

Evaluation Of The Effect Of Pulmonary Vein Isolation Treatment With Left Atrial Catheter Ablation Method On Atrial Conduction Times In Patients With Paroxysmal Atrial Fibrillation

ibrahim dönmez¹, fatma erdem¹, tolga memioğlu¹, and emrah acar¹

¹Bolu Abant İzzet Baysal University

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Abstract

Purpose:Atrial fibrillation(AF) causes structural, electrical, and cellular remodeling in the atrium. Evaluation of intra- and interatrial conduction time, which is measured by tissue doppler echocardiography, indicates structural and electrical remodeling in the atrium. The aim of this study was to evaluate the effect of pulmonary vein isolation applied with RF ablation therapy on intra- and interatrial conduction time and to investigate the structural and electrically remodeling after treatment. **Methods:**Fifty-two patients with symptomatic PAF despite at least one antiarrhythmic drug and without structural heart disease were included in the study. Two patients were excluded because of complications developed during and after the operation. Fifty patients (28 female; mean age: 51.68 ± 11.731 ; mean left atrial diameter: 36.79 ± 4.318) who underwent CARTO® 3D pulmonary vein isolation applied with the RF ablation system were followed-up. Intra- and the inter-atrial electromechanical delay was measured in all patients by tissue doppler echocardiography before and three months after RF ablation. **Results:**All intra- and interatrial conduction times were significantly decreased 3 months after RF ablation procedure(PA lateral $p = 0.022$; PA septum $p = 0.002$; PA tricuspid $p = 0.019$, interatrial conduction delay $p= 0,012$, intra-atrial conduction delay $p = 0.029$). **Conclusion:**The results of our study suggest that providing stable sinus rhythm by the elimination of the AF triggering mechanisms with RF ablation of pulmonary vein isolation may slow down,stop or even improve structural remodeling at substrate level secondary to AF even in patients who did not yet develop atrial fibrosis and permanent structural changes.

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İbrahim Dönmez

Faculty of Medicine, Department of Cardiology, Abant İzzet Baysal University, Golkoy, Bolu, 14280, Turkey

Fatma Hizal Erdem

Faculty of Medicine, Department of Cardiology, Abant İzzet Baysal University, Golkoy, Bolu, 14280, Turkey

Tolga Memioğlu

Faculty of Medicine, Department of Cardiology, Abant İzzet Baysal University, Golkoy, Bolu, 14280, Turkey

Emrah Acar

Faculty of Medicine, Department of Cardiology, Abant İzzet Baysal University, Golkoy, Bolu, 14280, Turkey

Corresponding Author

İbrahim Dönmez

Faculty of Medicine, Department of Cardiology, Abant İzzet Baysal University, Golkoy, Bolu, 14280, Turkey

Tel: 0 374 253 46 56 – 3194

Mail: dr_ibrahimdonmez@hotmail.com

ORCID No: 0000-0002-6913-9073

Abstract

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Methods: Fifty-two patients with symptomatic PAF despite at least one antiarrhythmic drug and without structural heart disease were included in the study. Two patients were excluded because of complications developed during and after the operation. Fifty patients (28 female; mean age: 51.68 ± 11.731 ; mean left atrial diameter: 36.79 ± 4.318) who underwent CARTO® 3D pulmonary vein isolation applied with the RF ablation system were followed-up. Intra- and the inter-atrial electromechanical delay was measured in all patients by tissue doppler echocardiography before and three months after RF ablation.

Results: All intra-and interatrial conduction times were significantly decreased 3 months after RF ablation procedure(PA lateral $p = 0.022$; PA septum $p = 0.002$; PA tricuspid $p = 0.019$, interatrial conduction delay $p = 0,012$, intra-atrial conduction delay $p = 0.029$).

Conclusion: The results of our study suggest that providing stable sinus rhythm by the elimination of the AF triggering mechanisms with RF ablation of pulmonary vein isolation may slow down,stop or even improve structural remodeling at substrate level secondary to AF even in patients who did not yet develop atrial fibrosis and permanent structural changes.

Keywords: Pulmonary vein isolation, Radiofrequency ablation, Atrial conduction time, Tissue doppler echocardiography

EVALUATION OF THE EFFECT OF PULMONARY VEIN ISOLATION TREATMENT WITH LEFT ATRIAL CATHETER ABLATION METHOD ON ATRIAL CONDUCTION TIMES IN PATIENTS WITH PAROXYSMAL ATRIAL FIBRILLATION

1 Introduction

Atrial fibrillation (AF) is a supraventricular tachyarrhythmia resulting from the irregular activity of the atria and is characterized by the atrial mechanic functional loss [1]. The ventricular rate is variable and irregular depending on the conduction function of the atrioventricular node. On electrocardiogram, rapid, irregular, fibrillation waves of different shapes and sizes are seen instead of P waves [2].

