Turk J Gastroenterol *2017; 28: 88-93*

Gastrointestinal Tract

Atrial fibrillation and sympathovagal balance in patients with gastroesophageal reflux disease

Mariana Floria[1,2], Oana Bărboi[1,3], Mihaela Grecu[4], Cristina Cijevschi-Prelipcean[1,3], Gheorghe Balan[1,3], Vasile Liviu Drug[1,3]

[1]Grigore T. Popa University of Medicine and Pharmacy, Iaşi, Romania
[2]III Medical Clinic of Sf. Spiridon University Hospital, Iaşi, Romania
[3]Hepatology and Gastroenterology Institute of Sf. Spiridon University Hospital, Iaşi, Romania
[4]CCTIFA Department of Cardiovascular Disease Institute, Iaşi, Romania

ABSTRACT

Background/Aims: Similar autonomic innervation of the esophagus and left atrium with sympathovagal imbalance seems to explain the association between non-valvular atrial fibrillation (AF) and gastroesophageal reflux disease (GERD). We aimed to assess this association via parameters of heart rate variability in time (SDNN) and frequency (low-frequency (LF)/high-frequency (HF) ratio) domains by 24-hour electrocardiographic (ECG) Holter monitoring.

Materials and Methods: One hundred thirty-five patients were prospectively included by a joint team consisting of a gastroenterologist and a cardiologist on the basis of the patients' complaints. A diagnosis of GERD was assessed by the gastroenterologist clinically. All patients also underwent upper gastrointestinal endoscopy.

Results: The patients were included in two groups: 61 patients with GERD (group I) and 74 patients without GERD (group II), with demographic data of 41% male, age 61.5±9 years, and body mass index (BMI) 28.8±4 kg/m^2 versus 46% male, age 58±9 years, and BMI 29±4 kg/m^2 (all p>0.05). In groups I and II the percentages of patients with AF were 33% and 39%, respectively (p=0.52). Patients with GERD had a relative risk of AF of 1.17 (95% confidence interval [CI] 0.78–1.75; p=0.34). Heart rate variability in terms of the time-domain parameter (SDNN) was statistically significantly lower in the GERD group (97.6±13.7 ms versus 139.9±44.6 ms; p=0.001). The mean value of the frequency-domain parameter (LF/HF ratio) was also lower in the GERD group (0.75±0.17 ms versus 0.76±0.24 ms), but without statistical significance (p=0.930).

Conclusion: Sympathovagal balance seems to be disrupted in patients with GERD, with dominance of the parasympathetic system and an increased risk of arrhythmias, although AF was not significantly more frequent in these patients.

Keywords: Atrial fibrillation, gastroesophageal reflux disease, autonomic imbalance, heart rate variability

Original Article

INTRODUCTION

Atrial fibrillation (AF) is the most common arrhythmia in medical practice. Its incidence has risen in countries with rapidly aging populations (1). Gastroesophageal reflux disease (GERD) is a frequent benign disorder of the upper gastrointestinal tract (2). Owing to the close positioning of the esophagus and the atria and their similar autonomic innervations, it has been proposed that the development of GERD could be associated with the occurrence of AF. Sympathovagal imbalance seems to be a principal mechanism of both AF and GERD (3,4). Hiatus hernia, esophagitis, and a dilated left atrium also seem to be implicated in this association, owing to a potential mechanical effect or inflammatory process. In spite of the fact that the association between GERD and AF is supported by clinical and experimental studies, this relationship is still considered controversial (3). Most studies about the association between AF and GERD are based on retrospective data from national registries or self-reporting questionnaires (3,4)

Address for Correspondence: Mariana Floria E-mail: floria_mariana@yahoo.com
Received: October 9, 2016 **Accepted:** January 15, 2017 **Available Online Date:** January 30, 2017
 • Available online at www.turkjgastroenterol.org • DOI: 10.5152/tjg.2017.16540

and did not evaluate autonomic imbalance in these patients. Heart rate variability (HRV) is a non-invasive tool that is very useful in the assessment of imbalance in autonomic tone (5). HRV decreases when sympathetic activity is predominant; conversely, HRV increases when parasympathetic activity is predominant (6). Therefore, it represents an important tool for assessment of the cardiovascular autonomic nervous system. Different methods are available for the analysis of HRV, of which the most frequently used are those in the time and frequency domains. There are fewer prospective data about autonomic (sympathovagal) imbalance and the risk of arrhythmias in patients with GERD.

