JOURNAL OF PHYSIOLOGY AND PHARMACOLOGY 2004, 55, Suppl 2, 77–90
www.jpp.krakow.pl

L. DOBREK[1], M. NOWAKOWSKI[2], M. MAZUR[1], R.M. HERMAN[2], P.J. THOR[1]

DISTURBANCES OF THE PARASYMPATHETIC BRANCH OF THE AUTONOMIC NERVOUS SYSTEM IN PATIENTS WITH GASTROESOPHAGEAL REFLUX DISEASE (GERD) ESTIMATED BY SHORT-TERM HEART RATE VARIABILITY RECORDINGS

[1] Department of Pathophysiology, Jagiellonian University Medical College, Cracow, Poland
[2] 3rd Department of Surgery, Jagiellonian University Medical College, Cracow, Poland

Gastro-esophageal reflux disease (GERD) is the result of the acid contents regurgitation back from the stomach into the esophagus. According to the endoscopic findings, GERD can be divided into two main forms: non-erosive (NERD) and erosive reflux esophagitis. The pathogenesis of GERD is associated with the impaired function of the antireflux barrier. Disturbances of the autonomic nervous system (ANS), especially parasympathetic part of the ANS, may be also involved in the pathogenesis of this disease. The aim of our study was to establish the parasympathetic activity in patients with reflux esophagitis and in patients with symptomatic endoscopically negative reflux. Working hypothesis was the question, whether the possible parasympathetic activity disturbances, which are observed in all GERD patients, may be regarded as the primary or secondary to the esophagitis. All the participants (20 pts. with NERD, 20 pts. with reflux esophagitis and 20 healthy controls) underwent esophageal manometry, 24-hour ambulatory pH-monitoring, resting heart rate variability (HRV) recording and the deep breathing (DB) test with the continuous HRV recording. The results of the spectral analysis both of the short-term, resting HRV recordings and DB-evoked revealed the disturbances of the main power spectra components - LF and HF in both groups of patients in comparison with the control group. In our opinion, the observed HRV spectra changes in both groups of patients support the hypothesis that not only is the parasympathetic activity impairment associated with the pathogenesis of GERD but it is also the primary factor contributing to the pathophysiological mechanism of reflux.

Key words: *GERD, NERD, HRV, DB test, autonomic nervous system, parasympathetic activity.*

INTRODUCTION

GERD is a highly prevalent gastrointestinal (GI) disorder, affecting the upper part of the gastrointestinal tract, and is one of the most common GI illnesses encountered in clinical practice. The term GERD applies to a group of symptoms and signs with possible concomitant morphological changes, which arise as a consequence of pathological reflux of stomach and duodenal contents into the esophagus (1). In attempting to develop an all-encompassing definition, the Genval Working Group arrived at the following: "all individuals who are exposed to the risk of physical complications from gastro-esophageal reflux or who experience clinically significant impairment of health-related well being (quality of life) due to reflux-related symptoms…" (2). Individuals with GERD have frequent, recurring, and prolonged episodes of reflux, usually at night (1). It usually causes the typical esophageal symptoms with the most common heartburn (pyrosis) being the hallmark symptom of GERD, however the clinical manifestations of GERD can be misleading. Other manifestations include acid regurgitation and dysphagia (3). Some patients with GERD have no standard symptoms while asthma, angina-like pain (NCCP - Non Cardiac Chest Pain) or pain in upper abdomen are all atypical presentations of GERD (1, 3).

Complications of GERD are variable and include erosive esophagitis, esophageal stricture, esophageal ulcer, Barret's esophagus (intestinal metaplasia of the esophagus), and adenocarcinoma of the esophagus (3).

The pathophysiological basis of GERD is complex and is an object of continuous investigation. Generally, it is associated with the impaired function of the antireflux barrier, which comprises many factors, both anatomical and physiological. The role of *H. pylori* infection is also postulated but there is no agreement on its contribution in GERD pathogenesis contrary to its role in the pathophysiology of duodenal ulcer disease (4). Reflux can occur due to transient relaxation of the lower esophageal sphincter (LES), reduced LES pressure allowing spontaneous reflux, or increased abdominal pressure (3). Factors important in removing refluxed material (peristalsis), resisting acid (salivary pH, esophageal epithelium and bicarbonate secretion), and the characteristics and quantity of gastric fluids produced are thought to play a role in pathogenesis of GERD (1, 3, 5). The vagus nerve provides parasympathetic control of the gastrointestinal tract (6). Vagal activity is a constant subject of many experimental research studies in animal models (7). Decreased vagal nerve activity, caused by disturbed autonomic regulation, is the most commonly considered factor contributing to the onset of GERD and this pathophysiological mechanism seems to be responsible for functional LES (Lower Esophageal Sphincter) failure. Normally, the tonic LES contraction is the essential element of the antireflux barrier mentioned above and it prevents the occurrence of reflux episodes in excessive number. The autonomic LES insufficiency generates TLESRs -

Transient Lower Esophageal Sphincter Relaxations, which is the reason for both physiologic and most of pathologic reflux episodes (8 - 12).