In the developed countries, the prevalence of AF is estimated between 1.5-2% in the general population and the mean age of patients with this disease is steadily increasing. Today, the mean age of AF patients is between 75 and 85 years. This arrhythmia is associated with a five-fold increase in the risk of stroke, a three-fold increase in the incidence of congestive heart failure, and high mortality. Hospitalization is common among AF patients. This arrhythmia is an important cardiovascular problem in modern society and its medical, social and economical aspects will further worsen in the next decades [3]. AF usually starts as paroxysmal AF (PAF) and transforms into persistent AF [4]. The mechanism of PAF consists of initiating factors[5, 6].

Two main targets in AF treatment are protection against thromboembolic complications, and rate and/or rhythm control. Appropriate treatment methods to control the symptoms or prevent cardiomyopathy that may occur due to tachycardia are similar. The use of warfarin or new generation oral anticoagulants in eligible patients reduces the risk of stroke. Among two important studies comparing rhythm and rate control, in the randomized controlled AFFIRM (Atrial Fibrillation Follow-up Investigation of Rhythm Management) study no difference could be demonstrated between the two groups in terms of mortality and stroke from all causes [7]. In the RACE (Rate Control versus Electrical cardioversion for persistent atrial fibrillation) study, it was shown that rate control was not worse than rhythm control in the prevention of cardiovascular mortality and morbidity [8]. However, in the subgroup analysis of the RACE study, left ventricular function was shown to worsen less or even to improve in patients with heart failure and rhythm control with catheter ablation for AF [9, 10]. Long-term rhythm control can be achieved with antiarrhythmics or ablation. In a meta-analysis of studies investigating rhythm control in paroxysmal AF, ablation was shown to be superior over antiarrhythmics in ensuring and maintaining sinus rhythm [11, 12]. Ablation can be performed in patients who are symptomatic despite optimal medical therapy [13, 14].

Atrial fibrillation is thought to occur as a result of the combination of electrophysiological, metabolic, ischemic, hemodynamic, and genetic factors [15, 16]. Persistent AF causes electrical remodeling characterized by shortening of atrial refractoriness caused by changes in the expression of ion channels in the atria, contractile remodeling resulting in disruption of atrial contraction, and structural remodeling leading to changes in the cellular structure of atrial myocytes. All these changes affect each other, leading to continuity of the AF process [15]. While electrical activity foci in the pulmonary vein (PV) cause the development of AF, structural changes occurring in the left atrium due to chronic or recurrent AF cause remodeling lead to especially fibrosis and continuing rhythm disturbance [17, 18]. Atrial conduction time that can be easily measured simply by tissue Doppler echocardiography can give us an idea about the arrhythmogenic substrate changes that make AF sustained [19, 20].

The objective of this study was to evaluate the effect of PV electrical activity foci isolation treatment with RF ablation method on the left atrial arrhythmogenic substrate through tissue Doppler echocardiography and to investigate the structural remodeling process due to AF by the termination of electrical remodeling using RF ablation method.

2 Material & Methods

A total of 52 patients aged [?] 18 years, who presented to and/or were hospitalized in the Abant İzzet Baysal University Medical Faculty, cardiology outpatient clinic, diagnosed with paroxysmal AF and who were symptomatic despite at least one antiarrhythmic drug were included in the study. Two patients were excluded from the study due to complications developed during and after the procedure. A detailed physical examination and 12-lead ECG were performed on all patients. All patients underwent transthoracic echocardiography before the procedure and transesophageal echocardiography within 48 hours before the procedure to confirm the absence of left atrial appendage (LAA) thrombus. Intra- and the inter-atrial electromechanical delay was studied with tissue Doppler method 3 months after the procedure. Identification of AF [?] 30 seconds following the procedure was considered a failure.

Patients with an acute coronary syndrome, previous myocardial infarction (MI) and coronary artery disease, congestive heart failure, decreased LV ejection fraction ($EF < 55\%$), chronic obstructive pulmonary disease, significant valvular disease, pacemaker implantation, hypertension (resting blood pressure [?] 140/90 mm Hg), diabetes mellitus, peripheral vascular diseases, respiratory or neurologic disorders, pericarditis, congenital heart disease, alcohol addiction, renal or hepatic disease and those with poor echocardiographic imaging were excluded from the study.

Before the beginning, the study protocol was approved by the local ethics committee of our hospital. All patients were informed about the objectives of the study in detail and gave informed signed consent forms. The study was conducted in accordance with the ethical principles of the Declaration of Helsinki.

2.1 Echocardiographic Examination and Measurement of Atrial Conduction Time

Echocardiographic examination was performed in all patients before pulmonary vein RF ablation and 3 months after the ablation with GE VividS6 system (GE Vingmed, Horten, Norway) using a probe of 2-4 MHz frequency. Echocardiographic examination was performed with the patient in the supine position and lying on the left side, using appropriate echocardiographic windows with M mode, two-dimensional (2D), pulse wave doppler, continuous wave doppler, color flow, and tissue doppler imaging (TDI) methods.