MATERIALS AND METHODS

Study Population

We aimed to compare prospectively HRV parameters in the time and frequency domains in patients with and without GERD and the presence of a diagnosis of AF on the basis of 24-hour electrocardiographic (ECG) Holter monitoring. In addition, we analyzed: 1) the relative risk (RR) of AF in patients with GERD and 2) parameters of left atrial structural remodeling (left atrial size) determined by transthoracic echocardiography. Patients were successively included by a joint team consisting of a gastroenterologist and a cardiologist if they met the inclusion and exclusion criteria of the study.

Inclusion criteria: Patients older than 18 years, without any prior gastroenterological evaluation (naïve patients), with symptoms suggesting GERD defined as mild symptoms of heartburn and/or regurgitation at least twice per week or moderate/severe symptoms occurring on more than 1 day per week that were perceived as "troublesome" by patients (according to the Montreal definition) (2).

Exclusion criteria: Patients younger than 18 years; patients with any type of documented valvular AF or under anticoagulation treatment; patients with chronic gastrointestinal diseases such as inflammatory bowel disease and celiac disease; patients with any valvular disease of more than mild intensity, thyroid disorders, previous myocardial infarction, transient ischemic attack, or stroke; patients who refused to be included; patients with a pacemaker/defibrillator, inflammatory disorders or under immunosuppressive therapy, active neoplasm, dementia, or other neurological or psychiatric disabling pathology; and all patients on non-steroidal anti-inflammatory drugs (including acetylsalicylic acid at a dose of greater than 100 mg/day) at enrollment and during the preceding 30 days. Treatment with proton pump inhibitors was interrupted 8 weeks before inclusion in the study. Antiarrhythmic drugs in patients with AF were not stopped during the study (owing to ethical reasons).

The diagnoses of non-valvular AF and GERD were defined according to current guidelines (1,2). Therefore, non-valvular AF referred to patients without moderate or severe mitral stenosis or artificial heart valves (1). GERD was diagnosed by the gastroenterologist clinically. The diagnosis of GERD was determined on the basis of clinical symptoms (according to the Montreal Consensus) (2): mild symptoms of heartburn and/or regurgitation at least twice per week or moderate/severe symptoms occurring on more than 1 day per week that were perceived as "troublesome" by patients. All patients underwent a gastroenterological and, after that, a cardiological assessment. They underwent upper gastrointestinal endoscopy, 24-hour ECG monitoring, and echocardiography, even if they were asymptomatic.

After a detailed medical history, the following clinical parameters were noted: age, sex, the presence of obesity (defined as a body mass index [BMI] of higher than 30 kg/m^2), dyslipidemia, hypertension, diabetes mellitus, heart failure, ischemic heart disease, and peripheral arterial disease.

Upper gastrointestinal endoscopy was performed by only one experienced gastroenterologist (Olympus Exera CV-160 endoscope) 48–72 hours before or after ECG Holter monitoring. The presence of hiatus hernia (as a condition favoring GERD), esophagitis, and Barrett's esophagus was noted.

Echocardiographic measurements were performed using two-dimensional transthoracic echocardiography with a Sonoscape SSI 8000 ultrasound machine (Providian Medical Equipment LLC, OH, USA). Diastolic left ventricular function (by the E/A ratio and E/Em ratio) and left atrial size were assessed as markers of left atrial structural remodeling. All measurements were made by an experienced operator only.

Heart rate variability parameters in the time and frequency domains were recorded by 24-hour ECG Holter monitoring using a two-channel tracker (EC-2H 2-Channel, Cardiospy, Labtech Holter ECG System, Hungary). Individuals went about their normal daily activities. In time-domain analysis the standard deviation of normal-to-normal (N-N) intervals (SDNN; ms) was determined. In the frequency domain, the frequency spectrum was assessed using a fast Fourier transform to determine the low-frequency (LF)/high-frequency (HF) ratio as an indicator of sympathovagal balance of the autonomic nervous system. All intervals of less than 200 ms and greater than 2000 ms were rejected as being artifacts. All HRV data were collected and interpreted by an experienced electrophysiologist.

