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Original Article / Özgün Araştırma

The association between frequent premature atrial contractions and recurrent stroke in a population of ischemic stroke

Serhat Günlü[1], **Adem Aktan**[2]

1 Cardiologist, Department of Cardiology, Dağkapı State Hospital, Diyarbakır, Turkey

2 Cardiologist, Department of Cardiology, Mardin Training and Research Hospital, Mardin, Turkey

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Abstract

Objective: Premature atrial contractions (PACs) are a prevalent cardiac occurrence. Recent research indicates that PACs are linked to atrial fibrillation (AF), ischemic stroke, and mortality. We aimed to investigate the association of PACs and the risk of recurrent stroke in patients with ischemic stroke in sinus rhythm.

Methods: The study was conducted as a cross-sectional study. 24-hour standard three-lead Holter ECG monitoring was performed for seven days and analyzed. Patients were separated into two groups based on the results of Holter ECG monitoring: those with subclinical AF and those with frequent PACs. Frequent PACs were characterized as more than fourteen PACs per hour and >3 PAC runs each 24 hours. Subclinical AF was defined as atrial fibrillation, atrial flutter, or atrial tachycardia events detected by implantable or wearable cardiac devices in people without AF symptoms and in whom clinical AF was not previously detected.

Results: 150 patients, consisting of 82 men (54.7% of the total) and 68 women (45.3%), with an average age of 60.9±13.5 years, were enrolled in the research. Based on the Holter findings, patients were separated into subclinical AF (n=54) and frequent PACs (n=96).During hospitalization, recurrent ischemic stroke was detected in 6 patients (11%) in the subclinical AF arm and 26 patients (26%) in the frequent PACs arm (p=0.03). Six patients died of whom 4 died after a recurrent stroke event in the hospital. In univariate analysis age [OR: 1.03, 95%CI (1-1.07), p=0.02], dyslipidemia [OR: 2.68, 95%CI (1.16-6.18), p=0.021] and frequent PACs [OR: 2.97, 95%CI (1.13-7.76), p=0.026] were found significant predictors of recurrent stroke. Furthermore, in multivariate logistic regression analysis only frequent PACs [OR: 2.69, 95%CI (1-7.17), p=0.048] was found independent predictors of recurrent stroke.

Conclusion: Frequent PACs on Holter analysis were significantly associated with recurrent ischemic stroke.

Keywords: Frequent PACs, subclinical AF, recurrent stroke, Holter-ECG.

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Correspondence / Yazışma Adresi: *Serhat Günlü, Department of Cardiology, Dağkapı State Hospital, Diyarbakır, Turkey e-mail: serhat8086@hotmail.com*

İskemik inme popülasyonunda sık erken atriyal kasılmalar ile tekrarlayan inme arasındaki ilişki

Öz

Amaç: Erken atriyal kasılmalar (EAK) yaygın bir kardiyak olaydır. Son araştırmalar, EAK'ların atriyal fibrilasyon (AF), iskemik inme ve mortalite ile bağlantılı olduğunu göstermektedir. Bu çalışmanın amacı sinüs ritminde iskemik inmeli hastalarda EAK'lar ile tekrarlayan inme riski arasındaki ilişkiyi incelemektir.

Yöntemler: Çalışma kesitsel olarak yürütülmüştür. Yedi gün boyunca 24 saatlik standart üç derivasyonlu Holter EKG takibi yapıldı ve analiz edildi. Holter EKG monitorizasyonu sonuçlarına göre hastalar subklinik AF ve sık EAK olmak üzere iki gruba ayrıldı. Sık EAK'lar, saatte 14'ten fazla EAK ve 24 saatlik periyotta 3 veya daha fazla EAK kaçışı olarak tanımlandı. Subklinik AF, AF semptomları olmayan ve daha önce klinik AF saptanmamış kişilerde kardiyak implante edilebilir veya giyilebilir cihazlar tarafından saptanan atriyal fibrilasyon, atriyal çarpıntı veya atriyal taşikardi atakları olarak tanımlandı.