2.2 M-mode echocardiography: Right ventricular end-systole and diastole sizes and ejection fraction, end-diastole septum and posterior wall thicknesses, and left atrial end-diastole dimensions were measured with M-mode echocardiography.

2.3 2D echocardiography: Wall motion of both ventricles, valvular structure and functions, and pericardial window were examined with 2D echocardiography. Mitral flow parameters were measured at the end of expiration by averaging three cardiac cycles.

2.4 Tissue Doppler Echocardiography: Simultaneous ECG recordings were taken during tissue Doppler echocardiographic examination. The time from the beginning of the P wave on the ECG to the onset of the A' wave in tissue Doppler (wave indicating atrial contraction) was defined as the PA distance (atrial electromechanical time) (Fig 1). Atrial electromechanical time was measured separately from the lateral mitral annulus, septal mitral annulus, and lateral tricuspid annulus; and defined as PA lateral, PA septum, and PA tricuspid, respectively. The difference between PA lateral and PA tricuspid (PA lateral – PA tricuspid) was defined as interatrial conduction delay; and the difference between PA septum and PA tricuspid (PA septum – PA tricuspid) as intraatrial conduction delay.

2.5 Transesophageal Echocardiography: All patients underwent TEE with in 48 hours before the ablation. The echogenic mass in the LAA that continued in more than one plane and distinguished from the surrounding tissues was considered thrombus, and patients with thrombus in the LAA were excluded.



Fig. 1 Measurement of atrial conduction time with tissue doppler echocardiography method

2.6 Electrophysiological Procedure

Pulmonary vein isolation was performed under anesthesia and noninvasive mild sedation. Vascular access was obtained using the bilateral femoral veins and left femoral artery. Intracardiac and superficial electrocardiograms were recorded at a rate of 100 mm/seconds (Prucka, GE Medical Systems). Transseptal punctures were made with the Brockenbrough needle transseptal needle (St. Jude Medical, Minnetonka, MN, USA)

under fluoroscopy. First, pulmonary vein electrical mapping was performed with a circular mapping catheter (Lasso, Biosense Webster, Diamond Bar, CA, USA) via the single transeptal sheath and pulmonary vein potentials (it was paced from the coronary sinus to separate from atrial potential [AP]) were determined. The ablation catheter (SF-Contact force, Biosense Webster, Diamond Bar, CA, USA) was inserted through the other transeptal sheath, right and left pulmonary vein isolation was performed, respectively. (Fig 2)

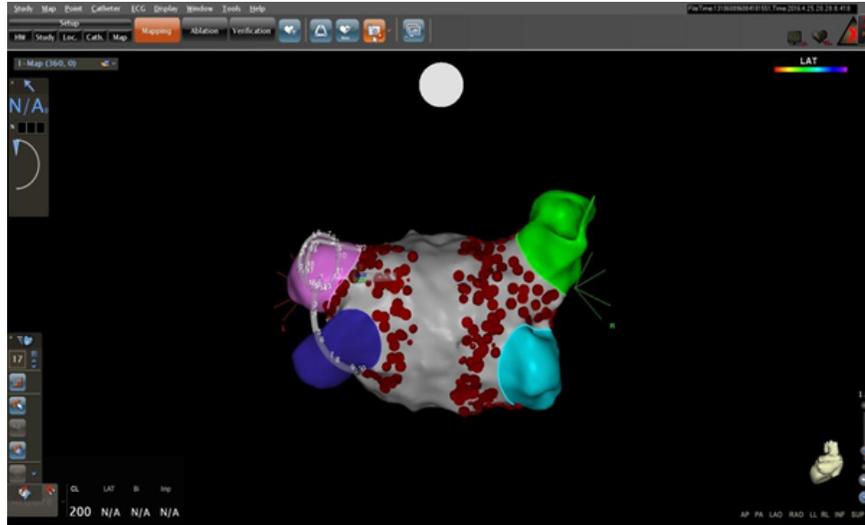


Fig. 2 Pulmonary vein isolation CARTO® image

2.7 Statistical Analysis

Biostatistical analysis of the data obtained was performed with SPSS (Statistical Package for Social Sciences) for Windows v. 21.0 package software. The normality of the data was analyzed with the Kolmogorov-Smirnov test. Continuous variables were expressed as mean \pm standard deviation and categorical variables with frequency and percentage (%). Descriptive statistics regarding normally distributed variables were expressed as mean \pm standard deviation. Whereas, non-normally distributed variables were given with median, minimum, and maximum values. In the statistical evaluations, correlations between categorical variables were examined with the Chi-square test, while Pearson’s correlation analysis was used to determine the direction and level of the correlations between the variables. Normally distributed variables were analyzed using Student t test, and non-normally distributed variables were analyzed using Mann-Whitney U and Kruskal-Wallis tests. $p < 0.05$ values considered statistically significant.

