A Case-Control Study of Risk Factors That May Contribute to the Occurrence of Paroxysmal Atrial Fibrillation

Paroksismal Atriyal Fibrilasyon Oluşumuna Katkı Sağlayan Risk Faktörleri: Vaka-Kontrol Çalışması

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ABSTRACT Objective: Information concerning paroxysmal atrial fibrillation (PAF) is scarce. There are several risk factors for the initiation of paroxysmal atrial fibrillation and the underlying mechanisms are multifactorial. Our study aimed to identify the risk factors that may contribute to the development of PAF. **Material and Methods:** One hundred and three consecutive patients who were detected to have PAF by 24-hour Holter monitoring (HM) were assigned in our study. The control group (n=87) comprised individuals with normal HM. All patients were evaluated for the presence of risk factors such as age, gender, hypertension, diabetes, history of coronary artery disease (CAD) and coronary artery bypass graft operation (CABG). Patients with aortic and mitral stenosis, hyperthyroidism, hypothyroidism, and pregnancy were excluded. Comprehensive clinical data were collected. **Results:** Mean age of the patients was 63±11 vs. 45±14 years (p< 0.001) in PAF and control groups, respectively. Fifty seven (55%) in PAF and 19 (21%) patients in control group were male subjects (p< 0.001). History of CAD (32% vs. 11%, respectively; p= 0.001), CABG (17% vs. 5%, respectively; p= 0.014) and cerebrovascular accident (CVA) or transient ischemic attack (TIA) (11% vs. 2%, respectively; p= 0.014) were more prevalent in PAF group when compared to control subjects. There was no difference in hypertension and diabetes between groups. Mean low density lipoprotein cholesterol (119±33 mg/dL vs. 109±29 mg/dL, respectively; p=0.26) and triglyceride (143±93 mg/dL vs. 144±98 mg/dL, respectively; p=0.95) levels were statistically insignificant between PAF and control subjects. **Conclusion:** Our results indicate that patients who develop PAF are old male subjects. History of CAD, CABG and CVA/TIA are more prevalent among PAF group when compared to control group.

Key Words: Atrial fibrillation; coronary artery disease

ÖZET Amaç: Çalışmamızın amacı paroksismal atrial fibrilasyon oluşumuna katkı sağlayan risk faktörlerini ortaya çıkarmaktır. **Gereç ve Yöntemler:** 24 saatlik Holter tetkikinde PAF tespit edilen 103 ardışık hasta çalışmaya dahil edildi. Kontrol grubunu Holter sonuçları normal olan 87 hasta oluşturdu. Tüm hastalar atriyal fibrilasyon risk faktorlerinin (yaş, cinsiyet, hipertansiyon, diabet, koroner arter hastalığı (KAH) ve koroner arter baypas operasyonu (KAB) hikayesi varlığı açısından değerlendirildi. Aort ve mitral darlığı, hipotiroidi, hipertiroidi ve gebelik dışlama kriterlerini oluşturdu. **Bulgular:** Ortalama yaş PAF grubunda 63±11 ve kontrol grubunda 45±14 (p< 0.001) idi. PAF grubunda 55 (%55), kontrol grupta 19 (%21) (p< 0.001) erkek hasta mevcuttu. KAH (%32 ve %11, sırasıyla; p= 0.001), KAB operasyonu (%17 ve %5, sırasıyla; p= 0.014) ve serebrovasküler olay (SVO) veya transient iskemik atak (TİA) (%11 ve %2, sırasıyla; p= 0.014) prevalansı PAF'lı grupta kontrol grubuna göre daha yüksekti. Hipertansiyon ve diabet her iki grupta da aynı idi. Ortalama düşük dansiteli lipoprotein (119±33 mg/dL ve 109±29 mg/dL, sırasıyla; p= 0.26) ve trigliserit (143±93 mg/dL vs. 144±98 mg/dL, sırasıyla; p= 0.95) seviyeleri iki grup arasında anlamlı fark göstermedi. **Sonuç:** Sonuçlarımız PAF gelişen hastaların daha çok yaşlı ve erkek olduğunu göstermektedir. KAH, KAB operasyonu ve SVO/TİA hikayesi PAF grubunda daha sık görülmektedir.

