

THE INFLUENCE OF CONCOMITANT ARTERIAL HYPERTENSION ON SEVERITY OF GASTROESOPHAGEAL REFLUX DISEASE

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Abstract

Gastroesophageal reflux disease (GERD) and arterial hypertension have a number of common risk factors, including lifestyle factors, diet, stress, etc. Therefore, the issues of comorbidity of these pathologies as well as their mutual impact on the severity of the disease are relevant.

***The purpose of research** was to study the peculiarities of intraesophageal pH-metry, the condition of the "lipid peroxidation-antioxidant protection", apelin level and concentration of nitric oxide in the daily urine in patients with isolated GERD and with its combination with arterial hypertension.*

***Results.** Increased body mass index (BMI) significantly influenced on the severity of heartburn at night in a group with concomitant arterial hypertension, $p = 0.042$. The presence of comorbidity with arterial hypertension had no effect on the data of intraesophageal pH-metry that allows to classify the existing disorders as severe gastroesophageal reflux disease in all patients regardless of concomitant arterial hypertension, $p > 0.05$. More pronounced activity of the oxidative stress was observed in patients with concomitant pathology that associated with higher levels of MDA compared to group with isolated GERD, $p = 0.001$. The concentration of NO in the daily urine and apelin level were higher in patients with isolated GERD, $p = 0.001$.*

***Conclusions.** More pronounced activity of oxidative stress, higher degree of depletion of the antioxidant defense system and the lower level of protective biomarker – apelin – were observed in patients with a combination of GERD and arterial hypertension.*

Key words: apelin, gastroesophageal reflux disease, arterial hypertension, intraesophageal pH-monitoring, nitric oxide, oxidative stress.

1. Introduction

Comorbidity of widely distributed noninfectious diseases is an actual problem of modern medicine [3]. Arterial hypertension is one of the most widespread diseases in countries with high economic level and one of the major risk factors for cardiovascular disease [1].

Along with it the special attention is paid to study of gastroesophageal reflux disease (GERD). In 1998, GERD has been included in the "five" diseases with the greatest extent of quality of life reduction. According to the latest data, the main symptom of GERD - heartburn - affects up to 40% of the US adult population and up to 10-25% - in Europe [4]. According to numerous population-based studies, GERD encompasses wide scope with prevalence in developed countries (10-20%) [5].

A frequent situation is combination of arterial hypertension and GERD [2] due not only to their distribution, but also the common risk factors for these diseases: psycho-emotional stress, smoking, alcohol abuse, poor diet with increased consumption of saturated fats, refined carbohydrates, insufficient use of micronutrients, obesity, physical inactivity, and others. Thus, in the study of Moraes-Filho JP et al. (2009) arterial hypertension was detected in 29% of persons with non-erosive reflux disease and 20.6% of patients with GERD [7]. In connection with the above study of pathogenetic links and features of the mutual influence of these two diseases is very important.

The purpose of research was to study the peculiarities of intraesophageal pH-metry, the condition of the "lipid peroxidation-antioxidant protection system", apelin level and concentration of nitric oxide in the daily urine in patients with isolated GERD and with its combination with arterial hypertension.

2. Materials and methods

The study enrolled 126 patients with a combination of essential hypertension II stage 1-3 degrees and GERD (1st group), mean age - (56.84±1.17), mean duration of arterial hypertension – (11.42±0.73) years. The second group consisted of 89 patients with isolated GERD, mean age - (42.0±1.6). The control group consisted of 20 healthy individuals, mean age - (22.8±0.2).

Determination of the stage and degree of arterial hypertension and risk stratification for prognosis were performed according to clinical guidelines for arterial hypertension of the European Society of Hypertension (ESH) and the European Society of Cardiology (ESC) 2013 [1]. The diagnosis of GERD was established according to The Montreal Consensus (2006) [8]. The patients with symptoms of heartburn (2 times a week or more) were selected in the study.

Anthropometric studies included measurement of height and weight of the patient with subsequent calculation of body mass index (BMI) by the conventional method according to the recommendations of the international group of WHO on obesity (IOTF WHO, 1997).

To assess the lipid peroxidation and antioxidant systems it was used the definition of malondialdehyde and SH-groups in the serum and of glutathione peroxidase in the blood hemolysate using standard procedures.

The metabolism of nitric oxide was determined by the content of its stable metabolites - nitrites and nitrates - in plasma and in daily urinary excretion (by day and night) by using spectrophotometric method with Gris reaction after reduction of nitrate to nitrite by zinc powder.

