Relationship between serum osteopontin level and atrial fibrillation recurrence in patients undergoing cryoballoon catheter ablation

Kriyobalon kateter ablasyonu uygulanan hastalarda serum osteopontin seviyeleri ile atriyum fibrilasyonu nüksü arasındaki ilişki

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ABSTRACT

Objective: Atrial fibrillation (AF) is the most common sustained arrhythmia and is associated with increased morbidity and mortality. Atrial fibrosis augments recurrence rate following AF catheter ablation. Osteopontin is a multifunctional molecule involved in several pathophysiological pathways, including fibrosis. Presently described is investigation of relationship between serum osteopontin level and AF recurrence after AF cryoablation.

Methods: The study was designed to be prospective and observational; 60 patients with paroxysmal (n=47) and persistent (n=13) AF were included. Osteopontin level was measured both before and 6 months after AF ablation with cryoballoon.

Results: Preprocedure and postprocedure osteopontin level did not differ between the 2 groups of AF patients (p=0.286, p=0.493, respectively). Postprocedure osteopontin level was significantly higher compared with preprocedure value (32.18 ng/mL vs 15.58 ng/mL; p=<0.001). Left atrial diameter, AF type, and preprocedure osteopontin level were related to AF recurrence (p≤0.05). An age-adjusted multivariate logistic regression analysis was conducted to determine independent predictors of AF recurrence. Among these, AF type (β=2.211; p=0.004; odds ratio [OR]: 9.124; 95% confidence interval [CI]: 2.026–41.094) was found to be the most important factor related to AF recurrence. Preprocedure osteopontin level also predicted AF recurrence independently (β=0.059; p=0.048; OR: 1.061; 95% CI 1.001–1.125).

Conclusion: Study results revealed persistency of AF and high preprocedure osteopontin level independently predicted AF recurrence in patients undergoing cryoballoon AF ablation. Association of a biochemical marker with AF recurrence might be beneficial to selection of appropriate patients for cryoballoon procedure and assessment of long-term procedural success.

ÖZET

Amaç: Atriyum fibrilasyonu (AF) mortalite ve morbidite artışı ile ilişkili en sık rastlanan ritm bozukluğudur. Atriyum fibrozu, AF'nin kateter ablasyonu sonrası nüks oranını artırır. Osteopontin, fibrozu da içeren çeşitli fizyopatololojik süreçlerde görev alan çok fonksiyonlu bir moleküldür. Atriyum fibrilasyonu kriyoablasyonu sonrasında serum osteopontin seviyeleri ile AF nüksü arasındaki ilişkiyi araştırdık.

Yöntemler: Çalışmamız ileriye dönük ve gözlemsel olarak tasarlandı; nöbetli (n=47) ve sürekli (n=13) AF'si olan 60 hasta çalışmaya dahil edildi. Serum osteopontin seviyeleri AF kriyoablasyonu işlem öncesi ve işleminden altı ay sonra ölçüldü.

Bulgular: İki AF hasta grubuna göre işlem öncesi ve sonrası osteopontin seviyeleri arasında farklılık saptanmadı (sırasıyla, p=0.286, p=0.493). İşlem sonrası osteopontin seviyeleri, işlem öncesi seviye ile kıyaslandığında anlamlı olarak yüksekti (32.18 ng/mL ve 15.58 ng/mL; p=<0.001). Sol atriyum çapı, AF tipi, işlem öncesi osteopontin seviyeleri AF ablasyonu sonrası nüks ile ilişkili saptandı (p≤0.05). Atriyum fibrilasyonu nüksünün bağımsız risk öngördürücülerini tespit etmek için yaşa göre düzeltilmiş çok değişkenli lojistik regresyon analizi yapıldı. Bunların arasında, AF tipinin (β=2.211 p=0.004, OO: 9.124, %95 GA [2.026–41.094]) AF nüksü açısından en önemli öngördürücü olduğu tespit edildi. İşlem öncesi osteopontin seviyeleri de AF nüksünü bağımsız olarak öngördü (β=0.059, p=.048, OO: 1.061, %95 GA [1.001–1.125]).

