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ORIGINAL ARTICLE

Bioimpedance monitoring of airway inflammation in asthmatic allergic children

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Abstract

Background: Asthma in childhood is characterized by chronic inflammation. Measurement of bioimpedance (BI) is a non-invasive way of detecting airway inflammation. The aim was to compare BI with exhaled nitric oxide (eNO) and lung function evaluations in asthmatic allergic children while not exposed to offending allergens.

Methods: 22 asthmatic children allergic to house dust mites have been enrolled while residents at high altitude in an environment free of house dust mites. They were evaluated at T0 after allergen exposure at home, at T1 and at T2 after 1 and 4 months of allergen avoidance, respectively.

Results: eNO decreased from 32.21 ± 5.70 ppb at T0 to 21.92 ± 4.36 ppb at T1, after one month at high altitude ($p = 0.038$), without a further decrease at T2. Data in electrical activity showed a significant decrease in conductivity of lower airways between T0 (48.53 ± 3.53 μA) and T1 (42.08 ± 3.47 μA) ($p = 0.023$). ΔB parameter (difference between conductivity of lower respiratory tract and average yield) showed significant decrease from T0 (20.75 ± 2.64 μA), and T1 (12.84 ± 2.52 μA) ($p < 0.01$), but no further decrease at T2. No difference in lung function parameters was observed.

Conclusion: Allergen avoidance regimen modifies inflammatory parameters in allergic asthmatics. Evaluation of extracellular bioelectrical conductivity seems to represent a promising non-invasive method to assess airway inflammation.

Introduction

Childhood asthma is a chronic inflammatory disease, characterized by recurrent episodes of wheezing, variable airway obstruction and inflammatory infiltration in the airway wall mucosa represented mainly by eosinophils, mast cells and lymphocytes[1]. Even mild asymptomatic asthmatic patients can still present a residual level of persistent airway inflammation and hyperreactivity, thus confirming the opportunity to consider treatment with anti-inflammatory agents also in mild patients[2].

Several markers of bronchial inflammation in paediatric asthma have been identified and studied. In particular, exhaled nitric oxide (eNO) has been proposed to be a more

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sensitive marker of deterioration of asthma than either symptoms or lung function. Indeed, eNO seems to be affected by inhaled corticosteroids and other anti-inflammatory treatments[3,4].

In a clinical model of allergen avoidance/exposure, it has been previously demonstrated that in house dust mite (HDM) allergic asthmatic children the clinical and inflammatory indices are clearly influenced by the presence/avoidance of offending allergens[5,6]. Therefore, the prolonged stay in an allergen-free environment may be accompanied by significant improvement of allergen-induced bronchial reactivity[7]; by a reduction of airway inflammatory indices such as eNO; sputum eosinophils; and serum eosinophil cationic proteins[5,6,8]. All this evidence shows that when children were naturally re-exposed to offending allergens there was a rapid increase of the inflammatory indices with a progressive deterioration of clinical parameters[5,6,8].

Measurement of bioimpedance (BI) is a novel non-invasive way of detecting body composition which has been successfully utilised in chronic disease evaluation[9-11]. The use of pulsating and polarised electric current at a frequency not higher than 10 Hz, may provide information on the impedance of body extra-cellular environment. This environment provides structural and metabolic support to the organs. It is rich in water and in highly conductive ions (Na^+ and Cl^-). Its electrolytic configuration changes in the presence of processes that alter the basic vital functions, such as during inflammation.

Since body components differ in electrical activity and changes in relative proportions alter impedance, we aim to verify the utility of the measurement of BI in mucosal inflammation which is characteristic of childhood chronic asthma. Therefore, the aim of the study was to investigate whether the measurement of BI, identifying parameters of mucosal electron changes, can reflect levels of airway inflammation in asthmatic children sensitised to HDM during natural avoidance/exposure regimens. A further endpoint was to evaluate possible correlations of BI with other validated inflammatory indices such as eNO and lung function test parameters.