It has not been fully described whether these disturbances are primary or secondary, in other words, do they already exist in patients with non-erosive reflux disease (endoscopy-negative reflux disease or symptomatic reflux disease) or is it a consequence of inflammatory changes.

The autonomic nervous system (ANS) tests and the role of autonomic regulations have become the subjects of many studies. They are mostly based on the measurement of the heart rate variability (HRV). HRV tests are non-invasive methods of evaluating the integrity and functional state of the ANS and may be carried out using the short-term ECG recordings or long-term measurement (Holter's ECG). Time domain or frequency domain analyses are the methods of HRV assessment. The first of them estimates fluctuations of R - R intervals on the ECG curve and the frequency domain method serves to create HRV power spectrum. It allows for a graphic presentation of autonomic and other, not all precisely defined, influences on ECG. Moreover that gives the possibility to calculate values, which show the activity of the sympathetic and parasympathetic arms of the ANS.

In the HRV spectrum the following components can be distinguished: VLF, LF and HF. LF (Low Frequency) is regarded to reflect the functional state of the sympathetic part of the ANS, while HF (High Frequency) represents the parasympathetic activity. The LF/HF ratio is the indicator of the autonomic sympatho-vagal balance. The meaning of the VLF (Very Low Frequency) spectral component has not been fully described yet (13, 14).

MATERIALS AND METHODS

Sixty persons (30 women and 30 men) including 40 patients, who presented typical symptoms of GERD with or without reflux esophagitis, participated voluntary in our research. All of them signed a written consent to undergo the procedures. The study was approved by the local ethics committee. 24-hour esophageal pH-monitoring, as a gold standard of GERD diagnosis (15 - 18) and HRV monitoring during resting conditions with deep breathing (DB) test were performed in each subject. According to the results of 24-hour esophageal pH-monitoring they were classified to the one of following groups: A - healthy volunteers (20 persons, 10 women and 10 men, the mean age 49,1), B - symptomatic NERD patients (20 persons, 10 women and 10 men, the mean age 51,9) and C - GERD patients with reflux esophagitis (20 persons, 10 women and 10 men, the mean age 52,7). The diagnostic procedure started with the history taking followed by physical examination and esophagogastroscopy. Later on esophageal motility was studied using esophageal manometry paying particular attention to determine the LES position. In the next step, 24-hour esophageal pH-metry was performed in ambulatory conditions. On the following day, after termination of pH-metry, each patient underwent resting heart rate variability recordings and the deep breathing test (DB) as a non-invasive method of autonomic nervous system activity estimation.

During esophageal manometry commercially available multilumen catheter with three channels placed in 5cm intervals from the tip was used (Synectics Sweden). It was perfused continuously

with water delivered by a pneumohydraulic pump connected to the pressure transducers. The recordings were stored and analysed on a personal computer using Polygram Synectics Sweden equipment. The position of LES was determined by station pull-through method. The catheter was passed nasally into the stomach to obtain intragastric pressure and then withdrawn in 1cm intervals to measure the lower esophageal sphincter pressure, which was taken as a mean of three channel values.

During pH-metry, the tip of pH-metry catheter was also passed nasally and positioned 5 cm above the upper border of manometrically determined position of the LES. It was terminated with single pH electrode and was connected to pH Digitrapper Mk III (Synectics Sweden). The reference electrode was placed on chest surface. Both electrodes were calibrated before the examination in standard buffer solutions (pH = 1 and pH = 7). During the study, patients were asked to note the precise time of meals and body position changes (supine vs. upright). Patients were instructed to follow their daily routine but they were not allowed to smoke and they were instructed to avoid consumption of food and beverages of pH<4. The next day the study was completed, the catheter was removed and the recording was stored on the PC and analysed using EsopHogram Synectics equipment. The reflux of stomach content was considered as a drop of pH < 4 in the distal esophagus. Standard parameters were taken under consideration.

