

Vasoactive intestinal polypeptide level in gastroesophageal reflux disease before and after surgical treatment

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A – research concept and design; B – collection and/or assembly of data; C – data analysis and interpretation; D – writing the article; E – critical revision of the article; F – final approval of the article

Key words:
gastroesophageal
reflux disease,
vasoactive intestinal
peptide.

Zaporozhye
medical journal,
2023. 25(4), 346-351

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From year to year, wide spread of gastroesophageal reflux disease (GERD) is attracting greater attention of specialists in the field of this pathology diagnosis and treatment. In-depth studies on etiological and pathogenetic factors in the GERD development are being conducted. Of particular interest is the role of humoral factors, one of which is vasoactive intestinal peptide (VIP). There are currently no data on the dynamics of this hormone during surgical treatment of GERD.

The aim of the study was to examine the dynamics of plasma VIP during surgical treatment of GERD and its influence on the lower esophageal sphincter (LES) function.

Materials and methods. Surgical treatment in the Nissen modification was performed for 35 patients with GERD. There were 26 women (74.3 %), men – 9 (25.7 %), mean age – 55.3 ± 11.3 years. Comparison group – 20 apparently healthy individuals: women – 14 (70.0 %); men – 6 (30.0 %), mean age – 56.7 ± 10.6 years. VIP was measured in venous blood plasma by an enzyme immunoassay (Vasoactive intestinal peptide ELISA, S-1201, BCM Diagnostics) using an immunoenzyme complex ImmunoChem-2100 (USA). The sampling of the studied samples in the main group was carried out before the operation and 2–3 months post-surgery.

Results. In the main group before the surgery, the level of VIP was 3.1 ± 1.1 ng/ml, after the surgery – 2.2 ± 1.0 ng/ml. In the comparison group, VIP was determined at the level of 2.1 ± 1.1 ng/ml. In GERD before the surgery, the VIP level was statistically different from the indicators in the comparison group and from postoperative values. After surgical treatment, VIP values were decreased to the level of apparently healthy individuals. There was a positive correlation between the VIP level and acid exposure time (AET), the total number of refluxes, the number of reflux events longer than 5 minutes, the maximum duration of refluxes and the degree of esophageal inflammation.

Conclusions. In the surgical treatment of GERD, the statistically significant decrease in the VIP level to that of apparently healthy individuals is determined. The moderate positive correlation between the levels of VIP, AET, the average number of refluxes, the number of reflux events longer than 5 minutes, and the maximum duration of refluxes confirms the inhibitory effect of VIP on LES tone. The relationship between the degree of esophageal inflammation and the VIP level confirms the indirect, through the action of VIP, inhibitory effect of the esophagitis severity on the LES tone.

Ключові слова:
гастроєзофагеальна
рефлюксна
хвороба,
вазоактивний
інтестинальний
пептид.

Запорізький
медичний журнал,
2023. Т. 25, № 4(139).
С. 346-351

Рівень вазоактивного інтестинального пептиду при гастроєзофагеальній рефлюксійній хворобі до та після хірургічного лікування

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Істотне поширення гастроєзофагеальної рефлюксійної хвороби (ГЕРХ) з кожним роком привертає дедалі більше уваги фахівців у галузі діагностики та лікування цієї патології. Здійснюють ґрунтовні дослідження етіологічних і патогенетичних факторів виникнення ГЕРХ. Особливий інтерес викликає роль гуморальних факторів, один із них – вазоактивний інтестинальний пептид (ВІП). Відомостей про динаміку цього гормону при хірургічному лікуванні ГЕРХ нині недостатньо.

Мета роботи – вивчити динаміку ВІП у сироватці крові при хірургічному лікуванні ГЕРХ та його вплив на функцію нижнього стравохідного сфінктера (НПС).

Матеріали та методи. Хірургічне лікування в модифікації Nissen здійснили 35 пацієнтам із ГЕРХ: 26 (74,3 %) жінок, 9 (25,7 %) чоловіків (середній вік – $55,3 \pm 11,3$ року). Група порівняння – 20 практично здорових осіб: 14 (70,0 %) жінок, 6 (30,0 %) чоловіків (середній вік – $56,7 \pm 10,6$ року). Дослідження ВІП здійснили шляхом імуноферментного аналізу в плазмі венозної крові. Зразки крові в пацієнтів основної групи брали перед операцією та через 2–3 місяці після неї. ВІП (Vasoactive intestinal peptide ELISA, S-1201, BCM Diagnostics) визначали на імуноферментному комплексі ImmunoChem-2100 (США).

