ORIGINAL ARTICLE

Applicability of Extracellular Electrical Impedance Tomography in Monitoring Respiratory Tract Inflammation

V Di Rienzo,[1] M Minelli,[2] R Sambugaro,[3] F Agostinis,[4] E Nucera,[5] D Schiavino,[5] G Patriarca[5]

[1] Allergy Unit, Azienda Sanitaria Locale, Frosinone, Italy
[2] Medicine Unit, Azienda Sanitaria Locale 1, Lecce, Italy
[3] Azienda Sanitaria Locale, Pavia, Italy
[4] Pediatric Unit, Hospital of Bergamo, Bergamo, Italy
[5] Allergy Department, Catholic University, Policlinico A Gemelli, Rome, Italy

Abstract

Background: The presence of persistent mild inflammation is widely considered to provide the immunopathogenic basis for bronchial, nasal, or sinusal inflammation between critical phases and in asymptomatic periods. Exhaled nitric oxide (NO) is currently the most reliable marker of rhinobronchial inflammation, but its routine assessment is difficult as the test is available only in highly specialized centers.

Objective: The aim of this study was to evaluate the agreement between a new diagnostic method (extracellular electrical impedance tomography) and immunological and clinical symptom scores, anterior rhinomanometry, peak expiratory flow rate (PEFR), serum eosinophil cationic protein (ECP) level, and blood eosinophil count in the clinical monitoring of respiratory tract inflammation before and after treatment of asthma or rhinitis.

Patients and Methods: Eighty-seven patients were studied; 73 had mild persistent asthma (PEFR ≥20% below predicted) and 14 had rhinitis. At baseline (T0), the patients underwent a medical examination to record symptom scores, PEFR, anterior rhinomanometry, an extracellular electrolytic conductivity test (bioimpedance tomography), serum ECP level and blood eosinophil count. Appropriate treatment was prescribed, following the guidelines of the Global Initiative for Asthma and the Allergic Rhinitis and Its Impact on Asthma. After 21 days of therapy (T1), the patients were re-evaluated for the same parameters.

Results and Conclusions: This study demonstrates the good agreement (Cohen's $\kappa = 0.689$) between the symptom scores of patients with rhinitis and the findings of extracellular tomography and very good agreement ($\kappa = 0.846$) between symptom scores of asthma patients and extracellular tomography. These findings validate the use of this new technique for the real-time monitoring and adjustment of treatment in these clinical settings.

Key words: Inflammation, mild persistent. Asthma. Rhinitis. Extracellular electrical impedance tomography. Bioimpedance. Artificial neural network. Allergo-Midax.

Resumen

Antecedentes: Se considera de forma general que la presencia de una inflamación leve persistente proporciona la base inmunopatógena de la inflamación bronquial, nasal o sinusal entre fases críticas y en períodos asintomáticos. El marcador más fiable de la inflamación rinobronquial es en la actualidad el óxido nítrico (NO) exhalado, pero su valoración repetida resulta difícil ya que la prueba sólo se realiza en centros altamente especializados.

Objetivo: El objetivo de este estudio fue valorar la concordancia entre un nuevo método diagnóstico (tomografía de impedancia eléctrica extracelular) y los resultados de síntomas clínicos e inmunológicos, rinomanometría anterior, flujo espiratorio máximo (FEM), nivel de proteína catiónica del eosinófilo en suero (PCE) y recuento de eosinófilos en el control clínico de la inflamación de las vías respiratorias antes y después de los tratamientos contra el asma o la rinitis.