Content of apelin-12 in the plasma was determined by ELISA using a kit of reagents "Apelin-12 (Human, Rat, Mouse, Bovine) EIA Kit" Phoenix Pharmaceuticals (USA).

24-hour intraesophageal pH-monitoring was performed using atsidogastrometr AGM-24 MP TC9441-002-13306657-2003 according to standard procedure with determination of percentage of total time during which the pH is less than 4 (% Total time pH<4) (normally less than 4.5), total number of refluxes

with pH of less than 4 per day (No. of episodes) (normally less than 47), total number of refluxes with pH of less than 4 and more than 5 minutes per day (No. of episodes > 5 min) (normally less than 3.5), the duration of the longest reflux with pH of less than 4 (Longest episode (min)) (normally less than 20) with followed calculation of the index De Meester (normally less than 14,7). Throughout the study all patients completed a self-monitoring diaries in order to identify the relationship of clinical symptoms with detect changes of pH-gram.

Analysis of the results was performed using a computer program IBM SPSS Statistics 21.0. For the purpose of mathematical data processing the following methods were used: primary descriptive statistics, t-Student test for dependent and independent samples, correlation analysis.

3. Results and discussion

The patients of comparison groups did not differ in the duration of GERD: in individuals with isolated course of the disease the duration of GERD was (9.9 ± 0.9) years, in the group with concomitant arterial hypertension – (8.7 ± 0.4) years, $p > 0.05$. It is interesting to note that in group of isolated GERD the duration of the disease was significantly higher in females ((12.0 ± 1.3) years) compared with males ((7.6 ± 1.0) years), $p = 0.01$. In the group of patients with combined pathology a similar tendency was observed, namely, the duration of GERD in females was (10.4 ± 0.7) years and the duration of arterial hypertension - (12.4 ± 1.0) ; in males, respectively - (7.3 ± 0.4) and (8.2 ± 0.5) years, $p < 0.001$. Furthermore, both the duration of GERD and arterial hypertension affect the severity of heartburn in patients with comorbidity. Thus, in patients with severe heartburn the duration of GERD was (10.2 ± 1.1) years and the duration of arterial hypertension - (12.5 ± 1.6) years, whereas, in patients with moderate heartburn the duration of GERD was significantly lower - (7.2 ± 0.6) years, $p = 0.02$, and the duration of arterial hypertension - (8.2 ± 0.7) years, $p = 0.023$. There was not established the significant dependence of severity of heartburn on the duration of the disease in the group of isolated GERD, however, the duration of GERD in these patients was significantly depended on age of the patients ($r = 0.614$, $p = 0.001$), affected the severity of nausea ($r = 0.274$, $p = 0.009$) and correlated with the presence of dizziness ($r = 0.218$, $p = 0.041$).

Comparison groups did not differ in BMI of patients: (27.4 ± 0.4) kg/m^2 and (27.5 ± 0.3) kg/m^2 respectively, $p > 0.05$. However, it should be noted that increasing BMI significantly influenced the severity of heartburn at night in the group with concomitant arterial hypertension, while the average BMI in individuals, who indicated the presence of nocturnal heartburn, was $(28,0 \pm 0,4)$ kg/m^2 , the patients without heartburn at night had an average BMI (27.0 ± 0.3) kg/m^2 , $p = 0.042$. In the group of patients with isolated GERD the impact of BMI on the existence of nocturnal heartburn was not revealed.

During the study indices of 24-hour intraesophageal pH-monitoring was compared. The percentage of total time during which the pH is less than 4 (% Total time $\text{pH} < 4$) in group of isolated GERD was (29.4 ± 0.9) %, in patients with concomitant arterial hypertension – (27.8 ± 0.9) %, $p > 0.05$. Also, the presence of comorbidity with arterial hypertension had no effect on total number of refluxes with pH of less than 4 per day (No. of episodes): (102.1 ± 4.1) и (103.0 ± 3.1) respectively, $p > 0.05$. Parameters such as “the total number of refluxes with pH of less than 4 and more 5 minutes per day (No. of episodes > 5 min)” and “the duration of the longest reflux with pH of less than 4 (Longest episode (min))” characterize the ability of the esophagus to cleanse itself. The increase of “No. of episodes > 5 min” ((28.4 ± 0.8) - in group of isolated GERD and (28.9 ± 0.8) - in group with concomitant arterial hypertension, $p > 0.05$) and the increase of “Longest episode (min)” ((26.9 ± 1.0) and (28.5 ± 0.7) min respectively, $p > 0.05$) make it possible to assume the existence of esophageal hypomotor dyskinesia in all the examinees. At the same time, the generalized index DeMeester allows to quantify the degree of deviation of pH values in a specific patient, that is, on the basis of objective data makes it possible to differentiate the physiological and pathological reflux. Increase

of the DeMeester index more than 14.72 indicates the presence of GERD. The obtained data allow classifying the revealed violations as severe gastroesophageal reflux in patients regardless of concomitant arterial hypertension (55.9 ± 1.6) and (55.5 ± 1.5) respectively, $p > 0.05$).