Результати. В основній групі до операції рівень ВІП становив $3,1 \pm 1,1$ нг/мл, після втручання – $2,2 \pm 1,0$ нг/мл. У групі порівняння ВІП визначили на рівні $2,1 \pm 1,1$ нг/мл. При ГЕРХ до операції рівень ВІП статистично відрізнявся від показника у групі порівняння та від післяопераційних значень. Після хірургічного лікування значення ВІП знизилися до рівня практично здорових пацієнтів. Виявили позитивний кореляційний зв'язок між рівнем ВІП і часом кислотної експозиції в стравоході, загальною кількістю рефлюксів, кількістю рефлюксів тривалістю понад 5 хвилин, максимальною тривалістю рефлюксів і ступенем запалення стравоходу.

Висновки. При хірургічному лікуванні ГЕРХ виявили статистично значуще зниження рівня ВІП до рівня практично здорових осіб. Помірний позитивний кореляційний зв'язок між рівнем ВІП, часом кислотної експозиції в стравоході, середньою кількістю рефлюксів, кількістю рефлюксів тривалістю понад 5 хвилин і максимальною тривалістю рефлюксів підтверджує інгібувальну дію ВІП на тонус нижнього стравохідного сфінктера. Взаємозв'язок ступеня запалення стравоходу та рівня ВІП підтверджує опосередкований (через дію ВІП) інгібувальний вплив ступеня тяжкості езофагіту на тонус нижнього стравохідного сфінктера. Підтверджено активну роль ВІП у патогенезі ГЕРХ і досягненні стійких результатів хірургічного лікування.

From year to year, wide spread of gastroesophageal reflux disease (GERD) is attracting greater attention of specialists in the field of this pathology diagnosis and treatment [1,2,3,4,5]. An active work continues on the development of new and improvement of already known treatment and diagnostic protocols aimed at preventing complications of GERD and improving the quality of life in patients [6,7,8]. Along with this, in-depth studies on the etiological and pathogenetic factors in the development of GERD are being conducted everywhere, the results of which will help solve some problematic issues in achieving a stable positive therapeutic effect [9,10,11]. One of particular interest is the role of humoral influence on the GERD pathogenesis and the possibility of using the obtained data to improve the results of both medical and surgical treatment [12,13].

Today, a number of hormones are known to regulate the functioning of the upper gastrointestinal tract muscles and also affect both the contraction and relaxation of the lower esophageal sphincter, the dysfunction of which plays one of the decisive roles in the development of GERD [14,15,16,17]. Among them, a special place is occupied by vasoactive intestinal peptide (VIP), which is one of the important neurotransmitters and neuromodulator that inhibits the reaction of the lower esophageal sphincter (LES) to various stimuli and, thus, contributes to its relaxation [13,18,19,20].

However, data on this hormone dynamics in the surgical treatment of GERD, one of the stages of which is the strengthening of the LES by crurorrhaphy and total fundoplication, are currently absent. The study on this influence will allow answering the question of achieving a stable postoperative positive effect and predicting the effectiveness of surgical treatment.

Aim

To study the dynamics of serum VIP during surgical treatment of GERD and its effect on the LES function.

Materials and methods

Laparoscopic crurorrhaphy and total fundoplication with Nissen modification were performed for 35 patients with GERD. There were 26 (74.3 %) women, men – 9 (25.7 %), aged 55.3 ± 11.3 years. The comparison group included 20 apparently healthy persons, among whom, there were 14 women (70.0 %) and 6 men (30.0 %), the mean age was 56.7 ± 10.6 . The studied groups were comparable in terms of sex ($p = 0.73$) and age ($p = 0.7$). The diagnosis of GERD was confirmed or ruled out using video gastroduodenoscopy (VGDS) and daily pH-impedancemetry, as well as questionnaires were filled out by all the patients. Inclusion criteria: presence of GERD, surgical treatment, no contraindications to surgery. Exclusion criteria – absence of GERD, exacerbation of other gastroenterological diseases, acute surgical pathology, patient preference of only drug treatments.

