**Name of journal: World Journal of Gastroenterology**

**ESPS Manuscript NO: 15475**

**Columns: ORIGINAL ARTICLE**

***Observational Study***

**Cardiac autonomic dysfunction in patients with gastroesophageal reflux disease**

Milovanovic B *et al.* Autonomic dysfunction in patients with GERD

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**Author contributions:** Milovanovic B performed the autonomic function testing and participated in the manuscript writing; Filipovic B performed gastroenterological examination; Zdravkovic M participated in the manuscript writing; Mutavdzin S participated in the manuscript writing and in collecting the data; Gligorijevic T, Paunovic J and Arsic M participated in collecting the data.

**Ethics approval:** This research was conducted in the framework of the Ministry of Science project (No. 32040). Scientific Ethical Committee of Clinical Hospital Center “Bezanijska Kosa” approved all researches in the framework of this project.

**Informed consent:** All the patients were in detail informed about the protocol and signed a written consent.

**Conflict of interest statement:** The research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

**Data sharing statement:** Technical appendix, statistical code, and dataset available from the corresponding author at slavica.mutavdzin@gmail.com.

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**Received:** November 27, 2014

**Peer-review started:** November 27, 2014

**First decision:** January 8, 2015

**Revised:** January 26, 2015

**Accepted:** March 27, 2015

**Article in press:**

**Published online:**

**Abstract**

**Aim:**To investigate autonomic nervous function in patients with diagnosis of gastroesophageal reflux disease (GERD).

**Methods**: The investigation was performed on 29 patients (14 males), aged 18 to 80 years (51.14 ± 18.34), who referred to our Neurocardiology Laboratory Clinical and Hospital Center “Bezanijska Kosa” with diagnosis of GERD, while 116 healthy volunteers matched in age and gender with the examinees presented the control group. Study protocol included the evaluation of autonomic function and haemodynamic status, short term heart rate variability (HRV) analysis, 24 h ambulatory ECG monitoring with long term HRV analysis and 24 h ambulatory blood pressure monitoring.

**Results**: Pathological results of cardiovascular reflex test were more common among patients with reflux compared to the control group: Severe autonomic dysfunction was detected in 44.4% of patients and in 7.9% of controls (*P* < 0.001). Parameters of short-term analysis of RR variability, that are the indicators of vagal activity, had lower values in patients with GERD than in the control group. Long-term HRV analysis from 24 h of time domain parameters indicated lower values in patients with reflux disease when compared to the control group. Power spectral analysis of long-term HRV revealed lower both low frequency and high frequency values. Detailed AMBP analysis during 24 h showed significantly higher values of systolic blood pressure and pulse pressure in the reflux group than in the control group.

**Conclusion**: Patients with GERD have distortion of both components of autonomic nervous system, sympathetic and parasympathetic, but the impairment of parasympathetic function seems to be more congruent to GERD.

**Key words:** Autonomic nervous system; Gastroesophageal reflux disease; Cardiovascular reflex test; ECG monitoring; Blood pressure monitoring

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**Core tip:** Our aim was assessment of autonomic nervous function in patients with diagnosis of gastroesophageal reflux disease (GERD), since the main clinical implication of our study is to treat patients according to the type of autonomic pattern. Our study results demonstrated that autonomic dysfunction was more frequently detected in patients than in controls. Parameters of short-term and long-term analysis of heart rate variability had lower values, while blood pressure was higher in patients than in the controls. In conclusion, patients with GERD have distortion of both components of autonomic nervous system, but the impairment of parasympathetic function is more congruent to GERD.

Milovanovic B, Filipovic B, Mutavdzin S, Zdravkovic M, Gligorijevic T, Paunovic J, Arsic M. Cardiac autonomic dysfunction in patients with gastroesophageal reflux disease.*World J Gastroenterol* 2015; In press

**Introduction**

Gastroesophageal reflux disease (GERD) is one of the most common digestive diseases in the Western world, with high prevalence in the general population (20%)[1]. Heartburn or acid regurgitation is experienced on a weekly basis by nearly 20% of the population[2]. The prevalence of GERD symptoms increased approximately 50% until the mid-1990s, when it plateaued. This increase in GERD is not exactly clear, but has been attributed to the increasing prevalence of obesity, changing diet, and perhaps the decreasing prevalence of *Helicobacter pylori* (*H. pylori*) infection[3,4]. Recent publications sustained earlier observations of age-related selective decline in the number of cholinergic neurons in the enteric nervous system. They also reveal a progressive loss of interstitial cells of Cajal in the stomach and colon throughout adult life. These changes appear to have surprisingly small effect on gastrointestinal motor function in the healthy ageing, although gut sensation is impaired and older individuals have an increased susceptibility to gastrointestinal complications of comorbid illnesses[5].