3 Results

A total of 52 patients with PAF despite at least one antiarrhythmic drug were included. One patient developed acute pericardial tamponade during 3D pulmonary vein isolation and the process was terminated. In another patient, pericardial tamponade was observed 12 hours after the successful process and upon percutaneous pericardiocentesis was insufficient due to effusion localization, the patient was taken to the surgery. Finally, 50 patients who underwent RF ablation with the CARTO® 3D pulmonary vein isolation system were analyzed. All patients had received at least one antiarrhythmic drug with 34 (68%) had received propafenone and the remaining 16 (32%) amiodarone.

Of all patients, 28 (56%) were female and the mean age of the patients was 51.68 ± 11.731 years. PAF attack was observed at follow-up after the ablation in six (12%) patients. Basal echocardiographic findings of the patients are given in Table 1.

Table 1 Basal echocardiographic findings of the patients.

	Minimum	Maximum	Mean
LVEDD	38	57	49.30±4.138
LVESD	20	38	29.70±4.170
IVS	7	14	9.64±1.495
PW	7	13	9.36±1.241
EF	56	67	64.91±2.057
LA	27	47	36.79±4.318
Dt	92	279	183.36±41.711
IVRT	46	133	85.37±19.733
ICT	52	130	79.09±17.251
ET	214	330	268.00±29.658
Tei INDEKS	0.303	0.8832	0.620284±0.131674
E	38	101	67.50±15.688
A	35	103	63.95±16.669
Et	4	18	8.93±3.029
At	4	16	9.24±2.618

LVEDD: Left ventricular end diastolic diameter, LVESD: Left ventricular end systolic diameter, IVS: Interventricular septum, PW: Posterior wall, EF: Ejection Fraction, LA: Left atrium size, Dt; Deceleration time, IVRT: Interventricular relaxation time, ICT: Interventricular Contraction Time, ET: Ejection Time, E: Mitral valve early diastolic peak rate, A: Mitral valve late diastolic peak rate, Em: Early diastolic myocardial rate, Am: Late diastolic myocardial rate.

3.1 Comparison of Atrial Conduction Times Before and After Ablation

Comparison of atrial conduction times measured with tissue Doppler echocardiographic examination before and 3 months after the ablation is shown in Table 2.

Table 2 Comparison of atrial conduction times measured with tissue Doppler method.

	Before ablation	3 months after ablation	Difference between before and after
PA lateral (ms)	72.90±15.3	68.41±12.37	4.48±1.84
PA septum (ms)	49.17±10.21	44.75±7.30	4.41±1.28
PA tricuspid (ms)	35.55±7.92	33.37±5.62	2.17±0.87
Interatrial conduction delay	35.11±12.13	29.70±10.70	5.40±1.99
Intra-atrial conduction delay	13.74±5.93	11.37±5.37	2.37±1.02

PA: Time from the beginning of the P wave on the ECG to the onset of the A' wave in tissue Doppler (wave indicating atrial contraction)

PA lateral, PA septum, PA tricuspid, intra- and interatrial conduction delay times were significantly decreased after the RF ablation procedure Fig 3.

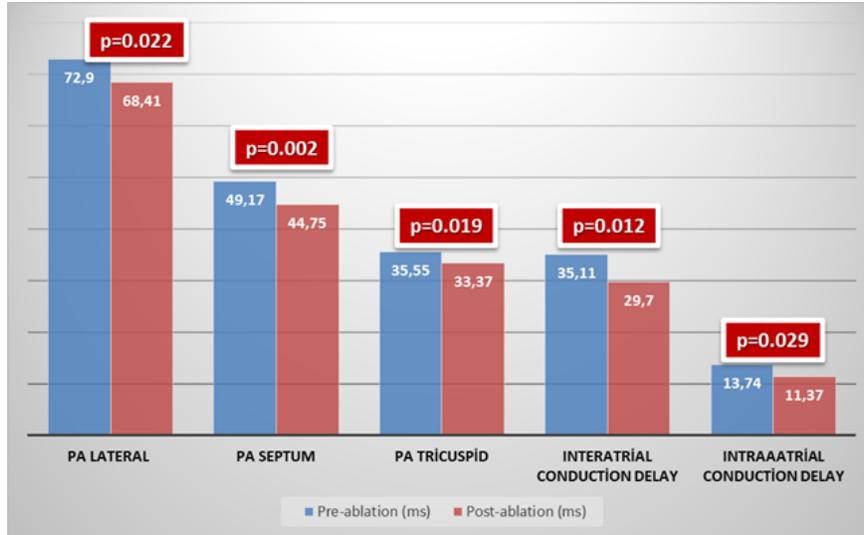


Fig. 3 Comparison of atrial conduction times before and after RF ablation.