Methods

Patients

Twenty two children (aged from 7 to 14 yrs, 16 males and 6 females) were enrolled into the study during the winter 2004-2005. Children had moderate asthma according to the definition of the American Thoracic Society[12] and the minimum medication required to achieve adequate control. All were sensitised to HDM, *Dermatophagoides pteronyssinus* and *farinae*, as demonstrated by positive skin prick tests and positive RAST (score $\geq$ 3). The study was conducted during a prolonged stay at high altitude while they were residents at the Instituto Pio XII, Misurina, at 1,756 m above sea level. At the residential house the routine analysis for HDM always failed to reveal the presence of mite-allergen while in contrast, in the area of the family houses, at sea level, relevant concentrations of mites have been shown through the year[5]. All patients were receiving regular treatment with inhaled corticosteroids during the study period (Fluticasone propionate 200 μg/die or Budesonide 400 μg/die). None of the children had respiratory infections for at least four weeks prior to entering the study.

Study design

This was set up as a controlled allergen exposure/avoidance follow-up pilot study. Evaluations were performed at T0 in January, after a three-week period for Christmas holidays in their family homes in the presence of the offending allergens, in February after one month (T1) and in May after four months at high altitude in the allergen free environment (T2). At day two after re-admission the cluster of evaluations (bioimpedance, lung function evaluation, eNO measurements) was performed.

The study was conducted from January to May, before the grass pollen season, in order to exclude effects by allergens different from HDM. Tests were always performed at the same time of the day.

Bioimpedance evaluation

Bioimpedance was evaluated by Allergo-Midax instrument (Biotekna srl, Eurospital s.p.a., Trieste, Italy), a non-invasive diagnostic device performing the bioelectric test in 8 minutes, as previously described[11]. Briefly, for each evaluation In order to evaluate the presence of inflammatory processes (by measuring conductivity "in loco") in the upper and lower respiratory tract, it was necessary to ascertain the average extra-cellular concentration of the total electrolytes in each patient at the time of examination. The concentration of electrolytes (directly proportional to the inflammatory state) was affected by individual hydration (more water equals more electrolytes) therefore, the average whole body and subsequently the upper and lower respiratory tract extra-cellular conductivity was calculated.

The bio-electric measurement of conductivity was carried out using a series of strip electrodes placed around the patient's head in the fronto-parietal-occipital region, one around the neck (cervical region), one around the waist (lumbar region), plus two handgrips and a footrest. All electrodes were placed in direct contact with the skin dividing the body into 17 zones and monitoring the organism's extra-cellular conductivity.

A test was carried out for each of the 10 pairs of electrodes with a succession of active and passive phases.

Active phase
During this phase a stimulus was applied producing a one volt polarised 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.

Passive phase
This follows on from the active phase and is characterised by the absence of electric stimuli. This phase serves to recover the original basal physiological conditions.

Conductivity was expressed in micro Ampere (μA) (range $\pm$ 100 μA with an error possibility of 1.5 μA).

The instrument gave three parameters: M = average extra-cellular conductivity, A = upper respiratory tract conductivity and B = lower respiratory tract conductivity.

The difference between the conductivity of the upper respiratory tract and the average yielded the parameter ΔA (A-M); the parameter ΔB was the difference between the lower respiratory tract conductivity and the average (B-M). All delta values greater than zero indicate in ammation in the respective upper or lower respiratory tract. For analysis we considered M, B and ΔB parameters.

Each test was sent telematically to a remote server and the signals processed by an arti cial neural network (ANN) and results sent back to the Allergo-Midax device for evaluation.

ENO measurements

ENO was measured using a chemiluminescence analyser (Logan LR 2149, Rochester, Kent, UK). Briefly, children were asked to perform a single slow exhalation through a mouthpiece against a resistance. A biofeedback device maintained a 5-6 L/min steady expiratory ow, assuring the closure of the soft palate and separating the nasopharynx from the oropharynx. ENO values were registered at the plateau of the end-exhaled reading according to the guidelines[13].

Lung function tests

The lung volume measurements were obtained using a water-sealed lung volume spirometer, which uses a washout system with removal of CO_2, an O_2 delivery control system and analysis of the helium dilution by a fast response cell (Baires, Biorevo mod., Biomedin, Padova, Italy).

