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Original Article / Özgün Araştırma

Effect of cardio-gastric interaction on atrial fibrillation in GERD patients

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Abstract

Objective: Atrial fibrillation (AF) and gastroesophageal reflux disease (GERD) are very common in daily clinical practice. Post-prandial AF episodes have been reported in GERD patients. Although it was reported in previous studies that it was caused by sympathovagal imbalance, there are no studies on cardiac conduction system involvement. In this study, we aimed to evaluate whether the risk of developing AF increases in untreated GERD patients with non-invasive electrophysiological tests.

Methods: The research was prospectively performed. Endoscopy was performed on the individuals due to reflux complaints. ECG was recorded at 25mm/s and 10 mm/mV amplitude, and 24-hour Holter ECG (three-channel; V1, V2, and V5) was performed. ECG parameters were measured and Holter ECG results were analyzed.

Results: A total of 120 individuals, 60 patients and 60 controls, were included. No significant statistically differences existed between groups for hypertension, diabetes, smoking, or dyslipidemia ($p>0.05$). In terms of heart rate, Pmax, Pmin, QTd, and QTcd, there were no significant differences across the two groups ($p>0.05$). P-wave dispersion (Pd) was substantially higher in the study group ($p=0.014$). Comparing the heart rate variabilities of 24-hour Holter ECG recordings across the groups, the standard deviation of R-R intervals (SDNN) was substantially higher in the study group ($p<0.001$). Low Frequency (LF) and LF/HF were significantly higher in the control group ($p<0.001$ and $p=0.003$, respectively). AF was detected in nine individuals on Holter ECG.

Conclusion: Pd duration and risk of developing AF were higher in GERD patients.

Keywords: Atrial fibrillation, heart rate variability, gastroesophageal reflux, Holter-ECG.

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GÖRH hastalarında kardiyo-gastrik etkileşimin atriyal fibrilasyon üzerine etkisi

Öz

Amaç: Atriyal fibrilasyon (AF) ve gastroözofageal reflü hastalığı (GÖRH) günlük klinik pratikte çok yaygındır. GÖRH hastalarında tokluk sonrası AF epizotları bildirilmiştir. Sempatovagal dengesizlikten kaynaklandığı daha önceki çalışmalarda bildirilmişse de kardiyak ileti sistemi tutulumu ile ilgili çalışma yoktur. Bu çalışmada non-invaziv elektrofizyolojik testler ile tedavi edilmemiş GÖRH hastalarında AF gelişme riskinin artıp artmadığını değerlendirmeyi amaçladık.

Yöntemler: Araştırma prospektif olarak yapıldı. Reflü şikayeti olan kişilere endoskopi yapıldı. EKG 25 mm/sn ve 10 mm/mV amplitüdünde kaydedildi ve 24 saatlik Holter EKG (üç kanallı; V1, V2 ve V5) yapıldı. EKG parametreleri ölçüldü ve Holter EKG sonuçları analiz edildi.

Bulgular: Araştırmaya 60'ı hasta ve 60'ı kontrol olmak üzere toplam 120 kişi dahil edildi. Gruplar arasında hipertansiyon, diyabet, sigara kullanımı veya dislipidemi açısından anlamlı istatiksel fark yoktu (p>0.05). Kalp hızı, Pmax, Pmin, QTd ve QTcd açısından iki grup arasında anlamlı fark yoktu (p>0,05). P-dalga dispersiyonu (Pd) çalışma grubunda oldukça yüksekti (p=0.014). Gruplar arasında 24 saatlik Holter EKG kayıtlarının kalp hızı değişkenlikleri karşılaştırıldığında, R-R aralıklarının standart sapması (SDNN) çalışma grubunda anlamlı olarak daha yüksekti (p<0.001). Düşük frekans (LF) ve LF/HF kontrol grubunda anlamlı olarak daha yüksekti (sırasıyla p<0.001 ve p=0.003). Holter EKG'de dokuz kişide AF saptandı.

Sonuç: GÖRH hastalarında Pd süresi ve AF gelişme riski daha yüksekti.

Anahtar kelimeler: Atriyal fibrilasyon, kalp hızı değişkenliği, gastroözofageal reflü, Holter-EKG.

