

INFLUENCE OF ANTISECRETORY THERAPY ON THE COURSE OF BRONCHIAL ASTHMA COMBINED WITH GASTROESOPHAGEAL REFLUX DISEASE

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The combination of gastroesophageal reflux disease (GERD) and respiratory diseases, particularly bronchial asthma (BA) is an actual issue in modern medicine. GERD revealed in approximately 40% of the adult population and in 70-80% among patients with BA; this situation remains stable during last decades [1, 2].

The peculiar interest is the pathological gastroesophageal reflux (GER), regarded as a trigger of asthma attacks, especially during the nighttime. Osler in 1892 first described that asphyxia was associated with aspiration of gastric contents. The research of Mendelson (1946), Friedland (1966) marked the beginning of further studies of the problems, thus there was the term "reflux-induced asthma". According to modern concepts, the pathogenesis of reflux-induced asthma is associated with two mechanisms. First — development of bronchospasm due to gastric content into the lumen of the bronchial tree; second — the induction of asthma attack by stimulating vagal receptors of distal esophagus (Goodall et al. 1981)

According to Goodall et al. the most significant in the development of reflux-induced asthma is a second mechanism of asthma attacks [3]. Increasing the number of pathological reflux accompanied by increased intragastric acid secretion (accordingly circadian rhythms production of hydrochloric acid) takes place predominantly between 0 and 4 hours in the morning. Throw-aggressive content results in stimulation of vagal receptors the distal esophagus reflexly inducing bronchoconstrictor effect.

The aim of research is studying the influence of antisecretory therapy on clinical and pathogenetic course of reflux-induced BA.

Materials and methods. 40 patients (18 men and 22 women) with asthma and revealed GERD were included in the study. All patients in age from 23 to 58 years, the average age was 49 years were divided into two comparable groups. The duration of GERD was $7,9\pm 2,6$ years, and BA — $12\pm 4,3$ years. Patients in both groups received basic asthma therapy, which included inhaled glucocorticosteroids (GCS) and long-acting selective β_2 - agonists. The second group of patients on the background of basic therapy additionally used proton pump inhibitor (PPI) — pantoprazole 40 mg/day. The duration of treatment with PPI was 8 weeks. The effectiveness of the therapy was evaluated after 8 weeks of treatment in the second group patients with GERD.

The diagnosis of asthma was established by GINA criteria based on typical complaints and anamnesis, the presence of reversible bronchial obstruction according to respiratory function (increase of forced expiratory volume in the first second 15% and more after using of bronchodilator — salbutamol 200 mcg). The verification of GERD was established on the basis of specific complaints anamnesis, clinical and laboratory data, results of endoscopy, intraesophageal pH-metry.

The efficiency of GERD treatment was evaluated by the change of clinical course of disease, relief of heartburn during the treatment, and in cases of reflux esophagitis — by the dynamics of erosive ulcers healing according to endoscopy. Influence of therapy on the course of BA was assessed by changes daytime and nighttime asthma symptoms, using of bronchodilators during the day, the dynamics of the values of FEV₁, VC, MVR₂₅, MVR₅₀, MVR₇₅ — forced expiratory flows at different levels of FVC (25%, 50%, 75%).

Biochemical studies such as the determination of proinflammatory cytokines IL-6 and tumor necrosis factor alpha (TNF- α) in the blood serum, as well as nitric oxide (NO) — nitrite and nitrate in plasma were held.

Results of study. The dynamics of daytime and nighttime symptoms had not revealed significant changes in the first group of patients with asthma receiving only

basic treatment without PPI (Table 1). Also in this group was marked resistance to the consumable bronchodilators.

In the second group of patients using PPIs had significantly reduction in the number of asthma attacks. It was most pronounced in respect of night attacks of asthma, the number of which under the influence of PPI after 8 weeks of treatment was reduced by 60%. It was also noted reduced consumption of short-acting bronchodilators. That it was connected with cupping the symptoms of GERD is indicated reduction in the frequency of night attacks, which is more typical for GERD associated forms of asthma.

The study of indicators of external respiration function parameters on the dynamics of changes in FEV₁, FVC and VC (Fig. 1, 2), showed significant improvement in bronchial patency in patients with asthma treated with PPIs compared with the first group. FEV₁ index in the first group was (in% predicted) 62,4±3,6 before treatment and 71,4±2,4 after the 8th week, in the second group — 63,1±2,4, and 81, 8±2,7 respectively (p <0.05). VC index in the first group was (in % predicted) 71,2±2,1 before treatment and 79,1±1,4 after treatment, the second group — 70,9±2,4 and 86,3±1 , 6, respectively, (p<0.05). Indicators of forced expiratory flow of different levels FVC (table. 2) revealed an increase in: MVR 25 — 11.9±0.1% in the first group (p<0,05), 18.9±of 0.5% in the second group (p<0,05); MVR 50 — 10.2±0.3% in the first group (p<0,05), 24.8± 0.5% in the second group (p<0,05); and MVR 75 — 7.4±0.1% in the first group (p<0,05), 26.6± 0.4 % in the second group (p<0,05).