Sonuç: Çalışmamızda, AF'nin sürekliliği ve daha yüksek işlem öncesi osteopontin seviyeleri AF kriyobalon ablasyon tedavisi yapılan hastalarda nüksü bağımsız olarak öngördürmüştür. Biyokimyasal bir belirtecin kriyoablasyon sonrası nüks ile ilişkili olması, ablasyon tedavisi için uygun hastaların seçimi ve uzun dönem işlem başarısını değerlendirmede faydalı olabilir.

The most common cause of sustained arrhythmia, atrial fibrillation (AF), is a significant condition associated with increased morbidity and mortality. It causes decreased quality of life, as well.[1] Incidence of AF increases with age, and prevalence of AF reaches up to 10% in adults older than 65 years of age.[1,2] Catheter-based ablation methods, such as cryoballoon and radiofrequency, are recommended for symptomatic patients refractory to antiarrhythmic therapy.[3,4] Success of AF ablation with cryoballoon depends on duration and type of AF (paroxysmal or permanent), along with other extrinsic factors such as left atrial (LA) diameter (LAD), LA fibrosis, and conditions related to general health of the patient, such as age, body mass index (BMI), and comorbidities.[5] Sustained AF results in atrial remodeling due to fibrosis and may serve as a trigger for persistency of AF.[6]

Osteopontin, which is a bone tissue extracellular matrix protein, has multiple functions as a molecule and is involved in various physiological and pathological processes, such as wound healing, fibrosis, and calcification.[7] Increased osteopontin plasma level is associated with inflammatory conditions, such as atherosclerosis, myocardial infarction, cardiomyopathies, ventricular arrhythmia, cancer, and dystrophic calcification.[8] Previous molecular studies demonstrated that patients with persistent AF have higher osteopontin level than patients without AF.[9] To the best of our knowledge, the association of plasma osteopontin level with AF recurrence after AF ablation has not been studied previously.

Recurrence is the main drawback of AF ablation procedure and patient selection criteria are important in order to avoid futile procedures. In this study, plasma level of osteopontin in patients undergoing AF cryoablation was evaluated before and 6 months after the procedure with the aim of testing clinical value for predicting recurrence after AF ablation.

METHODS

Study population

Plasma osteopontin level of 60 patients with paroxysmal or persistent AF who were symptomatic despite antiarrhythmic treatment and who underwent AF ablation with cryoballoon at our institution was measured. Paroxysmal AF was defined as self-terminating AF episode within 7 days, and persistent AF was defined as presence of AF episode lasting longer than 7 days. Written informed consent was obtained from each patient and the study was designed to be prospective and observational. Study protocol was approved by the local ethics committee.

Abbreviations:	
ACT	Activated clotting time
AF	Atrial fibrillation
BMI	Body mass index
ECG	Electrocardiography
LA	Left atrium
LAD	Left atrial diameter
MRI	Magnetic resonance imaging
PV	Pulmonary vein
PVI	Pulmonary vein isolation
RA	Right atrium

Exclusion criteria were moderate or severe valvular disease, documented coronary artery disease, chronic renal failure (estimated glomerular filtration rate <60 mL/min/1.73 m^2), chronic hepatic failure (alanine transaminase, aspartate transaminase >3x upper limit of normal), surgery within past 3 months, systemic rheumatic disease, malignancy, LA thrombus, or contraindication for oral anticoagulation.

