The Use of Heart Rate Variability Technique for Differential Diagnostics of Peptic Ulcer and Idiopathic Duodenal Ulcers

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The aim of the investigation was to study the peculiarities of autonomic regulation using spectral analysis of heart rate variability for differential diagnostics of peptic ulcer and idiopathic duodenal ulcer.

Materials and Methods. A stress level was assessed by vagosympathetic balance rate. Low-high frequency ratio in a frequency spectrum of heart rate was used as a marker of vagosympathetic balance of stress. Endoscopic findings were compared with Helicobacter pylori test, and autonomic status was studied using spectral analysis of heart rate variability.

Results. We found significant differences in low/high frequency ratio in the spectrum of heart rate of patients with Hp-positive and Hp-negative duodenal ulcers. The result proved stress nature of idiopathic ulcers. Idiopathic ulcers are characterized by significant increase of LF/HF that can serve as a differential diagnostic criterion for different types of duodenal ulcers.

Conclusion. Spectral analysis of heart rate variability can be used in differential diagnostics of peptic ulcers and idiopathic ulcers.

Key words: peptic ulcer diagnostics; heart rate variability; idiopathic duodenal ulcers; Helicobacter pylori.

From 2 to 10% of adult population suffer from peptic ulcers [1]. In Russia it is common practice to distinguish true peptic ulcer and symptomatic ulcers [2]. In foreign literature the term “idiopathic ulcers” is more frequently used instead of “symptomatic ulcers” [3].

Due to the recognition of a significant role of Helicobacter pylori in the pathogenesis and etiology of peptic ulcers in recent years, there came into use the classification demonstrating the detection of Helicobacter pylori in patients with peptic ulcers. The classification also includes the ulcers related to the administration of non-steroid anti-inflammatory drugs (NSAIDs) [4].

There are:

Helicobacter-positive ulcers;

ulcers related to NSAIDs;

ulcers related to neither Helicobacter pylori nor NSAIDs — idiopathic ulcers.

Peptic ulcer and idiopathic ulcers have much in common in their clinical manifestations, though the approaches to their treatment are different.

A leading factor causing idiopathic ulcers is stress. According to recent data [3], now there is an increasing worldwide incidence rate of idiopathic ulcers unrelated to common causes of the pathology: Helicobacter pylori, NSAIDs.

According to different sources, a proportion of idiopathic ulcers in total number of ulcers is variously estimated from 10 to 30% [5]. One of dramatic confirmations of stress effect on the appearance of ulcers is the observation of their incidence rate before and after earthquakes in Japan in 2011. A proportion of idiopathic ulcers in Japan increased in 2011 compared to 2010 from 13 to 24% [6]. The data determine the necessity to assess a stress level in the diagnosis and treatment of gastrointestinal diseases at different stages [7].

The analysis of heart rate variability (HRV) is the easiest and most available method among numerous human stress evaluation techniques. Circulatory system can serve as an indicator of any adaptive responses, and stress in particular. Thus, HRV analysis enables to assess both the result of body adaptive response, and also the involvement of regulatory mechanisms in this response [8].

HRV method is based on the recognition and measurement of time intervals between R-waves of an electrocardiogram (R–R intervals), plotting statistical series of R–R intervals followed by the analysis of the obtained numerical series using various mathematical methods.

Mathematical apparatus of HRV analysis includes a broad range of techniques: a statistical analysis of a series of R–R intervals including standard methods of descriptive statistics (calculation of root mean square deviation, variation coefficient, and other characteristics)

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and a distribution method (variational pulsometry); scatterography (Poincaré plot); digital filtration techniques; spectral analysis, etc.

Currently, the determination of HRV parameters has been considered the most informative noninvasive technique of quantitative estimation of autonomic regulation of heart [9], which helps to study the relationship of the brain and viscera. Low/high frequency (LF/HF) ratio is used as a sympathetic-parasympathetic balance index [10].

Neurogenic structures, such as autonomic nervous system, cortex-subcortex, reticular formation play a key role in gastroduodenal pathology formation. Autonomic nervous system has an effect on both gastrointestinal motility, and gastric juice secretion indices [7]. The use of HRV analysis can have great possibilities in the diagnostics of GIT pathology. However, there are just a few studies both in Russian and foreign medical literature devoted to autonomic homeostasis using the estimation of HRV spectral characteristics in gastroduodenal pathology [11].