INTRODUCTION

Atrial fibrillation (AF) is observed in 3-4% of the general population[1]. The prevalence in people over the age of 40 is between 20- 25%. As a result of risk factors such as coronary artery disease, hypertension, renal diseases and heart failure, which rise with the aging of the population, this rate multiplied by two to three times[2,3]. AF is one of the common arrhythmias detected in patients with acute ischemic cerebrovascular accident[4]. The development of AF is also influenced by diabetes, obesity, sleep apnea, and thyroid dysfunction[5]. AF is associated with significant morbidity and mortality[6]. AF management is predicated on maintaining sinus rhythm to avert disastrous outcomes[7].

A relationship between gastroesophageal reflux disease (GERD) and AF has been asserted. In clinical practice, we encounter GERD patients with heartburn or dysphagia. On the order hand, some individuals complain of palpitations after stomach acid flow-up into the oropharynx[8]. It has been reported that AF episodes are triggered after constipation, defecation, and consumption of cold water, alcohol, and fatty foods[9]. The mechanism of GERD-associated AF is explained by esophageal inflammation, mechanical irritation, and impaired anatomical innervation[10]. But, there are no studies on cardiac conduction system involvement. For these individuals, ECG parameters and Holter ECG can be utilized for explaining AF episodes in GERD patients.

In this present study, we sought to determine whether the risk of developing AF increases in untreated GERD patients with non-invasive electrophysiological tests.

METHODS

Study design and subject

The study was conducted prospectively between June 2022 and January 2023. Sixty consecutive patients older than 18 years of age who were diagnosed with GERD by endoscopy were included in the study. Patients with structural heart disease, acute coronary syndromes, chronic kidney disease or obstructive pulmonary disease, cancer, severe anemia, electrolyte imbalance, and drug use that may cause arrhythmia were excluded from

the study. The control group consisted of 60 individuals without a previous history of GERD and AF. The study was authorized by the ethics commission of Gazi Yaşargil Training and Research Hospital (date: 10/06/2022, permission number: 98). It complied with the Helsinki Declaration's ethical criteria for human testing (2013).

Study protocol

Complete blood count and biochemical tests were performed on all patients. In the cardiac examination, ejection fraction was measured with Simpson's method, ECG was recorded at 25mm/s and 10 mm/mV amplitude, and 24-hour Holter ECG (three-channel; V1, V2, and V5) was performed. ECG parameters were calculated under 400x magnification. Heart rate variables were obtained automatically by SCHILLER's medilog® Holter System. A cardiologist blind to the research evaluated ECG parameters and Holter ECG recordings. Holter ECG results were shown in Figure 1.

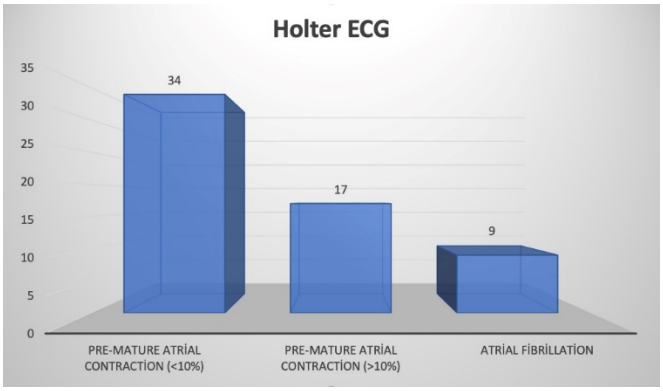

Figure 1. Number of GERD patients with AF based on Holter recordings

Pre-study power analysis

Study population calculation: 60 patients were included, assuming a significance threshold of 0.05, a power of 90%, and an estimated dropout rate of 10% utilizing G*Power 3 software.

Definitions

PACs are defined as three or more consecutive atrial contractions lasting less than 30 seconds[11]. Atrial fibrillation was defined as clinically AF occurrences recognized on surface ECG or subclinically AF events recorded by wearable devices such as Holter ECG[12]. The standard deviation of R-R intervals (SDNN), the number of R-R intervals that deviated by more than the total number of R-R intervals (pNN50), and the root mean square of successive differences (RMSSD) were obtained software system[13]. The total power was categorized as high frequency (HF) and low frequency (LF) components. The P dispersion was yielded by subtracting the shortest P wave length from the longest P wave duration[14]. QT and QTc dispersion were computed identically.

Statistics

For the analysis, the IBM SPSS 26.0 package application was utilized. Initial continuous data were given as means standard deviations or medians (interquartile range). Categorical data were represented using frequency and percentage and the chi-square test or Fisher's exact test was utilized. The variables' normal distribution was tested using the Kolmogorov–Smirnov and Shapiro–Wilk tests. If applicable, the T-test or the Mann–Whitney U-test was used to compare continuous data. Statistical significance was deemed at p-value <0.05.