Heart rate variability recordings were performed on each patient. Both resting and DB HRV signals were obtained from II limb lead. During DB period, the examined person breathed in a controlled way (5 sec inspiration and 5 sec expiration). ECG signal was collected on the PC and after removing artifacts in both recordings frequency domain analysis took place. The equipment used for the HRV analysis was EKG 2002 Proster Gliwice Poland. The main HRV power spectrum components were estimated. As the VLF range the frequency of 0,05 Hz and lower, LF 0,05-0,15 Hz and HF 0,15-0,5 Hz were accounted.

LF and HF values (both resting and obtained from DB period), the best factors of functional state of autonomic nervous system (ANS), were analysed statistically with the Bartlett's test (by the essence level $\alpha = 0,05$). Hypothesis of variances quality in all groups (with reference to analysed parameters), that means hypothesis of the lack of any differences between them (H_0) was verified. The alternative hypothesis was the one of variances inequality (H_1) that means the existence of statistically significant differences.

Than, in the case of rejection hypothesis H_0, similar hypothesis were verified with the Fischer's - Snedecor's test ($\alpha = 0,05$), but examining pairs of groups: A and B, A and C and B and C.

RESULTS

The results of 24-hour pH-monitoring allowed to distinguish 3 groups among all examinated subjects.

Group A included the asymptomatic persons with normal pH-recordings. The second group - B - comprised symptomatic NERD patients. The last group, marked further as a group C, was composed of symptomatic GERD patients with inflammatory changes in the esophageal lumen.

The percentage of time when esophageal pH was lower than 4 reached 21,2% in GERD patients (group C), while in group A only 2,3%. GERD patients had also nearly four times more total reflux episodes (353) compared to the healthy persons (81). NERD patients have 267,7 reflux episodes in total. The GERD patients had also the longest reflux episodes last on average 45,6 minutes. The

number of reflux episodes lasting longer than 5 minutes was also highest in group C (7,5), while this parameter in group B was (3,8) and very low in group A (0,3). The result of DeMeester's score obtained from patients' recordings (87,4) is highest again in group C and differs significantly from the healthy persons result (11,1).

In comparison to the GERD patients, patients with NERD had less reflux episodes lasting longer than 5 minutes (3,8 vs. 7,5) as well as shorter duration of the longest reflux episode (30,8 vs. 45,6). The percentage of time when pH < 4 was 12,4% vs. 21,2% in GERD patients and the DeMeester's value was 56,7. The results of the esophageal pH - monitoring are presented in *Table 1.*

Table 1. 24-hours pH-monitoring results. Acid reflux for all individuals

Parameter	Control (A)	NERD (B)	Esophagitis (C)	
Total number of reflux episodes	81,5 ± 44,5	267,7 ± 246,8	353,4 ± 326,8	p<0,05
The number of reflux episodes in upright position	64,6 ± 37,4	218,0 ± 199,1	289,8 ± 276,2	p<0,05
The number of reflux episodes in supine position	17,1 ± 32,8	50,4 ± 59,1	64,4 ± 64,1	p<0,05
The number of meal episodes	22,6 ± 26,9	31,5 ± 30,9	30,6 ± 38,7	NS
The number of postprandial episodes	39,9 ± 30,7	133,3 ± 132,9	191,1 ± 182,4	p<0,05
The number of reflux episodes lasting > 5 min	0,3 ± 0,6	3,8 ± 5,4	7,5 ± 8,0	p<0,05
The duration of longest reflux episode [min]	7,2 ± 16,9	30,8 ± 62,0	45,6 ± 75,2	p<0,05
Time of recordings with pH<4 [min]	32,5 ± 26,6	168,8 ± 231,4	299,8 ± 311,1	p<0,05
Fraction of recordings with pH<4 [%]	2,3 ± 1,9	12,4 ± 16,7	21,2 ± 22,1	p<0,05
DeMeester value	11,1 ± 5,7	56,7 ± 63,5	87,4 ± 80,1	p<0,05

HRV analysis:

The values of VLF during resting conditions differ in all groups (A - 906,3; B - 981,0; C - 505,8). During DB these differences persists (A - 884,8; B - 867,8; C - 1014,3). However, because of the fact, that clinical meaning of this HRV spectrum component is still unclear, we did not performed further analysis of this parameter. The LF value obtained from the ECG resting recordings in group C and B is significantly lower with comparison to the same parameter in group A (310,2 and 503,9 vs. 811,6 respectively). These results are presented in figures 1-3 as below (*Figs 1-3*)

During DB period LF increased in GERD patients (from 310,2 to 2369,1) and than this parameter reached high values in the group A and C (6652,1; 2369,1).

