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ORIGINAL ARTICLE

Observational Study

Cardiac autonomic dysfunction in patients with gastroesophageal reflux disease

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

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Abstract

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

METHODS: The investigation was performed on 29 patients (14 men), aged 18-80 years (51.14 ± 18.34), who were referred to our Neurocardiology Laboratory at the Clinical and Hospital Center "Bezanijska Kosa" with a diagnosis of GERD. One hundred sixteen healthy volunteers matched in age and sex with the examinees served as the control group. The study protocol included the evaluation of autonomic function and hemodynamic 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: Pathologic 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, which are the indicators of

vagal activity, had lower values in patients with GERD than in the control group. Long-term HRV analysis 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 low- and high-frequency values. Detailed 24 h ambulatory blood pressure analysis 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 sympathetic and parasympathetic components of the autonomic nervous system, but impaired parasympathetic function appears more congruent to GERD.

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

Core tip: Autonomic nervous function was assessed in patients with gastroesophageal reflux disease (GERD) for the purpose of treating patients according to their presenting autonomic pattern. The results demonstrate that autonomic dysfunction is more frequently detected in patients than in controls. Parameters of short-term and long-term analysis of heart rate variability had lower value 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.

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INTRODUCTION

Gastroesophageal reflux disease (GERD) is one of the most common digestive diseases in the Western world, with a 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 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 a surprisingly small effect on gastrointestinal motor function in normal ageing, though gut sensation is impaired and older individuals have an increased susceptibility to gastrointestinal complications from 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 activity. The association between gastrointestinal symptoms and cardiac dysrhythmias, as one of the autonomic system impairments in GERD patients, has been described as gastrocardiac syndrome[6,7]. Esophageal inflammation is not related to autonomic nervous system dysfunction *per se*, as vagal dysfunction is observed in 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 autonomic nervous system activity affect both contraction and transient relaxation of the lower esophageal sphincter (normally acting as a reflux barrier), leading to the occurrence and progression of GERD[9].

The primary aim of this study is to treat patients according to the type of autonomic pattern and adjustment of autonomic function. We hypothesize that there are significant differences between GERD patients and healthy volunteers in autonomic function as assessed by cardiovascular reflex tests.

MATERIALS AND METHODS

Demographic data

The investigation was performed on 29 (14 male and 15 female)patients aged 51.14 ± 18.34 years (range: 18-80 years) who were referred to our Neurocardiology Laboratory of the Clinical and Hospital Center "Bezanijska Kosa" with GERD. All the patients were informed about the protocol in detail and provided written consent. This 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 a 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, antidepressants, mood stabilizers, antiarrhythmics, or cimetidine. Patients were asked to stop all medications during the study.

The control group consisted of 116 healthy age- and sex-matched volunteers.

Study protocol

The protocol 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 ℃), without any preceding 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 *et al*[10] were the first step in the assessment of autonomic function. This includes two groups of tests: parasympathetic (heart rate response to Valsalva maneuver, deep breathing, and standing) and sympathetic tests [blood pressure (BP) 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 test.

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 was taken as the maximum RR interval in the 15 s following expiration divided by the minimum RR interval during the maneuver.

Heart rate response to deep breathing: Respiratory sinus arrhythmia was assessed by the performance of six deep breaths at 0.1 Hz frequency. The response was taken as the mean of the differences between the maximum and minimum instantaneous heart rates 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 the 30th beat after starting and the shortest RR interval corresponding with the 15th beat. The ratio was measured using a ruler and electrocardiograph trace, which was recorded continuously.

Sympathetic tests

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

BP response to sustained handgrip test: Sustained muscle contraction causes a rise in systolic and diastolic BP and heart rate. The test was performed with 30% of maximal voluntary contraction for 5 min with BP measurement. Increment of diastolic BP 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 BP during the test.

Mental stress test

Arithmetic calculation (addition of 17 up to1017) for 6 min with a previous 3-min rest period was used. Sympathetic dysfunction was present related to the absence of rise or changes of heart rate and BP during the mental stimulation.