Bulgular: Araştırmaya yaş ortalaması 60.9±13.5 yıl olan 82 erkek (%54.7) ve 68 kadın (%45.3) olmak üzere toplam 150 hasta alındı. Holter sonuçlarına göre hastalar subklinik AF (n=54) ve sık EAK'lar (n=96) olmak üzere iki gruba ayrıldı. Hastanede yatış sırasında subklinik AF kolunda 6 hastada (%11) ve sık EAK kolunda 26 hastada (%26) tekrarlayan iskemik inme gözlendi (p=0.03). Altı hasta öldü, bunlardan 4'ü hastanede tekrarlayan inme olayından sonra öldü. Tek değişkenli analizde yaş [OR: 1.03, 95%CI (1-1.07), p=0.02], dislipidemi [OR: 2.68, 95%CI (1.16-6.18), p=0.021] ve sık EAK'lar [OR: 2.97, 95%CI (1.13-7.76), p=0.026] tekrarlayan inmenin anlamlı öngörücüleri olarak bulundu. Ayrıca, çok değişkenli lojistik regresyon analizinde sadece sık EAK'lar [OR: 2.69, 95%CI (1-7.17), p=0.048] tekrarlayan inmenin bağımsız öngördürücüleri olarak bulundu.

Sonuç: Holter analizinde sık görülen EAK'lar, tekrarlayan iskemik inme ile önemli ölçüde ilişkiliydi.

Anahtar kelimeler: Sık EAK, subklinik AF, tekrarlayan inme, Holter-EKG.

INTRODUCTION

Globally, stroke is the second highest cause of death[1]. Ischemic stroke is the most prevalent form of stroke. Cardioembolic ischemic strokes account for 25–35 % of all ischemic strokes, and it is known that a significant number of cardioembolic ischemic strokes are caused by paroxysmal atrial fibrillation (AF) which can be difficult to diagnose[2]. Subclinical AF can also be encountered in long-term rhythm monitoring, but this is not enough to explain the etiology of cardioembolic strokes[3].

Premature atrial contractions (PACs) are generally seen in 8–20% of benign arrhythmias[4]. PACs have long been regarded as clinically insignificant when observed on a continuous ECG monitor (Holter). However, they have recently been researched to predict subclinical AF in healthy adults and stroke patients. Increased atrial ectopic activity is related to a raised risk of AF, but a direct association has not been established[5]. Beyond incident AF, a link was identified between frequent PACs and stroke, however, the prognostic importance of PACs in ischemic stroke patients remains unclear. It remains unclear whether excessive PACs are a risk for recurrent ischemic stroke[6]. Recent studies on ischemic stroke have shown a positive relationship between PAC frequency and recurrent ischemic stroke[7].

This study aims to research whether PACs, which are common in patients with sinus rhythm presenting with ischemic stroke, are linked to a raised risk of recurrent stroke.

METHODS

Study design and subject

Patients hospitalized in the intensive care unit with acute ischemic stroke between 2017 and 2021 were included in this study. The World Health Organization criteria were used to define

a stroke, and patients were enrolled in the study within 48 hours of stroke onset[8]. Magnetic resonance and computed tomography imaging scans made the distinction between hemorrhagic and ischemic strokes. The study included. 188 consecutive patients with ischemic stroke with sinus rhythm. Patients with preexisting AF, active cancer, chronic obstructive pulmonary disease, hyperthyroidism, and chronic renal failure were excluded from the study. Patients whose data was inaccessible and Holter analysis unsuccessful were also excluded from the study.

Study protocol

Routine blood tests were performed for all patients. An ECG was performed on each patient before treatment, using an electrocardiograph (model ECG-1350K Nihon-Kohden Corporation) at 25mm/s and 10 mm/mV amplitude. As part of standard care, patients underwent a 24-hour standard three-lead (V1, V2, and V5) Holter ECG (Northeast Monitoring, Maynard, MA) monitoring for up to seven days. Based on the Holter findings, patients were separated into subclinical AF and frequent PACs groups. Figure 1 shows the flow diagram of the patients.

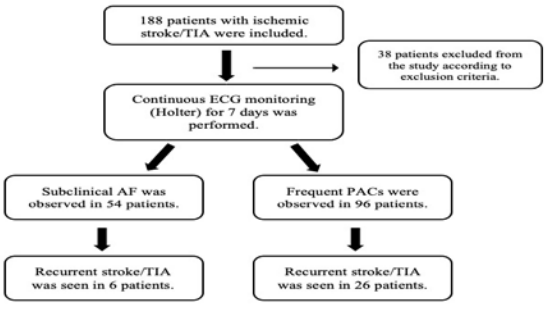

Figure 1. Study flow diagram.