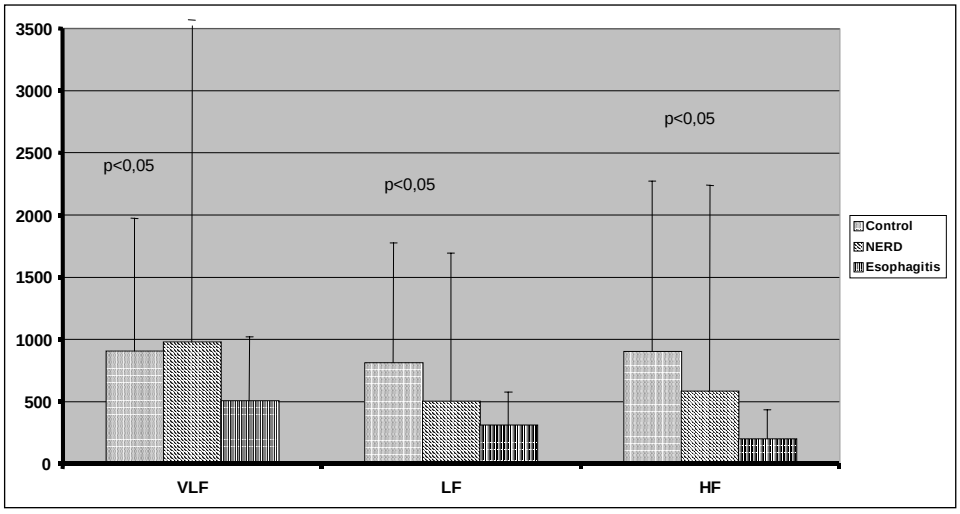

Fig. 1. Frequency domain analysis parameters during resting HRV recording (all individiuals).

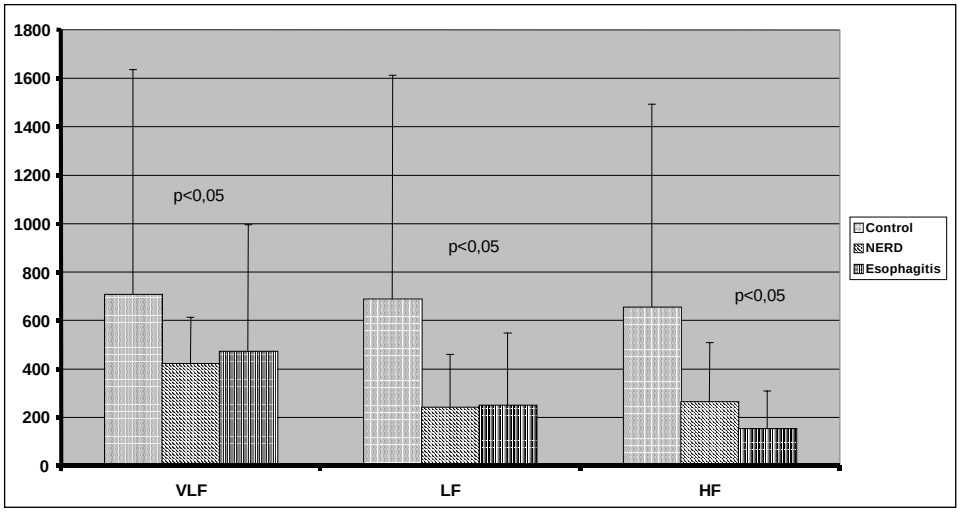

Fig. 2. Frequency domain analysis parameters during resting HRV recording (women).

HF from the resting recordings had much lower value in esophagitis patients comparing to NERD patients (group A - 901,7; B - 584,1; C - 201,0; $p < 0,05$). This component of HRV spectrum was expected to increase during DB and in fact this was observed during the study (854,6; 621,4; 884,5; $p < 0,05$ for group A, B and C, respectively). We have not observed any significant differences among sexes.

Results of the frequency domain analysis are presented in *Fig 4-6*. All obtained HRV results are in *Table 2*.

