Relationship Between Autonomic Nervous System Activity and Recurrence After Cryoballoon Ablation in Patients with Paroxysmal Atrial Fibrillation

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ABSTRACT

Introduction: In this study, we aimed to investigate the relationship between autonomic dysfunction (AD) determined according to the blood pressure (BP) and heart rate (HR) response in exercise treadmill test (ETT) prior to cryoballoon ablation (CBA), and the recurrence of atrial fibrillation (AF) after CBA in patients with paroxysmal AF.

Patients and Methods: Seventy-six patients (mean age 53 ± 11 years, 61.8% male) with paroxysmal AF who underwent CBA were enrolled. Before CBA the ETT was performed by all patients. BP and HR responses in ETT were compared between patients with and without AF recurrence.

Results: AD rate was significantly higher in the group with recurrence compared to the non-recurrent group (p< 0.001). In addition to AD, age, female gender, and lower exercise capacity were also associated with post-CBA AF recurrence (p> 0.05 for all). Examining AD parameters, systolic blood pressure at peak exercise (SBPpeak) (p< 0.001) and diastolic blood pressure at peak exercise (DBPpeak) (p< 0.001), slow heart rate recovery (HRR) (p< 0.001) were significantly higher in the recurrent group.

Conclusion: AD may be associated with AF recurrence after CBA in patients with paroxysmal AF. SBPpeak, DBPpeak, and slow HRR appear to be predictors of AF recurrence after ablation.

Key Words: Atrial fibrillation; autonomic nervous system; catheter ablation

Paroksismal Atriyal Fibrilasyonlu Hastalarda Ablasyon Sonrası Rekürrens ile Otonom Sinir Sistemi Aktivitesi Arasındaki İlişkinin Değerlendirilmesi

ÖZET

Giriş: Çalışmamızda lone atriyal fibrilasyonlu (AF) hastalarda, cryobalon ablasyon (CBA) öncesi yapılan egzersiz treadmil testinde (ETT) bakılan kan basıncı ve kalp hızı yanıtına göre tespit edilen otonomik disfonksiyon (OD) ile CBA sonrası AF rekürrensi arasındaki ilişkiyi değerlendirmeyi amaçladık.

Hastalar ve Yöntem: Çalışmaya cryobalon ablasyon yapılan 76 hasta (ortalama yaş 53 ± %11, 61.8 erkek) alındı. CBA öncesi tüm hastalara ETT yapıldı. AF rekürrensi ablasyon sonrası üç, altı, dokuz ve 12. aylarda değerlendirildi ve kaydedildi. ETT deki kan basıncı ve kalp hızı yanıtı AF rekürrens görülen ve görülmeyen hastalarda karşılaştırıldı.

Bulgular: OD oranı rekürrens olan grupta rekürrens olmayan gruba göre anlamlı olarak yüksek saptandı [17 (%89.5) vs. 19 (%33.3), p< 0.001]. OD dışında yaş, kadın cinsiyet, düşük egzersiz kapasitesi, CBA sonrası AF rekürrens ile ilişkili bulunmuştur (p> 0.05 for all). OD parametreleri incelendiğinde, maksimum egzersizdeki sistolik kan basıncı (188.89 ± 28.13 vs 157.60 ± 28.82, p< 0.001), maksimum egzersizdeki diyastolik kan basıncı (87.47 ± 16.89 vs. 72.02 ± 15.43, p< 0.001), yavaş kalp hızı iyileşmesi [11 (%57.9) vs. 8 (%14), p< 0.001] CBA sonrası AF rekürrensi ile ilişkili bulunmuştur.

Sonuç: OD lone AF'li hastalarda CBA sonrası AF rekürrensi ile ilişkili olabilir. Maksimum egzersizdeki sistolik kan basıncı, maksimum egzersizdeki diyastolik kan basıncı, yavaş kalp hızı iyileşmesi ablasyon sonrası AF rekürrens prediktörü olarak bulunmuştur.