Electrophysiological study

Transesophageal echocardiography (TEE) was performed on all patients before the procedure to rule out LA thrombus, regardless of anticoagulation state. Midazolam and phentanyl were provided for sedation and analgesia during ablation procedure. Blood pressure, heart rate, rhythm, and oxygen saturation were continuously monitored during procedure. Appropriate-sized introducer sheaths were placed into both femoral veins and femoral arteries. A pigtail-catheter was advanced to aortic root. A 7-F sheath was placed into left femoral vein and a decapolar diagnostic catheter (SJM IBI CS Catheter; St. Jude Medical, Inc., St. Paul, MN, USA) was introduced through this sheath and advanced to the coronary sinus. Catheter was used to pace the right atrium (RA) and phrenic nerve when necessary. Intracardiac and surface electrocardiograms were recorded at rate of 100 mm/second. Transseptal puncture was performed under fluoroscopic and TEE guidance with BRK transseptal needle (St. Jude Medical, Inc., St. Paul, MN, USA). When atrial position of the needle was verified with contrast injection and pressure measurement, transseptal sheath and dilator were advanced to LA. Afterward, needle was removed and guidewire was advanced to LA (in most cases, to left superior pulmonary vein [PV]). A 12-F deflectable sheath (Flex-Cath; Medtronic CryoCath, LP, Quebec, Canada) was placed in LA over the guiding wire. Intraprocedural anticoagulation was achieved with 7500 U unfrac-

tionated heparin bolus upon transseptal sheath entry to LA. Activated clotting time (ACT) was checked every 30 minutes and additional heparin was administered when necessary to keep ACT >300 seconds. All procedures were performed with 28-mm balloon catheter (10.5-F shaft; Medtronic CryoCath, LP, Quebec, Canada), and circular mapping catheter (Achieve mapping catheter; Medtronic, Inc., Minneapolis, MN, USA) was also used during the procedure to confirm pulmonary vein isolation (PVI).

Follow-up

Transthoracic echocardiographic examination was performed twice for each case, once postprocedure and again before hospital discharge in order to rule out pericardial effusion and other complications. Patients were monitored in intensive care unit for 24 hours after the procedure. All patients were treated with previously prescribed antiarrhythmic medications for 3 months postprocedure. Four follow-up visits were scheduled at 1, 3, 6, and 12 months. During each visit, cardiac rhythm was evaluated with 12-lead electrocardiography (ECG) and 24-hour ECG Holter monitoring. Antiarrhythmic medication was discontinued after 3 months in patients without AF recurrence. Patients who had palpitations but no arrhythmic episode on Holter recording were monitored with ECG event recorder. Patients having symptoms such as shortness of breath and cough were further evaluated with thorax computed tomography to detect any PV stenosis.

Early procedural success was defined as electrical isolation of all PVs, blanking period as 3 months post ablation, recurrence as symptomatic AF episode detected on ECG/monitor that lasted until cardioversion, or AF episode lasting longer than 30 seconds on 24-hour ambulatory ECG recording.[10]

Blood sampling

Venous blood samples were collected from left-antecubital vein before procedure while the patients were in fasting state and stored in ethylenediaminetetraacetic acid (EDTA) tubes. During sixth month follow-up visit, an extra blood sample was obtained for this study. EDTA tubes were centrifuged at 1000 rpm for 10 minutes and then plasma was collected and stored at -80°C. Osteopontin level in serum were measured with the Human Osteopontin Quantikine enzyme-linked immunosorbent assay kit (DOST00; R&D Sys-

tems Inc., Minneapolis, MN, USA), according to the manufacturer's protocol.

Statistical analysis

Categorical variables were presented as number of cases (percentage). Mean±SD and geometric means were used for continuous variables. Normal distribution was tested with Kolmogorov-Smirnov test. Logarithmic transformation was performed to evaluate preoperative osteopontin level, postoperative osteopontin level, ejection fraction (and AF duration) because of skewed distribution. Unpaired t-tests were used to compare continuous variables between the 2 groups. For preoperative and postoperative comparison of continuous and dependent variants, paired t-test was performed. To compare categorical variables, in 2x2 contingency tables, Yates correction for continuity was used when 1 or more cells had expected frequency of 5–25, and Fisher's exact test was used when 1 or more cells had expected frequency of 5 or less.