RESULTS

A total of 120 individuals, 60 patients and 60 controls, were included. 73 of them were female. The average age of the patient group was 44.1±9.8 years and 43.5±9.2 years control group. No significant clinical differences existed between groups for hypertension, diabetes, smoking, or dyslipidemia (p>0.05). There were no appreciable differences between the groups for hematological and biochemistry blood tests (p>0.05, Table I). There are no substantial variations between groups in terms of ejection fractions (p>0.05). In terms of heart rate, Pmax, Pmin, QTd, and QTcd, there were no significant differences across the two groups (p>0.05,

Table II). Pd was substantially higher in the study group (p=0.014). Comparing the heart rate variabilities of 24-hour Holter ECG recordings across the groups, no significant difference was seen in RMSSD, pNN50, HF (p>0.05). SDNN was substantially higher in the study group (p<0.001). LF and LF/HF were significantly higher in the control group (p<0.001 and p=0.003, respectively). AF was detected in nine individuals on Holter ECG. In 34 cases, more than 10% of premature atrial contractions were detected.

Table I: Clinical characteristics and laboratory parameters of patients

PARAMETERS	Study group, *n=60*	Control group, *n=60*	*P*-Value
Age (Years)	44.1±9.8	43.5±9.2	0.786
Gender, female, n (%)	37 (62.1)	36 (60.4)	0.813
Hypertension, n (%)	13 (22.3)	12 (20.6)	0.880
Diabetes mellitus, n (%)	12 (20)	15 (25)	0.427
DL, n (%)	21 (34.9)	19 (31.3)	0.621
Smoking, n (%)	9 (15)	6 (10.4)	0.452
White blood cell count (× 10^3 µL)	9.9±3.8	9.3±2.7	0.326
Hemoglobin (g/dl)	13.7±2.2	13.2±2.0	0.830
ALT (U/L)	18 (14.5)	16.5 (16)	0.235
AST (U/L)	20 (9.5)	18 (9.5)	0.533
CRP (mg/L)	0.4 (0.4)	0.32 (0.3)	0.539
Glucose (mg/dl)	87.0±19.5	87.9±20.4	0.898
Creatine (mg/dl)	0.98±0.31	0.94±0.19	0.430
Total cholesterol (mg/dl)	179.8±47.1	175.1±32.3	0.484
Triglyserides (mg/dl)	158.9±69.0	151.7±55.6	0.537
LDL (mg/dl)	112.0±30.9	103.6±28.5	0.105
HDL (mg/dl)	40.3±8.5	39.9±8.3	0.852
Atrial fibrillation	9 (15)	_	_
EF %	59.4±3.5	59.2±2.8	0.912

Data are expressed as appropriate as mean ± SD and median [interquartile range]. SBP: Systolic blood pressure, DL: dyslipidemia, ALT: alanine aminotransferase, AST: aspartate aminotransferase, CRP: C-reactive protein LDL: low-density lipoprotein, HDL: high-density lipoprotein, EF: Ejection fraction.

Table II: Heart rate variability and ECG parameters of groups

	Study group, *n*=60	Control group, *n*=60	*P*-Value
Heart rate (beats/min)	72±5	74±3	0.690
Pmax (ms)	120.6±6.5	118.7±7.9	0.252
Pmin (ms)	72.4±8.7	73.3±11.3	0.662
Pd (ms)	51.1±7.6	45.8±11.6	**0.014**
QTd (ms)	53.2±5.9	51.0±7.5	0.083
QTcd (ms)	67.9±8.1	65.2±9.4	0.104
SDNN (ms)	140.3±18.9	102.6±43.2	**<0.001**
RMSSD (ms)	32.6±22.5	28.7±8.9	0.582
pNN50 (%)	10.6±9.2	8.0±5.3	0.480
LF (nu)	55.8±12.4	67.6±15.6	**<0.001**
HF (nu)	27.2±7.6	25.2±11.2	0.346
LF/HF	2.24±1.3	3.54±1.8	**0.003**

Data are expressed as mean ± SD as appropriate. Pmax: P-wave maximum duration, Pmin: P-wave minimum duration, Pd: P-wave dispersion, QTd: QT dispersion, QTcd: Corrected QT dispersion, SDNN: Standard deviation of the NN (R-R) intervals, RMSSD: Root mean square of the successive differences, pNN50: The proportion of NN50 divided by the total number of NN (R-R) intervals, LF: Low frequency, HF: High frequency.

