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Exhaled nitric oxide in patients with esophagitis

Stężenie tlenu azotu w wydychanym powietrzu u chorych na zapalenie przełyku

Abstract

Introduction: Assessment of nitric oxide (NO) concentration in exhaled air is broadly used to monitor the airway inflammation in asthma. High levels of NO are also observed in paranasal sinuses and gastrointestinal tract (GT). Properly functioning esophageal sphincters are responsible for maintaining NO in the GT. So far, it has been unknown how much the GT disorders and especially the disorder of esophageal motility can affect FeNO (fractional exhaled nitric oxide) measurements. The aim of the study was to assess whether the gastroesophageal reflux disease has any impact on the level of NO in the exhaled air in patients who do not suffer from any airway diseases.

Material and methods: Gastroscopy with biopsy was performed in 51 patients, in whom asthma, allergic rhinitis and atopy were excluded. In 13 of them, no esophageal pathology was found and they were considered as the control group. In the remaining 38 patients, the severity of esophagitis was evaluated according to the Los Angeles classification.

Results: The concentration of NO in the exhaled air of patients with endoscopic gastroesophageal changes did not differ significantly from NO concentration in patients without inflammatory changes in the stomach and esophagus ($p = 0.68$). The presence of the hiatal hernia did not affect the FeNO concentration either ($p = 0.67$). There was no statistically significant correlation between the NO level and infection with *Helicobacter pylori* ($p = 0.18$).

Conclusions: The gastroesophageal pathologies did not affect the NO concentration in exhaled air significantly.

Key words: nitric oxide concentration in the exhaled air, FeNO, esophagitis

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Introduction

In the last 15 years, a new method of monitoring of the pulmonary inflammation (i.e. evaluation of nitric oxide concentrations in the exhaled air) has gained popularity. It is especially important for the therapy of bronchial asthma, as it has been found that the NO concentration in the exhaled air is proportional to the severity of inflammation in the bronchial wall, to eosinophilia in the induced sputum and to bronchial hyperreactivity. Increase in the NO level is connected with exacerbation, while decrease — with the use of anti-inflammatory treatment in asthmatic patient. Therefore, this is a method recommended for monitoring the disease course [1]. Changes in NO concentration in

the exhaled air are not specific for asthma. They are also found in other diseases, such as allergic rhinitis, eosinophilic bronchitis or Churg-Strauss syndrome, in atopic individuals and in case of breathing disorders during sleep [1, 2].

It is known that high concentration of NO is found in the sinuses and GI tract. The currently used tools for measurements of NO in the exhaled air restrict the NO flow from sinuses to the exhaled air [1, 3]. Properly functioning esophageal sphincter is supposed to maintain the NO in the GI tract [1, 4]. So far, it has been unknown how much the GT disorders, and especially the disorders of esophageal motility can affect FeNO measurements.

Determination of this correlation is very important, because increase in NO concentration resulting

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from GI tract diseases may lead to wrong therapeutic decisions in patients with asthma (unjustified increases of the doses of corticosteroids). Moreover, it is known that GI tract disorders can coexist with asthma [5–9]. Especially interesting is the influence of the gastroesophageal reflux disease on NO concentrations in the exhaled air, due to the disturbed function of the esophageal sphincters and a high morbidity in the group of asthma patients (about 30% of the examined individuals, and even 60% in the group of patients with severe asthma) [9].

The aim of the study was to find out whether the inflammatory changes of the esophagus may significantly influence the NO concentration in the exhaled air.

Material and methods

Patients hospitalised at the Department of Internal Medicine and Allergology in the years 2007–2009, who were planned for gastroscopy in the course of diagnostics of chronic urticaria, chronic cough, and symptoms suggestive of gastroesophageal reflux disease, were qualified to the study.

In order to exclude asthma and chronic obstructive pulmonary disease, spirometry was performed in all cases, together with the reversibility test using 200 mcg of fenoterol. History was taken as well. We excluded all patients who were diagnosed with disturbances of pulmonary ventilation and/or a positive result of the reversibility test. Patients with a history of chronic cough underwent an additional test — i.e. histamine challenge test. Only patients with $PC_{20} \geq 16$ mg% were included in the study. In order to rule out atopy, history was taken and skin prick tests with routine allergens (Allergopharma company) were performed.

