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Features of the Parameters of 24-Hours pH-Impedance and High-Resolution Esophageal Manometry in Patients with Barrett's Esophagus on Proton Pump Inhibitors

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Aim: to identify predictors of insufficient effectiveness of proton pump inhibitors based on the evaluation of the results of 24-hour pH-impedance and high-resolution esophageal manometry in patients with Barrett's esophagus.
Materials and methods. 52 patients with histologically confirmed Barrett's esophagus who are on therapy with proton pump inhibitors were examined. All patients underwent daily pH-impedance and high-resolution esophageal manometry.
Results. According to daily pH-impedance, group 1 consisted of 37 patients who responded satisfactorily to antisecretory therapy, group 2 of 15 patients who demonstrated insufficient response to acid-suppressive therapy, 11 of whom had no clinical manifestations. The total number of reflux averaged 55 in group 1 and 106 in group 2. The average number of acid reflux in group 1 was 5.68, in group 2 — 48.5. The average number of non-acid reflux prevailed in patients of group 2 and averaged 58, in group 1 the indicator averaged 47. Evaluation of the results of high-resolution esophageal manometry showed that violations of the structure and function of the esophago-gastric junction were detected in 21 patients out of 52. Disorders of the motility of the thoracic esophagus were detected in 31 patients out of 52. When comparing the frequency of motor disorders from the thoracic esophagus in groups 1 and 2, no significant differences were obtained. However, significantly more frequent registration of violations of the structure and/or function of the esophago-gastric junction was found in the group with unsatisfactory effectiveness of proton pump inhibitors.
Conclusion. In a number of patients with Barrett's esophagus, there is an insufficient effect of acid-suppressive therapy and at the same time an asymptomatic course of the disease, which may increase the risk of its progression. Predictors of insufficiently successful treatment of patients with Barrett's esophagus may be both insufficient pharmacological effect of proton pump inhibitors themselves, and motility disorders that cause the presence of non-acid reflux, decreased esophageal clearance, which in turn may cause the patient's symptoms to persist and adversely affect the condition of the esophageal mucosa.
Keywords: Barrett's esophagus, daily pH-impedance, high-resolution manometry
Conflict of interest: the authors declare no conflict of interest.

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Особенности параметров суточной pH-импедансометрии и манометрии пищевода высокого разрешения у пациентов с пищеводом баррета на фоне приема ингибиторов протонной помпы

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Цель исследования: выявление предикторов недостаточной эффективности ингибиторов протонной помпы на основании оценки результатов 24-часовой pH-импедансометрии и манометрии пищевода высокого разрешения у пациентов с пищеводом Баррета.
Материалы и методы. Обследованы 52 пациента с гистологически подтвержденным пищеводом Баррета, находящихся на терапии ингибиторами протонной помпы. Всем пациентам проводились суточная pH-импедансометрия и манометрия пищевода высокого разрешения.
Результаты. По данным суточной pH-импедансометрии 1 группу составили 37 пациентов, удовлетворительно ответивших на антисекреторную терапию, 2 группу — 15 пациентов, продемонстрировавших недостаточный ответ на кислотосупрессивную терапию, 11 из которых при этом не имели клинических проявлений. Общее количество рефлюксов в среднем составило 55 в 1 группе и 106 во 2 группе. Среднее количество кислых рефлюксов в 1 группе составило 5,68, у больных 2 группы — 48,5. Среднее количество некислых рефлюксов преобладало у пациентов 2 группы и составило в среднем 58, в 1 группе показатель в среднем составил 47. Оценка результатов манометрии пищевода высокого разрешения показала, что нарушения со стороны структуры и функции пищеводно-желудочного перехода были выявлены у 21 пациента из 52. Расстройства моторики грудного отдела пищевода были выявлены у 31 пациента из 52. При сравнении частоты встречаемости двигательных расстройств со стороны грудного отдела пищевода в 1 и 2 группах достоверных различий не получено. Однако обнаружена достоверно более частая регистрация нарушений структуры и/или функции пищеводно-желудочного перехода в группе с неудовлетворительной эффективностью ингибиторов протонной помпы.
Заключение. У ряда пациентов с пищеводом Баррета отмечается недостаточный эффект кислотосупрессивной терапии и при этом асимптомное течение заболевания, что может повышать риск его прогрессирования. Предикторами недостаточно успешного лечения пациентов с пищеводом Баррета могут являться как недостаточный фармакологический эффект самих ингибиторов протонной помпы, так и расстройства моторно-тонического характера, обуславливающие наличие некислых рефлюксов, снижение клиренса пищевода, что, в свою очередь, может обуславливать сохранение симптомов пациента и неблагоприятно влиять на состояние слизистой оболочки пищевода.
Ключевые слова: пищевод Баррета, суточная pH-импедансометрия, манометрия высокого разрешения
Конфликт интересов: авторы заявляют об отсутствии конфликта интересов.

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Introduction

Among the diseases of the esophagus, which represent a heterogeneous group of nosologies, special attention has been paid in recent decades to gastroesophageal reflux disease (GERD). The interest in this problem is due not only to the tendency to an increase in morbidity, the chronic nature of the course and a decrease in the quality of life of patients, but also to the role that GERD plays in the development of such a precancerous condition as Barrett's esophagus (BE). In BE, the multilayer flat non-corneating epithelium in the distal esophagus is replaced by a specialized glandular epithelium of the intestinal type, which ultimately increases the risk of esophageal adenocarcinoma (EAC).

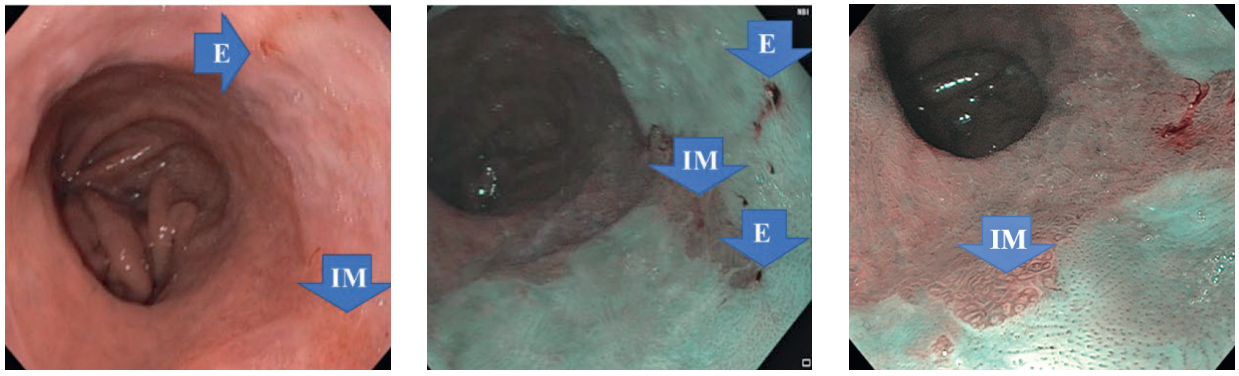
The prevalence of BE is not reliably known due to the fact that some patients who do not have active symptoms remain undiagnosed [1]. Nevertheless, large European population studies have demonstrated the prevalence of BE from 1.3 to 1.6 %, and one of the American studies in Minnesota showed the presence of BE in 8.5 % of cases in people over the age of 50 [2]. The frequency of detection of BE in the average population varies within 2,4–4.0 % [3, 4].