The aim of the investigation was to study the peculiarities of autonomic regulation using spectral analysis of heart rate variability for differential diagnostics of peptic ulcer and idiopathic duodenal ulcer.

Materials and Methods. HRV was analyzed by processing electrocardiograms taken using a VNS-Rhythm computed ECG recorder and a Poly-Spectrum original program (Neurosoft, Russia) according to the recommendations of Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology (1996) [12].

Poly-Spectrum records heart rate (HR) automatically reflecting the effect of heart contractions of both sympathetic component of autonomic nervous system (physiological task — "fight or flight", stress response maintenance), and also parasympathetic component (task — assimilation, restoration of energy consumption of the body on sympathetic activation). HR correlates primarily with sympathetic activity. Moreover, the program enables to receive data on the following HRV indices.

1. Using time domain methods (based on statistical techniques):

SDNN (standard deviation of NN intervals) is standard deviation of intervals between heart beats, shows both parasympathetic (primarily), and sympathetic influence;

RMSSD (root mean square of successive differences) — square root of sum of squared difference values;

pNN50 — the number of differences, which are over 50 ms, percentage of the total number of intervals.

RMSSD and pNN50 are considered to change unidirectionally and reflect sinus arrhythmia related to breathing; determined by the influence of parasympathetic component.

2. By means of correlation rhythmography or scatterography (Poincaré plot). A scatterogram is a graphic presentation of dynamic R–R intervals in the form of 'a cloud' by plotting a series of dots in rectangular coordinate system. And every current R–R interval is plotted on the Y-line, while every following R–R interval — along X-line. We determined the following parameters:

S — 'cloud' area;

L — 'cloud' length;

L/W — 'cloud' length/width ratio.

3. Using variation pulsometry. The technique consists in determining the distribution of R–R intervals as random variables. For this purpose a distribution curve is plotted — a bar graph. According to variation pulsometry, one can calculate a number of derived indices:

ABI — autonomic balance index (*ABI*=*AMo*/*X*); it determines sympathetic/parasympathetic ratio of cardiac activity control;

AHRI — autonomic heart rhythm index (*AHRI*=1/*Mo*·*X*); it enables to estimate autonomic balance: the lower *AHRI*, the more autonomic balance is shifted towards parasympathetic control predominance;

RAI — regulation adequacy index (*RAI*=*AMo*/*Mo*); it reflects the agreement between the level sinus node functioning and sympathetic activity;

SI — a stress index of regulatory systems (*SI*=*AMo*/2*X*·*Mo*); it shows the centrilization degree of cardiac rhythm control.

4. By means of spectral analysis of HRV. Spectral analysis enables to assess quantitatively the effect of different regulatory systems on cardiac work:

LF/HF — HRV low/high frequency ratio (characterizes sympathetic-parasympathetic balance).

In our survey we studied duodenal pathology, since the prevalence rate of duodenal ulcers is 4–20 times as higher than that of gastric ulcers. The findings were statistically processed using Microsoft Excel program and ANOVA. $P<0.01$ was considered as error probability.

A total of 257 patients underwent HRV analysis, among them there were 153 (55.6%) females, and 122 (44.4%) males. Patients' age was from 10.5 to 88 years, mean age being 52.9±15.9 years. Most patients (n=209) were suspected to have esophageal, gastric and duodenal pathology, 66 patients were examined for: occupational health examination, examination when referred to surgery (gynecological pathology, before coronography, etc.).

Endoscopy (AOHUA, VME model, China) was performed due to a suspected gastrointestinal pathology, as well as due to other reasons.

According to endoscopic findings (the presence or absence of duodenal ulcer) all patients were divided into two groups. A control group (n=220) included patients who had no duodenal ulcer according to clinical laboratory data.

All patients with duodenal ulcers were examined for Helicobacter pylori. They underwent cytological examination with Romanowsky–Giemsa staining of smears, and rapid urease test for Helicobacter pylori.

In case of a negative test, a patient was administered a test for Helicobacter pylori antibodies in peripheral blood (HEXAGON H. PYLORI test, HUMAN Diagnostics, Germany) [13].