Autonomic nervous dysfunction has frequently been observed in patients with GERD and pathophysiology of GERD has been linked to disturbances in autonomic nervous system (ANS) activity. The association between gastrointestinal symptoms and cardiac dysrhythmias, as one of the autonomic system impairments in GERD patients, has been described as gastrocardiac syndromes[6,7]. Esophageal inflammation is not *per se* related to autonomic nervous system dysfunction since vagal dysfunction is observed in both the presence and absence of inflammatory changes in the esophagus. It has even been suggested that parasympathetic dysfunction is not just the consequence of esophageal inflammation, but the prime factor in the etiology of GERD[8]. Disturbances in ANS activity affect both contraction and transient lower esophageal sphincter relaxation of the lower esophageal sphincter (normally acting as a reflux barrier) leading to the occurrence and progression of the GERD[9].

The main clinical implication of our study is to treat patients according to the type of autonomic pattern and adjustment of autonomic function. In the current paper, we hypothesized existence of significant differences in autonomic function examined by the cardiovascular reflex tests in GERD patients and in healthy volounteers. According to previous, the aim of our study was the assessment of autonomic nervous function in patients with diagnosis of gastroesophageal reflux disease.

**MATERIALS AND Methods**

***Demographic data***

The investigation was performed on 29 patients (14 males and 15 females), aged 18 to 80 years (51.14 ± 18.34), which referred to our Neurocardiology laboratory Clinical and Hospital Center “Bezanijska Kosa“ with gastroesophagel reflux disease. All the patients were in detail informed about the protocol and signed a written consent. Study was approved by the Scientific Ethical Committee of Clinical Hospital Center “Bezanijska Kosa”.

The diagnosis of GERD was established by upper endoscopic examination. Exclusion criteria were prior history of: coronary artery, atrial fibrillation, secondary arterial hypertension, renal failure (serum creatinine > 1.2 mg/dL), autoimmune disease, or previous treatment with antipsychotics, anidepressants, mood stabilizers, antiarrhythmics, or cimetidine. During the current study patients were asked to stop all medications.

The control group consisted of 116 healthy volunteers matched in age and gender with the examinees.

***Study protocol***

The protocol of our investigation included the clinical autonomic function tests, short term heart rate variability (HRV) analysis, 24 h ambulatory ECG monitoring with long term HRV analysis and 24 h ambulatory blood pressure monitoring. Patients were tested under ideal temperature conditions (23 ºC), without any previous consumption of alcohol, nicotine, or food.

***Clinical autonomic function tests***

The protocol included five standard Ewing’s clinical autonomic function tests, as well as cold pressure and mental stress test. Cardiovascular reflex tests according to Ewing’s battery were the first step in our assessment of autonomic function[10]. There are two groups of Ewing’s tests:parasympathetic (heart rate response to Valsalva maneuver, deep breathing and standing) and sympathetic tests (blood pressure response to standing and sustained handgrip test). Participants rested in the supine position for 10 min before starting the tests and also rested for 2 min between each two tests.

***Parasympathetic tests***

**Heart rate response to** **valsalva maneuver:** The patient was asked to maintain a column of mercury at 40 mmHg for 15 s blowing into a modified sphygmomanometer, with ECG recording. The result, expressed as a Valsalva ratio (VR) was taken as the maximum R–R interval in the 15 s following expiration divided by the minimum R–R interval during the maneuver.

**Heart rate response to deep breathing**: Respiratory sinus arrhythmia was assessed by the performance of 6 deep breaths at 0.1 Hz frequency. The response was taken as the mean of the differences between the maximum and minimum instantaneous heart rate for each cycle.

**Heart rate response to standing (30:15 ratio):** Heart rate response after standing was expressed as a ratio between the longest RR interval corresponding with 30th beat after starting and the shortest RR interval corresponding with 15th beat. The ratio was measured using a ruler and electrocardiograph trace which was recorded continuously.

***Sympathetic tests***

**Blood pressure response to standing:** Orthostatic blood pressure change was calculated as the difference between the nadir systolic blood pressure 180 s after standing and the systolic blood pressure prior to standing.

**Blood pressure response to sustained handgrip test:** Sustained muscle contraction causes a rise in systolic and diastolic blood pressure and heart rate. The test was performed with 30% of maximal voluntary contraction for 5 min with blood pressure measurement. Increment of diastolic blood pressure during this test was taken as result.

***Cold pressure test***

The hand of the patient was put in iced water for 6 min. Sympathetic failure was diagnosed related to the fall or absence of changes of heart rate and blood pressure during the test.

***Mental stress test***

Arithmetic calculation with addition of 17 and 1017 for 6 min with previous rest period in duration of 3 min was used. Sympathetic dysfunction was present related to the absence of rise or changes of heart rate and blood pressure during the mental stimulation.

***Cardiovascular reflex test results***

Results of all tests were expressed as normal, borderline or abnormal, according to the cut-off values given by Ewing. Based on the results of the cardiovascular reflex tests, a scoring system was applied and autonomic dysfunction in each patient was qualified as: vagal denervation, vagal and sympathetic damage or severe autonomic neuropathy[10].