Despite the fact that the duration of GERD in group of isolated GERD was higher in females, more severe violations according to the 24-hour intraesophageal pH-monitoring data were established for males. Thus, "the percentage of total time during which the pH is less than 4" in males was (31.3 ± 1.4) %, in females - (27.7 ± 1.0) %, $p = 0.035$; "total number of refluxes with pH of less than 4 per day" respectively differed according to gender - (113.2 ± 5.9) and (92.1 ± 5.3), $p = 0.009$; "the total number of refluxes with pH of less than 4 and more 5 minutes per day" - (30.3 ± 1.2) and (26.7 ± 0.9), $p = 0.017$; "the duration of the longest reflux with pH of less than 4" - (30.1 ± 1.6) and (24.0 ± 1.2) min, $p = 0.003$; DeMeester index - (60.2 ± 2.5) and (52.1 ± 1.9), $p = 0.012$. In the group with comorbidity (GERD and arterial hypertension) the significant differences between the intraesophageal pH-monitoring data has not been established according to gender.

In order to examine disorders in the "lipid peroxidation-antioxidant protection system" the following parameters were evaluated: malonic dialdehyde (MDA) - endogenous aldehyde formed as a result of polyunsaturated fatty acids metabolism and is the marker of oxidative stress, the concentration of nitrogen oxide (NO) in the blood plasma, and as markers of antioxidant protection the level of SH-groups in the serum and the concentration of glutathione peroxidase (GPO) in the hemolysate were considered. It is known that oxidative stress plays a significant role in the formation of endothelial dysfunction and is a significant pathogenetic link of development of both hypertension and GERD. The activity of the oxidative stress directly affects the severity of inflammation in GERD, there is an imbalance between the constitutive and inducible links of nitric oxide synthesis which creates the conditions for realizing its cytotoxic properties with subsequent tissue damage.

Assessing the findings, we can assume a more pronounced activity of oxidative stress in patients with comorbidity (GERD and arterial hypertension). Thus, for persons suffering from GERD and concomitant arterial hypertension the MDA concentration was significantly higher (4.40 ± 0.08) mcmol/l compared with group of isolated GERD (3.51 ± 0.09) mcmol/l, $p = 0.001$. In patients with concomitant arterial hypertension the MDA concentration was higher in females (4.67 ± 0.14) mcmol/l than in males (0.08 ± 4.16) mcmol/l, $p = 0.002$. The data is confirmed by the identification of decrease in SH-groups level in the serum of patients with comorbidity (495.11 ± 5.42) and (521.59 ± 5.60) mcmol/l respectively, $p = 0.001$), that may indicate the evolved exhaustion of antioxidant defense system. It should be noted that in the group of isolated GERD the tension of antioxidant protection was higher in females: SH-group concentration in serum was (493.84 ± 6.72) mcmol/l, while the concentration of SH-groups in males was slightly higher - (552.64 ± 6.44) mcmol/l, $p = 0.001$. The indicators of the NO concentration in the blood plasma in the compared groups were (24.84 ± 0.06) and (29.82 ± 0.53) mcmol/l respectively, $p = 0.001$. There were no significant differences between the levels of GPO in the examined patients (161.97 ± 4.61) and (158.78 ± 3.01) mcmol/min/gHb, $p > 0.05$), however, in the group of patients with concomitant arterial hypertension the GPO concentration was significantly higher in females (180.09 ± 6.38) mcmol/min/gHb, compared to males (146.59 ± 6.00) mcmol/min/gHb, $p < 0.001$. In the group of healthy individuals the MDA concentration was the lowest (2.71 ± 0.06) mcmol/l, the NO level in the blood was (23.72 ± 0.65) mcmol/l, and the rate of SH-groups was highest that indicated their inherent stability of the antioxidant protection - (676.92 ± 21.75) mcmol/l, the GPO concentration in hemolysate was highest - (261.88 ± 5.79) mcmol/min/gHb, $p < 0.001$.