Gastroscopy was carried out by means of a GIF — Q140 and Q145 Olympus gastroscope, after a previous local anaesthesia with lignocaine. Exacerbation of the inflammation was evaluated on the basis of the Los Angeles Classification [10, 11]:

- grade A — erosion*, 5 mm or less, not extending between folds;
- grade B — erosions more than 5 mm, not extending between the folds;
- grade C — erosions extending between folds but covering less than 75% of the circumference
- grade D — erosions extending between the folds and covering 75% or more of the circumference

During gastroscopy samples were collected from the esophagus and stomach, for histopatho-

logical examination. The objective was to exclude eosinophilic inflammation of the esophagus, to confirm the presence of infectious lesions, and to confirm the infection with *Helicobacter pylori*.

Nitric oxide concentration in the exhaled air (FeNO, fraction of exhaled nitric oxide) was determined at a flow of 50 ml/s, before elective gastroscopy, with an on-line method with the use of a NIOX analyser (Aerocrine) [1]. A mean from three repeatable readings was used for analysis [12]. According to the guidelines of the American Thoracic Society (ATS), spirometric tests (including histamine challenge test) were carried out after the analysis of FeNO. Patients did not smoke, eat or have any physical effort for at least four hours before the assay. The tests were performed in the morning hours (8.00–10.00 a.m.) [1].

Fifty-one patients were qualified for the study, including 10 with chronic idiopathic urticaria, 28 with gastroesophageal reflux disease and extraesophageal symptoms in the form of chronic cough, 8 with typical symptoms of gastroesophageal reflux disease, and 5 healthy subjects. Thirteen of them did not reveal any abnormalities of the esophagus (5 healthy subjects and 8 patients with chronic idiopathic urticaria). They formed the control group. Others were found with inflammatory changes of the esophagus (study group). None of the patients had any other chronic conditions, was on any medications (especially proton-pump inhibitors) or had any infections within the last 4 weeks. The patients were informed about the aim of the study and had to submit a written consent for participation. Demographic characteristics of the patients were presented in Table 1.

The statistical analysis was performed with the use of the Statistica 8 software. For group comparisons, nonparametric tests were used (Mann-Whitney U test) due to abnormal distribution of the features in the treatment groups. The descriptive statistics used medians (Me), as well as minimal (min) and maximal (max) values. The P value of less than 0.05 was considered as statistically significant.

The study was approved by the Institutional Bioethical Review Board of the Wrocław Medical University (approval No. KB-436/2007).

Results

During gastroscopy, 38 individuals (from among 51) were diagnosed with a different grade inflammatory process of the esophagus. Ten subjects were found with a reddening of the epicardia and a shift of the Z-line, three patients had linear mucosal breaks longer than 5 mm (grade B accor-

*erosions are defined as definite breaks in the mucosa with clear contrast with the normal looking mucosa, with or without exudates;

Table 1. Demographic characteristics of study population

Parameter	Study group	Control group	p
Number of study subjects	38	13	
Gender (female/male)	28/10	9/4	
Age (median. min–max)	45 (21–59)	40 (20–61)	0.79
FEV ₁ % predicted	105 (76–114)	98.9 (91.8–106)	0.9
FVC% predicted	116 (88–130)	107 (93–121)	0.72
Current smokers (%)	30	27	0.89

FEV₁ — forced expiratory volume in 1 second; FVC — forced vital capacity

ding to the Los Angeles classification), and others had linear mucosal breaks that did not exceed 5 mm (grade A). In the stomach, chronic inflammation was found in 30 subjects out of all studied individuals and in 5 subjects from the control group, while biliary gastritis was revealed in 2 individuals from the study group and 1 from the control group.

No statistically significant correlation was found between the presence of inflammatory lesions in the esophagus and NO concentration in the exhaled air ($p = 0.68$) (Fig. 1). FeNO level in the group of patients with esophagitis (Me — 12.6; max — 37.1; min — 4.9 ppb) and in the control group (Me — 11.6; max — 18.7; min. — 3.8 ppb) was within the normal ranges [13].