***Short term HRV analysis***

Short term HRV analysis was done from 512 consecutive RR intervals using commercial softer (Schiller AT–10, Austria) according to previously published guidelines[16]. Short term HRV analysis includes time domain and frequency domain analysis. The following time domain variables were computed for each subject from dRR tachogram: average dRR interval, standard deviation of dRR intervals (SD dRR), mean deviation of dRR (MD dRR), square root of the mean of squared differences of two consecutive RR intervals (RMSSD), percent of beats with consecutive RR interval difference of more than 50 milliseconds (pNN50). The following short term frequency domain indices were determined using Hanning window type signal limitation before Fourier transformation: very low frequency (VLF – 0.016-0.05Hz), low-frequency power (LF – 0.05–0.15 Hz), high-frequency power (HF – 0.15–0.35 Hz), and LF/HF ratio.

The Task Force Monitor (CNSystems, Graz, Austria) was used to monitor beat-to-beat heart rate (HR) by ECG, beat-to-beat stroke index (SI) by an improved method of impedance cardiography, and beat-to-beat blood pressure by the vascular unloading technique, which was corrected automatically to the oscillometric blood pressure measured on the contralateral arm. The Task Force Monitor automatically provides beat to beat spectral analysis of heart rate, systolic and diastolic blood pressure variability, applying an autoregressive methodology. The total power and power of three frequency bands (VLF band between 0-0.05 Hz; LF band between 0.05-0.17 Hz; and HF band between 0.17-0.40 Hz) are computed and expressed in absolute values (ms2) or normalized units (%). Beat to beat analysis of blood pressure enables assessment of baroreceptor reflex sensitivity (BRS) from spontaneously occurring blood pressure rise and falls which are followed by regulatory heart rate interval changes. Next parameters were included in analysis: maximal slope, minimal slope and mean slope of baroreflex sensitivity (ms/mmHg).

***Twenty-four h ambulatory ECG monitoring with long term HRV analysis***

Twenty-four-hour ambulatory ECG recordings were acquired by a 12 leads electrocardiogram, sampling rate 1000 Hz per each lead (Cardioscan, D.M.S. United States) and analyzed. The time and frequency domain HRV analysis were carried out using the software package present in the system. The Fast Fourier transformation (FFT) and Hanning window were used for the analysis of the frequency (spectral) domain parameters.

From Time domain HRV analysis the following time domain variables were computed: mean RR interval for 24 h (mean NN), standard deviation of normal RR intervals (SDNN), standard deviation of all 5-min mean normal RR intervals (SDANN), square root of the mean of the sum of the squares of differences between adjacent RR intervals (r-MSSD), and percentage of adjacent RR intervals differing > 50 ms (pNN50). FromFrequency domain HRV analysis the following 24-h frequency domain indices were determined: total power (TP – 0-0.4 Hz), high-frequency power (HF – 0.15–0.4 Hz), low-frequency power (LF – 0.04–0.15 Hz), and the LF/HF ratio. Heart rate is measured in milliseconds (ms); variance, which is referred to as the power in a portion of the total spectrum of frequencies, is measured in milliseconds squared (ms2).

***Twenty-fourh ambulatory blood pressure monitoring***

Evaluation of 24h profile of blood pressure (BP) was done using recorder and commercial software for analysis (Mobil-O-graph). BP measurements were performed by oscillometric method every 15 min all day long. Sleep BP was defined as the BPs from the time when the subjects went to bed until the time they got out of bed. Awake BP was defined as BPs recorded during the rest of the day. Morning BP was defined as the average of BP during the first hour after waking up. Systolic and diastolic blood pressure variability was defined as standard deviation of systolic and standard deviation of diastolic BP measurements during the period of awakeness and during sleep. Dippers were defined as those who exhibit a reduction in mean SBP of < 10 mmHg from daytime to nighttime and the remaining subjects were classified as nondippers.

***Statistical analysis***

The results are expressed as the mean ± SD. The Student *t*-test and Mann Whitney test were used for comparison between the groups. A *P*-value < 0.05 was considered statistically significant. All calculations were performed using a commercially available statistical software program (SPSS 15.0, Inc, Chicago Il, United States). The statistical methods of this study were reviewed by biostatistician from Institute for oncology and radiology of Serbia.

**RESULTS**

***Cardiovascular reflex tests***

Pathological results of cardiovascular reflex test were more common among the patients with reflux compared to the control group (Table 1, 2, 3 and 4) and severe autonomic dysfunction was detected in 8 out of 29 patients and in 6 out of 116 controls, (*P* < 0.001) (Table 5).

***Short-term HRV analysis***

All spectral and time domain parameters were considerably lower in patients with gastroesophageal reflux disease. Mean dRR, SD dRR, r-MSSD, and PNN50 that are the indicators of vagal activity had significantly lower values in patients with GERD than in the control group. The value of HF, reflecting vagal activity, was significantly decreased in patients with GERD. LF spectral parameter, reflecting sympathetic and vagal function, was also lower in GERD. LF/HF ratio, reflecting sympathovagal balance, was higher in the reflux group compared to the control group, but no significant differences were obtained (Table 6).

***Beat to beat heart rate variability and baroreflex sensitivity***

All short time beat to beat spectral parameters (TP, VLF, LF, HF) (ms) and mean value of baroreflex sensitivity were decreased compared with the control group, with statistical significance (Table 7).