Anahtar Kelimeler: Atriyal fibrilasyon; otonom sinir sistemi; kateter ablasyonu

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INTRODUCTION

Paroxysmal atrial fibrillation (PAF) is one of the most common cardiac arrhythmias encountered in patients with or without structural heart disease[1,2]. Pulmonary vein isolation (PVI) is a major treatment for patients with atrial fibrillation (AF) refractory to antiarrhythmic drugs (AADs)[3,4]. As an alternative to radiofrequency catheter ablation, cryoballoon ablation (CBA) offers an effective and safe PVI method by which the tissue around the pulmonary vein is ablated with the use of ultra-cold energy[5-7].

The association between autonomic tonus and the onset of AF has been confirmed in several studies[8-11]. AF episodes in patients with pulmonary vein-based focal ectopia have been shown to result from fluctuations in autonomic tonus[12]. Some studies have evaluated the effect of the change in autonomic tonus on the recurrence of paroxysmal AF after ablation. However, for a specific population of patients with paroxysmal AF, the relation between autonomic activity determined by the exercise treadmill test (ETT) and recurrence of AF after ablation has not been investigated to date.

It is known that exaggerated blood pressure response to exercise (EBPR) is associated with increased sympathetic activity[13,14] while decreased blood pressure response (DBPR) is linked to decreased sympathetic activity[15,16], and reduced heart rate recovery (HRR) response is related to reduced parasympathetic activity[17,18]. The present study aims to investigate the relationship between autonomic dysfunction (AD) determined according to the blood pressure (BP) and heart rate (HR) response in ETT prior to CBA, and the recurrence of AF after CBA in patients with paroxysmal AF.

PATIENTS and METHODS

Study Population

A total of 97 paroxysmal AF patients refractory or intolerant to treatment with AADs were enrolled in this study. Informed consent was obtained from all patients before any study-related procedures and the study was approved by the local ethics committee. Patients underwent pulmonary vein (PV) tomography and three-dimensional reconstruction before CBA. Twenty-one patients with complex PV anatomy were excluded from the study. All patients were confirmed to have no structural heart disease based on medical history, physical examination, 12lead rest ECG, ETT, and echocardiography. Patients with cardiovascular disease history, ischemic heart disease, cardiomyopathy, valvular heart disease, heart failure, diabetes mellitus, hypertension, hyperthyroidism, hypothyroidism were excluded from the study. Patients with left bundle branch block in ECG recorded during the exercise stress test and those with any rhythm other than sinus rhythm, patients with resting systolic BP (SBPrest)≥ 140 mmHg, resting diastolic BP (DBPrest)≥ 90 mmHg, anginal chest pain during the exercise test, ischemic ST change at baseline or during the exercise test (≥1 mm ST-segment deviation) were not included in the study.

Exercise Treadmill Testing

After the written informed consent process, symptom-limited ETT was conducted using the Bruce protocol[19]. Age-predicted maximal HR was calculated using the formula: 220-age. BP was measured by an automated monitor (Suntech Tango; Suntech Medical, Morrisville, NC, USA) throughout ETT using the same arm and cuff that was used for the resting BP. The 12-lead ECG was monitored continuously, with BP values measured every three minutes and measurements of HR and BP recorded at the end of each 3-min stage, at peak exercise, and at 1-min and 2-min intervals throughout the recovery phase. Total exercise time was also recorded. Functional capacity was estimated in metabolic equivalents (METs) on the basis of the speed and grade of the treadmill[20]. During the recovery phase, subjects continued to walk for 60 seconds at a speed of 1.5 mph and then sat down for three minutes with continued monitoring of 12-lead ECG and BP. EBPR was identified by peak recorded BP≥ 190/105 mmHg (women) or ≥210/105 mmHg (men)[21]. DBPR was defined as a drop in systolic BP below the pretest value or an increase with a subsequent decrease in systolic BP of >10 mmHg with increasing workload/intensity[22,23]. HRR was calculated by subtracting the heart rate at one minute after the exercise from the maximal heart rate. Slow HRR response was defined as ≤12 beats/min.[24-26]. The presence of EBPR, DBPR, or slow HRR was defined as AD[13-18].