Variables that showed evident significance (p<0.05) in univariate analysis were included in an age-adjusted multivariate logistic regression analysis (forward stepwise model) to determine independent predictors of AF recurrence. Results of the model were reported as odds ratio (OR), 95% confidence interval (CI), and beta and p values. P value of <0.05 was considered significant for all tests. SPSS software, version 11.0 (IBM Corp., Armonk, NY, USA), was used for statistical analysis.

RESULTS

Sixty patients with symptomatic persistent or paroxysmal AF who underwent cryoablation procedure were included. Twenty-four (40%) of the patients were female and 36 (60%) were male. Average age of the study population was 54±11years. Twenty-two (36.6%) patients had AF recurrence. Clinical and laboratory characteristics of the study population are provided in Table 1. Cardiovascular risk factors such as hypertension, diabetes mellitus, dyslipidemia, smoking, and drug use did not differ between the groups. AF type, LAD, and preprocedural osteopontin level were significantly different between the 2 groups (persistent 10 [76.9%] vs paroxysmal 3 [23.1%], p=0.002; 41±3.4 mm vs 38±4.1 mm, p=0.006; 13.29 ng/mL vs 19.65 ng/mL, p=0.035, respectively) (Table 1). Post-

Table 1. Comparison of clinical characteristics of patients with and without recurrence of atrial fibrillation

	Atrial fibrillation recurrence (+) (n=22)			Atrial fibrillation recurrence (–) (n=38)			*p*
	n	%	Mean±SD	n	%	Mean±SD	
Age (years)			55±10			53±11	0.517
Gender (male)	11	50		25	65.8		0.353
Hypertension	9	40.9		14	36.8		0.971
Diabetes mellitus	4	18.2		10	26.3		0.542
Hyperlipidemia	3	15		2	5.9		0.347
Current smoking	3	13.6		4	10.5		0.700
Thyroid disease	6	27.3		5	13.2		0.189
Body mass index (kg/m^2)			30±6.2			29±4.3	0.623
Ejection fraction			63.1			63.4	0.844
Left atrial diameter (mm)			41±3.4			38±4.1	0.006
Drugs							
Angiotensin converting enzyme inhibitors	4	19		7	20.6		1
Angiotensin receptor blockers	3	14.3		9	26.5		0.336
Beta bloker	17	81		30	88.2		0.464
Statin	3	14.3		2	5.9		0.359
Oral antidiabetic drugs	0	0		4	11.8		0.286
Propafenone	8	38.1		11	32.4		0.886
Amiodarone	7	33.3		7	21.2		0.501
Warfarin	7	33.3		9	26.5		0.811
New oral anticoagulants	10	47.6		14	41.2		0.851
Atrial fibrilation characteristics							
Atrial fibrilation type							
Persistent atrial fibrillation	10	45.5		3	7.9		0.002
Paroxysmal atrial fibrillation	12	54.5		35	92.1		
Atrial fibrillation duration, months*			2.8			3.01	0.749
Laboratory values							
Urea (mg/dL)			29±5			32±4	0.053
Creatinin (mg/dL)			0.8±0.18			0.8±0.16	0.911
Preprocedure osteopontin (ng/mL)*			19.65			13.29	0.035
Postprocedure osteopontin (ng/mL)*			36.11			30.54	0.409

*Geometric mean was used. SD: Standard deviation.

procedural osteopontin level did not differ between the 2 groups (30.54 ng/mL vs 36.11 ng/mL; p=0.409).

Univariate analysis revealed that LAD, AF type, and preprocedure osteopontin level were significantly associated with recurrence (p<0.05). Age-adjusted multivariate logistic regression analysis was performed to determine independent risk factors of AF recurrence. Among these, AF type was found to be the most important independent variable of AF recurrence (β=2.211; p=0.004; OR: 9.124; 95% CI: 2.026–41.094) (Table 2). Preprocedural osteopontin level was also determined to be an independent indicator of recurrence (β=0.059; p=0.048; OR: 1.061; 95% CI: 1.001–1.125) (Table 2) (Hosmer-Lemeshow test: p=0.261; Nagelkerke R^2=0.353).