When analysing the severity of inflammatory lesions according to the Los Angeles classification, no statistically significant differences were found either (Fig. 2). Quite a considerable difference (statistically insignificant) was observed between the patients with gastritis without mucosal breaks (Me — 17.56; max — 37.1; min — 7.11 ppb) and those with mucosal breaks (Me — 11.4; max — 28.4; min — 4.9 ppb). Authors of this work believe that the difference was connected with a small number of subjects in this group and a wide range of FeNO values. However, it cannot be excluded that the analysis of a more numerous population would reveal a statistically significant correlation.

Concentration of nitric oxide in the exhaled air in the group of patients with gastritis did not differ significantly from NO concentration in the group of patients without gastritis.

In 34 cases (89.5%), gastroscopy showed the presence of the hiatal hernia. This pathology of the esophagus did not cause any statistically significant changes in NO concentrations in the exhaled air either ($p = 0.56$) (Fig. 3).

No statistically significant correlation was found between FeNO values and histopathologically confirmed gastric infection with *Helicobacter pylori* ($p = 0.18$) (Fig. 4).

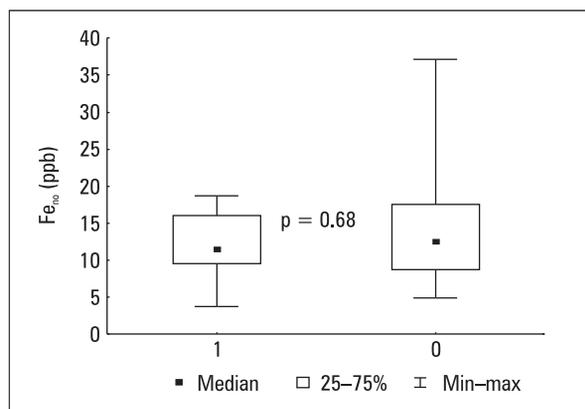


Figure 1. Comparison of NO concentration in exhaled air in patients with esophagitis (group 0) and control group (group 1)

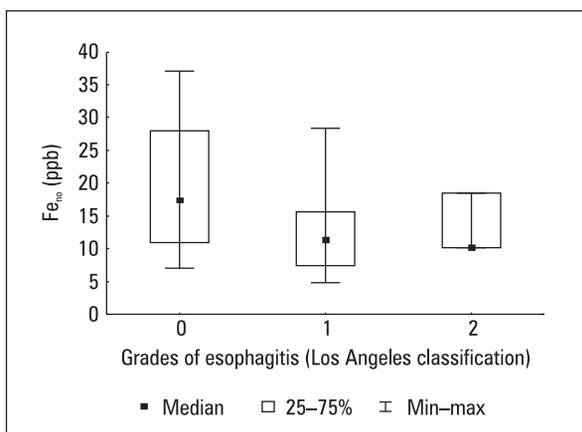


Figure 2. Comparison of NO concentration in exhaled air in patients with different grades of esophagitis (Los Angeles classification) 0 — without mucosal break, 1 — (grade A) mucosal break \leq 5 mm in length, 2 — (grade B) mucosal break $>$ 5 mm

Discussion

FeNO measurement in asthmatic patients is recognised as a non-invasive marker of inflammation. NO concentration in the exhaled air reaches a range of 5–100 ppb. At the same time,

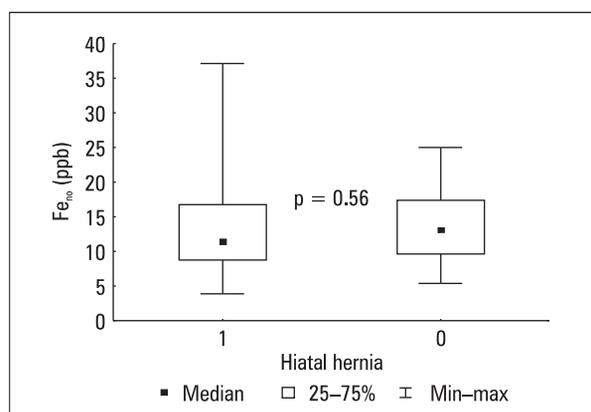


Figure 3. Comparison of NO concentration in exhaled air and patients with hiatal hernia (1) and without hiatal hernia (0)