Ablation Procedure

The cryoballoon procedure was performed similarly to the CBA technique described elsewhere[27,28]. Punctures in the right femoral vein, left femoral vein, and left radial artery were performed with the Seldinger technique in patients who had CBA. A 6-French (F) decapolar catheter was placed in the coronary sinus (CS) via the left femoral vein. A diagnostic guidewire was advanced to the aortic root through the left radial artery in order to mark the aorta during the transseptal puncture. A 7F-long sheath was advanced to superior vena cava over a 0.38-inch guidewire from the right femoral vein. Transseptal puncture was performed with a Brockenbrough needle (St Jude Medical) under fluoroscopic guidance. Transesophageal echocardiography was used for selected patients with challenging punctures. A steerable 12F sheath (FlexCath®, Medtronic, USA) was advanced to the left atrium.

We used a 28-mm cryoballoon (Arctic Front® Cryocath and Aortic Front Advance, Medtronic, USA) for the ablation proce-

dure. The balloon was introduced into the PV ostium over an Achieve guidewire (Achieve®, Medtronic Ablation Frontiers, LLC, Carlsbad, USA), which is utilized for mapping PV potentials before, during, and after cryoapplications. Contrast agent was injected into the distal side of the balloon to visualize occlusion through an arctic front catheter. Cryothermic energy was delivered for three minutes per application and two applications were performed for each PV. If PV potentials were still present, one extra cryoballoon application was attempted as needed. Before targeting the right pulmonary veins, the decapolar CS catheter was positioned in the superior cava for continuous phrenic nerve stimulation during cryoapplication. After the procedure, the exit and entrance block of all PVs were confirmed by pacing maneuvers.

Follow-Up

Patients were scheduled for follow-up visits at three, six, nine, 12 months after CBA. AF recurrence was defined as the presence of any AF episode lasting more than 30 seconds on 12-lead ECG or 24-hour ambulatory ECG monitoring at these visits. Patients received treatment with propafenone or amiodarone for six weeks following the ablation. After six weeks of follow-up, AADs were discontinued. All patients were orally anticoagulated for three months following ablation and those with CHA2DS2-VASc score ≥2 received continuous oral-anticoagulant therapy. Procedural success was defined as freedom from any atrial arrhythmia lasting longer than 30 seconds at six weeks after discontinuing AAD therapy.

Statistical Analysis

The Shapiro-Wilk test was used to test the normality of distribution of continuous variables. Paired and unpaired continuous variables were compared using paired t, student t-test, Wilcoxon, and Mann-Whitney U test as appropriate, respectively. Categorical variables were compared using the Chi-square, Fisher's exact, or McNemar test. A two-tailed $p< 0.05$ was considered statistically significant.

RESULTS

Table 1 shows the baseline characteristics of the patients enrolled in the study. The study population consisted of 76 patients (47 males, 61.8%) and the mean age of the patients was 53 ± 11 years. Twenty patients (26.3%) were smokers, average BMI was 24 ± 4.6 kg/m^2, with average SBPrest 121 ± 13 mmHg, DBPrest 76 ± 9 mmHg, HR 77 ± 15, left atrial diameter (LAD) 3.6 ± 0.9 cm, and left ventricular ejection fraction (LVEF) 62 ± 1.0%. The average procedure time was 66 (82-55) mins, with fluoroscopic time 19 ± 1.2 mins and application time 38 ± 9.6 mins, and the number of applications was 8 ± 0.9, and temperature 42.3 ± 1.6°C.

Table 1. Baseline clinical, procedural and laboratory characteristics of the patients