The concentration of NO in the daily urine was higher in patients with isolated GERD. Thus, the concentration of NO in the urine at day was (40.09 ± 0.69) mcmol/l, in patients with concomitant arterial hypertension - (31.26 ± 0.08) mcmol/l; at night period - (101.36 ± 1.01) and (57.69 ± 0.15) mcmol/l; in the daily urine - (141.45 ± 1.64) and (88.96 ± 0.17) mcmol/l respectively, $p=0.001$. The study of features of gender influence on the concentration of NO in the urine revealed higher values of NO for males in the group of isolated GERD: NO concentration in the urine in males at day was (41.98 ± 1.06) mcmol/l, in females - (38.39 ± 0.84) mcmol/l, $p=0.009$; at night - (103.86 ± 1.65) and (99.13 ± 0.14) mcmol/l, $p=0.021$; in the daily urine - (145.85 ± 2.61) and (137.52 ± 1.90) mcmol/l, $p=0.012$, respectively. In the control group the level of nitric oxide metabolites in urine at day - (25.68 ± 0.04) mcmol/l, at night - (40.70 ± 0.12) mcmol/l, in the daily urine - (66.43 ± 0.13) mcmol/l.

Interesting results were obtained by comparing the levels of such protective biochemical marker as apelin. Thus, apelin has many points of application: stimulation of gastric mucosal cells proliferation, secretion of cholecystokinin, a decrease of insulin secretion, histamine, hydrochloric acid by the parietal cells, etc. So, apelin is an important regulator of gastrointestinal tract functioning which contributes to the restoration of the mucosa and is involved in the regulation of smooth muscles functioning and metabolism. The vasodilator effect of apelin by the NO-dependent mechanisms of APJ-receptor stimulation was revealed. Furthermore, preventing the degradation of superoxide dismutase apelin is able to inhibit the production of free radicals [6]. It is noteworthy that the highest values of its concentration in the blood were characterized for the control group - (1133.42 ± 17.85) pg/ml. As for those with GERD, in combination with arterial hypertension the apelin level was slightly lower (755.15 ± 15.46) pg/ml compared with the data in isolated GERD (863.40 ± 19.87) pg/ml, $p=0.001$. In the group of patients with comorbidity (GERD and arterial hypertension) the apelin level was significantly higher in males (792.55 ± 21.29) pg/ml, than in females (710.41 ± 21.15) pg/ml, $p=0.008$. There were not significant gender differences in the levels of apelin among patients with isolated GERD.

4. Conclusions:

1. The presence of comorbidity with arterial hypertension had no effect on the intraesophageal pH-monitoring data that allows classifying the existing disorders as an severe gastroesophageal reflux in patients regardless of concomitant arterial hypertension (55.9 ± 1.6) and (55.5 ± 1.5) , respectively, $p > 0.05$).
2. At the same time, increased BMI significantly influenced the severity of heartburn at night in the group with concomitant arterial hypertension, thus, the average BMI in individuals with nocturnal heartburn was (28.0 ± 0.4) kg/m² and patients without nocturnal heartburn had a mean BMI (27.0 ± 0.3) kg/m², $p=0.042$.
3. More pronounced activity of the oxidative stress observed in patients with comorbidity, as indicated by higher levels of MDA (4.40 ± 0.08) mcmol/l compared to group of isolated GERD (3.51 ± 0.09) mcmol/l, $p=0.001$, and also by revealing of decrease in the level of SH-groups in the serum (495.11 ± 5.42) and (521.59 ± 5.60) mcmol/l, respectively, $p=0.001$). The degree of violations in the "lipid peroxidation-antioxidant protection system" was greater in females.
4. The concentration of NO in the daily urine was higher in patients with isolated GERD (141.45 ± 1.64) mcmol/l compared to the data at comorbidity with arterial hypertension (88.96 ± 0.17) mcmol/l, $p=0.001$.
5. In the case of concomitant arterial hypertension the apelin level was slightly lower (755.15 ± 15.46) pg/ml compared to the data at isolated GERD (863.40 ± 19.87) pg/ml, $p=0.001$.

5. Prospects of research:

Because of the high frequency of occurrence of GERD and arterial hypertension comorbidity and significant impact of these disorders on quality of life, common etiological trigger factors and pathogenesis

is necessary to investigate the features of mutual influence of these diseases on clinical manifestations and progression processes. The problem of the development of adequate correction methods and effective preventive measures of arterial hypertension and GERD is relevant and should be the subject of subsequent studies.

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