Cardiovascular reflex test results

Results of all tests were expressed as normal, borderline, or abnormal according to the cutoff values given by Ewing *et al*[10]. 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 performed from 512 consecutive RR intervals using commercial software (Schiller AT-10, Austria) according to previously published guidelines[11]. Short-term HRV analysis includes time and frequency domain analyses. The following time domain variables were computed for each subject from dRR tachogram: average dRR interval, standard and mean deviations of dRR intervals (SD dRR and MDdRR), square root of the mean of squared differences of two consecutive RR intervals (RMSSD), and percent of beats with consecutive RR interval difference of > 50 ms (pNN50). The following short-term frequency domain indices were determined using Hanning window-type signal limitation before Fourier transformation: very low-frequency power (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 HR by ECG, beat-to-beat stroke index by an improved method of impedance cardiography, and beat-to-beat BP by the vascular unloading technique, which was corrected automatically to the oscillometric BP measured on the contralateral arm. The Task Force Monitor automatically provides beat-to-beat spectral analysis of heart rate and systolic and diastolic BP variability by applying an autoregressive methodology. The total power (TP) and the power of the 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) were computed and expressed in absolute values (ms^2) or normalized units (%). Beat-to-beat analysis of BP enables assessment of baroreceptor reflex sensitivity from spontaneously occurring in a rise and fall of BP,

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: $\chi^2 = 8.48$, $df = 3$, $P = 0.014$.

Table 2 Autonomic cardiovascular tests reflecting parasympathetic damage *n* (%)

Autonomic cardiovascular reflex tests	Reflux (*n* = 19)	Controls (*n* = 77)	*P* value[1]
Valsalva maneuver	8 (42.1)	18 (23.4)	0.015
Heartrate variation during deep breathing	10 (52.6)	8 (10.4)	< 0.001
Heart rate response to standing test	6 (31.6)	36 (47.4)[2]	0.028
Vagal dysfunction	8 (42.1)	10 (13.0)	0.014

[1]Mann-Whitney test; [2]Data from one patient missing.

Table 3 Autonomic cardiovascular tests reflecting sympathetic damage *n* (%)

Autonomic cardiovascular reflex tests	Reflux (*n* = 18)	Controls (*n* = 77)	*P* value[1]
Orthostatic hypotension	1 (5.3)	2 (2.6)	0.822
Hand grip test	16 (88.9)	59 (76.6)	0.481
Sympathetic dysfunction	17 (94.4)	55 (72.4)[2]	0.047

[1]Mann Whitney test; [2]Data from one patient missing.

which are followed by regulatory heart rate interval changes. The following parameters were included in analyses: maximal slope, minimal slope, and mean slope of baroreflex sensitivity (ms/mmHg).

Twenty-four-hour ambulatory ECG monitoring with long-term HRV analysis

Twenty-four-hour ambulatory ECG recordings were acquired by a 12-lead electrocardiogram with a sampling rate of 1000 Hz (Cardioscan; DMSoftware Inc., CA,United States) and analyzed. The time and frequency domain HRV analyses were carried out using the software package present in the system. The Fast Fourier transformation 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). From Frequency 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 was measured in ms; variance, which is referred to as the power in a portion of the total spectrum of frequencies, was measured in ms^2.

Twenty-four hour ambulatory BP monitoring

Evaluation of the 24 h BP profile was conducted using recorder and commercial software for analysis (Mobil-O-graph; I.E.M., Stolberg, Germany). BP measurements were performed every 15 min by oscillometry. 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 BP variability was defined as standard deviation of systolic and standard deviation of diastolic BP measurements during the awake period and during sleep. Dippers were defined as those who exhibit a reduction in mean systolic BP 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's *t*-test and Mann Whitney *U* 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; SPSS Inc., Chicago IL, United States).The statistical methods of this study were reviewed by a biostatistician from the Institute for Oncology and Radiology of Serbia.