Definitions and Holter recordings

The Holter ECG was worn by trained and experienced personnel. An experienced observer who was blind to patient data analyzed the Holter recordings.

Two types of atrial ectopic activity were examined: several isolated PACs and runs of PACs, identified as three or more consecutive PACs with a cycle length of 30 seconds or less[9]. An isolated PAC is characterized by a premature P (the coupling interval to the preceding QRS complex was required 75% of the average RR interval preceding the event) and similar or identical QRS complexes to ordinary sinus beats[10]. We defined frequent PACs based on a threshold established at the highest percentile for the amount of PAC runs and the frequency of PACs. This definition of PAC frequency is commonly utilized by others[11]. Accordingly, frequent PACs were defined as >3 runs of PACs per 24 hours and >14 PACs per hour.

Subclinical AF was defined according to the 2021 ESC guideline12. Clinically AF: established asymptomatic or symptomatic AF using surface ECG. A minimum of 30 seconds or a complete 12-lead ECG is required to diagnose clinical AF. Subclinical AF was defined as atrial fibrillation, atrial flutter, or atrial tachycardia events detected by implantable or wearable cardiac devices in people without AF and AF symptoms.

Additionally, in our investigation, a recurrent stroke was defined as a new stroke event that occurred during hospitalization following the initial event.

Statistics

The IBM SPSS 26.0 package program was used for the analysis. According to the Holter results, patients were separated into two groups: those with subclinical AF and those with frequent PACs. The demographic and laboratory data of the two groups were analyzed. Initial continuous variables were represented by mean ± standard deviation or median (interquartile range). The normality distribution of the variables was analyzed utilizing the Kolmogorov–Smirnov, and Shapiro–Wilk tests. Categorical variables were shown as frequency and percentages. For

categorical variables, the chi-square test or Fisher's exact test was utilized. As appropriate, the student t-test or the Mann–Whitney U-test was employed to compare continuous variables. Univariate and multivariate logistic regression analyses were used to evaluate independent predictors of covariates that cause recurrent stroke predictors. Covariates with a p-value <0.05 were added, to the multivariate model. If the p-value of a test was less than 0.05, it was deemed statistically significant.

RESULTS

150 patients, consisting of 82 men (54.7% of the total) and 68 women (45.3%), with an average age of 60.913.5 years, were enrolled in the research. Based on the Holter findings, patients were separated into subclinical AF (n=54) and frequent PACs (n=96). The patients' baseline demographic and hematological parameters were shown in Tables I and II respectively. Recurrent stroke was found higher in the frequent PACs group than in the subclinical AF group [26 (27%) vs. 6 (11%), p=0.03, respectively] (Table I). Six patients died of whom four died after a recurrent stroke event in the hospital. The bar chart of the groups was also visualized in Figure 2. There were no substantial differences in hematological and biochemical parameters as shown in Table II. To identify independent factors of recurrent stroke, univariate and multivariate analyses of logistic regression were conducted. In univariate analysis age [OR: 1.03, 95%CI (1-1.07), p=0.02], dyslipidemia [OR: 2.68, 95%CI (1.16-6.18), p:0.021] and frequent PACs [OR: 2.97, 95%CI (1.13-7.76), p=0.026] were found significant predictors of recurrent stroke. Furthermore, in multivariate logistic regression analysis only frequent PACs [OR: 2.69, 95%CI (1-7.17), p=0.048] was found independent predictors of recurrent stroke (Table III).

Table I: Clinical characteristics of the patients

PARAMETERS	Total *N=150*	Subclinical AF *N=54*	Frequent PACs *N=96*	*P*-Value
Age (Years)	60.9±13.5	60.3±11.2	61.2±14.6	0.691
Gender, female, n (%)	68 (45.3)	19 (35.2)	49 (51.0)	0.061
In-hospital mortality, n (%)	6 (4)	4 (7.4)	2 (2.1)	0.124
Hypertension, n (%)	62 (41.3)	17 (31.5)	45 (46.9)	0.066
Diabetes mellitus, n (%)	51 (34)	15 (27.8)	36 (37.5)	0.228
DL, n (%)	37 (24.7)	10 (18.5)	27 (28.1)	0.190
Smoker, n (%)	79 (52.7)	25 (46.3)	54 (56.3)	0.241
Recurrent stroke, n (%)	32 (21.3)	6 (11.1)	26 (27.0)	**0.030**

Data are expressed as mean SD, number (percentage), or median (interquartile range) as appropriate. DL: dyslipidemia.