Predisposing factors for the development of BE, as with GERD, are age over 50 years, male gender, Caucasian race, obesity, the presence of a long, i.e., 5 years or more, anamnesis of GERD, smoking, as well as a burdened hereditary history of BE and EAC [5–8].

Patients with BE are at risk of developing EAC, which is characterized by an increase in detection cases and high mortality [9]. According to M. Solaymani-Dodaran et al. in the presence of GERD, the probability of developing EAC increases by 1.7 times, and with concomitant BE by 10.6 times [10]. The probability of annual malignant transformation to EAC in patients with BE ranges from 0.5–2.1 % (that is, at least 1 out of 200 patients with BE per year) [4]. The risk of developing EAC in BE depends on the presence of dysplastic changes in the mucous membrane [9, 11]. Thus, in patients without dysplasia, this risk is 0.3 cases per 100 person-years, with low-grade dysplasia — 0.5 per 100 person-years, whereas with high-grade dysplasia — 6.6 per 100 person-years [12]. Due to the risk of progression of BE to EAC, it is extremely important to diagnose this complication of GERD in a timely manner.

Diagnosis of BE is primarily based on esophagogastroduodenoscopy data, which allows to identify endoscopic signs of BE and to perform a targeted biopsy of the esophageal mucosa with further

histological evaluation of the obtained material. To date, there are highly sensitive endoscopic methods (high-resolution endoscopy combined with narrow-spectrum NBI endoscopy, confocal laser endomicroscopy) that significantly increase the ability to differentiate areas of intestinal metaplasia, dysplastic changes in the esophageal mucosa, as well as early signs of EAC [13–15] (Fig. 1, 2).



A B C

Fig. 1. Esophagogastroduodenoscopy. Barrett's Esophagus [16]: A — inspection in white light with high resolution (WII HD). IM — intestinal metaplasia of the esophageal mucosa and E — erosion; B — inspection in high-resolution narrow-spectrum mode (NBI HD). IM — intestinal metaplasia of the esophageal mucosa and E — erosion; C — inspection in narrow-spectral mode with close focus (NBI Dual Focus). IM — intestinal metaplasia of the esophageal mucosa

Рис. 1. Эзофагогастродуоденоскопия. Пищевод Баррета [16]: А — осмотр в белом свете с высоким разрешением (WLI HD). КМ — кишечная метаплазия слизистой оболочки пищевода и Э — эрозии; В — осмотр в узкоспектральном режиме высокого разрешения (NBI HD). КМ — кишечная метаплазия слизистой оболочки пищевода и Э — эрозии; С — осмотр в узкоспектральном режиме с близким фокусом (NBI Dual Focus). КМ — кишечная метаплазия слизистой оболочки пищевода

According to modern Russian and foreign clinical guidelines, basic therapy of BE, as well as GERD in general, includes taking proton pump inhibitors (PPIs) once a day to control symptoms and heal reflux esophagitis. The appointment of PPIs 2 times a day is recommended only if the control of symptoms is ineffective [18].

Several observational studies have demonstrated that the presence of GERD symptoms is a significant risk factor for the development of EAC, which increases with increasing duration and severity of symptoms. The use of PPIs prevents neoplastic progression in patients with BE, which makes it possible to consider them as chemoprophylactic agents [3, 19, 20].

A meta-analysis conducted with the inclusion of 2813 patients with BE, 317 patients with EAC or with BE with a high degree of dysplasia, 84.4 % of whom received PPIs, showed that taking PPIs by 71 % reduced the risk of developing EAC or high degree of dysplasia in patients with BE (OR 0.29; 95 % CI 0.12–0.79) [21].

A recent meta-analysis by Y. Chen et al. (2021), conducted on the basis of the results of 12 studies (n = 155 769), also showed that the use of PPIs by patients with BE leads to a significant reduction in the risk of developing high-grade dysplasia and EAC (OR 0.47, 95 % CI: 0.32–0.71) [22].

However, the question of the role of PPIs in reducing the risk of neoplastic changes remains under discussion. Thus, a meta-analysis of 9 observational studies (5 cohort and 4 case-control studies), which included 5712 patients with BE, showed that taking PPIs does not affect the risk of developing EAC and/or high-grade dysplasia in patients with BE (OR 0.43, 95 % CI 0.17–1.08). The analysis of the duration of PPIs use and response revealed no significant tendency to closure from EAC or high-stage dysplasia: an example of PPIs > 2–3 years compared to < 2–3 years: OR 0.91 (95 % CI 0.25–3.31) compared to 0.91 (0.40–2.07) [23].

In addition, the approaches proposed by international recommendations to the management of patients who are not bothered by GERD symptoms and without PPIs also differ. Only the American College of Gastroenterologists recommends the routine use of PPIs in asymptomatic patients, while other guidelines recommend the appointment of PPIs only for the control of GERD symptoms [18].

The management of patients with BE requires a personalized therapeutic approach based not only on the dynamic assessment of clinical, endoscopic and histological data, but also on the use of modern functional diagnostic methods that allow assessing a number of pathogenetic aspects of BE, such as daily pH impedance and high-resolution esophageal