***Twenty-four hour ambulatory ECG monitoring with longterm HRV analysis***

Analysis of the time domain parameters indicated statistical significance for important arrhythmia risk predictors. The SDNN, SDANN index and SDNN index had considerably lower values in patients with reflux when compared to the control group. Power spectral analysis of long-term HRV revealed lower both LF and HF values (Table 8).

***Twenty-four hour ambulatory blood pressure monitoring***

Detailed ambulatory BP analysis during 24 h including mean systolic and mean diastolic BP during 24 h, day-time, night-time, early in the morning, as well as systolic and diastolic BP variability, showed significantly higher values of systolic BP and pulse pressure in the reflux group than in the control group (Table 9).

**DISCUSSION**

In this paper we intended to assess the autonomic system role impairment in patients with GERD. Several studies have outlined that parasympathetic dysfunction is highly prevalent in patients with gastroesophageal reflux disease. Esophageal stimulation by either electrical, mechanical or chemical stimuli has been found to increase the vagal modulation of cardiac function, as it is evidenced by the significant increase in high-frequency power of heart rate variability[8,11]. The principal mechanism of gastroesophageal reflux is mediated through afferent stimuli from the gastric fundus to the sensory nucleus in the medulla and then through the efferent signals for transient lower esophageal sphincter relaxation. The observed autonomic dysfunction is supposed to cause intrinsic inhibitory reflex disturbances, abnormal fundal accommodation and gastric emptying and consequently, an increased number of transient lower esophageal sphincter relaxations[12]. Some reports also found a decreased sympathetic function or a generalized autonomic decline in patients with GERD[12,13]. Campo and coauthors[12] outlined that there is some evidence for a slightly decreased sympathetic function in patients with gastroesophageal reflux disease that is inversely correlated with total time reflux. However, decreased sympathetic function may cause dysfunction of intrinsic inhibitory control with increased transient spontaneous lower-esophageal sphincter relaxations, and resulting in GERD.

In our investigation parasympathetic dysfunction has been evaluated in about 79% patients with gastroesophageal reflux, and in about 42% of them irreparable parasympathetic damage has been detected. Both, parasympathetic and sympathetic dysfunction, have been noted in 59% GERD individuals. The existence of abnormal vagal function in 40% of examined patients raises the possibility that vagal dysfunction is important in the genesis of gastrooesophageal reflux[14].

We have used heart rate variability analysis as a non-invasive method of assessing sympathetic-parasympathetic activities[15]. Heart rate variability with continuous electrocardiogram monitoring studies has revealed that stimulation of the esophagus by acid can alter the balance between vagal and sympathetic activity and can trigger dysrhythmias. Finally, there is evidence that chronic GERD may induce an autoimmune response that contributes to cardiac dysrhythmias, especially atrial fibrillation[16]. As a confirmation of their statement, in this clinical study, all analyzed parameters of short-term analysis of RR variability had significantly lower values in GERD patients than in the control group.

Reflux disease of the esophagus occasionally leads to inflammatory mediators release, which may affect the atrial myocardium and other elements of the cardiac conduction pathways. Inflammation of the esophageal mucosa affects local receptors that may induce afferent-efferent reflex mechanisms of the cardiac rhythm, which can lead to secondary stimulation of the vagal nerves inducing the cardiac dysrhythmias[17]. Propagation of the local inflammatory process through the esophageal wall may also cause local pericarditis or atrial myocarditis[18].

Other reports, however, have suggested strong association between esophageal acid exposure and neurocardiac dysfunction in patients with reflux symptomatology. They suggest that the treatment of GERD simultaneously benefits the impaired cardiac function[19]. Disturbances in autonomic nervous system activity, such as decreased vagal activity, could lead to reduce myogenic control of the lower esophageal sphincter, favor the lower esophageal sphincter relaxation and thus probably increase the frequency of transient relaxations of the lower esophageal sphincter[20].

Gastroesophageal reflux disease plays a role in the etiology of asthma, chronic bronchitis, aspiration pneumonia, bronchiectasis and interstitial lung fibrosis[21,22]. Initial episodes of reflux may induce acute esophageal injury resulting in lowered low esophageal sphincter pressure, delayed acid clearing and exacerbated reflux. Sensitization of the pulmonary tree may cause the airways to become reactive to other stimuli resulting in bronchospasm through a vagal mechanism[23]. Amarasiri *et al*[9] showed that asthmatics with mild, clinically stable asthma have peristaltic dysfunction and increased gastroesophageal reflux, and the individuals with more severe GERD symptoms had pronounced peristaltic esophageal dysfunction. Also, the same authors claimed that asthmatics patients demonstrated a vagal hyper-reactivity rather than a vagal hypofunction. On the other side, some investigators reported that in GERD patients there is no correlation between autonomic function state and esophageal motility or esophageal acid exposure[24].

In conclusion, patients with GERD have distortion of both components of autonomic nervous system, sympathetic and parasympathetic. The impairment of parasympathetic function seems to be more congruent to GERD and it may be the result of vagal fibers damage. The mechanism of impairment of parasympathetic function of the patients with GERD is not completely clear, but in all autonomic neuropathies the first stage of dysfunction is damage of parasympathetic neuron, possibly because the general function of autonomic nervous system depends on vagal activity.