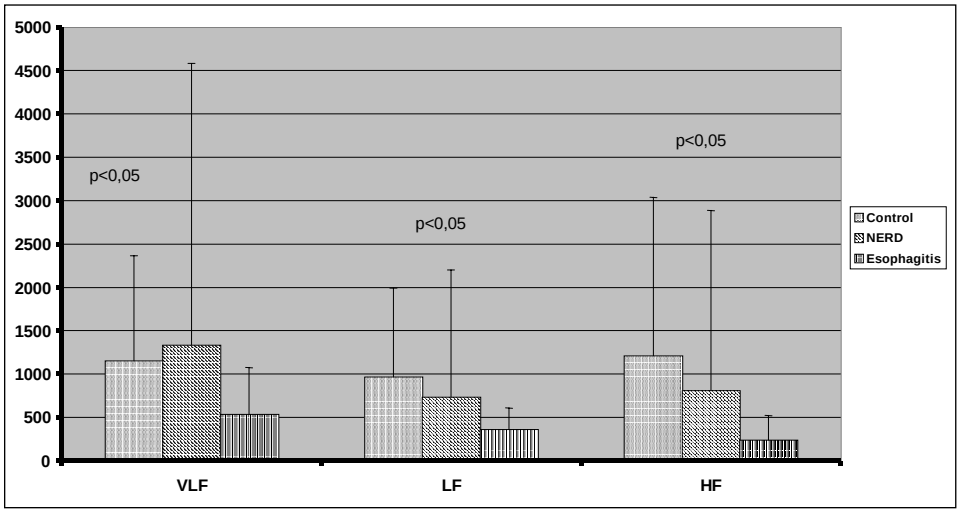

Fig. 3. Frequency domain analysis parameters during resting HRV recording (men).

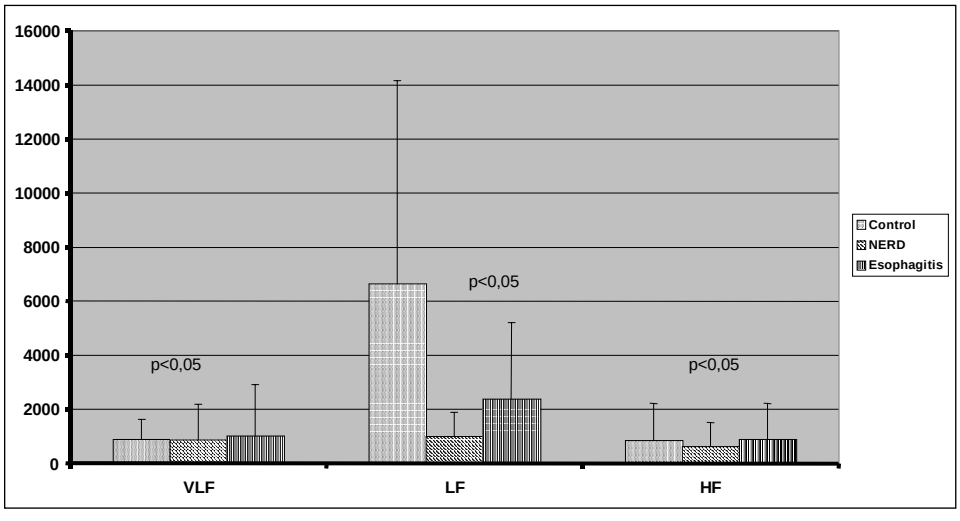

Fig. 4. Frequency domain analysis parameters during DB (all individuals).

DISCUSSION

We had expected to detect characteristic abnormalities in HRV parameters, which would support the hypothesis that diminished vagal activity contributes to GERD pathogenesis. The observed changes, suggesting potential parasympathetic activity dysfunction or both arms balance dysfunction, seem to be confirmed in literature data. One of the first reports covering this subject was made by Heatley *et al.* (19), who discovered in 1980 vagal activity disorders in patients with gastro-