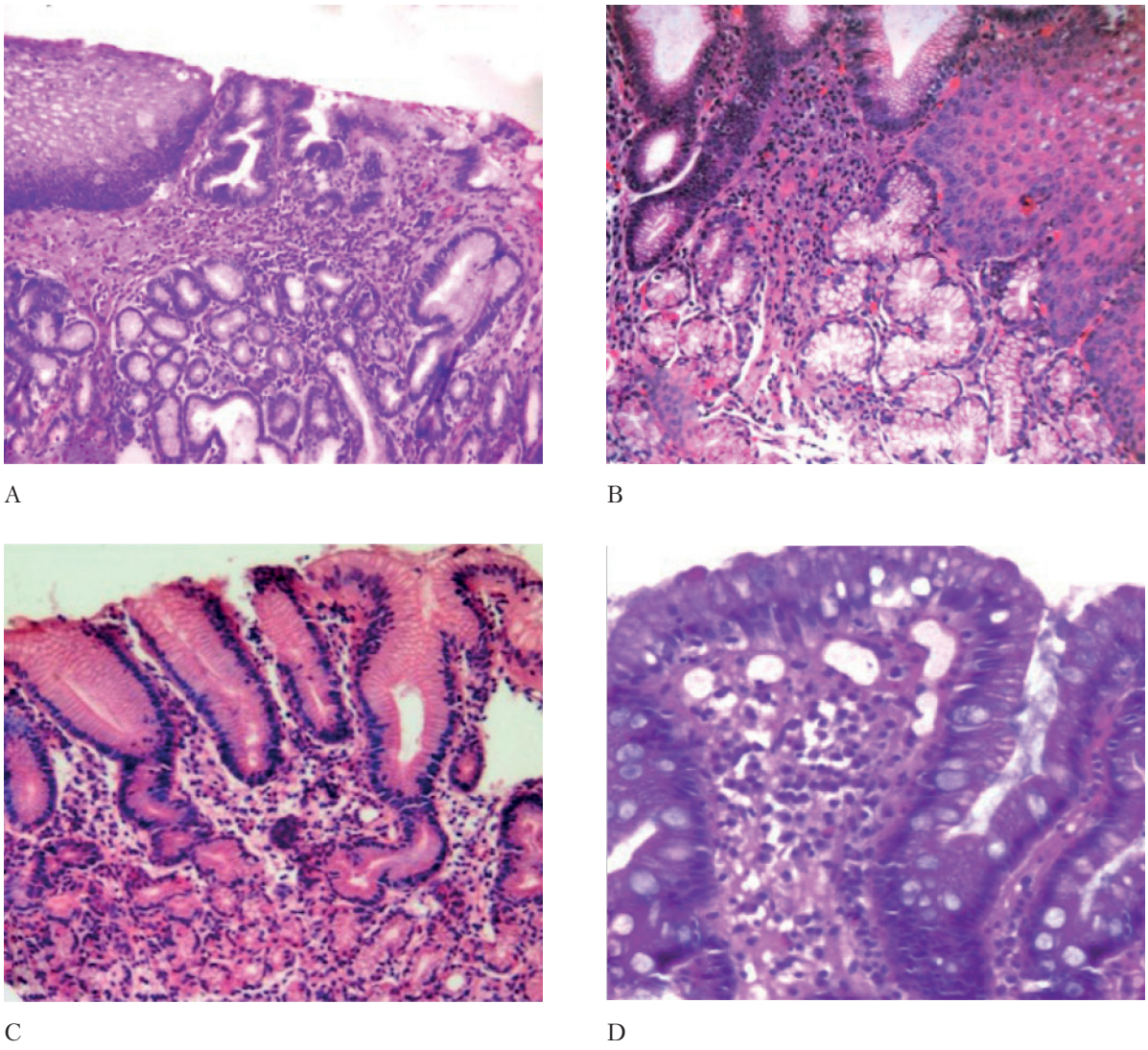


Fig. 2. Histological types of metaplastic cylindrical cell (glandular) mucosa of the distal esophagus [17]: A — cardiac, B — cardiac acid–producing, C — fundal types and D — intestinal metaplasia. Staining with hematoxylin and eosin, A — ×60, B, C — ×120, D — ×200

Рис. 2. Гистологические типы метаплазированной цилиндроклеточной (железистой) слизистой оболочки дистального отдела пищевода [17]: A — кардиального; B — кардиального кислотопродуцирующего; C — фундального типов и D— кишечная метаплазия. Окраска гематоксилином и эозином, A — ×60, B, C — ×120, D — ×200

manometry [24–27]. And despite the fact that there are currently no recommendations on their routine use, they occupy a significant place in the management of patients with BE.

The pathogenetic basis of GERD is gastroesophageal reflux and not only acidic, but also non-acidic. It is known that both acidic and duodenal components are present in most of the stomach contents thrown into the esophagus, and bile reflux can play a synergistic role in the damaging effect on the esophageal mucosa. The daily pH-impedance is a combination of traditional pH-metry, which registers acid reflux by episodes of pH < 4, and the impedance, which allows detecting casts by their physical properties (liquid, gas, mixed) regardless of pH values (including at pH > 4). Currently, pH-impedance measurement is the "gold standard" for the diagnosis of GERD, especially in the absence of convincing endoscopic data [28, 29]. In addition, with the help of pH-impedance, it is possible to assess the presence or absence of a connection between the patient's symptoms and reflux, as well as to analyze the effectiveness of antisecretory therapy, which is especially important for patients with BE.

At the same time, as is known, the evaluation of the effect of PPIs is necessary in cases where it is not possible to stop the symptoms of GERD. However, in 40–45 % of patients, typical complaints may be absent due to hypersensitivity of the esophagus to reflux. Thus, clinically, it is not always possible to judge the effectiveness of PPI therapy, therefore, the question arises about the need to perform a daily study in asymptomatic patients for an objective assessment of the adequacy of acid suppression [4, 30, 31].

It is worth noting that the results of clinical studies conducted to date indicate the importance of not only esophageal acidification, but also motor disorders in the genesis of BE and its subsequent transformation into EAC [32, 33]. According to domestic and international recommendations, the examination plan for patients with GERD includes esophageal manometry [3, 34, 35].

Manometry is not a direct method of diagnosing GERD, however, it provides valuable information about the state of the motility of the esophagus and its sphincter apparatus. First of all, high-resolution esophageal manometry becomes relevant in the refractory course of GERD, when PPI therapy does not give sufficient effect or turns out to be ineffective at all. With persistent symptoms of GERD, manometry can detect various motor disorders of the esophagus, as well as violations of the structure and/or function of the esophago-gastric junction — ineffective of esophageal motility, absent contractility, decreased tone of the lower esophageal sphincter (LES), the presence of a hiatal hernia (HH). Also, the manometric method allows to exclude other esophageal diseases accompanied by symptoms similar to GERD (eosinophilic esophagitis, achalasia, distal esophagospasm), and helps in the dynamic evaluation of the effectiveness of therapy aimed at correcting motor disorders [26]. Esophageal manometry is of particular importance in the case of solving the issue of antireflux surgical treatment of patients with GERD [2, 24, 26]. In this case, the method makes it possible to differentiate GERD and similar motility disorders in clinical manifestations, as well as to assess the motor function of the esophagus, including the reserve of contractility of the esophagus using functional tests, which is necessary when assessing the risks of surgical intervention and choosing a particular surgical method [36].

In the laboratory of functional research methods in gastroenterology of the A.I. Yevdokimov Moscow State University of Medicine and Dentistry, a study was performed to analize the parameters of daily pH-impedance and high-resolution esophageal manometry in patients with BE while taking antisecretory drugs. The first stage of the study was published in 2021 [27].

The aim of the study — to identify predictors of insufficient efficacy of PPIs in patients with BE, based on the results of the parameters of daily pH-impedance and high-resolution esophageal manometry.

Materials and methods

Research design

A prospective single-center study on the background of drug intervention.

The study involved male or female patients aged 27 to 72 years with histologically verified intestinal metaplasia, taking PPIs as basic therapy for 3 months to 1.5 years. The length of the BE segment, according to endoscopic data, exceeded 1 cm. Patients with dysplasia of varying degrees were not included in the study.

Conditions of the event

The study was conducted on the basis of the Laboratory of functional research methods in gastroenterology of the A.I. Yevdokimov Moscow State University of Medicine and Dentistry in the Department of Gastroenterology and Palliative Therapy of the private healthcare institution Central Clinical Hospital RZD-Medicine and in the Moscow Clinical Scientific and Practical Center named after A. S. Loginov.

Description of medical intervention

All patients signed an informed consent form for daily pH-impedance and high-resolution esophageal manometry. To perform the daily pH-impedance, an outpatient pH-recorder Ohmega (Medical Measurement Systems, The Netherlands) and disposable pH-impedance catheters for adults with 6 impedance channels and 2 pH channels (MMS-6Z2P-A02) were used, one of which was positioned in the stomach, the second 5 cm above the LES. High-resolution esophageal manometry was performed using a solid-state 36-channel catheter, and the data obtained were analyzed using specialized software Medical Measurement Systems, The Netherlands. The manometric study was conducted against the background of the exclusion of drugs that can affect the motility of the esophagus. The standard method of manometry was used with 10 swallows of water of 5 ml in the patient's supine position.