Measurements of VIP were carried out with the help of enzyme immunoassay in blood plasma, which was stored in a freezer at a temperature of -80°C . Venous blood samples were collected for analysis from the main group patients 2–3 weeks before and 2–3 months after the operation. Plasma VIP was measured (Vasoactive intestinal peptide

ELISA, S-1201, BCM Diagnostics) by an immunoenzymatic assay in an ImmunoChem-2100 immunoenzymatic complex (USA) at the Department of Clinical Laboratory Diagnostics of Zaporizhzhia State Medical and Pharmaceutical University. VIP concentrations were expressed in ng/ml [21].

Statistical interpretation of the study results was performed using the Statistica for Windows 13 software package (StatSoft Inc., No. JPZ804I382130ARCN10-J). The obtained results with normal distribution were presented as an arithmetic mean and a mean square deviation, $M \pm s$. Non-normally distributed data were described by the median (x) and interquartile range (25th (a) to 75th (b) percentiles). The data were expressed in the form of x (a; b). Differences and relationships between groups were assessed with non-parametric methods using the Mann–Whitney test, the Kruskal–Wallis test, the Wilcoxon test, the Spearman test, as well as using the “Differential tests” submodule in the “Basic Statistics and Tables” module. Statistical significance of the differences was set at $p < 0.05$.

Results

In the main group, the level of VIP was 3.1 ± 1.1 ng/ml before the operation, and it was decreased to 2.2 ± 1.0 ng/ml postoperatively. In the comparison group, in apparently healthy people, VIP was detected at the level of 2.1 ± 1.1 ng/ml. In patients with GERD, the preoperative level of VIP was statistically different from that in the control group and the postoperative values. At the same time, postoperative VIP values after successful surgical treatment decreased to the level of apparently healthy persons (Table 1).

We studied the features of refluxes, acid exposure time (AET), their relationship with the level of VIP in the studied groups, the dynamics before and after the surgery, determined during daily pH-impedance monitoring (Table 2).

Table 2 shows that AET before the surgery significantly exceeded normal values and statistically significantly decreased after surgical treatment to the level of healthy individuals in the control group. At the same time, there was a moderate correlation between the level of VIP and AET (Fig. 1).

The total number of refluxes before the surgery was also higher than physiological values and statistically significantly decreased post-surgery to the level of healthy individuals (Table 2). In this case, there was also a moderate correlation between the VIP level and the number of refluxes (Fig. 2).

The same trend was observed when analyzing the dynamics of reflux events longer than 5 minutes before and after the surgery in comparison with the control group (Table 2). At the same time, there was a moderate correlation between the VIP level and the number of these refluxes (Fig. 3).

The maximum reflux duration before the surgery in patients with GERD was 26.0 (9.0; 46.0) minutes, while it was decreased to 5.0 (2.0; 11.0) minutes post-surgery, that practically did not differ from the maximum reflux duration in the group of healthy people (Table 2). Meanwhile, the correlation analysis between the maximum reflux duration and the VIP level also showed a moderate correlation in the study (Fig. 4).

The mean reflux duration in GERD patients before the surgery was 4.1 (2.0; 5.0) minutes and decreased