In the correlation analysis of atrial conduction times before and after RF ablation; a significant negative correlation was found in all values including PA lateral ($r=-0.763$; $p<0.001$), PA septum ($r=-0.734$; $p<0.01$), PA tricuspid ($r=-0.812$; $p<0.001$), interatrial conduction time ($r=-0.594$; $p=0.00$) and intra-atrial conduction time ($r=-0.563$; $p=0.002$).

3.2 Comparison of Atrial Conduction Times Before and After Ablation According to Sexes

Comparison of atrial conduction times before and after ablation according to sexes is shown in Table 3.

Table 3 Comparison of pre- and post-ablation atrial conduction times according to sexes.

	Before ablation	3 months after ablation	P values
MALE	MALE	MALE	MALE
PA lateral (ms)	69,60±20,522	65,700±15,319	0,401
PA septum (ms)	48,40±13,914	43,60±8,448	0,133
PA tricuspid (ms)	36,80±10,799	33,30±6,617	0,158
Interatrial conduction delay (ms)	30,60±14,065	24,70±8,472	0,214
Intraatrial conduction delay (ms)	11,60±5,892	10,10±4,332	0,325
FEMALE	FEMALE	FEMALE	FEMALE
PA lateral (ms)	74,63±12,015	69,842±10,704	0,011
PA septum (ms)	49,58±8,064	45,368±6,80	0,005
PA tricuspid (ms)	34,89±6,172	33,421±5,231	0,026
Interatrial conduction delay (ms)	37,76±10,377	32,647±11,005	0,018
Intra-atrial conduction delay (ms)	15,00±5,766	12,117±5,904	0,057

When atrial conduction times before and after RF ablation were compared according to sexes; no significant difference was found between the two group in male patients, while there was a significant difference in all parameters except for intra-atrial conduction delay in female patients (Fig 4).

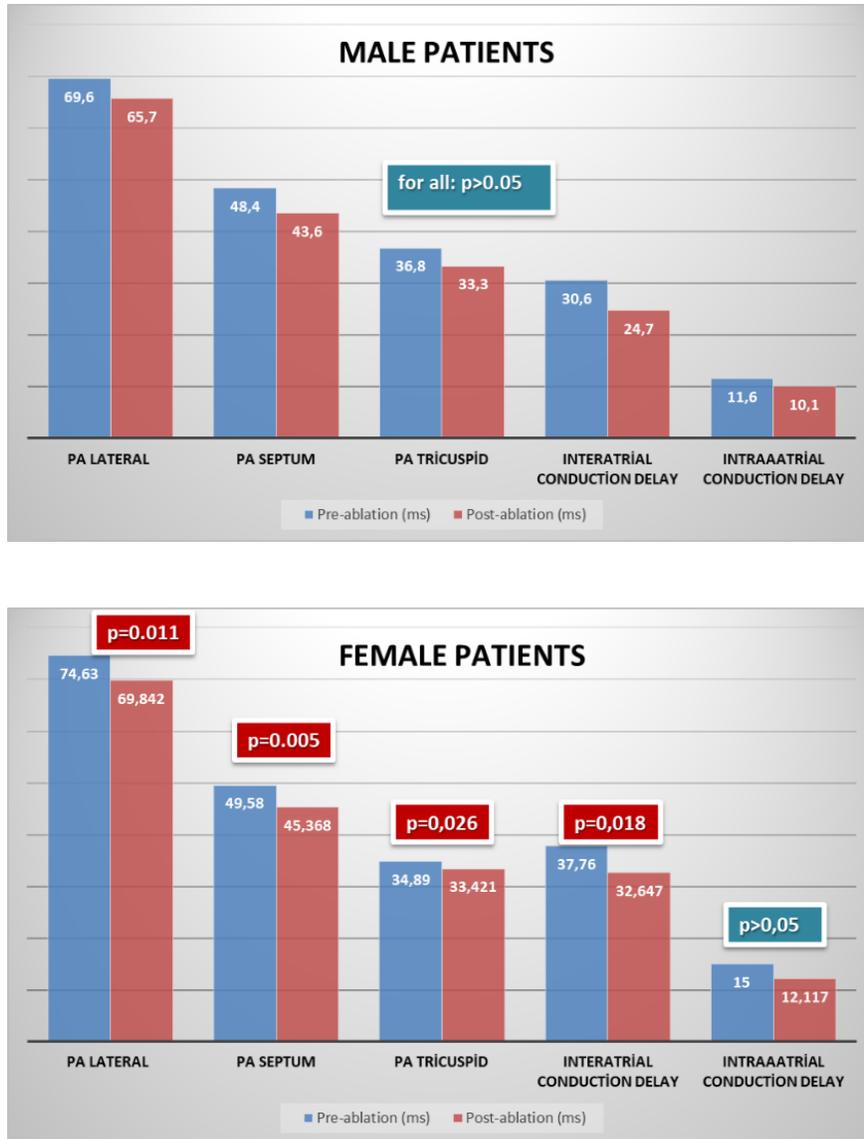


Fig. 4 Comparison of pre- and post-ablation atrial conduction times according to sexes.

