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Evaluation of the effects of 3D mapping ablation on atrial conduction times in patients with paroxysmal atrial fibrillation

Atrial fibrillation ablation and atrial conduction times

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Abstract
Aim: Atrial fibrillation (AF) causes structural, electrical, and cellular remodeling in the atrium. Evaluation of intra- and interatrial conduction time, indicates structural and electrical remodeling in the atrium. This study aimed to evaluate the effect of pulmonary vein isolation applied with radiofrequency ablation (RF) therapy on intra- and interatrial conduction time and to investigate the structural and electrically remodeling after treatment.
Material and 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 inter-atrial electromechanical delay was measured in all patients using 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).
Discussion: The results of our study suggest that providing stable sinus rhythm with RF ablation may slow down, stop or even improve structural remodeling at substrate level secondary to AF even in patients with paroxysmal AF who did not yet develop atrial fibrosis and permanent structural changes.

Keywords
Pulmonary Vein Isolation, Radiofrequency Ablation, Atrial Conduction Time, Tissue Doppler Echocardiography

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Introduction

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

In 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. 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. AF usually starts as paroxysmal AF (PAF) and transforms into persistent AF[2]. The mechanism of PAF consists of initiating factors [3, 4].

Two main targets in AF treatment are protection against thromboembolic complications and rate or rhythm control. 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 [5]. The RACE (Rate Control versus Electrical cardioversion for persistent atrial fibrillation) study showed that rate control was not worse than rhythm control in preventing cardiovascular mortality and morbidity [6]. However, in the subgroup analysis of the RACE study, left ventricular function improved in patients with heart failure and rhythm control with catheter ablation for AF [7]. Long-term rhythm control can be achieved with antiarrhythmics or ablation. In a study evaluating recurrence of atrial fibrillation (AF) in The Catheter Ablation versus Antiarrhythmic Drug Therapy for Atrial Fibrillation (CABANA), it was stated that catheter ablation was effective in reducing recurrence of any AF by 48% and symptomatic AF by 51% compared to drug therapy over 5 years of follow-up. Furthermore, AF burden was also significantly reduced in catheter ablation patients, regardless of their baseline AF type [8]. Despite optimal medical therapy, ablation can be performed in symptomatic patients [9].

Atrial fibrillation is thought to occur due to electrophysiological, metabolic, ischemic, hemodynamic, and genetic factors. 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 [10]. While electrical activity foci in the pulmonary vein (PV) cause the development of AF, structural changes in the left atrium due to chronic or recurrent AF cause remodeling, leading to fibrosis and continuing rhythm disturbance [11]. 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 [12, 13].

The objective of this study was to evaluate the effect of PV electrical activity foci isolation treatment with the 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.

Material and Methods

A total of 52 patients aged ≥ 18 presented to and were hospitalized in the Abant Izzet Baysal University Medical Faculty, cardiology outpatient clinic, diagnosed with paroxysmal AF and 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 and transesophageal echocardiography within 48 hours to confirm the absence of left atrial appendage (LAA) thrombus. Intra- and inter-atrial electromechanical delay was studied with the tissue Doppler method three months after the procedure. Identification of AF ≥ 30 seconds following the procedure was considered a failure.

Patients with 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 study's objectives and signed consent forms. The study was conducted under the ethical principles of the Declaration of Helsinki.

Echocardiographic Examination and Measurement of Atrial Conduction Time

Echocardiographic examination was performed in all patients before pulmonary vein RF ablation and three months after the ablation with the 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.

M-mode echocardiography: Left ventricular end-systole and diastole sizes and ejection fraction, end-diastole septum and posterior wall thicknesses were measured with M-mode echocardiography.

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

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 on tissue Doppler (wave indicating atrial contraction) was defined as the PA distance (electromechanical atrial time) (Figure 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 interatrial conduction delay.

Transesophageal Echocardiography: All patients underwent TEE within 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 a thrombus, and patients with thrombi in the LAA were excluded.

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 100 mm/second (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 transseptal 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 transseptal sheath; right and left pulmonary vein isolation was performed, respectively (Figure 2).

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 ± standard deviation and categorical variables with frequency and percentage (%). Descriptive statistics regarding normally distributed variables were expressed as mean ± 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. Normally distributed variables were analyzed using the Student t-test, and non-normally distributed variables were analyzed using Mann-Whitney U and Kruskal-Wallis tests. Pearson's correlation analysis was used to determine the direction and level of the correlations between the variables. $p<0.05$ values considered statistically significant.

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 then 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%) having 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

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

	Before ablation	Three months after ablation	Difference between before and after ablation	P values
PA lateral (ms)	72.90±15.3	68.41±12.37	4.48±1.84	0.022
PA septum (ms)	49.17±10.21	44.75±7.30	4.41±1.28	0.002
PA tricuspid (ms)	35.55±7.92	33.37±5.62	2.17±0.87	0.019
Interatrial conduction delay	35.11±12.13	29.70±10.70	5.40±1.99	0.012
Intra-atrial conduction delay	13.74±5.93	11.37±5.37	2.37±1.02	0.029

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 2b. Comparison of pre-and post-ablation atrial conduction times according to sexes.