The dynamics of pro-inflammatory cytokines in plasma in both groups of patients have shown a significant reduction in IL-6 and TNF- α before treatment (Fig. 3, 4). In patients of first group IL-6 was reduced by 34.1% and TNF- α by 38.7% compared to before treatment. In the second group of patients treated with PPI decrease of IL-6 in blood was 73.4%, and TNF- α — 57.5% compared to before treatment.

Study of NO metabolites in the blood plasma of patients with GERD-induced asthma was revealed in the first group of patients, reduction in the content of end NO

metabolites only 25.8% from the baseline. At the same time in the second group the concentration of NO metabolites was significantly decreased by 38.5% from baseline. The difference in the amount of nitrites and nitrates in the blood plasma of patients of the first and second observation groups was statistically significant — 12.7% ($p < 0.05$).

Pearson rank correlation analysis between FEV1, vital capacity and nitrites and nitrates, IL-6 and TNF- α were carried out. As seen from the results of analysis, in the first and second groups of patients during 8 weeks of therapy, between the ratio of FEV1, content of end nitric oxide metabolites in plasma and proinflammatory cytokines was strongly negative correlation (Table 3).

The same negative correlation was observed between the ratio of VC and the mentioned inflammatory biochemical markers in GERD-induced asthma (Table 4).

Conclusion. Thus, studies have shown that the using of antisecretory agents in the treatment of patients with GERD-induced asthma leads to reduce the frequency of asthma attacks and reduce the frequency of use of β_2 agonists short acting, improving the quality of life of patients and pulmonary functional parameters. Improving the efficiency of the therapy probably provided reduction plasma levels of nitric oxide end metabolites and proinflammatory cytokines

Table 1

Dynamics of clinical manifestations of patients during the treatment

Patients	Number of day attacks		Number of night attacks		Using of bronchodilators	
	Before	After 8 weeks	Before	After 8 weeks	Before	After 8 weeks
1st group	2,6 \pm 0,4	1,9 \pm 0,3*	1,6 \pm 0,1	0,9 \pm 0,3*	6,4 \pm 0,4	4,8 \pm 0,5*
2nd group	2,7 \pm 0,3	1,4 \pm 0,2*	1,5 \pm 0,2	0,6 \pm 0,1*	6,6 \pm 0,2	3,5 \pm 0,4*

Note * — difference significant against figure before treatment ($p < 0, 05$)

Table 2

Indicators of MVR 75, MVR 50, MVR 25 in patients with GERD-induced asthma during the treatment

	Pykfluometric indicators	Before treatment	After treatment
1st group	MVR 75	52,6±2,1	56,4±3,1*
	MVR 50	42,3±3,4	46,6±1,8*
	MVR 25	41,5±3,1	46,4±2,4*
2nd group	MVR 75	51,7±3,0	65,4±3,3*
	MVR 50	43,7±2,7	54,5±2,4*
	MVR 25	40,6±3,3	48,3±2,8*

Note * — difference significant against figure before treatment (p<0, 05)

Table 4

Correlation relationships between FEV1 ratio and biochemical parameters in patients with GERD-induced asthma

Ratio 1	Ratio 2	Correlation relationships
FEV1	NO metabolites	r= -0,8
	IL-6	r= -0,7
	TNF- α	r= -0,8

Table 4

Correlation relationships between the ratio of VC and biochemical parameters in patients with GERD-induced asthma

Ratio 1	Ratio 2	Correlation relationships
VC	NO metabolites	r= -0,7
	IL-6	r= -0,7
	TNF- α	r= -0,9