In this study experiments were performed in compliance with the ethical principles of the University Ethics Committee (approval number 2005/2014). Informed consent was obtained from each patient before inclusion in the study. This study conforms to the Declaration of Helsinki.

Statistical Analysis

Categorical data are presented as frequencies and percentages; continuous variables are expressed as the mean±standard deviation. Categorical, ordinal, and numerical variables were compared between groups using the χ^2, Cochran, and Wilcoxon rank sum

tests, Kruskal–Wallis, and Anova test, respectively. All statistical tests were two-tailed and performed with Statistical Package for the Social Sciences 15.0 software (SPSS, Inc., Chicago, IL, USA). A p-value of less than 0.05 was considered as statistically significant.

RESULTS

Between July 2014 and February 2015, 135 patients were prospectively and successively included: 61 patients with GERD (study group I) and 74 patients without GERD (control group II); 41% versus 46% were male, ages were 61.5±9 versus 58±9 years, and BMI values were 28.8±4 kg/m^2 versus 29±4 kg/m^2 (all p-values were greater than 0.05).

Clinical data for both groups are presented in Table 1. No significant differences were found in clinical parameters between the GERD patients and controls. The frequencies of AF were 33% and 39% in groups I and II, respectively (p=0.52). Patients with GERD had an RR of AF of 1.17 (95% confidence interval [CI] 0.78–1.75; p=0.34).

Patients with GERD Versus Those without GERD

Comparative data for the ECG Holter, echocardiography, and upper gastrointestinal endoscopy parameters of the two groups included in the study are presented in Table 2.

The mean value of SDNN was statistically significantly lower in patients with GERD than in those without GERD: 97.6±13.7 ms versus 139.9±44.6 ms (p=0.001). In terms of the frequency-domain parameters of HRV, the mean value of the LF/HF ratio was lower, but statistically non-significant, in patients with GERD than in those without GERD, with values of 0.75±0.17 and 0.76±0.24, respectively (p=0.930).

The E/A ratio was statistically significantly different in patients with GERD versus those without GERD (0.97±0.40 versus 1.31±0.67; p=0.007). There was no statistically significant difference in terms of left atrial area (as a marker of left atrial structural remodeling) in patients with GERD versus those without GERD (25±5.4 cm^2 versus 25±5 cm^2; p=0.781).

We found 32 patients with esophagitis among patients with GERD and only 8 patients among those without GERD (odds ratio (OR)=9.61, 95% CI 3.74–22.15; RR=2.62, 95% CI 1.86–3.68; p=0.0019). Hiatus hernia was not statistically significantly more frequent in patients with GERD than in those without GERD (11 versus 13 patients; OR=1.03, 95% CI 0.43–2.50; RR=1.02, 95% CI 0.63–1.65; p=0.999). None of the patients had esophagitis more severe than Los Angeles class A. Only one patient was diagnosed with Barrett's esophagus (in the GERD group).

Patients with AF and GERD

A comparison between the ECG Holter, echocardiography, and upper gastrointestinal endoscopy parameters in patients with AF+GERD (n=36) and AF-GERD (n=39) versus sinus rhythm (SR)+GERD (n=25) and SR-GERD (n=35) is presented in Table 3.

Table 1. Clinical parameters and RR in patients with GERD (group I, n=61) versus those without GERD (group II, n=74)

Parameter	Group I n (%)	Group II n (%)	Odds ratio (95% CI)	Relative risk (95% CI)
Male gender	25 (41.0)	28 (37.8)	1.14 (0.57-2.28)	1.07 (0.74-1.56)
Age≥60 years	38 (62.3)	34 (45.9)	1.94 (0.97-3.88)	1.45 (0.98-2.14)
Obesity	24 (39.3)	33 (44.6)	0.81 (0.38-1.70)	1.13 (0.77-1.65)
Dyslipidemia	43 (70.5)	58 (78.4)	0.66 (0.28-1.54)	1.24 (0.84-1.84)
Hypertension	43 (70.5)	58 (78.4)	0.66 (0.28-1.54)	1.24 (0.84-1.84)
Diabetes mellitus	11 (18.0)	11 (14.9)	1.26 (0.46-3.44)	0.89 (0.56-1.41)
Heart failure	17 (27.9)	18 (24.3)	1.20 (0.53-2.79)	0.91 (0.60-1.36)
Ischemic heart disease	19 (31.1)	15 (20.3)	1.78 (0.76-4.20)	0.74 (0.51-1.09)
Peripheral arterial disease	2 (3.3)	1 (1.4)	2.44 (0.17-69.8)	0.68 (0.30-1.54)
Atrial fibrillation	20 (32.8)	29 (39.2)	0.76 (0.35-1.63)	1.17 (0.78-1.75)