Concurrently with the above mentioned, all patients underwent HRV test. In accordance with international standards, HRV test is performed within 5 min, not earlier than 1.5–2 h after meals, in a quiet darkened room. 12 h before testing patients should take back from drinking alcohol and coffee, as well as advised be free of stresses (physical, psychological). Cardiac rhythm is recorded in the morning, between 9 and 12, in comfortable conditions (temperature is about 22°C). Before testing physiotherapeutic procedures and drug treatment should be discontinued considering drug clearance. Immediately prior to heart rate recording there should be a 5–10-minute adaptation period. If an adaptation period appears to be insufficient, a deformed area is excluded from testing, otherwise the analysis is terminated. A patient is in supine position.

HRV analysis requires only high quality rhythmograms with sinus rhythm and few artifacts and extrasystoles (up to 10% of the total number of R–R intervals). Before calculating HRV indices, these 'interferences' are to be corrected. It is unreasonable to analyze rhythmograms if a pacemaker is displaced (low atrial rate, atrioventricular rhythm). The filtering of interferences consists in excluding such sequent R–R interval, which differs from the previous one by more than 20%.

The present study was approved by the Ethics Committee of Nizhny Novgorod State Medical Academy, and complies with the declaration of Helsinki (adopted in June, 1964 (Helsinki, Finland) and revised in October, 2000 (Edinburg, Scotland)). Written informed consent was obtained from all patients.

Results. The first stage was to study the informative value of the suggested HRV indices based on their statistical analysis. The second stage aimed at checking clinical laboratory comparisons.

17 HRV indices were statistically analyzed using Poly-Spectrum. The tool Correlation of Microsoft Excel 2010 revealed their relationship. Many parameters appeared to be closely related, interdependent, with the same basis that was why it was unnecessary to use many parameters. For instance, SDNN correlates with RMSSD, pNN50, S, L, ABI by 80–94%; RAI correlates with SI by 93%, etc. This information enabled to simplify further investigations due to the exclusion of some similar parameters. SDNN, LF/HF, L/W, indicators variational pulsometry Baevsky (ABI, RAI, AHRI) were recognized as the most informative and were used for the following work.

At the second stage, using endoscopic findings we first checked if the patients with Helicobacter pylori had ulcers. 30 of 55 patients with endoscopically confirmed duodenal ulcers were found to have Helicobacter pylori.

We checked the availability of HRV analysis to diagnose peptic ulcer. For this purpose we compared HRV indices in two groups: patients with duodenal ulcers of any etiology (n=55), and patients without duodenal ulcers (n=220) (Table 1).

These findings and the calculation of Pearson correlation coefficient between HRV indices and the presence of duodenal ulcer in a patient enabled to show that LF/HF ratio is most closely related to duodenal ulcer (See Figure, Table 2). The ratio is likely to reflect patient's sympathico-parasympathetic balance (and a stress response level). Pearson correlation coefficient

Table 1

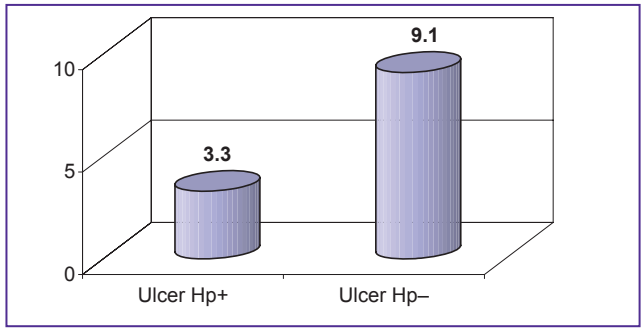
Heart rate variability indices in patients with duodenal ulcers and in controls (M±σ)

Parameters	Patients with duodenal ulcers (n=55)	Control group (patients without duodenal ulcers) (n=220)
Age (years)	46.4±15.0	54.6±15.8
HR	84.6±13.0	74.1±14.8
SDNN	22.7±13.5	29.9±19.7
LF/HF	6.0±3.5	2.6±2.3
L/W	4.2±1.2	3.0±1.2
ABI	0.1±0.1	0.2±0.2
RAI	118.2±71.6	97.2±61.9
AHRI	17.1±11.8	10.7±7.2

Table 2

Parameters of heart rate variability in patients with duodenal ulcer depending on the presence or absence of Helicobacter pylori (M±σ)