RESULTS

Cardiovascular reflex tests

Pathologic results of cardiovascular reflex tests were more common among the patients with reflux compared to the control group (Tables 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 GERD. Mean and standard deviations of the dRR, square root of the

Table 4 Complete autonomic dysfunction *n* (%)

Complete autonomic dysfunction	Reflux	Controls	*P* value[1]
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]Mann-Whitney test.

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

Degree of autonomic dysfunction	Reflux	Controls	*P* value[1]
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

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

Parameter	Reflux	Controls	*P* value[1]
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
pNN50%	3.62 ± 6.26	9.82 ± 10.29	0.009
RMSSD (ms)	19.81 ± 12.81	35.87 ± 21.78	0.001
VLF (ms^2)	67.76 ± 65.56	129.33 ± 129.19	0.036
LF (ms^2)	56.29 ± 65.64	135.07 ± 142.90	0.015
HF (ms^2)	35.62 ± 51.27	102.52 ± 115.53	0.011
LF/HF	3.07 ± 2.34	2.27 ± 2.82	0.225

[1]*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 power; LF: Low-frequency power; HF: High-frequency power.

mean of squared differences of two consecutive RR intervals, and percent of beats with consecutive RR interval difference of > 50 ms, which are the indicators of vagal activity, had significantly lower values in patients with GERD than in the control group (all $P < 0.05$) (Table 6). The value of HF, reflecting vagal activity, was significantly decreased in patients with GERD ($P < 0.05$). 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 difference was obtained.

Beat-to-beat heart rate variability and baroreflex sensitivity

All short-term beat-to-beat spectral parameters (TP, VLF, LF, HF) and the mean value of baroreflex sensitivity were significantly decreased in the GERD patients compared with the control group (all $P < 0.05$) (Table 7).

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

Parameter	Reflux	Controls	*P* value[1]
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 (ms^2)	132888.77 ± 56675.91	745.72 ± 2409.152	0.021
LF-RRI (ms^2)	319.18 ± 347.13	864.78 ± 1036.92	0.016
HF-RRI (ms^2)	225.73 ± 263.42	656.44 ± 996.35	0.047
Total power (ms^2)	1383.55 ± 65646.66	2264.58 ± 3231.24	0.034
LF/HF	3.32 ± 2.88	2.83 ± 3.72	0.561
Baroreflex sensitivity (ms/mmHg)			
Minimal slope	3.62 ± 3.99	4.43 ± 3.32	0.317
Maximal slope	40.50 ± 31.57	47.06 ± 32.29	0.385
Mean slope	12.11 ± 7.00	17.11 ± 9.77	0.024

[1]*t*-test. HF: High-frequency power; LF: Low-frequency power; LFnu-RRI: Percent of normalized LF interval component; Hfnu-RRI: Percent of normalized HFinterval component; VLF-RRI: Very low-frequency interval component of heart rate variability; LF-RRI: LF interval component of heart rate variability; HF-RRI: HF interval component of heart rate variability.

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

Parameter	Reflux	Controls	*P* value[1]
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
SDANNindex (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 (ms^2)	2683.56 ± 2081.23	4446.65 ± 2151.45	0.001
VLF (ms^2)	1851.73 ± 1318.44	2964.81 ± 1557.53	0.004
LF (ms^2)	615.72 ± 624.36	1048.73 ± 462.23	0.001
HF (ms^2)	197.15 ± 203.88	408.51 ± 291.02	0.002

[1]*t*-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 ms; VLF: Very low-frequency interval; LF: Low-frequency interval; HF: High-frequency interval.

Twenty-four-hour ambulatory ECG monitoring with long-term HRV analysis

Analysis of the time domain parameters indicated statistical significance for important arrhythmia risk predictors. The standard deviation of normal RR intervals, standard deviation of all 5-min mean normal RR intervals and their indices had considerably lower values in patients with reflux when compared to the control group (Table 8). Power spectral analysis of long-term HRV revealed lower both LF and HF values.