All p values were greater than 0.05 (Student's t-test)

Table 2. Comparative data for ECG, echocardiography, and upper gastrointestinal endoscopy parameters in patients with GERD (group I) versus those without GERD (group II)

Parameter	GROUP I (n=61)	GROUP II (n=74)	p value (Student's t-test)
ECG Holter			
SDNN$^+$ (ms)	97.6±13.7	139.9±44.6	0.001
LF/HF ratio^{++}	0.75±0.17	0.76±0.24	0.930
Echocardiography			
E/A ratio§	0.97±0.40	1.31±0.67	0.007
E/Em ratio§§	8.1±2.3	7.8±2.9	0.592
Left atrial area (cm^2)	25±5.4	25±5	0.781
Upper Gastrointestinal Endoscopy			
Esophagitis (%)	52.5	10.8	0.001
Hiatus hernia (%)	18.0	17.6	0.999

§E/A ratio: ratio of E-wave velocity to A-wave velocity; §§E/Em ratio: ratio of E-wave velocity to Em velocity; $^{++}$LF/HF ratio: low-frequency/high-frequency ratio; $^+$SDNN: standard deviation of normal-to-normal (N-N) intervals.

In patients with AF the mean value of SDNN was statistically significantly lower in those with GERD than in those without GERD, with values of 114±58 ms and 273±100 ms, respectively; p=0.001.

In terms of frequency-domain parameters of HRV, there were no differences in the mean value of the LF/HF ratio between the four groups (p=0.749). In the presence of AF, the mean value of the LF/HF ratio was higher in those with GERD than in those without GERD, with values of 0.71±0.16 and 0.69±0.17, respectively; however, the p-value was statistically non-significant (p=0.862).

Table 3. Comparative data for ECG, echocardiography, and upper gastrointestinal endoscopy parameters in patients with AF versus SR depending on the diagnosis of GERD

Parameter	AF+GERD n=36	AF–GERD n=39	SR+GERD n=25	SR–GERD n=35	p value Anova test
ECG Holter					
SDNN[+] (ms)	114±58	273±100	88±53	146±33	0.001
LF/HF ratio[++]	0.71±0.16	0.69±0.17	0.76±0.24	0.72±0.17	0.749
Echocardiography					
E/A ratio[§]	1.02±0.49	1.65±0.87	0.94±0.34	1.10±0.42	0.001
E/Em ratio[§§]	8.7±2.3	8.5±3.9	7.3±2.1	7.2±1.3	0.046
Left atrial area (cm^2)	25.8±5.1	27.3±5.1	23.9±5.8	22.9±3.4	0.002
Upper Gastrointestinal Endoscopy					
Esophagitis (%)	50.0	7.7	56.0	14.3	0.001*
Hiatus hernia (%)	19.4	15.4	16.0	20.0	0.942*

*Kruskal–Wallis Test. AF+GERD: patients with AF and GERD; AF-GERD: patients with AF without GERD; SR+GERD: patients with SR with GERD; SR-GERD: patients with SR without GERD.

[§]E/A ratio: ratio of E-wave velocity to A-wave velocity; [§§]E/Em ratio: ratio of E-wave velocity to Em velocity; [++]LF/HF ratio: low-frequency/high-frequency ratio; [+]SDNN: standard deviation of normal-to-normal (N-N) intervals.

The parameters of left ventricular diastolic dysfunction such as the E/A ratio, E/Em ratio, and left atrial area were statistically significantly different in the four groups of patients. There was a statistically significant difference in terms of left atrial area (as a marker of left atrial structural remodeling) in patients with AF+GERD versus those with AF-GERD, with values of 25.8±5.1 cm^2 versus 27.3±5.1 cm^2 (p=0.04).