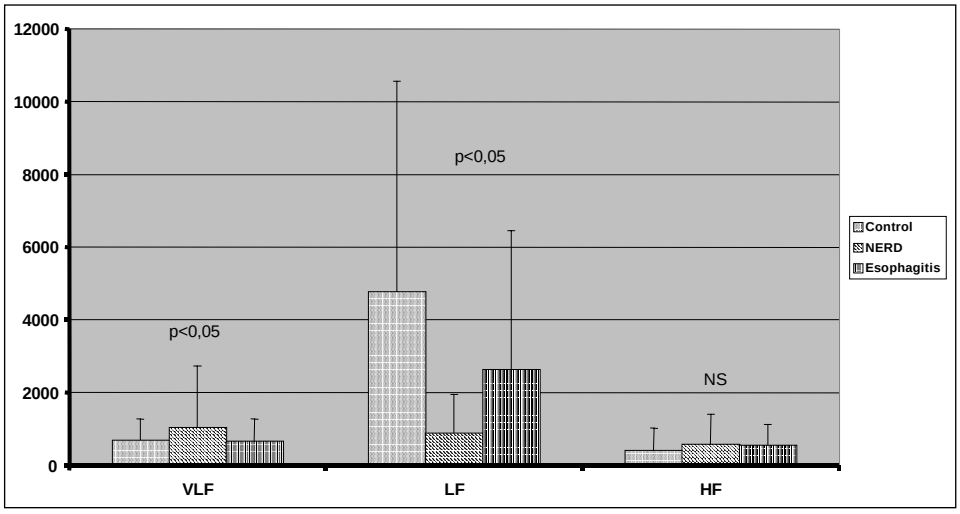

Fig. 5. Frequency domain analysis parameters during DB (women).

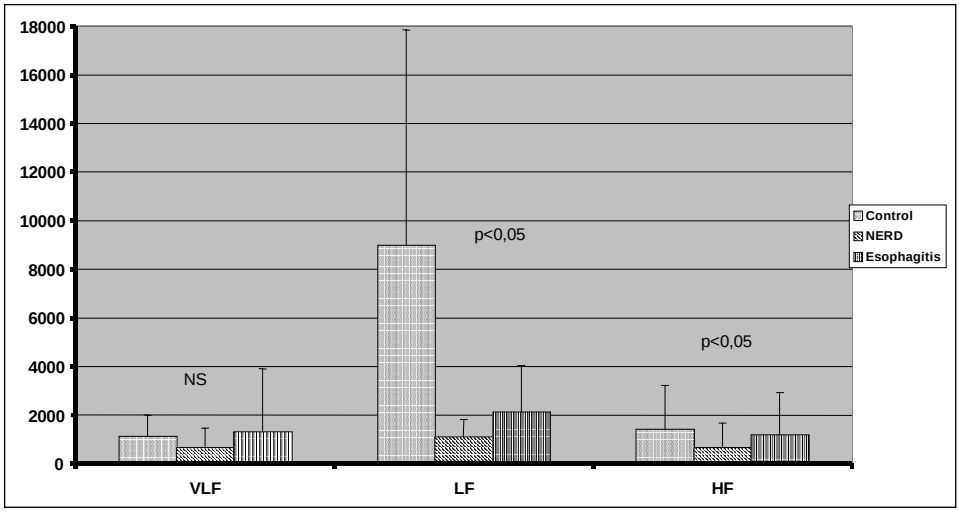

Fig. 6. Frequency domain analysis parameters during DB (men).

esophageal reflux disease while studying pentagastrine gastric secretory activity in post-insulin hypoglycemia and changes in pulse variability during forced inspiration and expiration (although this was not classic DB test). They found efferent vagal activity dysfunction in one-fourth of the patients with GERD. Yet they did not examine patients with inflammatory and non-inflammatory variant of GERD separately, which we did. Our results show that both patients with and without esophageal inflammatory changes present abnormally low HF component in resting conditions as compared to healthy controls. Therefore it can be

Table 2. Frequency domain analysis results of resting HRV recording and during DB test. All individuals.

Parameter	Control (A)	NERD (B)	Esophagitis (C)	
VLF [ms^2]	906,3 ± 1068,4 *884,8 ± 745,9*	981,0 ± 2589,8 *867,8 ± 1320,7*	505,8 ± 514,7 *1014,3 ± 1899,1*	p<0,05 *p<0,05*
LF [ms^2]	811,6 ± 965,4 *6652,1 ± 7505,6*	503,9 ± 1191,5 *989,1 ± 900,2*	310,2 ± 267,6 *2369,1 ± 2850,1*	p<0,05 *p<0,05*
HF [ms^2]	901,7 ± 1374,5 *854,6 ± 1365,0*	584,1 ± 1655,5 *621,4 ± 893,3*	201,0 ± 233,0 *884,5 ± 1330,6*	p<0,05 *p<0,05*
TP [ms^2]	2619,7 ± 3111,9 *8391,5 ± 8982,4*	2069,0 ± 5417,2 *2478,4 ± 2855,7*	1017,0 ± 843,6 *4267,9 ± 4941,5*	p<0,05 NS
LF/HF	1,2 ± 0,62 *13,6 ± 10,6*	2,1 ± 2,34 *6,8 ± 8,8*	2,1 ± 1,38 *7,2 ± 6,8*	NS *p<0,05*