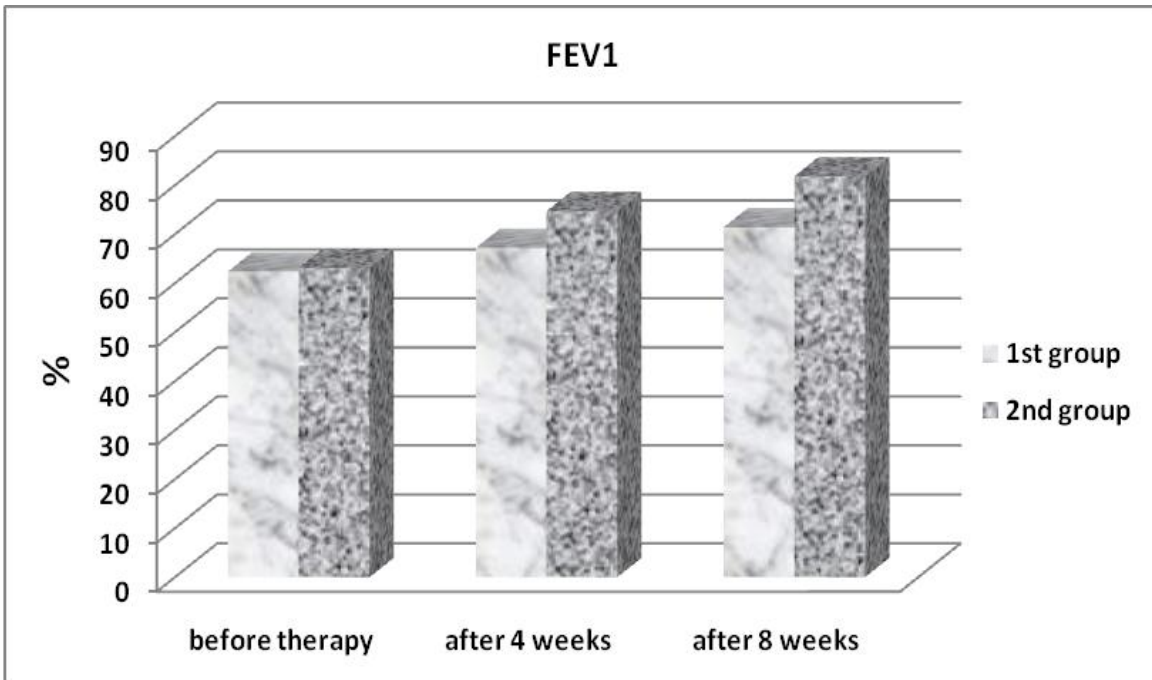


Fig. 1. Dynamics of FEV1 in the treatment of GERD-induced asthma.

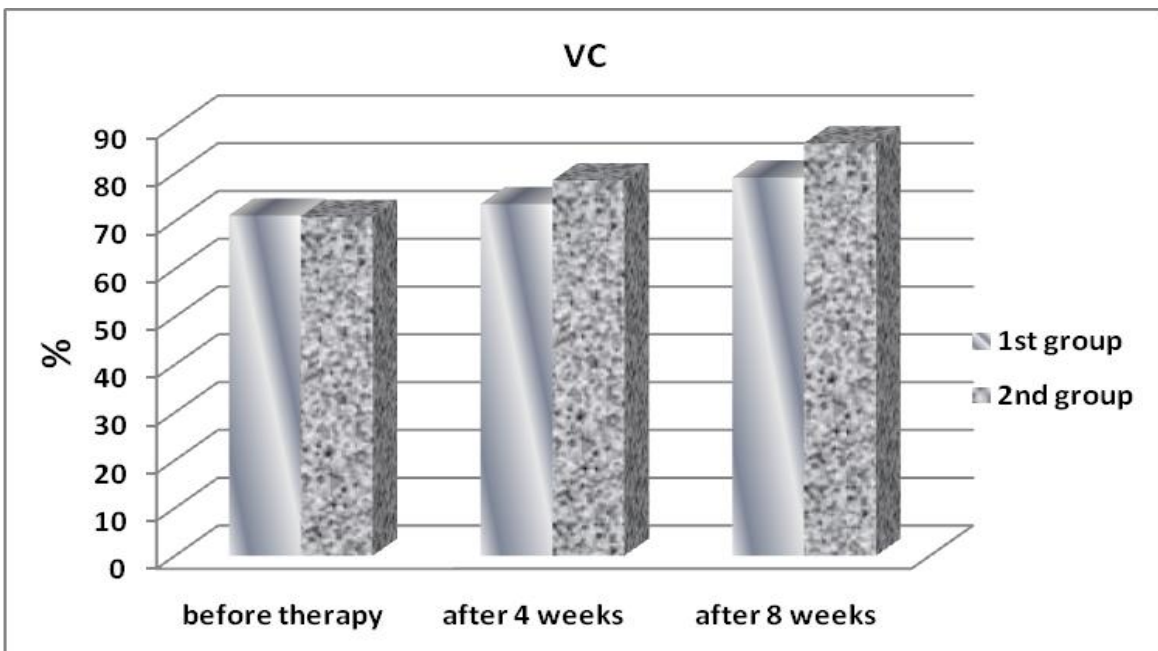


Fig. 2. Dynamics of VC in the treatment of GERD-induced BA.