	n= 76
Age (years)	53 ± 11
Gender, n (male %)	47 (61.8%)
Current smoking, n (%)	20 (26.3%)
BMI (kg/m^2)	24 ± 4.6
SBPrest (mmhg)	121 ± 13
DBPrest (mmhg)	76 ± 9
HRrest (beat)	77 ± 15
LAD (cm)	3.6 ± 0.9
LVEF (%)	62 ± 1.0
Ablation procedure	
Procedure time (mins)	66 (82-55)
Fluoroscopic time (mins)	19 ± 1.2
Application duration (mins)	38 ± 9.6
Number of applications	8 ± 0.9
Temperature (ºC)	-42.3 ± 1.6
Balloon Type	
Arctic FrontTM Medtronic Cryocath n (%)	32 (42.1%)
Aortic Front Advance n (%)	44 (57.9%)
Laboratory	
White Blood Cells (μl)	7.8 ± 1.6
Hemoglobin (g/dL)*	13.12 ± 1.60
Creatinine (mg/dL)	0.8 ± 0.8
Medications	
Beta blocker, n (%)	33 (43.4%)
Amiodarone, n (%)	5 (6.6%)
Propafenon, n (%)	24 (31.6%)
Asa, n (%)	4 (5.3%)
Dabigatran, n (%)	2 (2.6%)
Rivaroxaban, n (%)	5 (6.6)
Apixaban	2 (2.6)
Edoxaban	2 (2.6)

BMI: Body mass index, DBPrest: Diastolic blood pressure at rest, HRrest: Heart rate at rest, LAD: Left atrial diameter, LVEF: Left ventricular ejection fraction, SBPrest: Systolic blood pressure at rest.

AD was detected in 36 (47.3%) patients. DBPR and EBPR were observed in 8 (22.2%) and 19 (52.8%) of the patients, respectively. Moreover, slow HRR was detected in 19 (52.8%) out of 36 patients. In 10 (27.8%) of the 36 patients, AD was detected according to both HRR and BP responses.

Table 2. Clinical, procedural, and laboratory characteristics and comparison of patients with and without autonomic dysfunction

	AD+	AD-	
	n= 36	n= 40	p
Age (years)	53.97 ± 12	52.23 ± 10	0.509
Gender, n (male %)	22 (61.1%)	25 (62.5%)	0.544
Current smoking, n (%)	12 (33.3%)	8 (20%)	0.188
BMI (kg/m^2)	24 ± 3.9	24 ± 4.9	0.980
LAD (cm)	3.7 ± 0.3	3.6 ± 0.4	0.225
LVEF (%)	62 ± 2.8	61 ± 4	0.215
SBPrest (mmhg)	121.00 ± 13	122.20 ± 13	0.693
DBPrest (mmhg)	76.97 ± 9.5	75.63 ± 10.2	0.556
SBPpeak (mmhg)	174.36 ± 40	157.38 ± 17	**0.018**
DBPpeak (mmhg)	78.22 ± 21	73.78 ± 11	0.260
HRrest (beat)	74 ± 16	80.10 ± 13	0.096
HRpeak (beat)	185.11 ± 22	152.85 ± 20	0.373
Exercise capacity(mets)	9.7 ± 2.4	10.8 ± 2.2	0.055
Recurrence, n (%)	17 (47.2%)	2 (5%)	**<0.001**
Ablation procedure			
Procedure time (mins)	65 (83-54)	67 (84-53)	0.710
Fluoroscopic time (mins)	18 ± 5.4	19 ± 5.8	0.440
Application duration (mins)	39 ± 5.8	38 ± 5.6	0.970
Number of applications	8 ± 0.8	8 ± 0.9	0.890
Temperature (ºC)	-42.5 ± 1.7	-42.1 ± 1.5	0.910
Balloon Type			
Arctic Front® Medtronic Cryocath n (%)	15 (41.6%)	17 (42.5%)	0.416
Aortic Front Advance n (%)	21 (58.4)	23 (57.5%)	0.790
Laboratory			
White Blood Cells (μl)	7.1 ± 1.8	8.3 ± 1.7	0.062
Hemoglobin (g/dL)*	12.85 ± 1.25	13.33 ± 1.95	0.142
Creatinine (mg/dL)	0.8 ± 0.1	0.9 ± 0.3	0.060
Medications			
Beta blocker, n (%)	18 (50%)	15 (37.5%)	0.272
Amiodarone, n (%)	2 (5.6%)	3 (7.5%)	0.733
Propafenone, n (%)	12 (33.3%)	12 (30%)	0.755
Asa, n (%)	1 (2.8%)	3 (7.5%)	0.357
Dabigatran, n (%)	0	2 (5%)	
Rivaroxaban, n (%)	5 (6.6%)	4 (10%)	0.205
Apixaban	0	2 (5.6%)	
Edoxaban	1 (2.8%)	1 (2.5%)	0.940