Pacientes y Métodos: Ochenta y siete pacientes participaron en el estudio; 73 presentaban asma leve persistente (FEM >20% por debajo de lo previsto) y 14 tenían rinitis. En la fase de establecimiento de los valores de referencia (T0), los pacientes se sometieron a

un chequeo para registrar los resultados de síntomas, el FEM, también a una rinomanometría anterior, a una prueba de conductividad electrolítica extracelular (tomografía de bioimpedancia), análisis del nivel de PCE en suero y recuento de eosinófilos en sangre. Se prescribió el tratamiento apropiado, siguiendo las directrices de la *Global Initiative for Asthma and the Allergic Rhinitis and Its Impact on Asthma*. Al cabo de 21 días de terapia (T1), se volvieron a evaluar los mismos parámetros en los pacientes.

Resultados y Conclusiones: El estudio demostró la buena concordancia (κ de Cohen = 0,689) entre las puntuaciones de síntomas de los pacientes con rinitis y los resultados de la tomografía de impedancia eléctrica y una concordancia muy buena (κ = 0,846) entre las puntuaciones de síntomas de los pacientes con asma y los resultados de la tomografía de impedancia eléctrica. Estos resultados validan el uso de esta nueva técnica para el control en tiempo real y la modificación del tratamiento en estos entornos clínicos.

Palabras clave: Inflamación leve y persistente. Asma. Rinitis. Tomografía de impedancia eléctrica extracelular. Bioimpedancia. Red neuronal artificial. Allergo-Midax.

Introduction

Bioimpedance is a bioelectrical examination technique based on the principle that different tissues have different conductive and resistive properties when a mild electric current is applied. Although described almost half a century ago [1], this technology has only recently started to be applied clinically, for example to assess total body water after re-hydration [2] or the depletion of fluids prior to [3] and after surgery, to evaluate peritoneal dialysis [4], to noninvasively measure cardiac output [5], or to study pulmonary masses [6].

The traditional assessment tools that are most similar to impedance tomography are electrocardiography and electroencephalography. Whilst the latter measure the difference in potential produced by heart or brain activity (endogenous depolarization), bioimpedance tomography measures the conductivity of the extracellular environment under exogenous stimuli. The use of pulsating and polarized electric current at a frequency not higher than 10 Hz, provides information on the impedance of the extracellular environment. This environment provides structural and metabolic support for the organs. It is rich in water and highly conductive ions (Na^+ and Cl^-) and its electrolytic configuration changes in the presence of processes that alter basic vital functions such as during inflammation. By using the extracellular environment, the system is noninvasive as it does not interact with the intracellular environment.

Another component of the system is the "neural" interpretation technique using artificial neural networks (ANNs), which are inspired by biological neural systems. They consist of a large number of processors with a basic computational capability connected to other units of the same kind [7]. The use of ANNs is spreading rapidly in the medical world [8-10].

The Allergo-Midax instrument (Biotekna srl, Eurospital spa, Trieste, Italy) used in this study is a noninvasive diagnostic medical device that carries out extracellular bioimpedance tomography on the upper and lower respiratory tracts and provides ANN interpretation of the data. Inflammation produces arteriolar muscle relaxation and increased blood flow (active hyperemia). Increased capillary and venule permeability is encountered due to inflammation and eosinophilic chemical mediation [11]. The sum of the above-mentioned effects increases electrolyte concentrations in the extracellular compartment and therefore increased electrical conductivity. The system is able to gather data in 8 minutes and identify the general extracellular and local conductivity of the upper and lower respiratory tract through specifically positioned electrodes. The Allergo-Midax device processes the acquired pattern telematically and reports in real time.

There is no doubt that the evaluation of exhaled nitric oxide (NO) is, at present, the most reliable marker of bronchial inflammation and inflammatory rhinosinusitis [12, 13]. The availability of instruments to measure exhaled NO only in highly specialized centers led us to investigate alternative routes in order to improve real time monitoring of patients under treatment for asthma or rhinitis, to better evaluate the inflammatory state in patients who underestimate symptoms, and to monitor the patient so as to adjust anti-inflammatory and antiasthmatic drug therapy.