When left atrial diameter and the parameters investigated in this study were evaluated with Pearson's correlation analysis; there was no significant correlation between left atrial diameter and post-ablation PA lateral ($r=0.153$; $p=0.320$), PA septum ($r=0.61$; $p=0.695$), PA tricuspid ($r=0.66$; $p=0.670$), interatrial conduction delay ($r=0.169$; $p=0,279$), and post-ablation PA lateral ($r=0,156$; $p=0,402$), PA septum ($r=0.10$; $p=0,960$), PA tricuspid ($r=0,015$; $p=0,956$), interatrial conduction delay ($r=-0.009$; $p=0,960$) and intra-atrial conduction delay ($r=0.001$; $p=0,991$).

4 Discussion

AF is a disease characterized by the disruption of cardiac mechanical functions due to irregular atrial activation. There are initiating factors that cause the onset of AF and an anatomical substrate that maintains it. An important feature of AF is that the arrhythmia sustains itself when it begins. This is possibly caused by remodeling occurring in the atrium. Atrial remodeling occurs

at electrophysiological, cellular, and anatomic levels [21, 15]. Many studies have shown the association between intra- and interatrial conduction blocks and AF [22, 23]. It is thought that a shortening in the atrial effective refractory period, inconsistency of the atrial effective refractory period with changes in heart rate, and a prolongation in atrial conduction time occur as a result of electrical remodeling in AF [24]. Delay in interatrial and intra-atrial conduction causes atrial refractoriness to be inhomogeneous.

In a study by Deniz et al. [25], it was shown that left intra-atrial mechanical delay increased in patients with PAF and it was an independent risk factor of PAF. Kumagai et al [26] showed that inter and intra-atrial conduction was prolonged following electrical cardioversion in patients with lone AF. In a study by Evranos et al. [27] with patients who underwent cryoballoon, the intra-atrial delay before and 3 months after the procedure was found to be a predictor of late AF recurrence.

There may be fibrosis in the left atrium in AF, which causes anisotropy, maintain anisotropic atrial conduction delay, changes intra-atrial refractoriness, and leads to the continuity of reentrant arrhythmia. The persistence of AF during the structural atrial remodeling process leads to a reduction in the amount of connexin 40 and thus causing regional conduction abnormalities that lead to reentrant pathways to maintain themselves [28]. Radiofrequency (RF) catheter ablation has recently been introduced as an important therapeutic option in patients with drug-resistant atrial fibrillation (AF), with about a 75% success rate [29, 30]. In our study, significant decreases were observed in intra- and interatrial conduction times after RF ablation (PA lateral p: 0.022; PA septum p: 0.002; PA tricuspid p: 0.019; interatrial conduction delay p:0.012; and intra-atrial conduction delay p:0.029). This result suggests that providing stable sinus rhythm by the elimination of the AF triggering mechanisms with RF ablation of pulmonary vein isolation may slow down, stop or even improve structural remodeling at substrate level secondary to AF even in patients who did not yet develop atrial fibrosis and permanent structural changes. There is a linear relationship between electrophysiological, structural, and cellular remodeling with the increase of AF duration during the day in PAF patients, and this process progresses towards permanent AF [15]. However, it is unclear whether AF can produce additional forms of remodeling, especially when arrhythmia remains sustained for long periods [31]. As also seen in our study, preservation of sinus rhythm after pulmonary vein RF ablation is expected to affect this process.

Sex differences may affect diagnostic and therapeutic interventions in a wide variety of medical conditions including cardiac arrhythmias [32]. In our study, when atrial conduction times were compared before and after RF ablation according to sexes; no significant difference was observed between the two groups in male patients, while there were significant differences in all parameters except for intra-atrial conduction delay in female patients. The reason was probably due to the low number of male patients (14 patients; 28%) who had atrial conduction time measurement after the procedure.

5 Study Limitations

In this study, the number of patients was relatively small. Long-term results could be better analyzed with a larger series of patients and longer follow-up. Clearer information about fibrosis and left atrial structural changes could be obtained with the addition of cardiac MRI in addition to echocardiography.

6 Conclusion

As the clinical emphasis in this study; successful RF ablation eliminates initiating mechanisms and provides significant positive gains in a complex cardiovascular disease like AF. Intra- and inter-atrial conduction times that are considered indicators of this significantly decreased after ablation. This result increases the expectation of a decrease in complications related to AF in addition to rhythm control after a successful RF ablation.