Esophagitis was diagnosed in 16 patients with AF+GERD and 2 patients with AF-GERD (RR=8.53, 95% CI 2.14–34.0; p=0.001). Esophagitis was statistically significantly more frequent in patients with GERD irrespective of the presence of AF or SR. Hiatus hernia was not more frequent in patients with GERD than in those without GERD independently of the presence of AF or SR. Hiatus hernia was confirmed in 23.3% of patients with AF+GERD and 9.4% of patients with AF-GERD (RR=2.49, 95% CI 0.71–8.75; p=0.251).

DISCUSSION

Cardiovascular involvement in GERD has been little studied in the literature. One of the main pathophysiological mechanisms in paroxysmal AF is the presence of a trigger (7). The development of AF requires a trigger and an anatomic or functional substrate capable of both the initiation and perpetuation of AF. Haissaguerre et al. (8) have observed that AF is often triggered by an ectopic beat arising from the pulmonary veins. This observation induced the electrophysiologist community to refocus its attention on the posterior wall of the left atrium with the pulmonary veins and on the autonomic innervation of that region. Gastroesophageal reflux could be a trigger for AF via sympathovagal imbalance (9).

Another cornerstone in the pathophysiology of AF is the presence of a substrate or a substantially modified atrial myocardium owing to structural, electrical, and mechanical remodeling of the left atrium. The appearance of a trigger could alter the substrate. However, left atrial remodeling, which is a cornerstone of AF, may be a final common phenotype of multiple disease pathways caused by diverse pathophysiological mechanisms. Presently, it will be important to identify certain mechanistic subtypes of AF and not to consider AF as a single disease (10). This idea is increasingly frequently encountered when discussing AF as an inhomogeneous disease (10).

In this study, there were no differences between risk factors for AF (hypertension, ischemic heart disease, and diabetes mellitus) in patients with GERD versus those without GERD. In addition, there was no statistical difference in the percentage of patients with AF in the GERD group in comparison with the group without GERD. Thus, AF was not significantly more frequent in patients with GERD. To date, only one study, which was published by Bunch et al. (11) in 2008 based on a self-reporting questionnaire and included more than 5,000 patients, concluded that GERD did not involve a higher risk of AF after the exclusion of other risk factors. Our study is the second to show that AF is not significantly more frequent in patients with GERD. In comparison with the study by Bunch et al. (11), we assessed autonomic balance via parameters of HRV and left atrial structural remodeling in these patients.

Although diastolic dysfunction was more frequent in the GERD group, left atrial area, as a marker of chronic diastolic dysfunction, was not greater in this study group. When left atrial remodeling was analyzed in the four subgroups of patients, left atrial area was statistically significantly larger in patients with AF than in those with SR, irrespective of the presence of GERD. Thus, left atrial remodeling seems to be related to AF but not to GERD. Therefore, it is difficult to suspect left atrial remodeling as a possible substrate for AF in patients with GERD, in spite of the speculation that a dilated and palpitating left atrium may induce compression or irritation in the neighboring lower esophagus.

In the literature, when discussing HRV time-domain methods are more frequently used in comparison to frequency-domain methods when short-term recordings are investigated. SDNN is the most representative parameter of HRV in the time domain. A value of SDNN of less than 50 ms is considered indicative of high risk; a value of between 50 and 100 ms indicates moderate risk, whereas a value of over 100 ms is considered normal (6). A low value of SDNN indicates low HRV. A reduction in HRV has been reported in several cardiovascular and non-cardiovascular diseases (6). A decrease in HRV has received increasing attention as a prognostic indicator of risk associated with a variety of chronic diseases, behavioral disorders, mortality, and aging (6). In our study, a lower value of SDNN suggests lower HRV in patients with GERD and implicitly, an increased

risk of arrhythmias. In addition, the mean value of SDNN represents a moderate risk of arrhythmia in patients with GERD; in those without GERD, the mean value of SDNN implies no risk of arrhythmia.