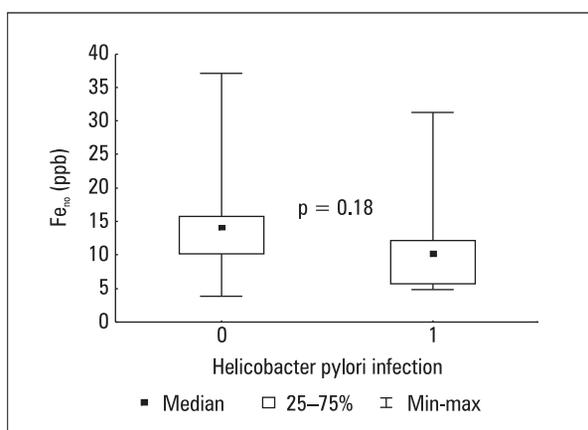


Figure 4. Comparison of NO concentration in exhaled air in patients infected with *Helicobacter pylori* (1) and without *Helicobacter pylori* infection (0)

human body includes reservoirs in which the concentration of this marker is several times higher than in the airways (1000–30 000 ppb) [1, 3, 4]. They include paranasal sinuses and gastrointestinal tract. Exhalation technique during NO concentration measurements helps in maintaining the air in sinuses and prevents from its passing to the exhaled air. NO level in the GI tract reaches 2000 ppb, i.e. approximately 100 times more than in the respiratory tract [4]. NO passing from the GI tract to the exhaled air would result in an overestimation of the parameter and thus in a wrong evaluation of asthmatic patient's health state. Efficient antireflux mechanisms of the GI tract are supposed to protect the exhaled air from being polluted with NO. However, the influence of the gastroesophageal reflux disease (in which those mechanisms are ineffective) or of the gastritis itself on NO levels in the exhaled air is still unknown.

It is important to explain this problem, because the gastroesophageal reflux disease is one of the most common abnormalities of the GI tract. Its incidence in the general population was assessed at 20–30% (pH-metry) [13]. It was much higher in the group of asthmatic patients, i.e. about 50% (14.8–81.8%) [5–9].

In the recent years, two papers have been published [14, 15], which analysed the influence of the gastroesophageal reflux disease on FeNO in asthmatic patients. The studies were conducted on a small sample of patients (approx. 9 in a group) and did not evaluate the grade of esophagitis. The analysis of the influence of GI tract diseases on FeNO in the group of patients with asthma is more difficult than in patients without asthma, due to the influence of the refluxed stomach contents on the injuries of the bronchial mucosa, activation of the vagus nerve, and development of neurogenic inflammation. All these factors increase the inflammatory process of the bronchi. In spite of that, the above mentioned studies did not reveal any influence of the gastroesophageal reflux disease on NO concentrations in patients with asthma.

This study included patients without atopy, asthma, COPD (chronic obstructive pulmonary disease) and rhinitis. Owing to that, the analysis of the influence of gastritis on FeNO was easier. No influence of esophagitis on FeNO was found in this group of patients either. However, it should be underscored that no other tests were carried out (pH-metry, impedance) which would exclude the gastroesophageal reflux disease in the control group (without inflammatory changes in the esophagus). The fact that NO levels in both groups were within the normal ranges suggests that this esophageal pathology has no influence on NO concentrations.

Helicobacter pylori was found in 6 subjects (15.7%) with inflammatory changes of the esophagus, and in one healthy person. This low incidence of infection is in accordance with previous articles, reporting on a reverse correlation between the infection with *Helicobacter pylori* and the incidence of the gastroesophageal reflux disease [16]. At the same time, no influence of *Helicobacter pylori* infection on FeNO was found.

The presence of the hiatal hernia was not shown to increase NO concentrations in the exhaled air either. The hiatal hernia disturbs many antireflux mechanisms; therefore it is very common among patients with gastroesophageal reflux disease. Chronic gastritis found in many patients was not connected with significant differences in FeNO either.

Authors of this work believe that no influence of these GI tract diseases on FeNO is most probably due to a positive pressure in the chest, which prevents the NO from passing to the exhaled air.

This year witnessed a publication [17] which analysed FeNO values in a large sample of patients with chronic cough (540 subjects). No statistically significant difference was found in NO concentrations between healthy individuals and patients with gastroesophageal reflux disease and without asthma. This is important for the evaluation of the reliability of FeNO as a marker of an existing inflammation of the bronchi in patients with asthma.

Conclusions

Esophagitis, also with concomitant chronic gastritis, does not influence FeNO significantly.

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