Materials and Methods

A multicenter study was carried out on a total of 87 patients (37 females, 50 males, mean age 29.55 years) between April and June 2005. Seventy-three patients had mild persistent asthma (peak expiratory flow rate [PEFR] ≥20% below predicted) and 14 had intermittent rhinitis (40% below reference values). Patients carrying a pacemaker or who were pregnant were excluded. The study was approved by the ethics committees of all participating hospitals and informed consent was obtained from all patients.

All patients underwent clinical and diagnostic screening (T0) and were subsequently prescribed medical treatment according to the guidelines of the Global Initiative for Asthma (GINA) [14] and Allergic Rhinitis and Its Impact on Asthma [15]. The patients were re-examined after 21 days (T1) of appropriate treatment: mometasone (100 μg/d in each nostril for 3 weeks in patients with rhinitis) and fluticasone spray (500 to 1000 μg/d), for three weeks, in asthmatic patients, inhaled salbutamol (1-4 puffs/day, 100 μg/puff) as needed. At both stages (T0 and T1), a bioimpedance evaluation of the upper and lower respiratory tract was carried out with the Allergo-Midax instrument to evaluate that marker's agreement with the clinical and other diagnostic parameters used (symptom

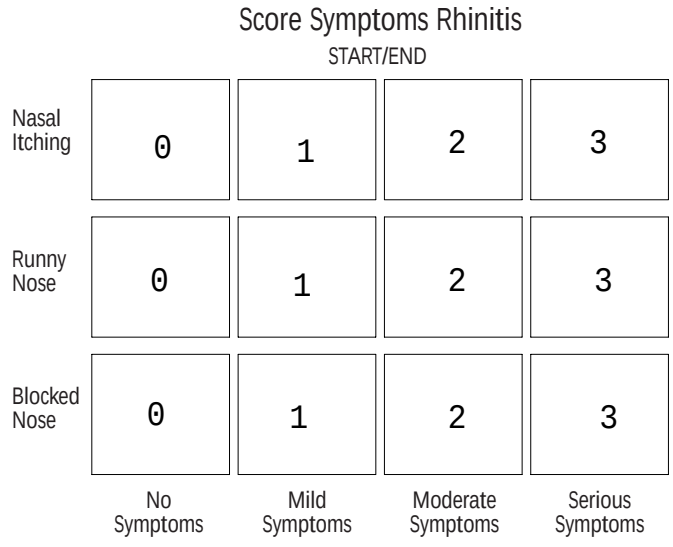

Figure 1. Chart for recording nasal symptoms. The total score ranged from 0 to 9 at each recording (T0 and T1).

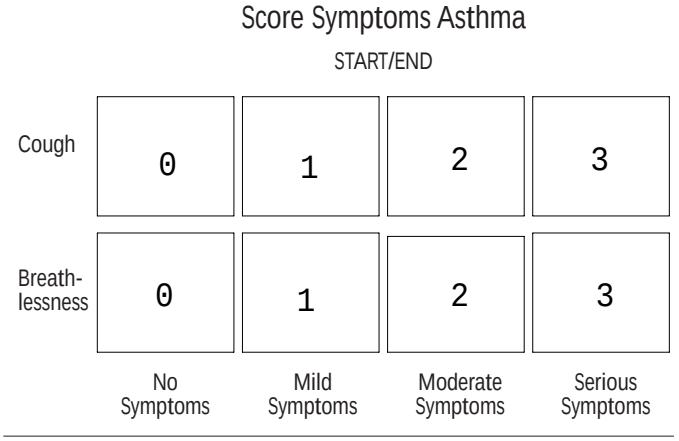

Figure 2. Chart for recording asthma symptoms. The total score for each recording (at T0 and T1) ranged from 0 to 6.

score, anterior rhinomanometry, PEFR, serum eosinophil cationic protein [ECP] level, and blood eosinophil count).