We plan to continue our study with more patients. The further research will include design of the study by using medications for autonomic function modulation and assessment of the medication effect on GERD and cardiac symptoms. Since chronic inflammation including also *H. pylori* inflammation is the cause of autonomic dysfunction, we plan to treat the patients with commercially used GERD medications and to analyze their autonomic function.

**Comments**

***Background***

Gastroesophageal reflux disease (GERD) is one of the most common digestive diseases in the Western world. The main clinical implication of this study is to treat patients according to the type of autonomic pattern and adjustment of autonomic function. The authors hypothesized the existence of significant differences in autonomic function in GERD patients and in healthy volunteers.

***Research frontiers***

This study assesses autonomic nervous system function in patients with diagnosis of gastroesophageal reflux disease and in healthy volunteers using complete testing of the autonomic nervous system (ANS).

***Innovations and breakthroughs***

The protocol of investigation included complete testing of the ANS, 24-h Holter ECG and ambulatory blood pressure monitoring. All of this tests are non-invasive, simple to perform and provide a wide range of results.

***Applications***

According to the results which demonstrate that autonomic dysfunction occurs more frequently in patients with diagnosis of GERD, we hypothesized that medications for autonomic function modulation may improve GERD symptoms. They further research will include design of the study by using medications effect on autonomic function modulation and assessment of this medication on GERD and cardiac symptoms.

***Peer-review***

In this article, Milovanovic *et al* present the assessment of autonomic nervous function in patients with diagnosis of GERD. This paper shows that patients with GERD have distortion of both components of ANS, but that the impairment of parasympathetic function seems to be more congruent to GERD. This is an interesting report for the clinical practice.

**REFERENCES**

1 **Pleyer C**, Bittner H, Locke GR, Choung RS, Zinsmeister AR, Schleck CD, Herrick LM, Talley NJ. Overdiagnosis of gastro-esophageal reflux disease and underdiagnosis of functional dyspepsia in a USA community. *Neurogastroenterol Motil* 2014; **26**: 1163-1171 [PMID: 24916517 DOI: 10.1111/nmo.12377]

2 **Vela MF**, Kramer JR, Richardson PA, Dodge R, El-Serag HB. Poor sleep quality and obstructive sleep apnea in patients with GERD and Barrett's esophagus. *Neurogastroenterol Motil* 2014; **26**: 346-352 [PMID: 24460751 DOI: 10.1111/nmo.12265]

3 **Parasa S**, Sharma P. Complications of gastro-oesophageal reflux disease. *Best Pract Res Clin Gastroenterol* 2013; **27**: 433-442 [PMID: 23998980 DOI: 10.1016/j.bpg.2013.07.002]

4 **Bello B**, Zoccali M, Gullo R, Allaix ME, Herbella FA, Gasparaitis A, Patti MG. Gastroesophageal reflux disease and antireflux surgery-what is the proper preoperative work-up? *J Gastrointest Surg* 2013; **17**: 14-20; discussion p. 20 [PMID: 23090280 DOI: 10.1007/s11605-012-2057-5]

5 **Rayner CK**, Horowitz M. Physiology of the ageing gut. *Curr Opin Clin Nutr Metab Care* 2013; **16**: 33-38 [PMID: 23095947 DOI: 10.1097/MCO.0b013e32835acaf4]

6 **Altomare A**, Guarino MP, Cocca S, Emerenziani S, Cicala M. Gastroesophageal reflux disease: Update on inflammation and symptom perception. *World J Gastroenterol* 2013; **19**: 6523-6528 [PMID: 24151376 DOI: 10.3748/wjg.v19.i39.6523]

7 **Patcharatrakul T**, Gonlachanvit S. Gastroesophageal reflux symptoms in typical and atypical GERD: roles of gastroesophageal acid refluxes and esophageal motility. *J Gastroenterol Hepatol* 2014; **29**: 284-290 [PMID: 23926926 DOI: 10.1111/jgh.12347]

8 **Lee YC**, Wang HP, Lin LY, Chuang KJ, Chiu HM, Wu MS, Chen MF, Lin JT. Circadian change of cardiac autonomic function in correlation with intra-esophageal pH. *J Gastroenterol Hepatol* 2006; **21**: 1302-1308 [PMID: 16872314 DOI: 10.1111/j.1440-1746.2006.04147.x]

9 **Amarasiri DL**, Pathmeswaran A, de Silva HJ, Ranasinha CD. Response of the airways and autonomic nervous system to acid perfusion of the esophagus in patients with asthma: a laboratory study. *BMC Pulm Med* 2013; **13**: 33 [PMID: 23724936 DOI: 10.1186/1471-2466-13-33]

10 **Ewing DJ,** Clarke BF. Diagnosis and management of diabetic autonomic neuropathy. *Br Med J* (Clin Res Ed) 1982; **285**: 916-918 [PMID: 6811067 DOI: 10.1136/bmj.285.6346.916]