The main outcome of the study

The features of acidification and motility of the esophagus were studied in patients with BE on the background of taking PPIs. In the final analysis, patients were divided into 2 groups depending on the effect of antisecretory therapy, determined both by clinical data and by the percentage of time with pH <4 in the esophagus per day (acid exposure time, AET).

Methods of registering outcomes

According to the purpose of the study, in the presented groups of patients, such indicators of daily pH-impedance as AET, the total number of refluxes, as well as the number of acidic (with pH <4) and non-acidic (with pH > 4) refluxes were evaluated comparatively.

One of the main indicators of pH-impedance is AET. According to the Lyon Consensus, at a value of < 4 %, this indicator is considered reliably normal, and at a value of > 6 %, it is reliably pathological. All values in the range of 4–6 % belong to the so-called "gray zone", that is, they are considered insufficiently convincing [34]. When evaluating this parameter in patients with BE, we tended to take values in the range of 4–6 %, rather as a pathological AET due to the greater risk of progression of changes in the esophageal mucosa in BE than in other forms of GERD.

The total number of refluxes per day was also estimated. This parameter is not a key one, but it plays an additional role in diagnostics. The Lyon Consensus defines as a significantly increased daily number of reflux > 80 episodes, and if they are < 40 per day, it regards as a physiological number [34]. Acidic and non-acid reflux was also quantified. Acid reflux is characterized by throwing stomach contents into the esophagus with a pH < 4, non-acid reflux – with a pH > 4.

The study included high-resolution esophageal manometry with an assessment of the structure (presence or absence of HH) and the function of the esophago-gastric junction (EGJ) (presence or absence of hypotension of the LES), as well as the motility of the thoracic esophagus (presence or absence of peristalsis disorders). The manometric data were interpreted according to the criteria of the Chicago Classification of Motor Disorders 3.0 (2015) [37].

To assess the presence or absence of HH, the structure of the EGJ was evaluated. High-resolution manometry makes it possible to visualize both components of EGJ, namely the LES and the crura diaphragm (CD), which form the resting pressure of EGJ and act as a single locking mechanism preventing gastroesophageal reflux (Fig. 3A). In the case when a single pressure zone of the LES and CD (I morphological type of EGJ) is visualized, the HH is missing. When there is a separation of the pressure zones of the LES and CD in the area of EGJ, we can talk about the presence of HH (II and III morphological types of EGJ) [38] (Fig. 3B).

In order to assess the tone of the LES, the resting pressure of the LES is measured in a 30-second time interval when the patient does not swallow. The normal values of the resting pressure of the LES are 10–45 mmHg. The resting pressure of the LES < 10 mmHg. corresponds to hypotension of the LES [38] (Fig. 3C).

The peristaltic activity of the thoracic esophagus was manometrically assessed for the presence or absence of ineffective motility or complete absent contractility.

Ineffective motility of the esophagus is diagnosed when more than 50 % of swallows are ineffective. This is estimated primarily on the basis of such an indicator as the distal contricticle integral (DCI). DCI is a pressure (mmHg), which is created by the wall of the thoracic esophagus distal to the transition zone in 1s of time on a section of 1 cm long. The pressure from 20 mmHg is taken into account on the pressure scale up to the maximum. Normal DCI values are 450–8000 mmHg×cm×s. In the case when 50 % of swallows are represented by either failed peristalsis (DCI < 100 mmHg×cm×s), or weak (DCI 100–450 mmHg×cm×c) the presence of ineffective motility skills is ascertained [38] (Fig. 4B).

In patients whose manometric data show no signs of esophageal contractions in 100 % of swallows (DCI < 100 mmHg×cm×c) with normal relaxation of the LES, the absent contractility is noted [38] (Fig. 4C).

Ethical expertise

The study was conducted in accordance with the principles of the Helsinki Declaration of the World Medical Association. The protocol of this study was approved by the Interuniversity Ethics Committee (Protocol No. 04-19). Each patient received detailed information about the study and signed an informed consent to participate in the study.

Statistical analysis

Statistical processing was carried out using specialized software MedCalc 20.014 (Belgium) in the Microsoft Windows 11 environment (USA). The data is presented in the form of an arithmetic mean or median and a 95 % confidence interval (CI). Statistical hypotheses were tested using the nonparametric Mann – Whitney U-test and the parametric Fisher test. The results obtained were regarded as reliable at $p < 0.05$.

Results

The main results of the study and their discussion

The study included 52 patients with verified BE without dysplasia, including 34 men and 18 women. The average age of the patients included in the final analysis was 48.0 years (95 % CI 41.5–52.0) (Table 1). All examined patients received PPIs as basic therapy.

It is worth noting that according to anamnestic data, 8 (15 %) of 52 patients have never experienced symptoms of GERD, and the diagnosis of BE was established when performing a planned endoscopic

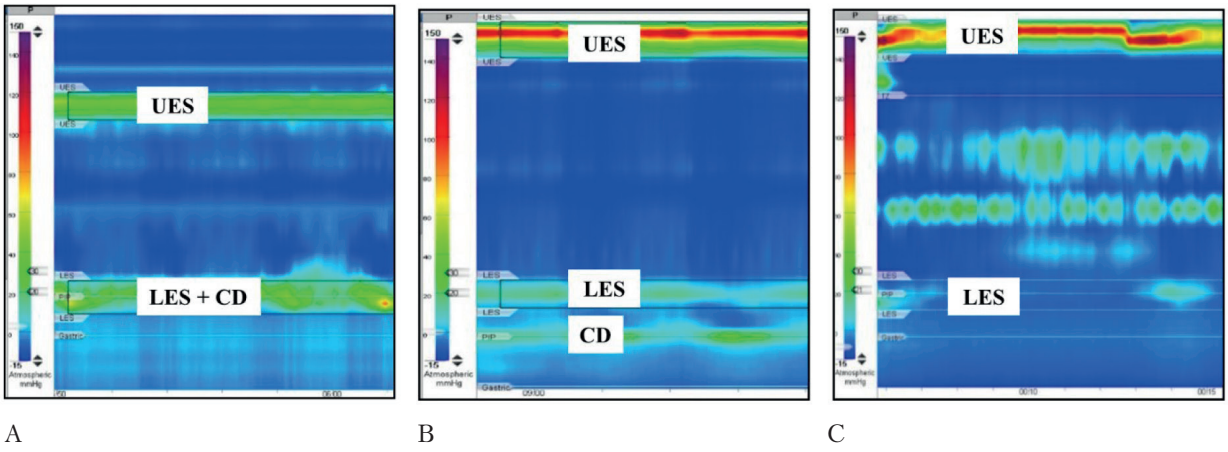


Fig. 3. High-resolution manometry. Esophago-gastric junction (EGJ). UES — upper esophageal sphincter; LES — lower esophageal sphincter; CD — crura diaphragm. A — normal structure of EGJ. The EGJ is represented by a single pressure zone, including the LES and CD; B — violation of the structure of EGJ. EGJ is represented by two pressure zones: the upper one is the pressure of the LES, the lower one is the pressure of the CD, which corresponds to a hiatal hernia; C — hypotension of LES. The LES resting pressure is 4 mmHg (norm 10—45 mmHg).
Own data of the Laboratory of functional research methods in gastroenterology.
Рис. 3. Манометрия высокого разрешения. Пищеводно-желудочный переход (ПЖП). UES — верхний пищеводный сфинктер; LES — нижний пищеводный сфинктер; CD — ножки диафрагмы. A — нормальная структура ПЖП. ПЖП представлен единой зоной давления, включающей LES и CD; B — нарушение структуры ПЖП. ПЖП представлен двумя зонами давления: верхняя — давление LES, нижняя — давление CD, что соответствует грыже пищеводного отверстия диафрагмы; C — гипотония LES. Давление покоя LES 4 мм рт. ст. (норма 10—45 мм рт.ст.)
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examination either as part of a medical examination or for other reasons.