The LF/HF ratio is a marker of imbalance between the sympathetic and parasympathetic systems. An increase in this ratio reflects dominance of the sympathetic system, whereas a decrease indicates dominance of the parasympathetic system. In this study, the lower value of the LF/HF ratio in patients with GERD than in those without GERD signifies dominance of the parasympathetic nervous system, although this was statistically non-significant. However, by analysis of the subgroups, in patients with AF we observed a higher mean value of the LF/HF ratio in patients with GERD; this could signify a decrease in parasympathetic activity, which was probably due to other mechanisms such as heart failure, although this was statistically non-significant.

Esophagitis was more frequent in patients with GERD, as was expected. It seems that the pattern of autonomic function differs depending on the presence of erosive esophagitis (12). The LF/HF ratio appears to be significantly lower in patients with non-erosive GERD compared with those with erosive GERD (13). However, in comparison with patients with non-erosive GERD, autonomic tone in patients with endoscopically confirmed esophagitis (even without symptoms) is lower. Probably, the structural state of the esophagus is important in the status of autonomic function (not symptomatology) (14).

Obesity is associated with both AF and GERD. Body fat seems to be associated with HRV (15). In this study obesity in terms of BMI was not different between the study and control groups. However, the RR of GERD induced by obesity was 1.13 (95% CI 0.77–1.65).

To date, we know that autonomic neuropathy in GERD patients may have a mixed character (16). Dobrek et al. (17) showed one year previously that an impairment in parasympathetic activity was associated with the pathogenesis of GERD; in addition, it was also the primary factor contributing to the pathophysiological mechanism of GERD, owing to modulation of the activity of the vagus nerve, which plays an important role in maintaining the physiological function of the lower esophageal sphincter (18).

This is the second study to show that AF is not significantly more frequent in patients with GERD. According to the data from our study, sympathovagal balance seems to be disrupted in patients with GERD; in this group of patient's dominance of the parasympathetic system could be involved. The same conclusion, which was reached for a smaller number of patients, was recently published (19). However, neither the presence of AF nor left atrial structural remodeling was assessed in these patients.

Study Limitations

It is difficult to interpret the parameters of HRV without taking into account all cardiovascular comorbidities and other daily factors. However, in our study there were no differences regarding cardiovascular diseases between patients with GERD and those without GERD. Antiarrhythmic drugs can reduce HRV; antiarrhythmic treatment was not interrupted because of ethical reasons. The assessment of HRV before and after treatment with proton pump inhibitors, not only in the absence of this treatment, could bring new information, because therapy with proton pump inhibitors may have proarrhythmic or antiarrhythmic effects (20,21). A larger study population will be necessary.

Sympathovagal balance seems to be disrupted in patients with GERD, with dominance of the parasympathetic system and an increased risk of arrhythmias, although AF was not significantly more frequent in these patients.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Grigore T. Popa University of Medicine and Pharmacy (Approval number 2005/2014).

Informed Consent: Written informed consent was obtained from patients who participated in this study.

Peer-review: Externally peer-reviewed.

Author contributions: Concept – M.F., V.L.D.; Design – M.F., V.L.D., M.G.; Supervision - G.B., C.C.P., V.L.D.; Materials – M.F., O.B., M.G.; Data Collection and/or Processing – R.A.; Analysis and/or Interpretation – M.F., M.G., V.L.D.; Literature Review – M.F.; V.L.D.; Writer – M.F.; Critical Review – V.L.D., C.C.P., G.B.

Acknowledgments: Thanks to Lidia Rusu for her support in statistical analysis of the data from this study.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: This study was supported by grant no. POSDRU/159/1.5/S/133377 from the University of Medicine and Pharmacy Grigore T. Popa, Iasi, Romania.

REFERENCES

1. January TC, Wann LS, Alpert JS, et al. American College of Cardiology/American Heart Association Task Force on Practice Guidelines: 2014 AHA/ACC/HRS Guideline for the Management of Patients With Atrial Fibrillation: Executive Summary. JACC 2014; 64: 2246-80. **[CrossRef]**
2. Vakil N, van Zanten SV, Kahrilas P, Dent J, Jones J, Global Consensus Group. The Montreal Definition and Classification of Gastroesophageal Reflux Disease: A Global Evidence-Based Consensus. Am J Gastroenterol 2006; 101: 1900-20. **[CrossRef]**
3. Floria M, Bărboi O, Rezuș C, et al. Atrial Fibrillation and Gastro-Oesophageal Reflux Disease - Controversies and Challenges. Curr Pharm Des 2015; 21: 3829-34. **[CrossRef]**
4. Roman C, Bruley des Varannes S, Muresan L, Picos A, Dumitrascu DL. Atrial fibrillation in patients with gastroesophageal reflux disease: A comprehensive review. World J Gastroenterol 2014; 20: 9592-9.

5. Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology. Heart rate variability: Standards of measurement, physiological interpretation and clinical use. Eur Heart J 1996; 17: 354-81. **[CrossRef]**
6. Pumprla J, Howorka K, Groves D, Chester M, Nolan J. Functional assessment of heart rate variability: Physiological basis and practical applications. Int J Cardiol 2002; 84: 1-14. **[CrossRef]**
7. Calkins H, Kuck KH, Cappato R, et al. 2012 HRS/EHRA/ECAS Expert Consensus Statement on Catheter and Surgical Ablation of Atrial Fibrillation: Recommendations for Patient Selection, Procedural Techniques, Patient Management and Follow-up, Definitions, Endpoints, and Research Trial Design. Europace 2012; 14: 528-606. **[CrossRef]**
8. Haissaguerre M, Jais P, Shah DC, et al. Spontaneous initiation of atrial fibrillation by ectopic beats originating in the pulmonary veins. N Engl J Med 1998; 339: 659-66. **[CrossRef]**
9. Reddy YM, Singh D, Nagarajan D, et al. Atrial fibrillation ablation in patients with gastroesophageal reflux disease or irritable bowel syndrome-the heart to gut connection! J Interv Card Electrophysiol 2013; 37: 259-65. **[CrossRef]**
10. Dewland TA, Vittinghoff E, Harris TB, et al. Inflammation as a mediator of the association between race and atrial fibrillation. Results from the Health ABC Study (Health, Aging, and Body Composition). JACC Clin Electrophysiol 2015; 1: 248-55. **[CrossRef]**
11. Bunch TJ, Packer DL Jahangir A, et al. Long-term risk of atrial fibrillation with symptomatic gastroesophageal reflux disease and esophagitis. Am J Cardiol 2008; 102: 1207-11. **[CrossRef]**
12. Montenero AS, Mollichelli N, Zumbo F, et al. Helicobacter pylori and atrial fibrillation: a possible pathogenic link. Heart 2005; 91: 960-1. **[CrossRef]**
13. Chen CL, Orr WC, Yang CC, Kuo TB. Cardiac autonomic regulation differentiates reflux disease with and without erosive esophagitis. Scand J Gastroenterol 2006; 41: 1001-6. **[CrossRef]**
14. Lee YC, Wang HP, Lin LY, et al. Heart rate variability in patients with different manifestations of gastroesophageal reflux disease. Auton Neurosci 2004; 116: 39-45. **[CrossRef]**
15. Hillebrand S, Swenne CA, Gast KB, et al. The role of insulin resistance in the association between body fat and autonomic function. Nutr Metab Cardiovasc Dis 2015; 25: 93-9. **[CrossRef]**
16. Dobrek L, Nowakowski M, Syguła A, et al. 24-hour heart rate variability in patients with gastroesophageal reflux disease. Folia Med Cracov 2005; 46: 53-64.
17. 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.
18. Błaut U, Dobrek Ł, Laskiewicz J, Thor PJ. Disturbances of the autonomic nervous system in gastroesophageal reflux disease. Folia Med Cracov 2001; 42: 63-73.
19. Stollberger C, Finsterer J. Treatment of esophagitis/vagitis-induced paroxysmal atrial fibrillation by proton-pump inhibitors. J Gastroenterol 2003; 38: 1109. **[CrossRef]**
20. Milovanovic B, Filipovic B, Mutavdzin S, et al. Cardiac autonomic dysfunction in patients with gastroesophageal reflux disease. World J Gastroenterol 2015; 21: 6982-9.
21. Linz D, Hohl M, Vollmar J, Ukena C, Mahfoud F, Böhm M. Atrial fibrillation and gastroesophageal reflux disease: the cardiogastric interaction. Europace 2016 May 31. pii: euw092. [Epub ahead of print].**[CrossRef]**