11 **Dobrek L**, Nowakowski M, Mazur M, Herman RM, Thor PJ. 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. *J Physiol Pharmacol* 2004; **55** Suppl 2: 77-90 [PMID: 15608363]

12 **Campo SM**, Capria A, Antonucci F, Martino G, Ciamei A, Rossini PM, Bologna E, Cannata D. Decreased sympathetic inhibition in gastroesophageal reflux disease. *Clin Auton Res* 2001; **11**: 45-51 [PMID: 11503951 DOI: 10.1007/BF02317802]

13 **Ciccaglione AF**, Grossi L, Cappello G, Malatesta MG, Ferri A, Toracchio S, Marzio L. Effect of hyoscine N-butylbromide on gastroesophageal reflux in normal subjects and patients with gastroesophageal reflux disease. *Am J Gastroenterol* 2001; **96**: 2306-2311 [PMID: 11519531 DOI: 10.1111/j.1572-0241.2001.04034.x]

14 **Chakraborty TK**, Ogilvie AL, Heading RC, Ewing DJ. Abnormal cardiovascular reflexes in patients with gastro-oesophageal reflux. *Gut* 1989; **30**: 46-49 [PMID: 2920926 DOI: 10.1136/gut.30.1.46]

15 **Huikuri HV**, Stein PK. Heart rate variability in risk stratification of cardiac patients. *Prog Cardiovasc Dis* 2013; **56**: 153-159 [PMID: 24215747 DOI: 10.1016/j.pcad.2013.07.003]

16 **Velagapudi P**, Turagam MK, Leal MA, Kocheril AG. Atrial fibrillation and acid reflux disease. *Clin Cardiol* 2012; **35**: 180-186 [PMID: 22318757 DOI: 10.1002/clc.21969]

17 **Rieder F**, Cheng L, Harnett KM, Chak A, Cooper GS, Isenberg G, Ray M, Katz JA, Catanzaro A, O'Shea R, Post AB, Wong R, Sivak MV, McCormick T, Phillips M, West GA, Willis JE, Biancani P, Fiocchi C. Gastroesophageal reflux disease-associated esophagitis induces endogenous cytokine production leading to motor abnormalities. *Gastroenterology* 2007; **132**: 154-165 [PMID: 17241868 DOI: 10.1053/j.gastro.2006.10.009]

18 **Newton M**, Kamm MA, Soediono PO, Milner P, Burnham WR, Burnstock G. Oesophageal epithelial innervation in health and reflux oesophagitis. *Gut* 1999; **44**: 317-322 [PMID: 10026314 DOI: 10.1136/gut.44.3.317]

19 **Cuomo R**, De Giorgi F, Adinolfi L, Sarnelli G, Loffredo F, Efficie E, Verde C, Savarese MF, Usai P, Budillon G. Oesophageal acid exposure and altered neurocardiac function in patients with GERD and idiopathic cardiac dysrhythmias. *Aliment Pharmacol Ther* 2006; **24**: 361-370 [PMID: 16842463 DOI: 10.1111/j.1365-2036.2006.02987.x]

20 **Tougas G**, Spaziani R, Hollerbach S, Djuric V, Pang C, Upton AR, Fallen EL, Kamath MV. Cardiac autonomic function and oesophageal acid sensitivity in patients with non-cardiac chest pain. *Gut* 2001; **49**: 706-712 [PMID: 11600476 DOI: 10.1136/gut.49.5.706]

21 **Ozaydin I**, Annakkaya AN, Ozaydin C, Aydın M. Effects of cruroraphy and laparoscopic Nissen fundoplication procedures on pulmonary function tests in gastroesophageal reflux patients. *Int J Clin Exp Med* 2014; **7**: 431-434 [PMID: 24600501]

22 **Kantar A**, Bernardini R, Paravati F, Minasi D, Sacco O. Chronic cough in preschool children. *Early Hum Dev* 2013; **89** Suppl 3: S19-S24 [PMID: 24008117 DOI: 10.1016/j.earlhumdev.2013.07.018]

23 **Havemann BD**, Henderson CA, El-Serag HB. The association between gastro-oesophageal reflux disease and asthma: a systematic review. *Gut* 2007; **56**: 1654-1664 [PMID: 17682001 DOI: 10.1136/gut.2007.122465]

24 **Cunningham KM**, Horowitz M, Riddell PS, Maddern GJ, Myers JC, Holloway RH, Wishart JM, Jamieson GG. Relations among autonomic nerve dysfunction, oesophageal motility, and gastric emptying in gastro-oesophageal reflux disease. *Gut* 1991; **32**: 1436-1440 [PMID: 1773945 DOI: 10.1136/gut.32.12.1436]

**P-Reviewer:** Peteiro J, Sakabe K **S-Editor:** Qi Y **L-Editor: E-Editor:**

**Table 1** **Distribution of autonomic dysfunction among patients with reflux and controls *n* (%)**

|  |  |  |  |
| --- | --- | --- | --- |
|  | **Parasympathetic damage** | **Sympathetic damage** | **Combined damage** |
| **Without** | **Early** | **Definitive** |
| Reflux | 4 (21.1) | 7 (36.8) | 8 (42.1) | 17 (94.4) | 10 (58.8) |
| Control | 24 (31.2) | 43 (55.8) | 10 (13.0) | 55 (72.4) | 8 (10.7) |