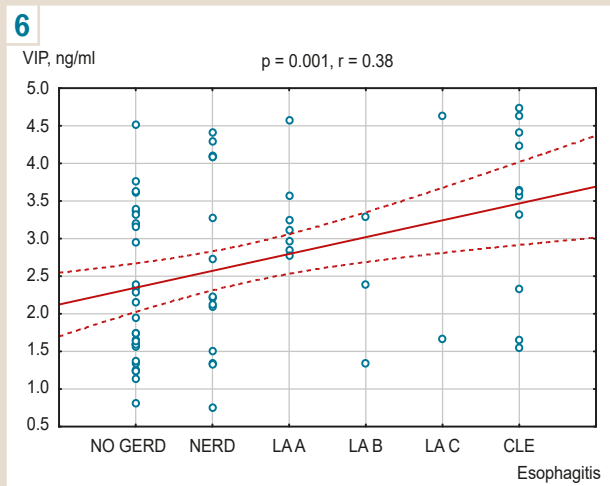
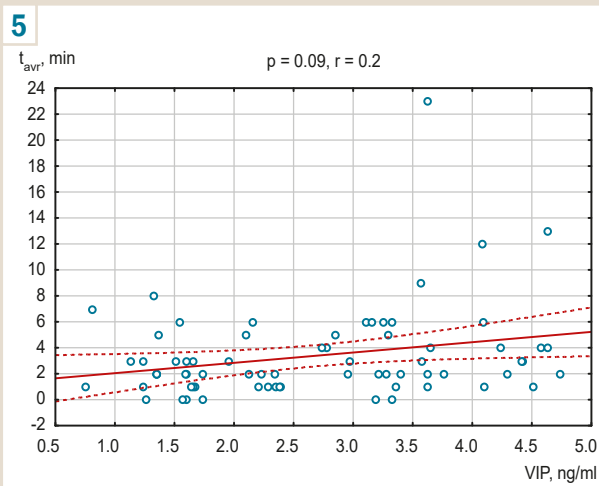
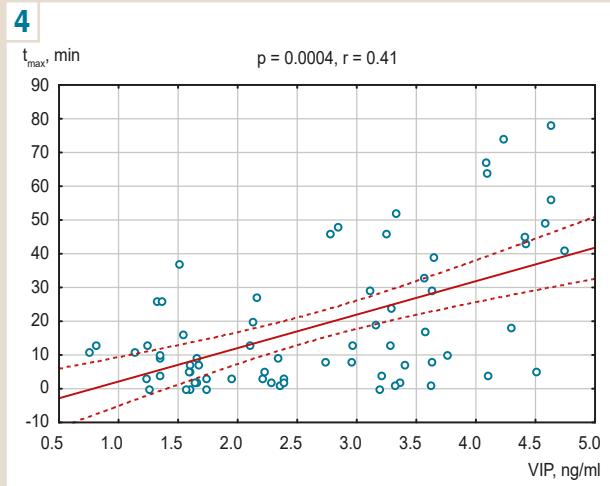
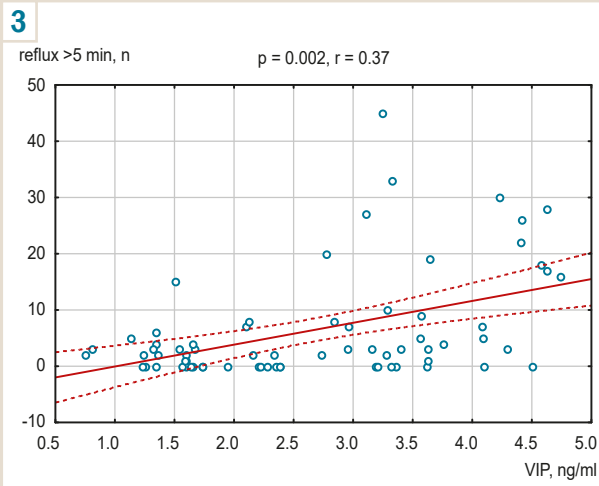
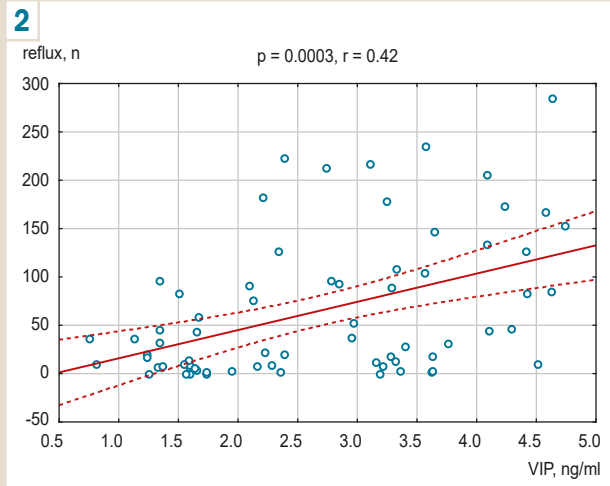
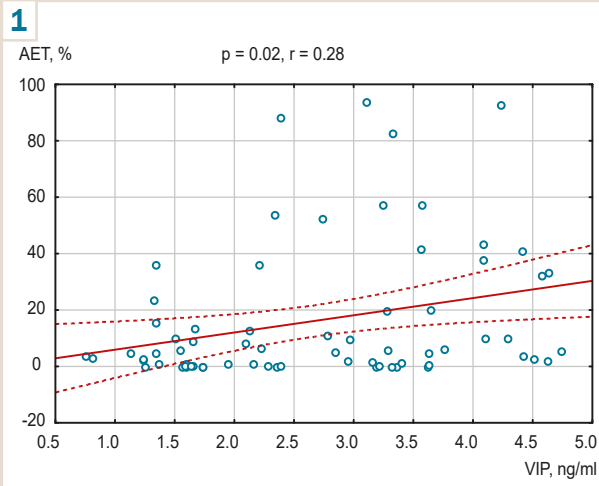


Fig. 1. Correlation between acid exposure time in the lower third of the esophagus and the VIP level.