AD: Autonomic dysfunction, BMI: Body mass index, DBPpeak: Diastolic blood pressure at peak exercise, DBPrest: Diastolic blood pressure at rest, HRpeak: Heart rate at peak exercise, HRrest: Heart rate at rest, LAD: Left atrial diameter, LVEF: Left ventricular ejection fraction, SBPpeak: Systolic blood pressure at peak exercise, SBPrest: Systolic blood pressure at rest.

Table 2 compares the characteristics of patients with and without AD. Mean age, percentage of the male sex, smoking rate, average BMI, LAD, and LVEF were similar in these two groups (p> 0.05 for all). SBPrest, DBPrest, diastolic blood pressure at peak exercise (DBPpeak), heart rate at rest (HRrest), heart rate at peak exercise (HRpeak), and exercise capacity were similar in both groups (p> 0.05 for all). Systolic blood pressure at peak exercise (SBPpeak) was significantly higher in the group of patients with AD (174.36 ± 40 vs. 157.38 ± 17, p= 0.018). The rate of AF recurrence after ablation was significantly higher in the group with AD than in the group without AD (17 (47.2%) vs. 2 (5%), p= <0.001). Procedural and laboratory parameters were found to be comparable across the two groups (p> 0.005 for all). Drug use was similar in both groups (p> 0.05 for all).

Table 3 compares the characteristics of patients with AD. In patient groups diagnosed with AD based on BP response alone, HRR alone, or both, all features were similar (p> 0.05 for all) except for SBPrest. SBPrest was significantly higher in the group with AD detected by both BP and HRR (117.94 ± 8.1 vs. 117.22 ± 13.6 vs. 129.60 ± 15.61, p= 0.040).

Table 4 compares the characteristics of patients with and without recurrence after CBA. The mean age in the recurrent group was significantly higher than that in the nonrecurrent group (58 ± 11 vs 51 ± 10, p= 0.010). The percentage of males was significantly lower in the group with recurrence (7 (36.8%) vs 40 (70.2%) p= 0.010). Exercise capacity was significantly lower in the group with recurrence (8.9 ± 2.7 vs 10.7 ± 2, p= 0.004). AD rate was significantly higher in the group with recurrence compared to the nonrecurrent group (17 (89.5%) vs. 19 (33.3%), p< 0.001). Procedural aspects, laboratory parameters, and drug use were similar in the two groups (p> 0.05 for all).

Table 5 shows the comparison of AD parameters separately, in the groups with and without recurrence. The number of patients with slow HRR in the recurrent group was significantly higher than that in the nonrecurrent group (11 (57.9%) vs. 8 (14%), p< 0.001). SBPrest, DBPrest, HRrest, HRpeak, were similar in both groups (p> 0.05 for all). SBPpeak (188.89 ± 28.13 vs 157.60 ± 28.82, p< 0.001) and DBPpeak (87.47 ± 16.89 vs. 72.02 ± 15.43, p< 0.001) were significantly higher in the recurrent group.

DISCUSSION

In our study, the relationship between AD and AF recurrence after CBA was examined by using the ETT as a detection tool.

i. Post-CBA AF recurrence rate was significantly higher in the patient group with AD than in the group without AD.

ii. Examining AD parameters, post-CBA AF recurrence was found to be associated with slow HRR, SBPpeak, and DBPpeak.

iii. In addition to AD, age, female gender, and lower exercise capacity were also associated with post-CBA AF recurrence.