	Before ablation	Three months after ablation	P values
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
Intra atrial conduction delay (ms)	11,60±5,892	10,10±4,332	0,325
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

Table 3. Correlation analyses of RF Ablation with difference between before and after atrial conduction times

	RF Ablation	
Variables	**r**	**p**
PA lateral (ms)	0,763	0,001
PA septum (ms)	0,734	0,001
PA tricuspid (ms)	0,812	0,001
Inter-atrial conduction delay (ms)	0,594	0,001
Intra-atrial conduction dela (ms)	0,563	0,002

RF: radiofrequency, 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)



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

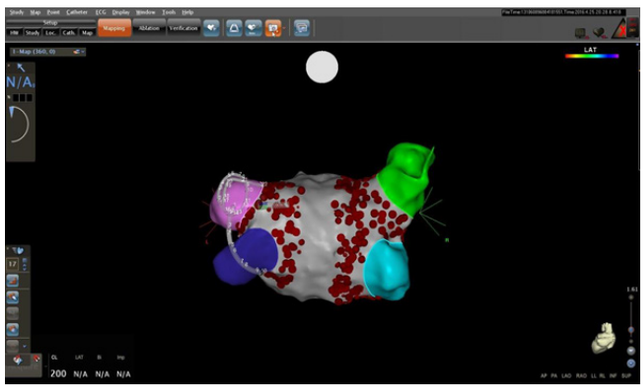


Figure 2. Pulmonary vein isolation CARTO® image

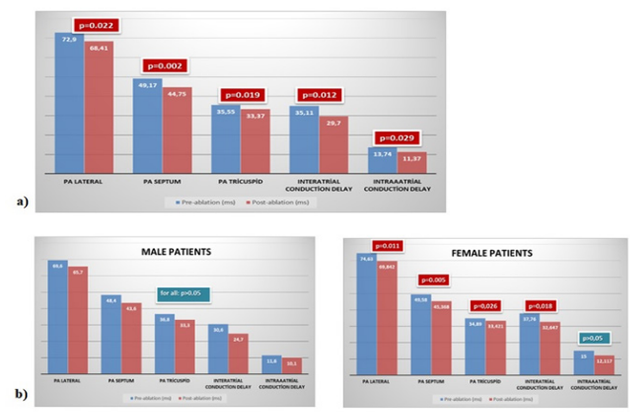


Figure 3. Comparison of atrial conduction times
a) Comparison of atrial conduction times before and after RF ablation.
b) Comparison of pre-and post-ablation atrial conduction times according to sexes.

follow-up after the ablation in six (12%) patients.

Basal echocardiographic findings of the patients are given in Table 1.

Comparison of Atrial Conduction Times Before and After Ablation

A comparison of atrial conduction times measured with tissue Doppler echocardiographic examination before and three months after the ablation is shown in Table 2a.

PA lateral, septum, tricuspid, intra-, and interatrial conduction delay times significantly decreased after the RF ablation procedure (Figure 3a.)

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

A comparison of atrial conduction times before and after ablation according to sexes is shown in Table 2b.

When atrial conduction times before and after RF ablation were compared according to sexes, no significant difference was found between the two groups in male patients, while there was a significant difference in all parameters except for intra-atrial conduction delay in female patients (Figure 3b).

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) (Table 3).

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 essential feature of AF is that the arrhythmia sustains itself when it begins. It is possibly caused by remodeling occurring in the atrium. Atrial remodeling occurs at electrophysiological, cellular, and anatomic levels [14]. Many studies have shown the association between intra- and interatrial conduction blocks and AF [15]. 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 [16]. Delay in interatrial and intra-atrial conduction leads to heterogeneity of atrial refractoriness.

A study by Bayar et al. showed that left intra-atrial mechanical delay increased in patients with PAF and was an independent risk factor for PAF [17]. Van Staveren et al. showed that inter and intra-atrial conduction was prolonged following electrical cardioversion in patients with lone AF [18]. In a study by Lizewska et al. with patients who underwent cryoballoon, the intra-atrial delay before and after the procedure was a predictor of late AF recurrence [19].

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 maintaining

themselves [20]. 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 [21]. 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 eliminating 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 toward permanent AF [4, 10]. However, it is unclear whether AF can produce additional forms of remodeling, especially when arrhythmia remains sustained for extended periods [22]. 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 various medical conditions, including cardiac arrhythmias [23]. 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. At the same time, there were significant differences in all parameters except for intra-atrial conduction delay in female patients. The reason was probably the low number of male patients (14 patients; 28%) who had atrial conduction time measured after the procedure.

Limitation

In this study, the number of patients was relatively small. Long-term results could be better analyzed with a more extensive series of patients and longer follow-ups. Clearer information about fibrosis and left atrial structural changes could be obtained by adding cardiac MRI and echocardiography.

Conclusion

As the clinical emphasis in this study, providing stable sinus rhythm with successful RF ablation may slow down, stop or even improve structural remodeling at substrate level secondary to AF in patients with PAF who did not yet develop atrial fibrosis and permanent structural changes.

Scientific Responsibility Statement

The authors declare that they are responsible for the article's scientific content including study design, data collection, analysis and interpretation, writing, some of the main line, or all of the preparation and scientific review of the contents and approval of the final version of the article.

Animal and human rights statement

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. No animal or human studies were carried out by the authors for this article.

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Conflict of interest

None of the authors received any type of financial support that could be considered potential conflict of interest regarding the manuscript or its submission.

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