Fig. 2. Correlation between the average number of refluxes and the VIP level.

Fig. 3. Correlation between the number of reflux events longer than 5 minutes and the VIP level.

Fig. 4. Correlation between the maximum reflux duration and the VIP level in GERD.

Fig. 5. Correlation between the mean reflux duration and VIP level.

Fig. 6. Correlation between the VIP level and the inflammation severity of the lower third esophageal mucosa.

Table 1. The level of VIP in the main and control groups of patients

Parameter, units of measurement	Control group (n = 20)	GERD group (n = 35)	
		Before the operation	After the operation
VIP, ng/ml	2.1 ± 1.1	3.1 ± 1.1*	2.2 ± 1.0**

*: p < 0.05 in comparison with the control group and postoperative data; **: p < 0.05 in comparison with preoperative data; p: value of statistical significance.

Table 2. VIP level, acid exposure time in the esophagus, features of reflux in patients of both groups

Parameter, units of measurement	Control group (n = 20)	GERD group (n = 35)	
		Before the surgery	After the surgery
VIP, ng/ml	2.1 ± 1.1	3.1 ± 1.1*	2.2 ± 1.0**
Acid exposure time, %	0.2 (0.0; 1.5)	20.0 (9.5; 43.2)*	0.7 (0.0; 2.5)**
Total number of refluxes, n	9.0 (2.0; 19.0)	96.0 (59.0; 173.0)*	9.0 (3.0; 18.0)**
Number of reflux events longer than 5 minutes, n	0.0 (0.0; 1.5)	7.0 (3.0; 19.0)*	0.0 (0.0; 3.0)**
Maximum reflux duration, min	3.0 (2.0; 8.0)	26.0 (9.0; 46.0)*	5.0 (2.0; 11.0)**
Mean reflux duration, min	2.0 (1.0; 2.0)	4.1 (2.0; 5.0)*	2.0 (1.0; 3.0)**

*: p < 0.05 in comparison with the control group and postoperative data; **: p < 0.05 in comparison with preoperative data; p: value of statistical significance.

Table 3. Characteristics of the VIP level and the number of patients with reflux esophagitis / CLE in the studied groups

Parameter, units of measurement	Control group (n = 20)	GERD group (n = 35)	
		Before the surgery	After the surgery
VIP, ng/ml	2.1 ± 1.1	3.1 ± 1.1*	2.2 ± 1.0**
Reflux-esophagitis / CLE	no	21*	2**

*: p < 0.05 in comparison with the control group and postoperative data; **: p < 0.05 in comparison with preoperative data; p: value of statistical significance.

Table 4. Comparative characteristics of the VIP level before surgery depending on the form of esophageal inflammation

Parameter	Control group (n = 20)		GERD group (n = 35)	
	Number of patients	VIP	Number of patients	VIP
No GERD	20 (100 %)	2.1 ± 1.1	–	–
GERD	–	–	14 (40.0 %)	2.8 ± 1.2*
Erosive esophagitis (LAA, B, C)	–	–	12 (34.3 %)	3.0 ± 1.0*
CLE	–	–	9 (25.7 %)	3.6 ± 1.1*

*: p < 0.05 in comparison with the control group; p: value of statistical significance.

to 2.0 (1.0; 3.0) minutes post-surgery, that did not differ from the group of apparently healthy individuals (Table 2). However, there was no statistically significant correlation between these variables (Fig. 5).

Table 3 shows that simultaneously with the decrease in the number of patients with esophagitis / Columnar Lined Esophagus (CLE) after surgery, the VIP level also decreased.

Correlation analysis between the lower third esophageal mucous membrane inflammation and the VIP level in the studied patients of the main group showed a moderate positive correlation between the VIP level and the degree of esophageal inflammation (Fig. 6).

The level of VIP was increased statistically significantly with an increase in the severity of esophagitis and was different from that level in the controls, which is clearly shown in Table 4.