Women

Parameter	Control (A)	NERD (B)	Esophagitis (C)	
VLF [ms^2]	708,7 ± 927,0 *692,8 ± 579,5*	422,3 ± 191,4 *1040,9 ± 1689,4*	472,1 ± 524,1 *661,8 ± 608,2*	p<0,05 *p<0,05*
LF [ms^2]	689,6 ± 921,9 *4775,0 ± 5795,7*	240,7 ± 220,1 *885,7 ± 1062,1*	249,0 ± 300,3 *2628,9 ± 3820,9*	p<0,05 *p<0,05*
HF [ms^2]	655,4 ± 837,8 *410,3 ± 607,2*	265,6 ± 243,3 *570,7 ± 840,8*	154,0 ± 155,1 *544,2 ± 544,7*	p<0,05 NS
TP [ms^2]	2053,7 ± 2542,4 *5878,1 ± 6625,4*	928,6 ± 552,5 *2497,3 ± 3522,0*	875,1 ± 913,2 *3834,9 ± 4440,5*	p<0,05 *p<0,05*
LF/HF	1,3 ± 0,6 *13,3 ± 9,7*	1,5 ± 1,6 *2,7 ± 2,4*	1,4 ± 0,9 *3,9 ± 2,8*	NS *p<0,05*

Men

Parameter	Control (A)	NERD (B)	Esophagitis (C)	
VLF [ms^2]	1153,4 ± 1207,5 *1124,9 ± 873,0*	1332,2 ± 3254,6 *675,4 ± 796,7*	531,1 ± 542,3 *1322,7 ± 2581,3*	p<0,05 NS
LF [ms^2]	964,1 ± 1026,4 *8998,5 ± 8850,3*	731,2 ± 1471,6 *1104,1 ± 725,3*	356,2 ± 250,9 *2141,8 ± 1898,7*	p<0,05 *p<0,05*
HF [ms^2]	1209,7 ± 1826,8 *1409,9 ± 1813,3*	810,4 ± 2076,4 *677,8 ± 996,6*	236,1 ± 283,5 *1182,3 ± 1752,0*	p<0,05 *p<0,05*
TP [ms^2]	3327,3 ± 3666,9 *11533,4 ± 1066*	2873,7 ± 6784,6 *2457,3 ± 2096,0*	1123,4 ± 834,1 *4646,7 ± 5620,0*	NS *p<0,05*
LF/HF	1,1 ± 0,6 *14,0 ± 12,0*	2,8 ± 2,7 *11,4 ± 11,1*	2,7 ± 1,5 *10,1 ± 8,1*	NS *p<0,05*

presumed that vagal activity dysfunction is present in both inflammatory and non-inflammatory variant of gastro-esophageal reflux disease.

Ogilvie et al. in their study indicated decreased vagal activity in patients with reflux esophagitis using standard DB test (20). We also decided to use this kind of parasympathetic branch activation. Similarly to Ogilvie's results, disproportion observed in resting HRV spectrum aggravated in DB test. In our study especially LF component achieved low value.

With introducing Ewing's battery tests set, firstly used to diagnose diabetic neuropathy, there has been a turning point in possibilities of the non-invasive diagnosis of the autonomic nervous system disorders in different patients. Chakraborty in cooperation with Ewing *et al.* (21) were the first to perform the whole set of tests to fully estimate the expected autonomic neuropathy in patients with reflux disease. Moreover they performed the pupillary test consisting in estimation of pupil contraction and relaxation time in reaction to the light stimulus, which is related to normal parasympathetic activity. In DB test they indicated disturbances in 38% of patients suggesting, similarly to the former citations, the presence of parasympathetic dysfunction. The pupillary test was normal in patients with GERD, which indicates, that disturbances noticed in tests estimating parasympathetic functional state (DB test, HR variability during Valsava maneuver or 30/15 ratio in tilt test) do not have generalised character (at least at the beginning of the disease), but are limited to the cardiovascular part of the parasympathetic branch of the autonomic nervous system. According to the authors, this neuropathy of parasympathetic character is a primary disorder, playing role in the early part of the pathogenesis of intensified reflux in these patients (decrease in vagal activity lowers myogenic control of LES) and is not a result of inflammatory changes in the esophagus.