Statistical analysis

The study hypothesis was tested by examining internal changes of bioimpedance evaluation, eNO, FEV_1 during the study period. Comparison for contiguous times of the exposure-avoidance study was planned *a priori* and the analysis of variance (ANOVA) was used for comparing observations. Correlations between the values in BI, levels of eNO and the values of FEV_1 were tested by Spearman's correlation test.

The Local Hospital Ethical Committee approved the study, and the children and their parents gave informed consents.

Results

All children performed the clusters of parameters and concluded the study.

The results obtained are expressed as group mean ± standard error of the estimate (± S.E.M.); p value is equal to comparison for contiguous times.

FEV1 values (L/s) showed no signi cant variation between the study periods being 2.75 ± 0.15 in January, 2.78 ± 0.13 in February and 2.95 ± 0.14 in May. In January, when the children returned to the residential house after three weeks at home in the presence of HDM, eNO was 32.21 ± 5.70 ppb. As expected there was a statistically signi cant decrease after one month at high altitude (21.92 ± 4.36 ppb) ($p = 0.038$), which was maintained in May without further decrease (23.08 ± 4.57 ppb).

Data in electrical activity obtained by Allergo-Midax are expressed as M (average extra-cellular conductivity), B lower respiratory tract conductivity and the parameter ΔB, expressing the difference between the conductivity of the lower respiratory tract and the average yield (B-M). No difference between periods was observed in the M parameter (27.77 ± 2.86 μA at T0, 29.23 ± 3.23 μA at T1 and 28.76 ± 3.63 μA at T2). There was a signi cant decrease in B conductivity between T0 (48.53 ± 3.53 μA) and T1 (42.08 ± 3.47 μA) ($p = 0.023$) when the children were not exposed for the rst month to the offending allergen. The decrease was sustained through the study period being 41.20 ± 3.77 μA at T2, without any further statistical difference. ΔB parameter showed a significant decrease from T0 in January (20.75 ± 2.64 μA), when the children arrived at the Institute after the period of allergen exposure, and T1 in February (12.84 ± 2.52 μA) ($p < 0.01$), but no further decrease at T2 was observed (12.44 ± 2.55 μA), with no signi cant difference between T1 and T2.

The analysis of the correlations between all the evaluated parameters showed no signi cant correlation between in ammatory and lung function results.

Discussion

In the present study we confirm that effective allergen avoidance can really modify in ammatory parameters in allergic asthmatic children; as previously described[8], the changes in in ammatory markers could be more sensitive and vary more rapidly than lung parameters such as FEV1. This was demonstrated in the present study not only by evaluation of eNO but also by assessment of BI conductivity. It can be assumed that the natural allergen-induced bronchial inflammation could have altered the extra-cellular concentration of the total electrolytes in each patient, leading to increases in the B and the ΔB values, as has been observed at T0 evaluation. The reverse was probably the case after one and four months of allergen avoidance: the bronchial in ammation was reduced and accompanied by reduction in eNO and in lower respiratory tract conductivity as detected by signi cant changes of B and ΔB values. At the same time the M median values of BI of the whole body did not change, showing speci city of BI change evaluations. In a recent paper in adult mild asthmatics a good agreement between electrical conductivity data and peak ow variations and symptom score was demonstrated[11]. Authors did not measure eNO and concluded that the evaluation of extracellular bioelectrical conductivity proved a reliable and simple diagnostic parameter that can provide information for real time management of the disease irrespective of whether eNO assessment is possible[11]. In our study we have shown that the two different in ammatory parameters may be modi ed with the same statistically signi cant trend by allergen exposure/avoidance. Of course this does not allow to consider BI evaluation as an alternative to eNO, however it accounts for the validity of the method and reinforces the need for further evaluation. Bronchial BI and eNO did not correlate in our study population at the different time points; this is not surprising since they may be related to different aspects of the bronchial inflammation, as previously demonstrated for several different parameters[5,8].

In conclusion, we can observe that BI evaluation could add new information regarding the allergic modifications that characterize allergic asthma in childhood. Indeed, the evaluation of extracellular bioelectrical conductivity by Allergo-Midax seems to represent a promising non-invasive method to assess inflammation in the lower airways, even in childhood. Therefore, further studies are necessary to support the utility and reproducibility of the BI evaluation in diagnosing and treating allergic asthmatic patients.

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