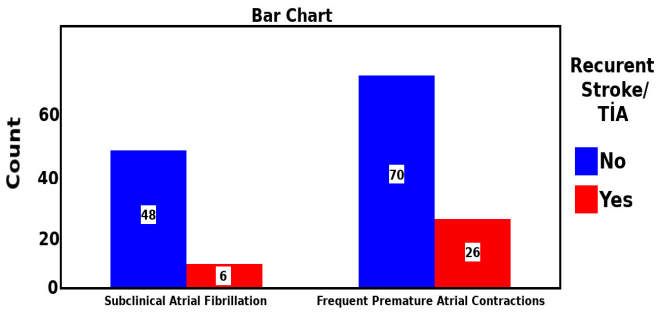

Figure 2. Bar chart of groups according to the number of patients with recurrent stroke

Table II: Hematological and biochemical parameters of patients

PARAMETERS	Total*N=150*	Subclinical AF *N:54*	Frequent PACs *N=96*	*P*-Value
White blood cell count (×10^{3}µL)	11.6±3.05	11.9±2.74	11.5±3.22	0.410
Neutrophils (×10^{3}µL)	6.3 (3.3)	6.46 (3.34)	6.30 (3.39)	0.813
Lymphocytes (×10^{3}µL)	2.7 (2.3)	3.55 (2.63)	2.53 (1.84)	0.044
Hemoglobin (g/dl)	13.4±1.64	13.7±1.38	13.3±1.76	0.119
Sodium (meq/L)	140 (5.0)	140 (5)	140 (3.75)	0.619
Potassium (meq/L)	4.15±0.57	4.23±0.44	4.11±0.63	0.224
Glucose (mg/dl)	120 (34.2)	122 (33.2)	118 (31.5)	0.333
Creatine (mg/dl)	0.87 (0.32)	0.86 (0.33)	0.88 (0.33)	0.801
Total cholesterol (mg/dl)	164 (68.2)	166 (71.7)	164 (68)	0.355
Triglyserides (mg/dl)	109 (46)	118 (63.2)	100 (44.5)	0.340
LDL (mg/dl)	106 (42.5)	112 (44.4)	105 (46.5)	0.154
HDL (mg/dl)	42 (16.3)	42 (17.3)	42 (14.3)	0.664
eGFR	95.5 (37.9)	96.5 (36.4)	94 (38.5)	0.925

Data are expressed as mean ± SD and median [interquartile range] as appropriate. LDL: low-density lipoprotein, HDL: high-density lipoprotein, eGFR: estimated glomerular filtration rate.

Table III: Independent predictors for recurrent stroke by multivariate logistic regression analysis

Parameters	Univariate analysis		Multivariate analysis	
	OR (95% CI)	*P*-Value	OR (95% CI)	*P*-Value
Age	1.03 (1.0-1.07)	**0.020**	1.03 (0.99-1.06)	0.059
Sex	0.78(0.35-1.73)	0.547	*	
Dyslipidemia	2.68 (1.16-6.18)	**0.021**	2.10 (0.87-5.06)	0.095
Hypertension	1.83 (0.83-4.04)	0.130	*	
Diabetes mellitus	1.44 (0.64-3.21)	0.374	*	
Smoker	0.45 (0.20-1.02)	0.056	*	
Frequent PACs	2.97 (1.13-7.76)	**0.026**	**2.69 (1.0-7.17)**	**0.048**

PACs; premature atrial contractions.

DISCUSSION

In this cross-sectional research of ischemic stroke patients in sinus rhythm, frequent PACs were observed to be related to a raised risk of recurrent stroke.

Excessive sympathetic stimulation develops due to autonomic dysfunction. The catecholamines are released. ECG abnormalities and myocardial injury are observed because of contractile dysfunction and electrolyte imbalance due to oxidative stress and calcium release. The developing systemic inflammatory response leads to microvascular spasms in the endothelium with the release of cytokines, which can lead to ischemic events by damaging atherosclerotic plaques[13-15]. Occasionally, PACs and AF can occur as a result of autonomic dysfunction due to excessive release of catecholamines after ischemic cerebrovascular obstructive disease. This event can lead to recurrent strokes.