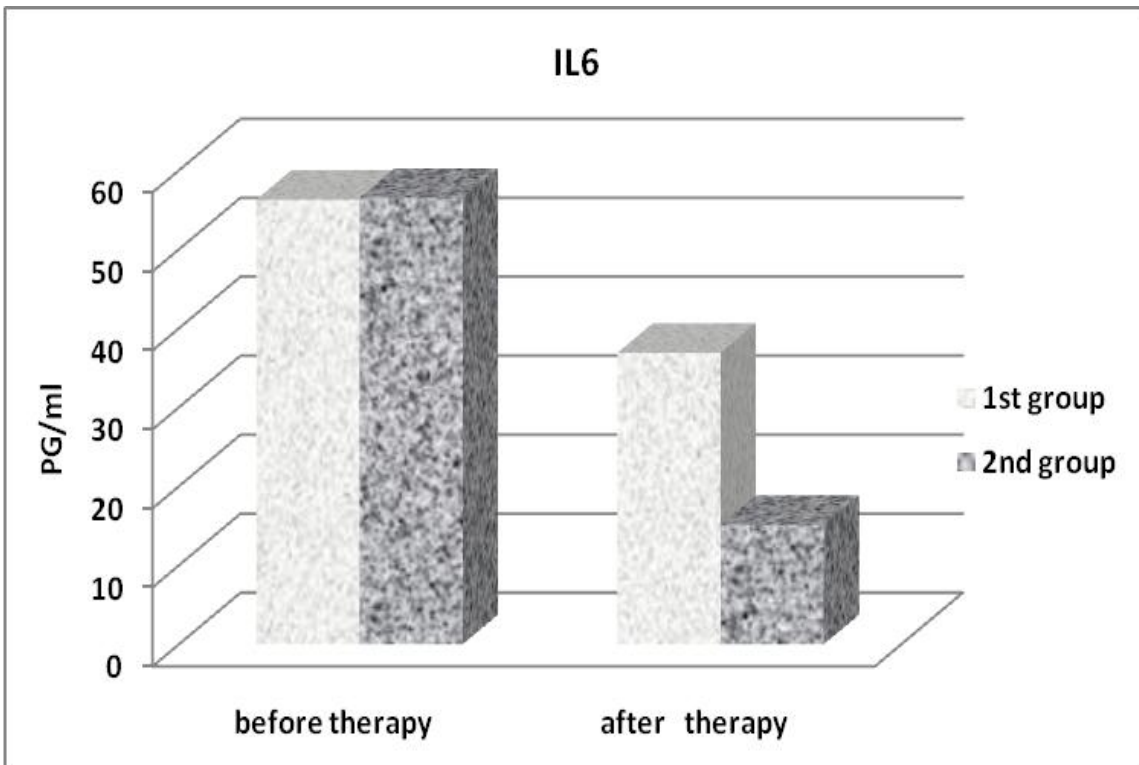


Fig. 3. The content of IL-6 in blood plasma of patients with GERD-induced BA in the dynamics of treatment.