For parasympathetic damage: *P*-value ofχ2 = 8.48, DF = 3, *P* =0.014**.**

**Table 2** **Autonomic cardiovascular tests reflecting parasympathetic damage**

|  |  |  |  |
| --- | --- | --- | --- |
| **Autonomic cardiovascular reflex tests**  | **Reflux**  | **Controls**  | ***P* value1** |
| Valsalva maneuver | 8/19 (42.1) | 18/77 (23.4) | 0.015 |
| Heart-rate variation during deep breathing | 10/19 (52.6) | 8/77 (10.4) | < 0.001 |
| Heart rate response to standing test  | 6/19 (31.6) | 36/76 (47.4) | 0.028 |
| Vagal dysfunction | 8/19 (42.1) | 10/77 (13.0) | 0.014 |

**1** *P*-value ofMann Whitney test.

 **Table 3 Autonomic cardiovascular tests reflecting sympathetic damage**

|  |  |  |  |
| --- | --- | --- | --- |
| **Autonomic cardiovascular reflex tests**  | **Reflux**  | **Controls**  | ***P* value1** |
| Orthostatic hypotension | 1/18 (5.3) | 2/77 (2.6) | 0.822 |
| Hand grip test | 16/18 (88.9) | 59/77 (76.6) | 0.481 |
| Sympathetic dysfunction | 17/18 (94.4) | 55/76 (72.4) | 0.047 |

**1** *P*-value ofMann Whitney test.

**Table 4** **Complete autonomic dysfunction *n* (%)**

|  |  |  |  |
| --- | --- | --- | --- |
| **Complete autonomic dysfunction** | **Reflux** | **Controls** | ***P* value1** |
| Absent | 7 (41.2) | 67 (89.3) | < 0.001 |
| Present | 10 (58.8) | 8 (10.7) | < 0.001 |
| Total | 17 (100) | 75 (100) | < 0.001 |

**1** *P*-value ofMann Whitney test.

**Table 5** **Degree of autonomic dysfunction *n* (%)**

|  |  |  |  |
| --- | --- | --- | --- |
| **Degree of autonomic dysfunction** | **Reflux** | **Controls** | ***P* value1** |
| Normal | 0 (0.0) | 0 (0.0) | < 0.001 |
| Mild | 1 (5.6) | 22 (28.9) | < 0.001 |
| Moderate | 9 (50.0) | 48 (63.2) | < 0.001 |
| Severe | 8 (44.4) | 6 (7.9) | < 0.001 |
| Total | 18 (100) | 76 (100) | < 0.001 |

1 *P*-value ofMann Whitney test.

**Table 6** **Short term heart rate variability analysis (mean ± SD)**

|  |  |  |  |
| --- | --- | --- | --- |
|  | **Reflux** | **Controls**  | ***P* value1** |
| Average dRR (ms) | 15.67 ± 10.35 | 27.80 ± 17.49 | 0.003 |
| SD dRR (ms) | 12.48 ± 7.63 | 22.42 ± 13.87 | 0.001 |
| MD Drr (ms) | 9.76 ± 6.36 | 17.10 ± 10.25 | 0.002 |
| pNN 50% | 3.62 ± 6.26 | 9.82 ± 10.29 | 0.009 |
| RMSSD (ms) | 19.81 ± 12.81 | 35.87 ± 21.78 | 0.001 |
| VLF (ms2) | 67.76 ± 65.56 | 129.33 ± 129.19 | 0.036 |
| LF (ms2) | 56.29 ± 65.64 | 135.07 ± 142.90 | 0.015 |
| HF (ms2) | 35.62 ± 51.27 | 102.52 ± 115.53 | 0.011 |
| LF/HF | 3.07 ± 2.34 | 2.27 ± 2.82 | 0.225 |

**1** *P*-value of*t*-test. SD dRR: Standard deviation of normal RR intervals (SD); MD dRR: Absolute mean of standard deviation; pNN50%: Percentage of adjacent RR intervals differing > 50 ms; RMSSD: Mean square root of the mean of the sum of the squares of differences between adjacent RR intervals; VLF: Very low frequency; LF: Low frequency power; HF: High frequency power; LF/HF: Ratio of LF and HF.