The exact duration of clinically significant AF, which might raise thromboembolic risk, is uncertain and is being researched in multicenter trials, such as ARTESIA[16]. In the CRYSTAL-AF study, an episode of atrial fibrillation was defined as 30 seconds[17]. It has been reported that more than 25% of all strokes result from paroxysmal AF[18]. AF is difficult to detect because of its paroxysmal nature and the fact that it is frequently asymptomatic. Raza et al. calculated the rate of AF development at the age of 40–75 years as 24%[19]. In our study, the mean age was found 60.9±13.5 years and the rate of AF development was calculated as 36% between the ages of 40–75 years. This difference is caused by subclinical AF was not calculated. After all, it could not be determined accurately.

Frequent PACs, which are placed somewhere between sinus rhythm and AF, are increasingly attracting attention[20,21]. Ofoma et al. argued that AF-related stroke develops as a result of PACs[22]. A recent study reported that PACs developed due to early ventricular contractions (PVCs); subclinical AF was observed, and ischemic stroke developed due to it[23]. Conversely, another study reported that frequent PACs trigger PVCs and cause cryptogenic stroke[24]. In contrast, Engström et al. identified frequent PACs as independent risk factors for stroke[25]. Larsen et al. reported that the risk of ischemic stroke was approximately twice as high in patients with frequent PACs[26]. In our study, recurrent stroke due to frequent PACs developed at a rate of 26% without the development of subclinical AF on Holter ECG for 7 days follow-up ($p<0.05$). As a result of 14-day ambulatory heart rhythm monitoring, Rooney et al. found a relationship between PACs load and cognitive function in patients without AF rhythms[27]. They found that these patients had a cognitive executive function, with a brain age of 5-7 years older. MRI images of dementia showed that it developed as a result of stroke[28]. Veltkamp et al. stated that 15% of patients with excessive PACs had a recurrent ischemic stroke in the first year[29]. In our study, this rate was 21%.

Still poorly understood are the factors that contribute to a high risk of recurrent stroke. Zheng et al. reported that hypertension, excessive PACs, atrial fibrillation, diabetes

mellitus, and coronary heart disease were linked to an increased risk of stroke recurrence[30]. According to Zhao et al, strict glycemic control might enhance the prognosis of stroke patients and prevent recurrency[31]. Kitagawa et al. reported that intensive blood pressure lowering tended to reduce stroke recurrence[32]. The updated meta-analyses supported a target blood pressure of less than 130/80 mm Hg in recurrent stroke prevention[33].

In studies, there is no standardized approach to defining recurrent stroke. Authors have used varying criteria or have not reported the criteria. In the routine data research conducted by van den Bussche et al., a minimum of seven days was employed between discharge following the initial stroke and readmission[34]. A majority of researchers have used a minimum interval of twenty-one days between the initial event and recurrence[35]. In our study, this period was accepted as 7 days.

Absolute and relative risks of a second stroke are highest early after the initial stroke but remain increased for several years afterward[36]. In the study of Aked et al., recurrent stroke risk was 13% early after the first stroke by 1 year[37]. After the initial year, the annual average risk was approximately 4%. In line with this, O'Neal et al. reported a raised risk of recurrent ischemic stroke in patients who had frequent PACs at an 8-year follow-up[38]. Secondary prevention efforts should be undertaken as soon as possible and continued for many years for maximum benefit[39]. Current guidelines do not recommend antiarrhythmic treatment for frequent PACs. Considering that PACs are precursors of recurrent stroke, anticoagulants, and antiarrhythmics should be started.

Our study has several limitations. The study population was small. Holter was performed for only 7 days. It is not known whether patients in the frequent PACs group develop AF or recurrent stroke after discharge. In the future, it could be possible to use implantable loop recorders. The threshold for frequent PACs was arbitrary because there is no accepted threshold. In previous investigations, however, the same cutoffs used for frequent PACs were proven to be diagnosis beneficial for stroke patients.

CONCLUSION

In our patient cohort with ischemic stroke in sinus rhythm, frequent PACs were significantly related to a raised risk of recurrent stroke. This result suggests that the assumption of PACs as a benign finding on the Holter should be reconsidered. More studies are needed to determine the cutoff value for frequent PACs causing the recurrent stroke.

Ethical Committee Approval: The Ethics Commission of Gazi Yaşargil Training and Research Hospital authorized the study and waived the necessity for informed consent (No: 2022-37 Date: February 25th, 2022) The present manuscript was conducted in line with the provisions of the Declaration of Helsinki (2013).

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

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