Symptom scores were assessed as shown on Figures 1 (rhinitis) and 2 (asthma) and the patient measured PEFR twice a day as suggested by guidelines; the examiner measured PEFR in the morning at T0 and at T1 (after 21 days had passed). For statistical analysis, PEFR measurements at T0 and at T1 were the only ones taken into consideration.

Allergo-Midax is a non-invasive diagnostic device that conforms to the Council of the European Communities Directive 93/42/EEC for medical devices. The only restriction on its use is that it can not be used on patients with a pacemaker (or any other life-saving electronic device) or on pregnant women.

In order to evaluate the presence of inflammatory processes (by measuring conductivity in loco) in the upper and lower respiratory tracts, it is necessary to ascertain the average extracellular concentration of the total electrolytes in each patient at the time of examination. First, the average extracellular conductivity is calculated; subsequently conductivity at a local level–-the upper and lower respiratory tracts–-is calculated.

The measurement of bioelectrical conductivity is carried out by a series of strip electrodes placed around the patient's head on the frontal–parietal–occipital region, one around the neck (cervical region), one around the waist (lumbar region). Hands are in contact with 2 hand grips and feet are on a footrest. Together they divide the body into 17 zones and monitor the organism's extracellular conductivity. There are two electrodes in each of the 3 strips. We therefore have frontal electrodes on the left and right, cervical electrodes on the left and right, upper peripheral electrodes (left and right hands), lumbar electrodes (left and right lumbar region), lower peripheral electrodes, (left and right feet) for a total of 10 electrodes.

A test is carried out for each of the 10 pairs of electrodes with a succession of active and passive phases. During the active phase a stimulus is applied which produces a 1-volt polarized current at an increasing frequency up to 10 Hz. The trend over time provides parameters such as the maximum conductivity and the difference between the maximum conductivity reached and the value registered at the end of this active phase. A subsequent passive phase is characterized by the absence of electrical stimuli. This phase serves to recover the original basic physiological conditions. Conductivity is expressed in μA (range, 0 –80 μA).

The instrument gives three parameters. The M parameter is the average extracellular conductivity. The A parameter is the upper respiratory tract conductivity. The B parameter is the lower respiratory tract conductivity. The difference between the conductivity of the upper respiratory tract and the average yields the parameter ΔA (A-M); the parameter ΔB is the difference between the lower respiratory tract conductivity and the average (B-M). Clearly, all Δ values greater than zero indicate inflammation in the respective upper or lower respiratory tract. By using variation in these values as markers it is possible to monitor the inflammatory state of the upper and lower respiratory tracts with all the consequent benefits.

Statistical Analysis

In order to evaluate agreement between tests or scoring systems yielding nominal results (positive/negative, increase/decrease), agreement between the trend (increase/decrease) in ΔA or ΔB and the symptom score at times T0 and T1, Cohen's κ statistic was used to give an estimation of agreement [16], such that a κ of 0.20 indicated very poor agreement; a κ between 0.21 and 0.40 indicated scarce agreement; κ between 0.41 and 0.60, modest agreement; κ between 0.61 and 0.80, good agreement; and κ between 0.81 and 1, very good agreement.

The relationship between variations in PEFR and conductivity in asthmatic patients were analyzed from the average of parametric tests using analysis of variance. The variation in symptoms was evaluated with a nonparametric test (Wilcoxon test). In both cases values of *P* less than .01 were considered significant.

Results

The symptom scores of 87 patients (Figures 1 and 2) at time T0 and T1 were compared with the variation in electrical conductivity obtained with the Allergo-Midax. Good agreement was obtained ($\kappa = 0.689$) in the group of rhinitis patients and very good agreement ($\kappa = 0.846$) in the asthmatic group.

In one group of 22 asthmatic patients who, despite treatment, showed signs of worsening of the asthma over the 21 days of observation (Figure 3), conductivity (Figure 4) varied ($\kappa = 1$) in perfect agreement with the worsening PEFR values ($P < .01$) and the statistically significant increase in the symptoms score ($P < .01$).