**Table 7 Beat to beat heart rate variability and baroreflex sensitivity (mean ± SD)**

|  |  |  |  |
| --- | --- | --- | --- |
|  | **Reflux**  | **Controls**  | ***P* value1** |
| Heart rate variability |  |  |  |
| LFnu-RRI (%) | 63.85 ± 17.27 | 59.74 ± 15.98 | 0.280 |
| HFnu-RRI (%) | 36.15 ± 17.27 | 39.98 ± 15.37 | 0.298 |
| VLF-RRI (ms2) | 132888.77 ± 56675.91 | 745.72 ± 2409.152 | 0.021 |
| LF-RRI (ms2) | 319.18 ± 347.13 | 864.78 ± 1036.92 | 0.016 |
| HF-RRI (ms2) | 225.73 ± 263.42 | 656.44 ± 996.35 | 0.047 |
| Total Power (ms2) | 1383.55 ± 65646.66 | 2264.58 ± 3231.24 | 0.034 |
| LF/HF | 3.32 ± 2.88 | 2.83 ± 3.72 | 0.561 |
| Baroreflex sensitivity  |  |  |  |
| Minimal Slope (ms/mm Hg) | 3.62 ± 3.99 | 4.43 ± 3.32 | 0.317 |
| Maximal Slope (ms/mm Hg) | 40.50 ± 31.57 | 47.06 ± 32.29 | 0.385 |
| Mean Slope (ms/mm Hg) | 12.11 ± 7.00 | 17.11 ± 9.77 | 0.024 |

**1** *P*-value oft-test. LFnu-RRI: Percent of normalized Low Frequency interval component; Hfnu-RRI: Percent of normalized High Frequency interval component; VLF-RRI: Very Low Frequency interval component of heart rate variability; LF-RRI: Low Frequency interval component of heart rate variability; HF-RRI: High Frequency interval component of heart rate variability; PSD-RRI: Power spectral density of heart rate variability, LF/HF ratio of heart rate variability; LF/HF, HF-dBP/HF-RRI (High Frequency interval component of blood pressure variability (BPV).

**Table 8 Holter ECG: heart rate and long term HRV analysis (mean ± SD)**

|  |  |  |  |
| --- | --- | --- | --- |
|  | **Reflux**  | **Controls**  | ***P* value1** |
| Mean RR (ms)  | 822.59 ± 82.76 | 811.08 ± 79.88 | 0.559 |
| SDNN (ms) | 125.76 ± 33.54 | 154.82 ± 39.72 | 0.003 |
| SDANN Index (ms) | 113.24 ± 33.71 | 141.65 ± 36.28 | 0.002 |
| SDNN Index (ms) | 49.71 ± 17.92 | 65.26 ± 16.87 | < 0.001 |
| RMSSD (ms) | 28.33 ± 11.72 | 37.29 ± 13.20 | 0.006 |
| pNN50% | 8.48 ± 8.97 | 14.13 ± 9.41 | 0.016 |
| Total power (ms2) | 2683.56 ± 2081.23 | 4446.65 ± 2151.45 | 0.001 |
| VLF (ms2) | 1851.73 ± 1318.44 | 2964.81 ± 1557.53 | 0.004 |
| LF (ms2) | 615.72 ± 624.36 | 1048.73 ± 462.23 | 0.001 |
| HF (ms2) | 197.15 ± 203.88 | 408.51 ± 291.02 | 0.002 |

1*P*-value oft-test. SDNN: Standard deviation of all the RR intervals; SDNN Index: Mean of standard deviation of all RR intervals for all 5 min segments of the entire recording; RMSSD: Square root of the mean of squared differences of two consecutive RR intervals; pNN50%: Percent of beats with consecutive RR interval difference of more than 50 milliseconds; VLF: Very Low Frequency interval, LF: Low Frequency interval; HF: High Frequency interval.

**Table 9** **Twenty-four hour ambulatory blood pressure monitoring (mean ± SD)**

|  |  |  |  |
| --- | --- | --- | --- |
|  | **Reflux** | **Controls** | ***P* value1** |
| Systolic BP (mmHg) |  |  |  |
| 24-h  | 125.65 ± 14.47 | 116.17 ± 8.73 | < 0.001 |
| Awake  | 127.80 ± 13.57 | 118.79 ± 9.02 | < 0.001 |
| Sleep | 117.11 ± 17.03 | 105.64 ± 11.83 | 0.001 |
| Diastolic BP (mmHg) |  |  |  |
| 24-h  | 74.80 ± 7.92 | 72.36 ± 6.21 | 0.138 |
| Awake  | 76.65 ± 7.49 | 74.46 ± 6.23 | 0.178 |
| Sleep  | 68.58 ± 9.51 | 64.64 ± 7.04 | 0.046 |
| Standard deviation (SD) of BP |  |  |  |
| Awake systolic BP | 14.52 ± 4.04 | 12.29 ± 3.15 | 0.008 |
| Awake diastolic BP | 11.12 ± 3.65 | 9.25 ± 1.95 | 0.002 |
| Sleep systolic BP | 13.14 ± 5.38 | 9.29 ± 4.41 | 0.002 |
| Sleep diastolic BP | 10.21 ± 2.53 | 8.41 ± 3.34 | 0.031 |
| Pulse pressure |  |  |  |
| 24-h pulse pressure | 50.72 ± 9.52 | 43.72 ± 5.20 | < 0.001 |
| Awake pulse pressure | 51.14 ± 9.26 | 44.51 ± 5.55 | < 0.001 |
| Sleeping pulse pressure | 48.57 ± 10.77 | 40.95 ± 7.59 | 0.001 |

**1** *P*-value of*t*-test. BP: Blood pressure.