The role of autonomic tone in AF development has been clinically recognized for several years[8,29]. ETT is one of the ways of evaluating autonomic nervous system activity in clinical cardiology. EBPR and low HRR response are known signs of increased sympathetic system activity, while DBPR is an indication of increased parasympathetic system activity[13-18,30]. To date, many studies have been conducted to investigate the relationship between AF and autonomic tonal variations, and the results have been controversial[31-36]. In some studies conducted by analyzing HR variability (HRV), increased sympathetic tone or vagal tone reduction was observed prior to postoperative PAF[31], before PAF during sleep[33], and in some paroxysmal AF patients[34]. In different studies, an increase in vagal tone was observed in some patients with paroxysmal AF and some particularly young patients with nocturnal AF[34,35,37]. The study by O'Neal et al. suggested that DBPR could be a risk factor for the development of AF[36]. In our study, paroxysmal AF patients with a mean age of 53 years were examined and 47.3% of them were diagnosed with AD. While 22.2% of these patients were monitored with DBPR, 52.8% were monitored with EBPR, and 52.8% with slow HRR. In our study, similar to previous studies, both vagal and sympathetic tone increases were present in patients with AF, and the proportion of patients with increased sympathetic tone was higher. This may be resulting from various factors such as diversity of the patient population, AFtriggering factors, differences in methods used to detect autonomic tone.

There are many parameters that affect post-CBA AF recurrence. Different results were obtained in studies that demonstrated the relationship between the change in autonomic tonus and postablation recurrence. In the study by Kanda and his colleagues, HRV analysis was carried out before and after CBA and the relationship between autonomic nervous system activity and recurrence was evaluated. Paroxysmal AF patients were included in the study and while the findings of their study show increased vagal tone in HRV parameters of patients with recurrence [increased root-mean-square differences of successive R-R intervals (RMSSD) and HF, decreased Low-Frequency power (LF)/High-Frequency power (HF)] and a decrease in these parameters for the group without recurrence after ablation, there was no reduction in the parameters (LF/HF) of sympathetic system activation in the group with recurrence[38]. In another study, chronotropic indexes, HRrest, and HRR index parameters measured in pre-CBA ETT were observed to decrease after ablation, and no difference was observed in these parameters between the group with recurrence and the nonrecurrence group[39].

Table 3. Comparison of patients with autonomic dysfunction

	According to only BP response	According to only HRR response	According to BP and HRR response	
	n= 17	n= 9	n= 10	p
Age (years)	53.76 ± 10	51.22 ± 14	56.80 ± 13	0.610
Gender, n (male %)	13 (10.4%)	6 (66.7%)	3 (30%)	0.053
Current smoking, n (%)	9 (52.9%)	2 (22.2%)	1 (10%)	0.053
BMI (kg/m^2)	24 ± 5.9	23 ± 4.8	25 ± 3.7	0.225
SBPrest (mmhg)	117.94 ± 8.1	117.22 ± 13.6	129.60 ± 15.61	**0.040**
DBPrest (mmhg)	77.71 ± 8.7	73.33 ± 11	79.00 ± 9.6	0.408
SBPpeak (mmhg)	178.41 ± 44.4	154.22 ± 10	185.60 ± 46.8	0.209
DBPpeak (mmhg)	77.24 ± 24.7	76.22 ± 13.9	81.70 ± 23	0.835
HRrest (beat)	68.53 ± 17.1	78.56 ± 12.5	80.3 ± 14.6	0.120
HRpeak (beat)	225.59 ± 29.7	148.22 ± 26	149.50 ± 26.16	0.613
Exercise capacity (mets)	10.35 ± 2.0	9.6 ± 2.3	8.8 ± 2.9	0.282
LAD (cm)	3.7 ± 0.2	3.8 ± 0.1	3.6 ± 0.4	0.380
LVEF (%)	62 ± 2.9	64 ± 0.9	63 ± 1.9	0.125
Recurrence, n (%)	6 (35.3%)	5 (55.6%)	6 (60%)	0.391
Ablation procedure				
Procedure time (mins)	61 (80-50)	59 (78-47)	64 (83-54)	0.320
Fluoroscopic time (mins)	18 ± 3.5	19 ± 2.5	20 ± 3,9	0.770
Application duration (mins)	38 ± 5.1	37 ± 4.5	39 ± 4.8	0.810
Number of applications	7 ± 0.9	8 ± 0.5	9 ± 0.3	0.122
Temperature (ºC)	-41.5 ± 1.5	-42.3 ± 1.2	-42 ± 1.7	0.880
Balloon Type				
Arctic FrontTM Medtronic Cryocath n (%)	6 (35.2%)	4 (44.4%)	5 (50%)	0.435
Aortic Front Advance n (%)	11 (66.7)	5 (55.5%)	5 (50%)	0.678
Laboratory				
White Blood Cells (μl)	8.1 ± 1.9	8.5 ± 1.3	7.6 ± 1.5	0.678
Hemoglobin (g/dL)*	13.23 ± 1.54	12.5 ± 1.73	12.8 ± 2.15	0.546.
Creatinine (mg/dL)	0.5 ± 0.2	0.7 ± 0.2	0.6 ± 0.9	0.440
Medications				
Beta blocker, n (%)	9 (52.9%)	5 (55.6%)	4 (40%)	0.752
Amiodarone, n (%)	0	0	2 (20%)	
Propafenone, n (%)	7 (41.2%)	2 (22.2%)	12 (33.3%)	0.60
Asa, n (%)	1 (5.9%)	0	0	
Dabigatran, n (%)	1 (100%)	9 (100%)	10 (100%)	36
Rivaroxaban, n (%)	0	0	1 (2.8%)	
Apixaban	1 (5.9%)	1811.1%)	0	
Edoxaban	0	0	1 (10%)	