Based on the results of daily pH-impedance patients were differentiated into two groups depending on the adequacy of the acid-suppressive effect of PPIs. AET was used as an instrumental criterion for evaluating the effectiveness of PPIs: up to 4 % — adequate antisecretory response (group 1), above 4 % — insufficient antisecretory response (group 2) (Fig. 5).

According to the results of daily pH-impedance, AET was 0.5297 % (95 % CI 0.2210—0.8384) in patients of group 1 and 7.84 % (95 % CI 5.2634—10.4166) in group 2 (Fig. 6).

Group 1 included 37 patients with an adequate response to PPI therapy, group 2 consisted of 15 patients with insufficient effect of antisecretory therapy, which required its correction. It should be noted that out of 52 patients, 10 people (19 %) noted the presence of complaints, despite taking antisecretory drugs. At the same time, in group 1, where PPIs were effective out of 37 patients, symptoms were present in 6, in group 2 with insufficient acid suppression in 4 patients (Table 2). Thus, it was found that the absence of clinical manifestations does not always indicate sufficient acid suppression, and at the same time, with adequate antisecretory the effect of PPIs in patients may persist complaints.

The total number of reflux averaged 55 in the group 1 of patients and 106 in the group 2. The average number of acid reflux in group 1 was 5.6757 (95 % CI 2.8827—8.4686), in group 2 patients — 48.5333 (95 % CI 34.8626—62.2041) (Fig. 7). The average number of non-acid reflux was also higher in group 2 patients and averaged 58, then as in group 1, this indicator was 47. Thus, in patients who adequately responded to PPI therapy, compared with patients with insufficient response, there is not only a naturally smaller number of acid reflux, but also non-acid reflux, and consequently, the total number of stomach contents thrown into the esophagus.

It is known that the composition of the reflux may include not only hydrochloric acid, but also duodenal contents, represented by bile acids, trypsin and lysolycetin, which can have a synergistic effect on the mucous membrane of the esophagus, damaging it. With such mixed refluxes, PPIs have a clinical effect not only due to the suppression of acid production itself, but also due to a decrease in the amount of gastric secretions, which reduces the volume of reflux [3, 39].

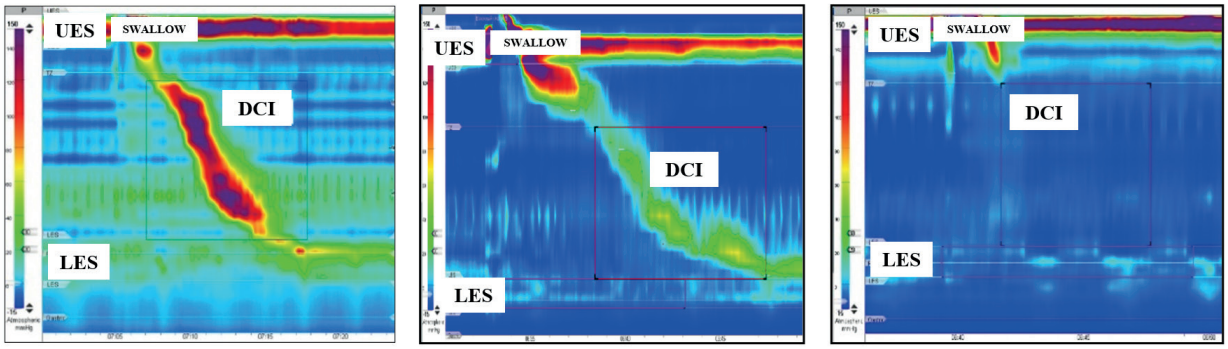

Fig. 4. High-resolution manometry. Motility of the thoracic esophagus. UES — upper esophageal sphincter; LES — lower esophageal sphincter; DCI — distal contricticle integral. A — normal motility: DCI — 2769 mm×Hgcm×sec (norm 450–8000 mmHg×cm×sec); B — ineffective motility: DCI — 360 mmHg×cm×sec (norm 450–8000 mmHg×cm×sec) — weak peristalsis; C — absent contractility: DCI — 0 mmHg×cm×sec (norm 450–8000 mmHg×cm×sec)
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Рис. 4. Манометрия высокого разрешения. Моторика грудного отдела пищевода. UES — верхний пищеводный сфинктер; LES — нижний пищеводный сфинктер; DCI — интегральная сократимость дистального сегмента. A — нормальная моторика: DCI — 2769 мм рт. ст.×см×сек (норма 450–8000 мм рт. ст.×см×сек); B — Нэффективная моторика: DCI — 360 мм рт. ст.×см×сек — ослабленная перистальтика; C — отсутствие сократимости: DCI — 0 мм рт.ст.×см×сек
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Table 1. Distribution of patients by age and gender
Таблица 1. Распределение пациентов по возрасту и полу

Group Группа	Absolute number, *n* Абсолютное число, *n*	Men, *n* (%) Мужчины, *n* (%)	Women, *n* (%) Женщины, *n* (%)	Age (95 % CI), years Возраст (95 % ДИ), лет
BE ПБ	52	34 (65.38)	18 (34.62)	48.0 (41.5–52.0)

Note. BE — Barrett's esophagus; *n* — number of patients; CI — confidence interval.
Примечание. ПБ — пищевод Баррета; *n* — количество пациентов; ДИ — доверительный интервал.

However, in conditions of acid suppression, non-acid reflux can be the reason for the persistence of complaints. Thus, according to pH-impedance, in 6 patients of group 1, symptoms were associated with refluxes with pH > 4, which required the addition of drugs from other groups to the treatment.

In 15 patients with BE, the effect of taking PPIs was insufficient (group 2). One of the main reasons for the insufficient effectiveness of PPI may be the violation of medical recommendations by patients for various reasons. The ineffectiveness of treatment is often associated with improper administration and non-compliance with the dose of PPIs and the timing of therapy [3, 40].

Five patients out of 15 in group 2 were recommended a half dose of PPIs, 6 patients did not follow the medication regimen, explaining this by a decrease in motivation to follow medical recommendations in the absence of symptoms, 4 patients took PPIs of old generations that did not provide full blocking of hydrochloric acid production (both by prescription of the attending physician, and independently changing the drug from a new one generations for economic reasons). Four patients of group 2 had complaints of burning behind the sternum while taking PPIs. According to the results of daily pH-impedance, a convincing association of symptoms with acid reflux was revealed. Antisecretory therapy was adjusted for all patients of group 2.