DISCUSSION

This study showed that the duration of Pd was longer and LF/HF ratio was lower in GERD patients compared to controls. PACs and AF episodes were observed on Holter monitoring in the study group. Additionally, patients with GERD had significant autonomic nervous system dysfunction compared to the control group in favor of the parasympathetic system.

A thin tissue layer separates the esophagus from the left atrium. This layer is composed of nerve plexuses and often branches over the left atrium[15]. Esophageal acid stimulation increases

vagal activity[16]. In individuals with GERD, focal alterations in the pulmonary vein resulting from the activation of the plexus ganglia initiate atrial fibrillation[17]. Studies have revealed different mechanisms. Mulia et al. reported that AF developed in 66% of patients who developed pericarditis and myocarditis as a result of local inflammation in patients with Barrett's esophagus[18]. Inflammation-associated AF was correlated with an increase in circulating inflammatory cytokines[19]. Hiatal hernia mechanically compresses the left atrium. Gharagozloo et al. stated that the symptoms of AF regressed in patients who underwent laparoscopic fundoplication[20]. Roy et al. concluded that hiatal hernia would be the cause of future AF, especially in young GERD patients[21]. Another mechanism is that acid stimulation reduces coronary blood flow and causes angina. Reduced cardiac perfusion induces atrial myocardial scarring and generates a substrate for AF[22]. George et al. reported that AF attacks were seen in GERD patients diagnosed with syndrome X[23].

ECG parameters are used as non-invasive predictors of dysrhythmia risk, and Holter ECG recording provides a helpful way for rhythm analysis. Bodur et al. noted that PACs as AF surrogates were observed in large numbers on Holter recordings of patients with GERD[24]. The results of our study were similar and the Pd duration, which has an independent predictive value for AF, was higher. In Tasci et al study, ventricular extra-systole contractions were higher in GERD patients[25]. Kaya et al. stated that QTd increased and repolarization anomalies were observed[26]. In contrast, QTd or QTcd values did not rise in our investigation, and ventricular arrhythmia was not observed in Holter recordings.

HRV is a strong predictor of the balance between the parasympathetic and sympathetic nervous systems. RMSSD, PNN50, and HF all indicate parasympathetic activity, while LF indicates sympathetic activity[27]. The LF/HF power ratio determines the sympathovagal balance, while the SDNN indicates the overall variability of heart rate[28]. According to previous studies on heart rate variability, stimulating the esophagus with acid increases vagal activity and leads to the development of arrhythmias. Firstly, Rebecchi et al. compared the HRV of the esophagus at rest and after contraction using electrical stimulation[29]. It was observed that the area of the HF band increased in the total power spectrum. This indicates that vagal activation reduces sympathetic modulation. Zarea et al. found a correlation between Holter ECG and 24-hour pH monitoring in terms of arrhythmia and increased acidity[30]. Wang et al. reported a negative relationship between GERD and LF/HF[31]. The same results were obtained in our study, and the SDNN values were higher. Maruyama et al. stated that the great majority of paroxysmal AF patients treated with proton pump inhibitors had decreased or eliminated AF-related symptoms[32]. On the other hand, the question of whether AF is a predisposing factor for GERD comes to mind in the cardio-gastric interaction. Multicenter studies by Tuerxun et al. showed that GERD was not associated with gender, coronary artery disease, dyslipidemia, and hypertension, and AF was an independent risk factor for GERD[33].

Our study has several limitations. The population was small. Holter was conducted for only 24 hours. Whether individuals in premature atrial contractions would develop AF after the trial is unknown. After GERD medication, the ECG and Holter data of the patients were not compared.

CONCLUSION

Prolongation of P wave dispersion, decrease in LF/HF ratio and AF monitoring on Holter ECG showed a significant relationship between GERD and AF. This result suggests that GERD patients with palpitations should be treated to prevent possible AF. To explain this relationship

in more detail, further prospective trials with a larger patient population are required.

Ethics Committee Approval: The study was authorized by the ethics commission of Gazi Yaşargil Training and Research Hospital (date: 10/06/2022, permission number: 98). It complied with the Helsinki Declaration's ethical criteria for human testing (2013).

Conflict of Interest: The authors declared no conflicts of interest.

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