Similarly, in 46 asthmatic patients who showed a statistically significant improvement in PEFR ($P < .01$) (Figure 5), a decrease in bioelectrical conductivity was observed (Figure 6) and associated with the decrease in the symptom score ($P < .01$).

There were no significant differences between times T0 and T1 in serum ECP levels (normal value <20 µg/L; mean 20 µg/L at T0 and 17.40 µg/L at T1) or blood eosinophil count (mean 3.3% at T0 and 3.5% at T1). Nonsignificant variations were obtained by evaluating the values of nasal air flow using anterior rhinomanometry at times T0 (mean 14.46 L/min) and T1 mean 13.89 L/min).

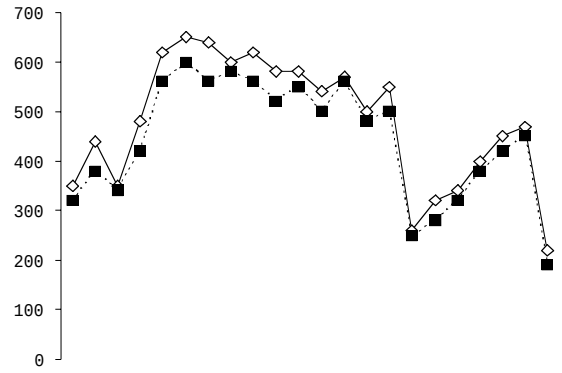

Figure 3. Changes in peak expiratory flow rate (PEFR) in 22 patients with worsening of asthma (T0, ◇; T1, ■).T0, PEFR = 478.73 ± 128.92 L/min. T1: PEFR = 441.81 ± 119.74 L/min. *P* < .01.

Discussion

Allergo-Midax is a noninvasive system that diagnoses the functional state in the upper and lower respiratory tracts by ANN analysis and interpretation of the bioelectrical signals. This study evaluated the sensitivity and specificity of the system's ability to evaluate inflammation in the respiratory tracts both prior to and after treatment of intermittent rhinitis and persistent mild asthma.

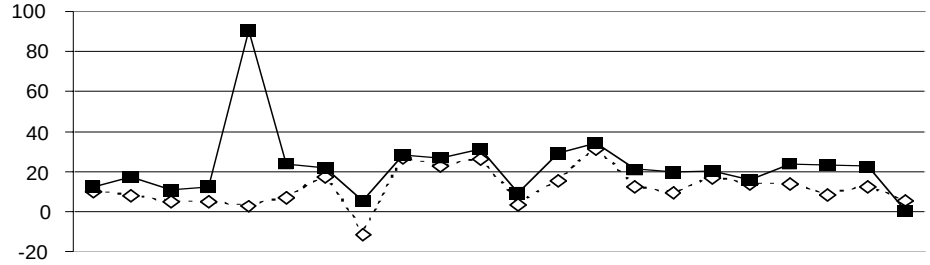

Figure 4. Changes in conductivity in 22 patients with worsening of asthma (T0, ◇; T1, ■).T0, ΔB = 11.98 ± 9.50 µA . T1, ΔB = 22.95 ± 17.27 µA. *P* < .01.

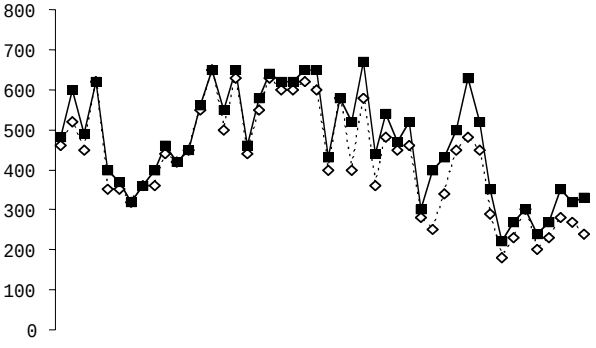

Figure 5. Changes in peak expiratory flow rate (PEFR) in 46 patients with improvement of asthma (T0, ◇; T1, ■).T0, PEFR = 427.17 ± 133.61 L/min. T1, PEFR = 469.56 ± 129.23 L/min. *P* < .01.