Special attention should be paid to patients with BE from group 2 who had no clinical manifestations, despite the insufficient effect of acid-suppressive treatment. Thus, the absence of GERD symptoms against the background of acid-suppressing therapy is not an absolute criterion for the effectiveness of PPIs for patients with BE.

A number of studies show that some patients with BE may have unexpressed GERD symptoms, and

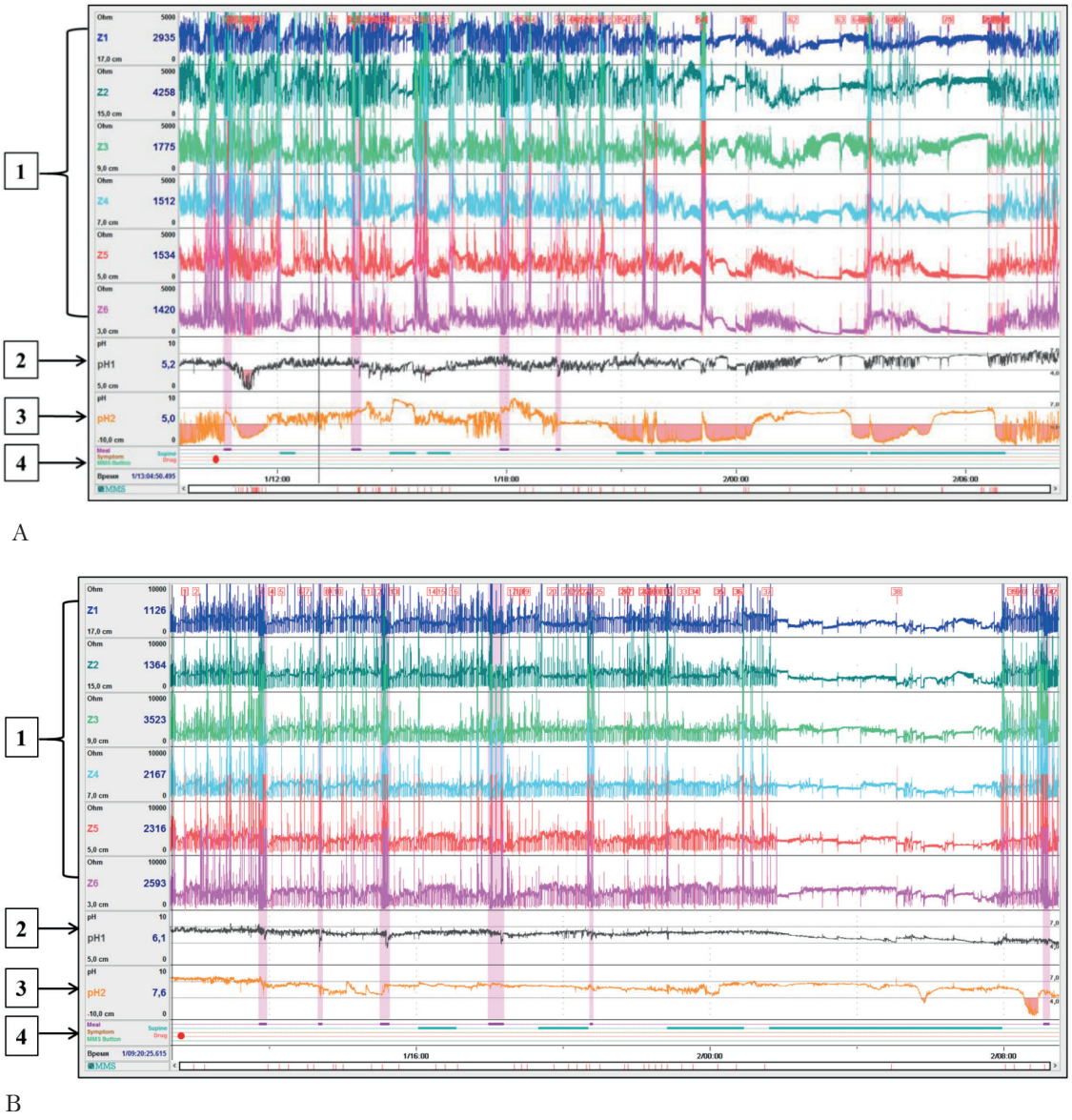

Fig. 5. General view of the daily pH-impedance. A. Inadequate acid suppression: 1 — impedance channels; 2 — pH curve of the esophagus: numerous decreases in pH < 4 (acid reflux), AET is 7.3 %; 3 — pH curve of the stomach: PPIs does not provide adequate acid suppression (time with pH < 4 in the stomach 44 %); 4 — diary panel, where a red circle marks the reception of PPIs; B. Adequate acid suppression: 1 — impedance channels; 2 — pH curve of the esophagus: episodes of pH decrease < 4 (acid reflux) are not observed, AET is 0.1 %; 3 — pH curve of the stomach: PPIs provides adequate acid suppression (time with pH < 4 in stomach 2.5 %); 4 — diary panel, where a red circle marks the reception of PPIs

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Рис. 5. Общий вид суточной pH-импедансграммы: А. Неадекватная кислотосупрессия: 1 — импеданс-каналы; 2 — pH-кривая пищевода: многочисленные снижения уровня pH < 4 (кислые рефлюксы), время с pH в пищеводе < 4 за сутки 7,3 %; 3 — pH-кривая желудка: ИПП не обеспечивает адекватной кислотосупрессии (время с pH < 4 в желудке 44 %); 4 — дневниковая панель, где красным кружком отмечен прием ИПП; Б. Адекватная кислотосупрессия: 1 — импеданс-каналы; 2 — pH-кривая пищевода: эпизодов снижения уровня pH < 4 (кислые рефлюксы) не наблюдается, время с pH в пищеводе < 4 за сутки 0,1 %; 3 — pH-кривая желудка: ИПП обеспечивает адекватную кислотосупрессию (время с pH < 4 в желудке 2,5 %); 4 — дневниковая панель, где красным кружком отмечен прием ИПП.

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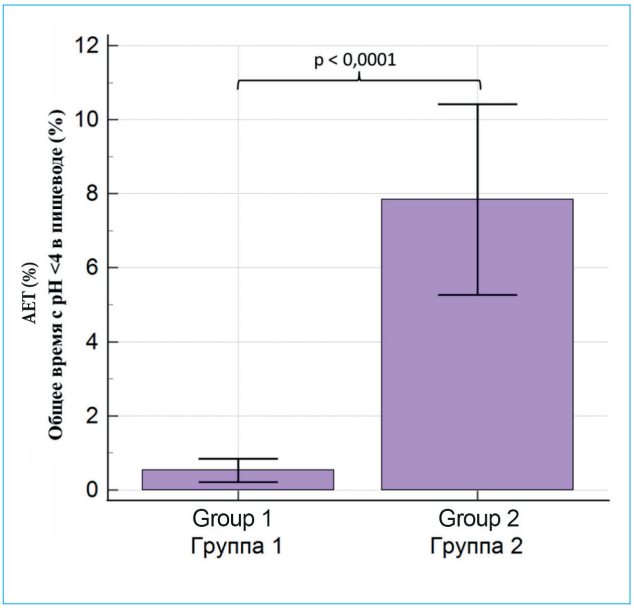