Research made by Cunningham *et al.* (22) confirmed former reports of the presence of the functional disturbances in patients with GERD related to vagal regulation of the lower esophageal sphincter tension, esophageal peristalsis and gastric emptying, which in many ways contribute to the onset of reflux disease. Researchers estimated the presence of autonomic neuropathy by performing in a group of 48 patients deep breathing test and the tilt test with calculating HR changes as a 30/15 ratio and measuring a drop in systolic pressure. They did not encounter any differences in autonomic nervous system activity in patients with different degree of inflammatory process in the esophagus, by that proving those changes are among etiologic factors, and not results of the existence of inflammatory changes in the esophagus. In our study not only did we confirm the presence of autonomic dysfunction in patients with inflammatory changes but we also showed the presence of this dysfunction in patients without any morphological changes in esophagogastroscopy. That is why we agree with Cunningham's hypothesis about primary role of parasympathetic dysfunction. Cunningham group was also the first to demonstrate the relationship between parasympathetic neuropathy in patients with GERD and distorted esophageal motility.

Hartley et al. (23) postulated, that presence of gastric emptying disorders, determined by autonomic regulation disturbances, allow to regard GERD as a disease primarily related to the gut motility disorders.

Decreased parasympathetic activity is linked with an increased TLESRs frequency (24). Moreover LES pressure can be lowered pharmacologically using anticholinergic drugs which is another fact contributing to the role of decreased parasympathetic activity in the pathogenesis of the esophageal reflux disease (25).

One must not forget that there have been some reports of a slightly decreased sympathetic activity in GERD patients, which was supposed to negatively correlate with the total time of reflux episodes (26). Decreased sympathetic activity can cause intrinsic inhibitory reflex disturbances and, similarly to parasympathetic dysfunction, increased number and time duration of TLESRs episodes resulting in pathological enhancement of reflux. Chakraborty *et al.* in the study mentioned above did not observe pathologic changes in tests estimating sympathetic stimulation e.g. the postural drop of arterial pressure during tilt test or an increase of diastolic pressure in isometric hand grip test.

We found that not only HF but also LF component was markedly reduced in both groups of patients and it did not normalise during DB test. LF is considered to be a marker of sympathetic modulation, or according to other authors, it displays both sympathetic and vagal influences (27, 28). Therefore initial low LF value may, similarly to HF, reflect low parasympathetic activity. However, we cannot exclude that also the sympathetic component of the ANS is involved in GERD pathogenesis. That hypothesis seems reasonable because autonomic dysfunction as that observed in diabetic, alcoholic or in vitamin B12 deficiency usually involves both components of the ANS (29 - 31). Available literature addressing the impact of some chemical and work-related factors on the human ANS indicates that parasympathetic activity appears to be more vulnerable to these factors than sympathetic activity does (32). The lack of parasympathetic response causes HF to remain low.

Summarizing, the results of our study are conformable to a well-documented theory of parasympathetic neuropathy in patients with GERD, which is regarded as a primary disturbance, present already in patients without inflammatory changes in the esophagus. This dysfunction can be counted between the pathogenetic factors of gastro-esophageal reflux disease.

CONCLUSIONS

In the view of presented study results, disturbances of the parasympathetic branch of the autonomic nervous system can be observed both in patients with and without inflammatory changes in the esophagus. It can be presumed that disturbances mentioned above are not simply just the results of inflammatory

process. They can be regarded as essential in the pathogenesis of gastro-esophageal disease as they can be involved in TLESRs generation, which is a major contributor to the development of GERD. However we believe that the role of sympathetic component (LF) in the disease pathogenesis is also possible and cannot be omitted. It seems that this topic needs further studies in order to find answers to all the remaining questions.

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Received: 27 March 2004
Accepted: 28 May 2004

Author's address: Marcel Mazur MD, Department of Pathophysiology, Jagiellonian University Medical College, Czysta Str. 18, 31-121 Cracow, Poland. Tel/fax 0048 12 633 39 47. E mail: marcelmazur@poczta.onet.pl

List of abbreviations used in text:

GERD - Gastro-esophageal Reflux Disease
NCCP - Non Cardiac Chest Pain
LES - Lower Esophageal Sphincter
TLESRs - Transient Lower Esophageal Sphincter Relaxations
ANS - Autonomic Nervous System
HRV - Heart Rate Variability
DB - "deep breathing"
VLF - Very Low Frequency
LF - Low Frequency
HF - High Frequency