Anahtar Kelimeler: Atriyal fibrilasyon; koroner arter hastalığı

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Paroxysmal atrial fibrillation is a condition in which there are intermittent periods of atrial fibrillation that usually terminate spontaneously. Between episodes, the intervening predominant baseline rhythm is sinus rhythm.[1] PAF often progresses to longer episodes. The result is 15-30% of advancement to permanent AF within 1-3 years.[2] Permanent AF is associated with morbidity and mortality that is almost doubled compared with the general population.[3] Stroke is among the most potentially devastating consequences of permanent AF.[4]

Although the mechanism of perpetuation of AF has not been fully elucidated, various triggers and predisposing factors have been proposed. There are strong evidences in favor of the pulmonary artery firing as the trigger in the majority of cases.[2] Enhanced automaticity, re-entry circuits, sympathetic or parasympathetic stimulation, bradycardia, atrial premature beats, tachycardia, accessory atrioventricular pathways, and acute atrial stretch are also defined as triggers.[5] Clinical factors that predisposes to PAF are inflammation, cardiac failure, hypertension (HTN), ischemic heart disease, hyperthyroidism, valvular heart disease, and cardiothoracic surgery.[6,7]

The etiology of PAF is multifactorial and a need to explore contributing factors still exists. Predisposing factors have to be understood better and fully fixed to prevent permanent AF. The purpose of our study is to investigate risk factors that contribute to the onset of PAF.

MATERIAL AND METHODS

We studied 103 consecutive patients with one or more self-terminating episodes of PAF, lasting more than 30 seconds on 24-hour Holter monitoring. The control group consisted of 87 cases with normal sinus rhythm or sinus tachycardia on 24-hour Holter monitoring. Indication for Holter was palpitations at rest for both groups. Subjects with aortic and mitral stenosis, hyperthyroidism, hypothyroidism, and pregnancy were excluded from the study. Risk factors for AF were recorded for both groups. Data regarding echocardiographic findings, medications, and clinical characteristics were collected.

HOLTER AND ECHOCARDIOGRAPHIC TECHNIQUE

A digital Holter recorder (DMS 300-8 Digital Holter Recorder; DMS, Nevada, USA) was used and digital analysis performed by the software (CardioScan 10 version 10.2.00011a, Stirling Technologies Inc., BC, Canada). PAF was defined as AF lasting for more than 30 seconds with sinus rhythm which spontaneously resumed before the end of recording. We excluded permanent AF and episodes lasting less than 30 seconds.

Two-dimensional and Doppler echocardiographic evaluations of both groups were collected. A Vivid 7 echo-machine and a 2.5 MHz matrix transducer with second harmonic imaging were used for data acquisition (GE Healthcare, Horten, Norway). Left ventricular ejection fraction was calculated by Teicholtz formula (EDD^2 (end-diastolic diameter) – EDS^2 (end-systolic diameter/ EDD^2) with M-mode at parasternal long axis view and by modified Simpson formula (EDV (end-diastolic volume) – ESV (end-systolic volume)/EDV) at apical four chamber view. Anterior-posterior left atrial diameter was measured at the end of atrial diastole at parasternal long axis view by M-mode and with the inner edge-inner edge convention.

STATISTICAL ANALYSES

Mean values for each group were compared by using the Student's *t-test* for continuous variables and the *Chi-square* test for categorical variables. Continuous variables were expressed as mean±SD. Frequencies of categorical variables were defined as percentages (%). Values of $p < 0.05$ were considered significant.

RESULTS

Tables 1 and 2 summarize the baseline clinical characteristics of the study population. Mean age of the patients was 63 ± 11 vs. 45 ± 14 years ($p< 0.001$) in PAF and control groups, respectively. PAF was more frequent in patients between 50 and 75 years

TABLO 1: Baseline clinical characteristics of the PAF and Control groups.

