value. Could it be possible that children with atopic asthma had more severe disease at the moment that they were enrolled and treated with IC? Because asthma was not well controlled in a significant number of these children, they had to receive systemic steroids. On the other hand, Jatakanon et al. showed that the use of a 100-mcg daily dose of budesonide led to a significant reduction in exhaled NO levels compared with baseline, with no significant change in lung function.[9] Other authors showed a dose-dependent effect on airway responsiveness to methacholine and on exhaled NO.[10] Exhaled NO levels did not correlate with FEV_1, FVC and FEF_{25-75} in the Jentzsch et al. study. It suggests that spirometry does not significantly correlate with atopic status or NO levels, results which are similar to those of other published studies.[11] NO levels were higher in subjects with atopic asthma using modest doses of IC, which may mean that this group probably has a worse quality of life.

We believe that there are several limitations in the study by Jentzsch et al. The sample size was relatively small and the cut-off for determining a positive skin test was not addressed. The authors did not detect any relationship between lung function tests, NO levels and long-term treatment with IC, but they did not fully assess symptoms, serial lung function and specific atopic status. Although the use of IC is generally successful in controlling asthma symptoms, the present study showed that there remained a small but significant number (6/24) of patients with persistent symptoms and frequent exacerbations that required systemic steroids. Finally, they found that exhaled NO was increased in patients with atopic asthma, but they did not report which was the most frequent positive allergen in their children. There is strong evidence that sensitization to some allergens is more strongly related to exhaled NO than sensitization to others.[12,13] There is evidence that exposure to perennial allergens, such as house dust mite, are more likely to cause airway inflammation than exposure to seasonal allergens. An Italian experiment revealed increased exhaled NO levels during natural allergen exposure.[12] Also, cat dander is a perennial allergen and has been associated with asthma symptoms. Exhaled NO is also increased in atopic children and among symptomatic subjects. Atopic individuals present higher levels of exhaled NO when compared with nonatopic ones. This suggests that exhaled NO may be a marker for atopy rather than provide information about airway inflammation.[14,15] Jentzsch et al. showed results

that suggest that atopy itself induces the production of different cell populations and/or the production of different cytokines, regardless of the use of anti-inflammatory drugs. Whether there exists an association between exhaled NO and airway inflammation, and how it might be expected to vary by season if allergen varied by season still needs detailed characterization. Previous studies have shown similar results – that exhaled NO is elevated in adults and children with asthma and atopy, with the highest levels found in patients with atopic asthma –, which suggests that NO reflects eosinophilic airway inflammation.

In conclusion, the findings of this very interesting study by Jentzsch et al. published in this issue of the Jornal do Pediatria[6] point out the importance of exhaled NO as a valuable tool for monitoring airway inflammation. Because exhaled NO is a noninvasive test, it is possible to make repeated measurements to assess the response to IC treatment and to inform the decision whether to change the IC dose. There are several reports that suggest that exhaled NO may be used to monitor anti-inflammatory treatment, since untreated patients may show high NO levels. It may also be used in an attempt to predict asthma exacerbations.[16-18] We believe that we clearly need further clinical research on exhaled NO to be able to plan strategies for effective treatment and perhaps for early intervention in the management of asthma in children. Further studies will show the feasibility of including these measurement methods into everyday clinical practice. Their inclusion in the conventional assessment of asthma control appears promising. Using these methods to evaluate the current inflammatory state seems mandatory when researching for new asthma therapeutic and management strategies. We believe that, in specialist practice, managing asthma in children relying only on symptoms and lung function is no longer the state of the art.

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