Parameters	Hp-positive ulcer (n=30)	Hp-negative ulcer (n=25)
Age (years)	46.1±17.6	46.8±11.3
HR	80.2±12.5	89.9±11.8
SDNN	27.6±15.5	16.9±7.2
LF/HF	3.3±1.7	9.1±2.1
L/W	3.6±0.8	5.0±1.2
ABI	0.2±0.1	0.10±0.05
RAI	77.4±29.7	167.1±76.8
AHRI	14.6±12.7	20.0±10.1



Comparison of LF/HF ratio in Hp-positive and Hp-negative duodenal ulcer group

Table 3

Examples of using spectral analysis of heart rate variability

Patients	Sex	Age (years)	Date	LF/HF	Hp-smear	Helic-test (Helicobacter pylori analysis)	Hp-antibodies
O.	Female	36.4	04.06.14	0.61	+	+	+
M.	Male	30.2	04.08.14	4.95	–	–	–
S.	Male	38.9	08.08.14	1.7	–	–	+
G.	Male	35.6	25.08.14	3.28	–	–	–
A.	Male	16.9	24.09.14	0.39	–	+	+
E.	Male	29.2	26.09.14	1.17	+	+	+

between the presence of ulcer and changed LF/HF ratio equaled 0.41 ($p<0.001$).

The correlation between other HRV indices and the presence of ulcer appeared to be significantly lower. The findings enabled to demonstrate LF/HF ratio to be the most sensitive HRV parameter for duodenal ulcer diagnosis.

At the final stage we studied HRV in patients with duodenal ulcers confirmed by endoscopy (n=55). The patients were divided into two groups: an Hp-positive group (n=30) and an Hp-negative group (n=25).

To determine the compatibility of the groups we used analysis of variance and Student t-test. We found significant differences in LF/HF values in a group with Hp-positive duodenal ulcer (3.3) and in a group with Hp-negative ulcer (9.1) — $p<0.00001$. The findings showed a marked HRV imbalance towards the dominating neurotony of sympathetic component of autonomic nervous system. No relation to Helicobacter pylori suggests terming Hp-negative ulcers as true “idiopathic” ulcers.

Let us consider the examination of patients with duodenal ulcers revealed by endoscopy using the suggested technique (Table 3).

The patients undergoing gastroscopy were taken antral smears, performed Helic-test for Helicobacter pylori, and taken blood test for antibodies to Helicobacter pylori. This very day their heart rate variability was assessed.

Table 3 shows the discrepancy in the results of different Helicobacter pylori tests. Therefore, it is not always possible to estimate the nature of duodenal ulcer.

Heart rate variability (LF/HF ratio, in particular) in patient M. (4.95) and patient G. (3.28) exceeded the norm (up to 2.2). Thus, these patients on the day of examination could be diagnosed “idiopathic ulcers” and administered proper treatment.

The results of Helicobacter pylori test in patients S. and A. were contradicting. HRV analysis did not showed idiopathic nature of ulcers: LF/HF was within normal limits (1.7) in patient S., and even lower — in patient A. (0.39). The tests for antibodies to Helicobacter pylori were positive.

Patient O. and patient E. had Helicobacter pylori positive results according to both the tests performed immediately after the examination and the blood tests for antibodies to Helicobacter pylori. LF/HF of both patients was within the normal limits (0.61 and 1.17). Thus, the dependence of ulcer on Helicobacter pylori in these patients was undisputed.

The administration of anti-Helicobacter therapy for the last four patients was reasonable.

The use of the diagnostic technique suggested enables to shorten significantly the time and increase the reliability of detection of idiopathic duodenal ulcers.

Thus, HRV analysis using Poly-Spectrum program enables to estimate the peculiarities of autonomic control in patients with gastrointestinal pathology. The technique is noninvasive and not time-consuming — it takes about 10 min per a patient.

Conclusion. LF/HF ratio is the most informative index for heat rate variability analysis in gastrointestinal diseases (especially, in duodenal ulcer). Idiopathic ulcers are characterized by significant increase of LF/HF values. It enables to suggest applying the technique to determine heart rate variability, LF/HF criterion in particular, to differentiate peptic ulcer and idiopathic duodenal ulcers.

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