BMI: Body mass index, BP: Blood pressure, DBPpeak: Diastolic blood pressure at peak exercise, DBPrest: Diastolic blood pressure at rest, HRrest: Heart rate at rest, HRR: Heart rate recovery, LAD: Left atrial diameter, LVEF: Left ventricular ejection fraction, SBPpeak: Systolic blood pressure at peak exercise, SBPrest: Systolic blood pressure at rest.

Table 4. Clinical, procedural, and laboratory characteristics and comparison of patients with and without recurrence

	Recurrence+	Recurrence-	
	n= 19	n= 57	p
Age (years)	58 ± 11	51 ± 10	0.010
Gender, n (male %)	7 (36.8%)	40 (70.2%)	0.010
Current smoking, n (%)	5 (26.3%)	15 (26.3%)	1
BMI (kg/m^2)	24 ± 3.9	24 ± 4.9	0.669
Exercise capacity (mets)	8.9 ± 2.7	10.7 ± 2	**0.004**
LAD (cm)	3.8 ± 0.1	3.7 ± 0.3	0.678
LVEF (%)	64 ± 2	63 ± 6.7	0.098
AD, n (%)	17 (89.5%)	19 (33.3%)	**<0.001**
Ablation procedure			
Procedure time (mins)	63 (80-51)	65 (82-53)	0.545
Fluoroscopic time (mins)	19 ± 6.4	20 ± 5.4	0.443
Application duration (mins)	39 ± 6.9	42 ± 5.1	0.119
Number of applications	7 ± 0.8	9 ± 0.5	0.080
Temperature (ºC)	-42.5 ± 1.7	-41.4 ± 1.4	0.190
Balloon Type			
Arctic FrontTM Medtronic Cryocath n (%)	7 (36.8%)	25 (43.8%)	0.575
Aortic Front Advance n (%)	12 (63.2)	32 (56.2%)	0.579
Laboratory			
White Blood Cells (μl)	11.6 ± 2.4	12.6 ± 1.4	0.231
Hemoglobin (g/dL)*	13.23 ± 1.33	12.53 ± 1.41	0.211
Creatinine (mg/dL)	0.7 ± 0.3	0.5 ± 0.4	0.098
Medications			
Beta blocker, n (%)	11 (57.9%)	22 (38.6%)	0.142
Amiodarone, n (%)	2 (10.5%)	3 (5.3%)	0.423
Propafenone, n (%)	7 (36.8%)	17 (29.8%)	0.569
Asa, n (%)	0	4 (7%)	
Dabigatran, n (%)	0	2 (3.5%)	
Rivaroxaban, n (%)	1 (5.3.%)	4 (7%)	0.789
Apixaban	2 (10.5%)	0	
Edoxaban	0	2 (3.5%)	

AD: Autonomic dysfunction, BMI: Body mass index, LAD: Left atrial diameter, LVEF: Left ventricular ejection fraction.