	PAF(n=103)	Control (n=87)	p
Age, years (mean±SD)	63±11	45±14	<0.001
Male, n (%)	57 (55)	19 (21)	<0.001
History of CAD, n (%)	33 (32)	10 (11)	0.001
History of CABG, n (%)	18 (17)	5 (5)	0.014
Hypertension, n (%)	48 (46)	33 (37)	0.22
DM, n (%)	25 (24)	12 (13)	0.069
Previous CVA/TIA, n (%)	12 (11)	2 (2)	0.014
Concomitant drug therapy, n (%)			
β-Blockers	51 (49)	10 (11)	<0.001
Calcium Channel Blockers	14 (13)	16 (18)	0.36
ACEI/ARB	49 (47)	19 (22)	0.0001
Lipid lowering therapy	32 (31)	22 (25)	0.37
Aspirin/Clopidogrel	52 (50)	13 (15)	<0.001

CAD: Coronary Artery Disease, CABG: Coronary Artery Bypass Graft, CVA/TIA: Cerebrovascular Accident/Transient Ischemic Attack, ACEI/ARB: Angiotensin converting enzyme inhibitors/Angiotensin receptor blockers.

TABLO 2: Laboratory and Echocardiographic Findings of the PAF and Control groups.

	PAF (n=103)	Control(n=87)	p
LDL-C (mg/dl)	119±33	109±29	0.26
Triglyceride (mg/dl)	143±93	144±98	0.95
TSH (μIU/ml)	1.2±0.9	1.2±0.9	0.52
WBC (K/mm^3)	7580±2352	7472±2086	0.73
Platelets (K/mm^3 x1000)	242±73	236±53	0.52
LA diameter (mm)	37±7	31±4	<0.001
LVEF (%)	57±15	64±2	<0.001

LDL-C: Low Density Lipoprotein Cholesterol, TSH: Thyroid stimulating hormone, WBC: White Blood Cell, LA: Left Atrium, LVEF: Left Ventricule Ejection Fraction

that peaked in age 70. Fifty seven (55%) in PAF and 19 (21%) patients in control group were male subjects (p< 0.001). History of coronary artery disease (CAD) (32% vs. 11%, respectively; p=0.001), coronary artery bypass graft (CABG) operation (17% vs. 5%, respectively; p= 0.014) and cerebrovascular accident (CVA) or transient ischemic attack (TIA) (11% vs. 2%, respectively; p= 0.014) were more prevalent in PAF group when compared to control subjects. There was no difference in hypertension and diabetes between groups. Mean low density lipoprotein cholesterol (119±33 mg/dL vs. 109±29, respectively; p= 0.26) and triglyceride (143±93 vs. 144 ± 98, respectively; p= 0.95) levels were statistically insignificant between PAF and control subjects. Mean values of left atrial (LA) diameter for PAF and control groups were 37±7 mm vs. 31±4 mm (p< 0.001), respectively. Mean left ventricular ejection fraction was 57±15% in PAF group and 64±2% in control subjects (p< 0.001).

DISCUSSION

This is a case-control study to examine the risk factors that may contribute to the onset of PAF. Previous studies have well put forward risk factors for AF, but the general conclusion is that it is difficult to assess an underlying cause in all AF patients.[8] Given the risk factors for AF, one may suppose that same risk factors would also be encountered in PAF. In the presented study, we aimed to examine whether established risk factors of AF also exist in patients with PAF.

Specific cardiovascular conditions associated with AF include valvular heart disease (most often mitral valve disease), CAD, and hypertension, particularly when left ventricular hypertrophy is present. There is a strong association between hypertension and CVA in AF, which is probably mediated primarily by embolism originating in the LA appendix,[9] but hypertension also increases the risk of noncardioembolic strokes in AF.[9,10] The effect of advancing age in increasing stroke risk in AF is multifactorial.[11] In patients with AF, aging is associated with LA enlargement.[12,13] History of heart failure and age>75 years are independent predictors of mortality in patients with AF.[14] Atrial fibrillation is a common early postoperative complication of cardiac or thoracic surgery.

Results of our study did not show difference in hypertension, diabetes, LDL-C, and triglyceride levels between study groups. Patients with PAF were older compared to normal subjects. Male gender, history of CAD, CABG, previous CVA/TIA, and left ventricular dysfunction were more prevalent in PAF group. These results except hypertension and diabetes are compatible with the major risk factors which are defined by the $CHADS_2$ score, that comprises congestive heart failure, hypertension, age >75, diabetes mellitus, and history of CVA or TIA.[15,16]

CONCLUSION

We determined a male preponderance among PAF patients. History of CAD, CABG and CVA/TIA are more prevalent among PAF group. LA is larger and LVEF less diminished in PAF group than that of control subjects.

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