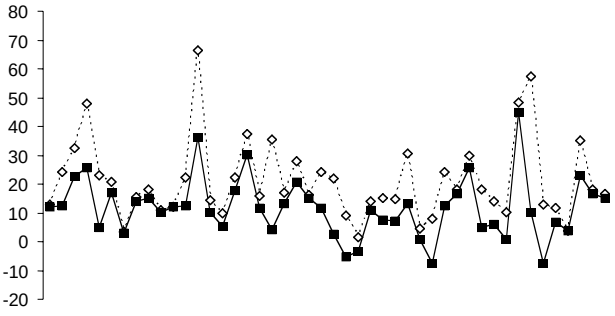

Figure 6. Changes in conductivity in 46 patients with improving of asthma (T0, ◇; T1, ■).T0, ΔB = 21.03 ± 13.75 µA. T1, ΔB = 11.81 ± 10.47 µA. *P* < .01.

The evaluation of NO in exhaled air remains the most reliable marker of respiratory tract inflammation. That method is only available in highly specialized centers, however, making it impossible to monitor the therapy of a patient with asthma or rhinitis in "real time" and on a daily basis.

Studies carried out on both adults and children have demonstrated that there is a higher production of NO in asthmatic patients than in healthy individuals [17] and that treatment with steroids is able to reduce endogenous production of this molecule [18-20]. It is equally well known that the general use of corticosteroids in children with asthma normalizes forced expiratory volume in 1 second; NO concentrations are reduced by 50%, but they still remain higher than in healthy patients [21]. This demonstrates that even in the absence of clinical signs, persistently high concentrations of NO are an indication of persistent bronchial inflammation [22]. It can also be deduced that it is not always possible to associate improvement in the respiratory function with a reduction in exhaled NO.

On the basis of these findings, the evaluation of extracellular bioelectrical conductivity proved to be a reliable and simple diagnostic parameter that correlated with PEFR and symptoms. It can provide information for real-time management of treatment, irrespective of whether exhaled NO assessment of inflammation is possible. In fact, in the group of 22 asthmatic patients who showed worsening of symptoms during the 21 days of observation despite treatment, Allergo-Midax was not only able to follow the course of disease but also suggested an immediate adjustment in therapy both in terms of dosage and in choice of the treatment. Similarly, for the 46 asthmatic patients who showed an improvement in PEFR, the system also managed to indicate improvement in disease course.

Studying extracellular bioelectrical conductivity with the Allergo-Midax device can translate into an evident benefit in the form of adaptation to provide the best possible therapy at any given moment (in terms of dosage and duration of treatment) in line with the therapeutic needs of a patient suffering from asthma and/or rhinitis. Further studies are needed to confirm these very interesting preliminary results.