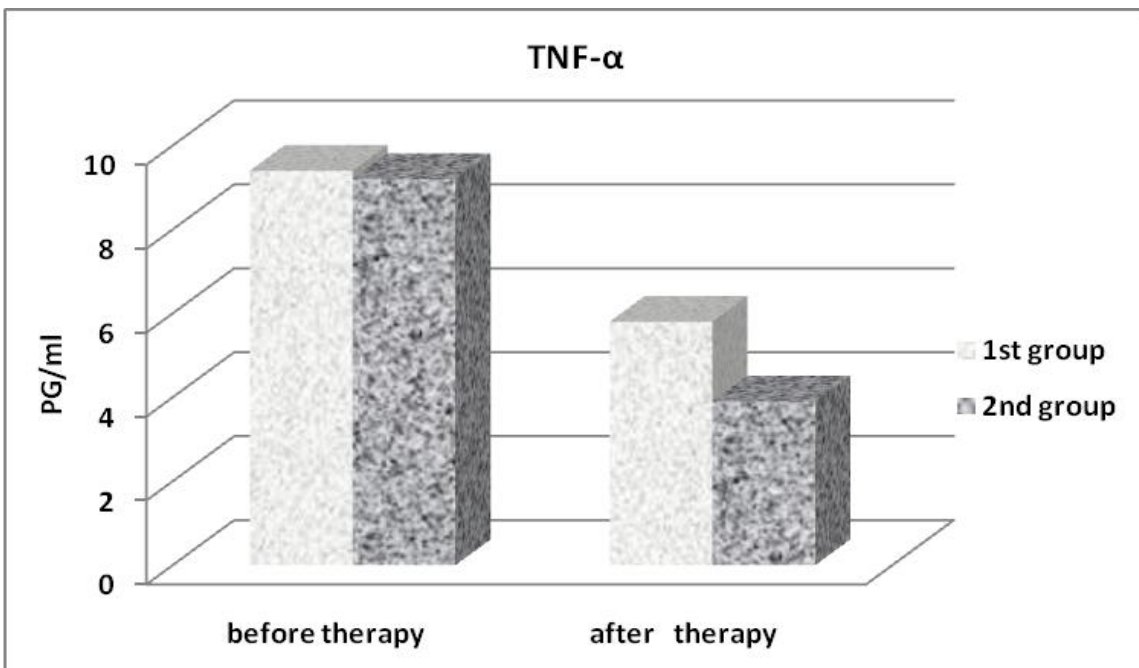


Fig. 4. The content of TNF-α in plasma of patients with GERD-induced asthma during the treatment.

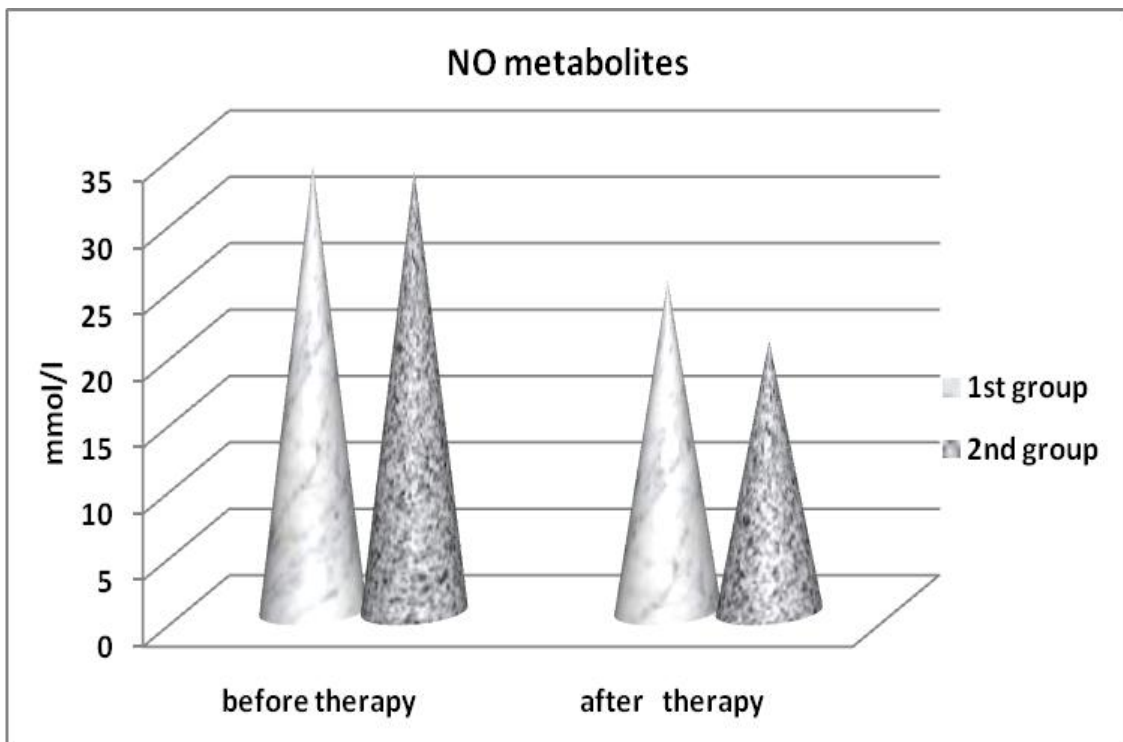


Fig. 5. The content of nitrates and nitrites in the blood plasma of patients with GERD-induced asthma during the treatment.

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The results of therapy of 40 patients with bronchial asthma combined with gastroesophageal disease are presented in the article. It is shown that using of antisecretory therapy helped reduce the number of end nitric oxide and proinflammatory cytokines in the blood plasma. The results of the therapy of these patients also improved symptoms of asthma, as manifested in reduction of frequency of asthma attacks, decreased use of beta-agonists and improvement of parameters of pulmonary ventilation.