Discussion

The gastrointestinal tract is one of the organs most susceptible to hormonal influences, both in terms of the variety of hormones acting on it and the range of effects. In recent years, a number of biologically active peptides has also been proven, which, not being classical hormones, act on the gastrointestinal tract in the same way as hormones. Among them are many important neurohormones that have

different effects on the LES tone, which plays a leading role in the development of GERD. Some hormones only modulate the LES response to various stimuli. But both of them are actively involved in the pathogenesis of GERD and play an essential role in the development and implementation of effective treatments for this disease [14].

VIP is one of the most principal neurotransmitters that affect the functioning of the stomach muscles and LES [18,22,23].

The inhibitory effect of this hormone on the LES tone contributes to the development of pathological gastroesophageal reflux [14,15,19,24].

In the course of our study, the plasma VIP level in GERD patient before surgical treatment was statistically higher than that in apparently healthy patients. After surgical treatment (total fundoplication and crurorrhaphy), the plasma level of VIP in patients did not differ from the level of apparently healthy individuals. A similar trend was previously noted by us in the study on the prostaglandin E2 dynamics, which also has an inhibitory effect on LES [25]. The effectiveness of surgical treatment was confirmed by both questioning and assessing the quality of patient life, as well as instrumentally by performing VGDS, histological examination of biopsy material and daily pH-impedancemetry. The mechanism of reducing VIP after effective treatment to the level of apparently healthy individuals has not been fully studied to date and requires continued work in this direction. However,

given the known data on its effect on the LES tone, it can be assumed that a decrease in this hormone after surgery reduces its inhibitory effect on the LES tone, thereby contributing to an increase in its basal tone and a decrease in spontaneous relaxation. All the above has a positive effect on the effectiveness of GERD treatment, resulting in the achievement of a stable effect after surgical treatment.

So, as a study result, we have obtained the positive correlation between the VIP level and AET, showing a positive effect of the VIP level on increasing AET in the esophagus during a day. Similarly, the positive moderate correlation was noted between the total number of refluxes, the number of reflux events longer than 5 minutes, the maximum duration of refluxes, demonstrating the influence of VIP on a decrease in the LES basal tone and, at the same time, on an increase in its spontaneous relaxation, leading to an increase in AET and the number of refluxes. And the inhibitory effect of VIP on the stomach smooth muscles enhanced this effect, slowing down the evacuation from the stomach and contributing to an increase in intragastric pressure [19]. During surgical treatment, pathological reflux was eliminated, and the LES tone was increased, due to which the esophageal mucosa was restored in almost all patients. The level of VIP was also decreased to the level of apparently healthy individuals (Table 3). There was the positive moderate correlation between the level of VIP and the degree of esophageal inflammation indicating the increased VIP level with higher degree of inflammation in GERD (Fig. 6). This confirms the data on the active involvement of VIP in the inflammatory process [20,24,26].

In our study, this shows the key role of VIP in the light of understanding its impact on the pathogenetic vicious circle of GERD development: reflux – inflammation – increased VIP level – increased LES hypotension/increased gastric hypotension – increased reflux. Surgical elimination of reflux leads to the esophageal mucosa restoration and consequently to the decrease in the level of VIP, thus reducing the inhibitory effect of VIP on the LES tone and stomach muscles, contributing to improved effectiveness and duration of successful surgical treatment for GERD.

Conclusions

1. The statistically significant decrease in the VIP level to that observed in the group of apparently healthy individuals has been determined after the surgery with the effective elimination of gastroesophageal reflux compared with the preoperative data.

2. The moderate positive correlation between the level of VIP, AET, the average number of refluxes, the number of reflux events longer than 5 minutes and the maximum duration of refluxes has confirmed the inhibitory effect of VIP on the LES tone, the resting tone and spontaneous relaxation of which play a decisive role in the development of refluxes and the reflux of gastric contents into esophagus in GERD.

3. The relationship between the degree of esophageal inflammation and the level of VIP has confirmed this hormone involvement in the inflammatory process and shown the indirect, through the influence of VIP, inhibitory effect of the esophagitis severity on the LES tone.

4. The obtained study data have confirmed the important role of VIP in the pathogenesis of GERD and the achievement of stable effective results in the surgical treatment of this disease.

Conflicts of interest: authors have no conflict of interest to declare.
Конфлікт інтересів: відсутній.

Надійшла до редакції / Received: 03.04.2023

Після доопрацювання / Revised: 28.04.2023

Схвалено до друку / Accepted: 09.05.2023

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