References

1. Thomasset AL. Measure du volume des liquides extra-cellulaires par la methode electo-chimique signifiaction biophysique de l'impedance a 1 kilocycle du corpis humain. Lyon Med. 1965;214:131-43.
2. McDonald JJ, Chanduvì B, Velarde G, Cama R, Diaz F, Carrello L, Torre V, Watanabe J, Villrreal J, Ramirez-Ramos A, Mantle R, Gilman RH. Bioimpedance monitoring of rehydration in cholera. Lancet. 1993, 341:1049-51.
3. Ackland GL, Singh-Ranger D, Fox S, McClaskey B, Down JF, Farrar D, Sivaloganathan M, Mythen MG. Assessment of preoperative fluid depletion using bioimpedance analysis. Br J Anaesth. 2004;92:134-6.
4. Zhu F, Hoenich NA, Kaysen G, Ronco C, Schneditz D, Murphy L, Santacroce S, Pangilinan A, Gotch F, Levin NW. Measurement of intraperitoneal volume by segmental bioimpedance analysis during peritoneal dialysis. Am J Kidney Dis. 2003;42:167-72.
5. Cotter G, Moshkovitz Y, Kalusky E, Cohen AJ, Miller H, Goor D, Vered Z. Accurate, noninvasive continuous monitoring of cardiac output by whole-body electrical bioimpedance. Chest. 2004;125:1431-40.
6. Kimura S, Morimoto T, Uyama T, Monden Y, Kinouchi Y, Iritani T. Application of electrical impedance analysis for diagnosis of a pulmonary mass. Chest. 1994;105:1679-82.
7. Crick F. The recent excitement about neural networks. Nature. 1989;337:129-32.8) Dybowski R, Gant V. Artificial neural networks in pathology and medical laboratories. Lancet. 1995;346:1203-7.
9. Terrin N, Schmid CH, Griffith JL, D'Agostino RB, Selker HP. External validity of predictive models: a comparison of logistic regression, classification trees, and neural networks. J Clin Epidemiol. 2003;56:721-9.
10. Bibi H, Nutman A, Shoseyof D, Shalom M, Peled R, Kivity S, Nutman J. Prediction of emergency department visits for respiratory symptoms using an artificial neural network. Chest. 2002;122:1627-32.
11. Herbert CA, Edwards D, Boot HR. In vitro modulation of eosinophil-dependent enhancement of the permeability of epithelium. Br J Pharmacol. 1993;104:391.
12. Kharitonov SA, Yates D, Robbins RA, Logan-Sinclair R, Shinebourne EA, Barnes PJ. Increased nitric oxide in exhaled air of asthmatic patients. Lancet. 1994;343:133-5.
13. Hamid Q, Springall DR, Riveros-Moreno V, Chanez P, Howarth P, Redington A, Bousquet J, Godard P, Holgate S, Polak JM. Induction of nitric oxide synthase in asthma. Lancet. 1993;342:1510-13.
14. Bousquet J. Global initiative for asthma (GINA) and its objectives. Clin Exp Allergy. 2000;30 (Supp 1):2-5.
15. Bachert C, van Cauwenberge P. The WHO ARIA (allergic rhinitis and its impact on asthma) initiative. Chem Immunol Allergy. 2003;82:119-26.
16. Cohen J. A coefficient of agreement for nominal scales. Educational and Psychological Measurement. 1960;20:37-46.
17. Alving K, Weitzberg E, Lundberg JM. Increased amount of nitric oxide in exhaled air of asthmatics. Eur Respir J. 1993;6:1268-70.
18. Kharitonov SA, Yates DH, Barnes P. Inhaled glucocorticoids decrease nitric oxide in exhaled air of asthmatic patients. Am J Respir Crit Care Med. 1996;153:454-7.
19. Artlich A, Hagenah JU, Jonas S, Ahrens P, Gortner L. Exhaled nitric oxide in chidhood asthma. Eur J Pediatr. 1996;155:698-701.
20. Massaro AF, Gaston B, Kita D, Fanta C, Stamler JS, Drazen JM. Expired nitric oxide levels during treatment of acute asthma. Am J Respir Crit Care Med. 1995;152:800-3.
21. Baraldi E, Azzolin N, Zanconato S, Dario C, Zacchello F. Corticosteroids decrease exhaled nitric oxide in children with acute asthma. J Pediatr. 1997;131:381-5.
22. Larsen GL. Asthma in children. N Engl J Med. 1992;326:1540-5.

Manuscript received March 20, 2006; accepted for publication June 7, 2006.

Giampiero Patriarca

Servizio di Allergologia
Policlinico A.Gemelli
Largo Gemelli, 8
00168 Roma, Italy
E-mail: allergologia@hotmail.com