Fig. 6. Comparative data on the assessment of AET
Рис. 6. Сравнительные данные по оценке общего времени с pH < 4 в пищеводе

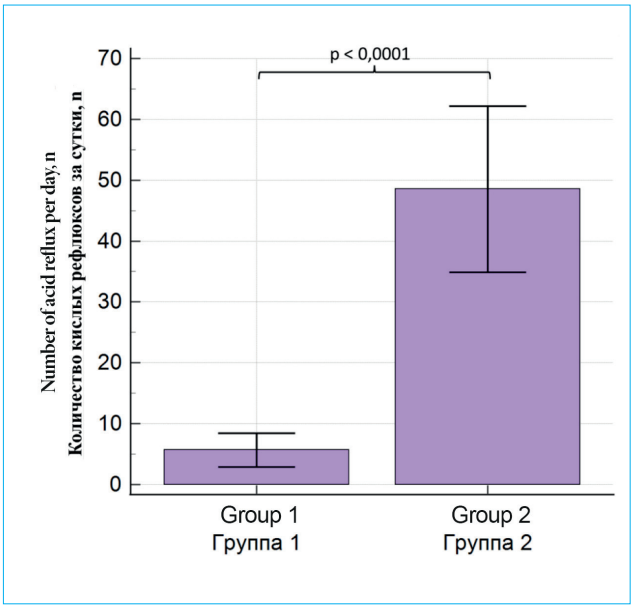

Fig. 7. Comparative data on the assessment of the number of acid reflux per day
Рис. 7. Сравнительные данные по оценке количества кислых рефлюксов за сутки

Table 2. Distribution of patients according to the antisecretory effect of PPIs and the presence of complaints

Таблица 2. Распределение пациентов по антисекреторному действию ИПП и наличию жалоб

Group 1, *n* = 37 (AET < 4 %) Группа 1, *n* = 37 (процент времени с PH < 4 в пищеводе за сутки < 4 %)		Group 2, *n* = 15 (AET > 4 %) Группа 2, *n* = 15 (процент времени с PH < 4 в пищеводе за сутки > 4 %)	
Symptoms + Симптомы +	Symptoms – Симптомы –	Symptoms + Симптомы +	Symptoms – Симптомы –
6 (16 %)	31 (84 %)	4 (27 %)	11 (73 %)

Note. *n* — number of patients.
Примечание. *n* — количество пациентов.

often (40–45 %) there are no complaints at all, even despite a higher AET [30, 41, 42]. Thus, the absence of symptoms in a patient with BE does not indicate the absence of GERD in general, nor of BE, nor of the effectiveness of antisecretory therapy, since about half of patients with BE do not experience symptoms characteristic of GERD even before the appointment of PPIs [1].

These features of the clinic are explained by the reduced sensitivity of the receptors of the esophageal mucosa in patients with BE to reflux. Johnson D.A. et al. in an early study, it was demonstrated that the chemoreceptors of the esophageal mucosa in patients with BE are less sensitive to hydrochloric acid solution compared to those in patients with erosive esophagitis, which was estimated by the time of occurrence and severity of pain in response to a chemical stimulus. [43]. In another study, it was revealed that patients with BE demonstrated lower sensitivity of the mechanoreceptors of the esophageal mucosa when inflating balloons compared to healthy individuals, patients with other forms of GERD and patients with functional heartburn [44].

Various concepts have been proposed to explain the causes of mucosal hyposensitivity in patients with BE. Thus, M.G. Brandt et al. suggested that it is the replacement of the normal esophageal epithelium with a specialized cylindrical one that leads to the protection of sensitive nerve endings of the esophageal mucosa from sensitization [45]. There have been suggestions that the reduced sensitivity to acid perfusion is due to the lower permeability to hydrogen ions of the altered esophageal mucosa in patients with BE [46]. In a study by P.W. Weijenborg

et al. it has also been shown that patients with BE are less sensitive to acid than other forms of GERD. However, the difference in the integrity of the mucous membrane, as the cause of the different sensitivity of the esophagus to acid perfusion, was not identified [47].

A recent study by C. Lottrup et al. demonstrates the peculiarities of sensitivity to various stimuli of the esophageal mucosa in groups with BE and control persons. The nature of the reaction to mechanical, thermal, electrical and chemical effects was studied. In general, the group with BE showed hyposensitivity to all stimuli, except chemical, compared with healthy individuals. Sensitivity to acidic effects in the group with BE was comparatively higher. It is worth emphasizing that patients with other GERD phenotypes were not included in the study and a comparative assessment of sensitivity was not carried out in them. In addition, in this study, a comparison was made within the group with BE, where 57 % of patients had GERD symptoms and 43 % of patients were asymptomatic. Asymptomatic patients showed reduced sensitivity to all stimuli compared to those who had symptoms. Thus, this work showed that patients with GERD complicated by BE constitute symptomatic and asymptomatic subgroups demonstrating different sensory profiles [42].

The age factor may also cause a relatively lower sensitivity of the esophageal mucosa. In the studies of R. Fass et al., A. Grade et al. it has been shown that in patients aged 65 years and older, sensitivity is lower than in the age group of 50 years and younger [48, 49].

According to high-resolution esophageal manometry, disorders of EGJ and motility of the thoracic esophagus were detected in 35 patients out of 52. When assessing the structure (presence or absence of HH) and function (tone of the LES) EGJ disorders were detected in 21 patients out of 52: 13 had only HH, 2 had hypotension of the LES, 6 patients had both HH and hypotension of the LES (Fig. 3). Disorders of the motor function of the thoracic esophagus were noted in 31 patients out of 52: 21 showed signs of ineffective motility, 10 showed signs of absent contractility (Fig. 4).

In a number of studies, it has been shown that disorders of the structure and function of EGJ and motility of the thoracic esophagus are often found in patients with BE and prevail in them compared to patients suffering from NERD and healthy individuals. Significant differences with the erosive reflux disease (ERD) group were not revealed [25, 32, 33, 38, 50].

Comparative analysis of groups 1 and 2 showed that disorders of the structure and/or function of EGJ were detected in 27 % of patients in group 1 and 73 % of patients in group 2.

The LES tone in group 1 patients was significantly higher (27.75 mmHg, 95 % CI 23.8122–31.7013) compared with patients in group 2 (14.67 mmHg, 95 % CI 9.1579–20.1754) (Fig. 8).

When comparing the frequency of occurrence of motor disorders from the thoracic esophagus, these are determined in 62 % of patients of group 1 and in 53 % of patients of group 2.

It is worth noting that in group 2 of patients, 5 patients had only HH, 2 patients had a combination of HH and hypotension of the LES, 4 had only disorders of the motility of the thoracic esophagus (ineffective motility in 3 cases and absent contractility in 1 case), 1 patient had a combination of hypotension of the LES and ineffective motility and 3 disorders of the motility of the thoracic esophagus (ineffective motility in 1 case, absent contractility in 2 cases) in combination with HH and hypotension of the LES (Fig. 9). Also, 11 out of 15 patients in this group had no symptoms against the background of inadequate action of PPIs, which could potentially cause a higher risk of progression of BE both due to a combination of factors aggravating the course of the disease (increased acid exposure in the esophagus, disorders of the structure and function of EGJ, disorders of the motility of the thoracic esophagus), and due to the absence of symptoms in conditions of ineffective acid suppression. This may be mistakenly assessed as a satisfactory effect and lead to untimely correction of treatment [51, 52].