Declarations:

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Informed Consent: All participants were informed about the objectives of the study and signed informed consent forms.

Availability of data and material: All data used in this study are included in the manuscript.

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TABLES

Table 1. Basal echocardiographic findings of the patients.

	Minimum	Maximum	Mean
LVEDD	38	57	49.30±4.138
LVESD	20	38	29.70±4.170
IVS	7	14	9.64±1.495
PW	7	13	9.36±1.241
EF	56	67	64.91±2.057
LA	27	47	36.79±4.318
Dt	92	279	183.36±41.711
IVRT	46	133	85.37±19.733
ICT	52	130	79.09±17.251
ET	214	330	268.00±29.658
Tei INDEKS	0.303	0.8832	0.620284±0.131674
E	38	101	67.50±15.688
A	35	103	63.95±16.669
Et	4	18	8.93±3.029
At	4	16	9.24±2.618

LVEDD: Left ventricular end diastolic diameter, LVESD: Left ventricular end systolic diameter, IVS: Interventricular septum, PW: Posterior wall, EF: Ejection Fraction, LA: Left atrium size, Dt; Deceleration time, IVRT: Interventricular relaxation time, ICT: Interventricular Contraction Time, ET: Ejection Time, E: Mitral valve early diastolic peak rate, A: Mitral valve late diastolic peak rate, Em: Early diastolic myocardial rate, Am: Late diastolic myocardial rate.

Table 2. Comparison of atrial conduction times measured with tissue Doppler method.

	Before ablation	3 months after ablation	Difference between before and after
PA lateral (ms)	72.90±15.3	68.41±12.37	4.48±1.84
PA septum (ms)	49.17±10.21	44.75±7.30	4.41±1.28
PA tricuspid (ms)	35.55±7.92	33.37±5.62	2.17±0.87
Interatrial conduction delay	35.11±12.13	29.70±10.70	5.40±1.99
Intra-atrial conduction delay	13.74±5.93	11.37±5.37	2.37±1.02

PA: Time from the beginning of the P wave on the ECG to the onset of the A' wave in tissue Doppler (wave indicating atrial contraction)

Table 3. Comparison of pre- and post-ablation atrial conduction times according to sexes.

	Before ablation	3 months after ablation	P values
MALE	MALE	MALE	MALE
PA lateral (ms)	69,60±20,522	65,700±15,319	0,401
PA septum (ms)	48,40±13,914	43,60±8,448	0,133

PA tricuspid (ms)	36,80±10,799	33,30±6,617	0,158
Interatrial conduction delay (ms)	30,60±14,065	24,70±8,472	0,214
Intraatrial conduction delay (ms)	11,60±5,892	10,10±4,332	0,325
FEMALE	FEMALE	FEMALE	FEMALE
PA lateral (ms)	74,63±12,015	69,842±10,704	0,011
PA septum (ms)	49,58±8,064	45,368±6,80	0,005
PA tricuspid (ms)	34,89±6,172	33,421±5,231	0,026
Interatrial conduction delay (ms)	37,76±10,377	32,647±11,005	0,018
Intra-atrial conduction delay (ms)	15,00±5,766	12,117±5,904	0,057

FIGURES



Fig. 1 Measurement of atrial conduction time with tissue doppler echocardiography method