In the present study, the patients who formed the study group were only paroxysmal AF patients who were confirmed to have no structural heart disease thereby representing a more specific group than other studies. In our study, the rate of AF recurrence was found to be high in the group of patients with AD detected by ETT. When the BP and HR parameters were examined separately, SBPpeak, DBPpeak, and slow HRR were found to be associated with AF recurrence, however, the change in these parameters was not evaluated after ablation. PVs have a rich neural network supplied by the bilateral vagus nerve and cervical sympathetic ganglia and truncus[40]. The autonomic nervous system regulates the atrial refractoriness and transmission velocity, which are important mechanisms in the development of AF[41]. Despite ablation in patients with high

Table 5. Comparison of autonomic dysfunction parameters of patients with and without recurrence

	Recurrence+	Recurrence-	
	n= 19	n= 57	p
HRR	11 (57.9%)	8 (14%)	**<0.001**
SBPrest (mmhg)	125.26 ± 12.28	120.42 ± 13.22	0.164
DBPrest (mmhg)	78.79 ± 9.13	75.42 ± 10.05	0.200
SBPpeak (mmhg)	188.89 ± 28.13	157.60 ± 28.82	**<0.001**
DBPpeak (mmhg)	87.47 ± 16.89	72.02 ± 15.43	**<0.001**
HRrest (beat)	73.47 ± 17.21	78.65 ± 14.32	0.199
HRpeak (beat)	214.26 ± 31.24	214.26 ± 31.24	0.139

DBPpeak: Diastolic blood pressure at peak exercise, DBPrest: Diastolic blood pressure at rest, Hedef HR: HRpeak heart rate at peak exercise, HRrest: Heart rate at rest, LAD: Left atrial diameter, LVEF: Left ventricular ejection fraction, SBPpeak: Systolic blood pressure at peak exercise, SBPrest: Systolic blood pressure at rest.

sympathetic activity, ongoing abnormalities in atrial transmission may cause AF recurrence. One of the post-PVI AF recurrence mechanisms is the triggering foci outside the PV[42]. Sympathetic activity is known to cause atrial arrhythmia by increasing automaticity and delayed afterdepolarizations[43]. Increased sympathetic activity in patients with EBPR and slow HRR may lead to triggering foci outside the PV.

EBPR is known to predict the development of long-term hypertension[44,45]. In addition, EBPR is more common in patients with masked hypertension[46,47]. The effects of hypertension on atrial tissue and the transmission system may emerge in the early stages in these patients and may affect the recurrence of AF. High SBPpeak has been associated with increased aortic and systemic large artery stiffness[48,49]. Various atrial abnormalities which indicate the risk factors that have not yet been fully recognized were detected in paroxysmal AF patients. These abnormalities include increased inflammation, diastolic dysfunction, increased fibrosis, and microvascular dysfunction[50-53]. Increased arterial stiffness in patients with EBPR may contribute to atrial myopathy even when LAD, the thickness of the atrium ventricular wall, and resting BP are all normal. Further studies are warranted to assess the relationship between AF recurrence and exercise BP response.

Study Limitations

The most important limitation of our study is the lack of evaluation of the change in autonomic tone after ablation. If ETT was performed during post-ablation follow-up visits, the effect of ablation on the change in autonomic tone could have been evaluated. Another limitation is that patients with normal resting BP who had no history of hypertension were included in the study, therefore it was not possible to rule out masked hypertension.

CONCLUSION

AD may be associated with AF recurrence after CBA in patients with paroxysmal AF. SBPpeak, DBPpeak, and slow HRR appear to be predictors of AF recurrence after ablation. Evaluating BP and HRR response to exercise may provide information for clinical practice after ablation.

Ethics Committee Approval: The approval for this study obtained from İstanbul Medipol University, Non-invasive Clinical Research Ethics Committee (Decision No: 1180, Date: 25.12.2019).

Informed Consent: This is retrospective study, we could not obtain written informed consent from the participants.

Peer-review: Externally peer-reviewed.

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