Conclusion

GERD is currently one of the most frequent diagnoses in gastroenterological practice. BE is a complication of GERD that increases the risk of a sequential transformation from intestinal metaplasia without dysplasia to low and high degree dysplasia and eventually to EAC. This makes it necessary to conduct adequate diagnostics and improve the effectiveness of drug treatment of GERD in general and patients with BE in particular, which improves the quality and life expectancy of patients.

The main role in determining individual patterns of esophageal acidification and motor characteristics is played by functional research methods such as daily pH-impedance measurement and high-resolution esophageal manometry.

In the framework of this study, predictors of the insufficient effectiveness of PPIs in patients with BE were studied based on the parameters of daily pH-impedance and high-resolution esophageal manometry. It has been shown that a number of patients with BE have insufficient pharmacological efficacy of antisecretory therapy even in the absence of clinical symptoms of GERD. In addition, according to pH-impedance, it was noted that with effective acid suppression, the persistence of complaints may be due to non-acid reflux, which

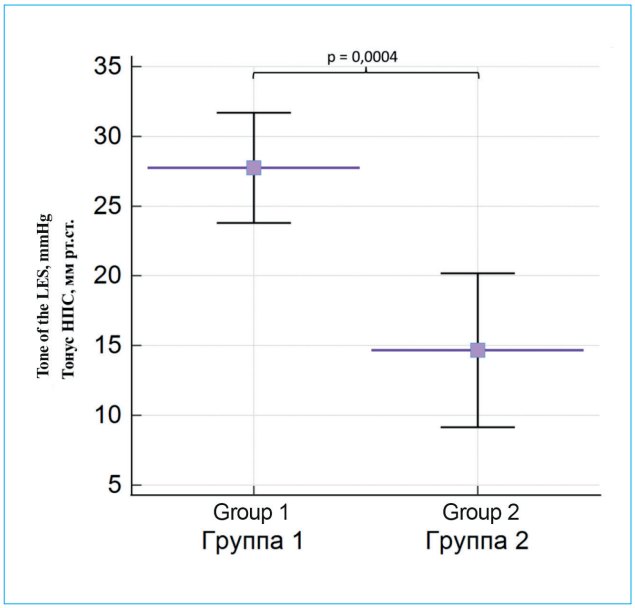

Fig. 8. Comparative data on the tone of the lower esophageal sphincter in the study groups
Рис. 8. Сравнительные данные по тонусу нижнего пищеводного сфинктера в исследуемых группах

may also require correction of treatment by additional prescribing of drugs of other groups or performing fundoplication. When analyzing the data obtained during high-resolution esophageal manometry, it was not possible to identify significant differences in the frequency of motor disorders between groups with the effectiveness of PPIs and with their unsatisfactory effect in our study. However, significantly more frequent registration of violations of the structure and/or function of EGJ was found in the group with insufficient effectiveness of antisecretory therapy. Thus, predictors of insufficiently effective therapy of patients with BE are both insufficient pharmacological action of the PPIs themselves, and motor disorders causing non-acidic gastroesophageal refluxes, reduced esophageal clearance, which in turn can support the patient's symptoms and affect the condition of the esophageal mucosa.

Based on the research work carried out, it was revealed that patients with BE are heterogeneous and, with general principles of management, require a differentiated approach to treatment. A personalized approach, based, among other things, on pH-impedance and esophageal manometry data,

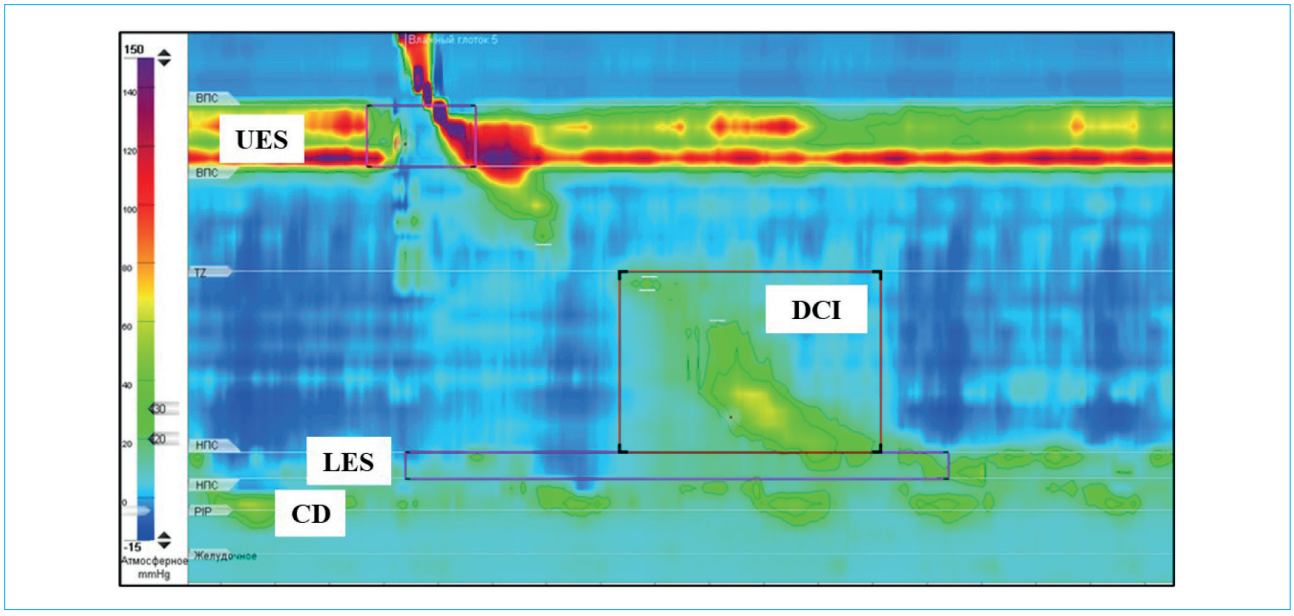

Fig. 9. High-resolution manometry. A combination of hypotension of the LES, the presence of HH and ineffective motility. UES — the upper esophageal sphincter. LES — lower esophageal sphincter — resting pressure 8 mmHg (norm 10–45 mmHg); CD — crura diaphragm. The divergence of the pressure zones created by the LES and CD, which corresponds to a heatal hernia 2.3 cm. DCI — distal contractical integral — 172 mmHg×cm×sec (norm 450–8000 mmHg×cm×sec) — weak peristalsis.
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Рис. 9. Манометрия высокого разрешения. Сочетание гипотонии нижнего пищеводного сфинктера, наличия грыжи пищеводного отверстия диафрагмы и неэффективной моторики. UES — верхний пищеводный сфинктер. LES — нижний пищеводный сфинктер — давление покоя 8 мм рт. ст. (норма 10–45 мм рт. ст.); CD — ножки диафрагмы. Расхождение зон давления, создаваемых НПС и НД, что соответствует грыже пищеводного отверстия диафрагмы 2,3 см. DCI — интегральная сократимость дистального сегмента — 172 мм рт. ст.×см×сек (норма 450–8000 мм рт. ст.×см×сек) — ослабленная перистальтика.
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