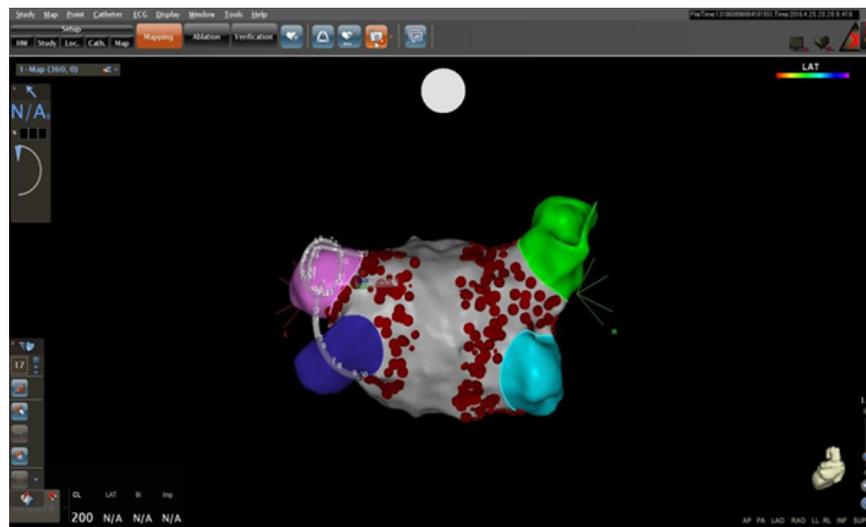


Fig. 2 Pulmonary vein isolation CARTO® image

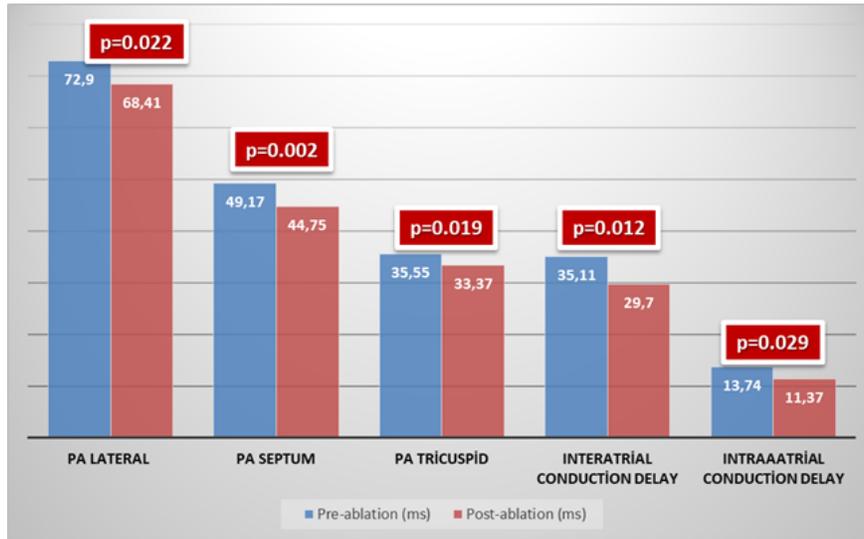
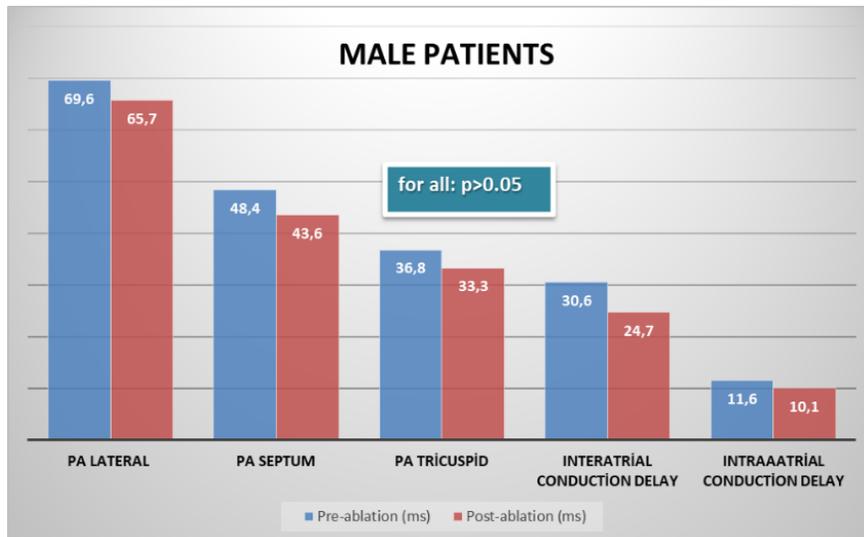


Fig. 3 Comparison of atrial conduction times before and after RF ablation.



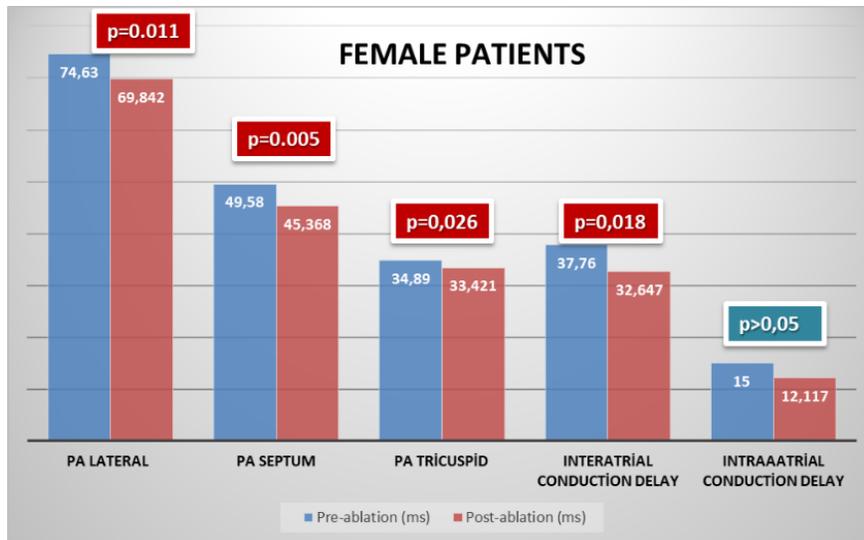


Fig. 4 Comparison of pre- and post-ablation atrial conduction times according to sexes.