Twenty-four-hour ambulatory BP monitoring

Detailed ambulatory BP analysis during 24 h included

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

Parameter	Reflux	Controls	*P* value[1]
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 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	50.72 ± 9.52	43.72 ± 5.20	< 0.001
Awake	51.14 ± 9.26	44.51 ± 5.55	< 0.001
Sleep	48.57 ± 10.77	40.95 ± 7.59	0.001

[1]*t*-test. BP: Blood pressure.

mean systolic and diastolic BPs during 24 h, daytime, nighttime, early in the morning, as well as systolic and diastolic BP variability. The results showed significantly higher values of systolic BP and pulse pressure in the reflux group than in the control group (Table 9).

DISCUSSION

The aim of this study was to assess the role of autonomic system impairment in patients with GERD. Several studies have outlined that parasympathetic dysfunction is highly prevalent in patients with GERD. Esophageal stimulation by either electrical, mechanical, or chemical stimuli increases the vagal modulation of cardiac function, as evidenced by the significant increase in HF of HRV[8,12]. 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[13]. Some reports also found a decreased sympathetic function or a generalized autonomic decline in patients with GERD[13,14]. Campo *et al*[13] outlined that there is some evidence for a slightly decreased sympathetic function in patients with GERD 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, resulting in GERD.

In this investigation, parasympathetic dysfunction was observed in about 79% of patients with gastro-esophageal reflux, in which about 42% had irreparable parasympathetic damage. Both parasympathetic and sympathetic dysfunctions have been noted in 59% of 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 gastroesophageal reflux[15].

HRV analysis was used as a noninvasive method of assessing sympathetic-parasympathetic activities[16]. HRV with continuous ECG monitoring shows that stimulation of the esophagus by acid can alter the balance between vagal and sympathetic activity and trigger dysrhythmias. Finally, there is evidence that chronic GERD may induce an autoimmune response that contributes to cardiac dysrhythmias, especially atrial fibrillation[17]. 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 release of inflammatory mediators, 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[18]. Propagation of the local inflammatory process through the esophageal wall may also cause local pericarditis or atrial myocarditis[19].

Other reports, however, have suggested a strong association between esophageal acid exposure and neurocardiac dysfunction in patients with reflux symptomatology. It was suggested that the treatment of GERD simultaneously benefits the impaired cardiac function[20]. Disturbances in autonomic nervous system activity, such as decreased vagal activity, could lead to reduce myogenic control of the lower esophageal sphincter, favor lower esophageal sphincter relaxation, and thus probably increase the frequency of transient relaxations of the lower esophageal sphincter[21].

GERD plays a role in the etiology of asthma, chronic bronchitis, aspiration pneumonia, bronchiectasis, and interstitial lung fibrosis[22,23]. Initial episodes of reflux may induce acute esophageal injury resulting in reduced lower 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[24]. 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 asthmatic patients demonstrated a vagal hyper-reactivity rather than a vagal hypofunction. On the other hand, some investigators reported that in GERD patients, there is no correlation between autonomic function and esophageal motility or

esophageal acid exposure[25].

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 fiber 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 neurons, possibly because the general function of the autonomic nervous system depends on vagal activity.

Further research will include additional patients and study designs that include the use of medications for autonomic function modulation and assessment of the medication effect on GERD and cardiac symptoms. As chronic inflammation, such as that resulting from *H. pylori* inflammation is a cause of autonomic dysfunction, future studies will analyze autonomic function in patients treated with commercially available GERD medications.

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 that autonomic function in GERD patients differs significantly from healthy volunteers.

Research frontiers

This study assesses autonomic nervous system function in patients diagnosed with GERD and in healthy volunteers using complete testing of the autonomic nervous system.

Innovations and breakthroughs

The protocol of investigation included complete testing of the autonomic nervous system, 24-h Holter ECG and ambulatory blood pressure monitoring. All of these tests are noninvasive, simple to perform, and provide a wide range of results.

Applications

According to the results showing that autonomic dysfunction occurs more frequently in patients with diagnosis of GERD, the authors hypothesized that medications for autonomic function modulation may improve GERD symptoms. Further research will include assessment of the effect of GERD medications on autonomic function 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 the autonomic nervous system, but that the impairment of parasympathetic function seems to be more congruent to GERD. This is an interesting report for the clinical practice.

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