Table 2. Multivariate logistic regression analysis of independent predictors of atrial fibrillation recurrence

	β	*p*	OR	95% CI
Atrial fibrilation type	2.211	0.004	9.124	2.026–41.094
Preprocedure osteopontin levels	0.059	0.048	1.061	1.001–1.125

Hosmer and Lemeshow test; p=0.261, Nagelkerke R Square: 0.353. CI: Confidence interval; OR: Odds ratio.

Early procedural success (isolation of all PVs) was 100%. When patients with and without recurrence were compared, mean procedural time (73±9 vs 70±11; p=0.210) and fluoroscopy time (14±2 vs 13±2; p=0.183) did not differ. Ablation catheter application time for each PV, balloon size, and mean freeze duration were also similar for these patients. When complications were analyzed from this perspective, in the recurrence group, 1 patient had PV stenosis, while among patients without recurrence, 1 patient had pericardial effusion and 1 patient had hematoma at sheath insertion site.

Preprocedural and postprocedural osteopontin level did not differ between types of AF (18, 19 ng/mL vs 14.90 ng/mL, p=0.335; 36.82 ng/mL vs 31.19 ng/mL, p=0.493, respectively). Postprocedure osteopontin level increased significantly compared to preoperative level (32.18 ng/mL vs 15.58 ng/mL; p=<0.001). Although postprocedure osteopontin level was not associated with recurrence in univariate and multivariate analysis, Pearson's correlation test indicated that log-preprocedure osteopontin level correlated with log-postprocedure osteopontin level (r=0.845; p<0.001).

DISCUSSION

Plasma level of osteopontin, which is a marker of fibrosis, was evaluated in patients who underwent cryoballoon ablation before and after the procedure. To the best of our knowledge, this is the first study investigating osteopontin impact on AF recurrence. Findings indicated that[1] despite an increase in osteopontin level, postprocedure osteopontin level is not associated with recurrence,[2] LAD, persistent AF, and increased preprocedure osteopontin level are associated with recurrence, and[3] permanent AF and increased preprocedure osteopontin level are independent predictors of recurrence.

Pathogenesis of AF is not well understood; however, recent evidence suggests fibrosis and inflammation are important mediators for its occurrence.[11] AF recurrence after catheter ablation is associated with persistent AF, AF duration, increased LAD, increased PV diameter, PV variation, early recurrence following ablation, LA fibrosis, age, BMI, active smoking, hypertension, and other comorbidities.[5] Our study also indicated that increased LAD and persistency of AF are related to AF recurrence.

Increased LAD and permanent AF are consequences of LA fibrosis.[12] Uijl et al. reported that increased LAD and LA fibrosis determined by echocardiography-derived, calibrated, integrated backscatter were associated with AF recurrence.[13] AF recurrence may also occur due to persistence or reconnection of ablated lines after catheter ablation and atrial remodeling-induced atrial fibrosis.[14] Atrial fibrosis causes cellular disarray and forms a potential cause of atrial activation abnormalities, consequently resulting in both initiation and permanence of AF.[14] Verma et al. reported that pre-existing LA scarring in patients undergoing AF ablation was associated with AF recurrence, increased LAD, and increased levels of inflammatory markers.[12]

Osteopontin, a multifunctional glycoprotein, was initially identified in osteoblasts.[7] Osteopontin is involved in numerous biological processes, such as regulation of extracellular matrix structure by modulating inflammatory cells through macrophage and cytokine release.[8] It is a major modulator of profibrotic alterations induced by angiotensin in heart failure.[15] Angiotensin release from atrial tissue is increased in patients with persistent AF.[9] In a gene expression profiling study, osteopontin transcript level was higher in patients with persistent AF compared with patients without AF.[9] There was no significant difference in osteopontin level between paroxysmal and persistent AF in our study, but comparison between a healthy control group and AF group was not performed. Persistent AF is more common in cases with long-lasting and irreversible atrial dysfunction; however, it is con-

flicting to detect similar osteopontin level in paroxysmal AF. Precipitating factors for AF-induced atrial remodeling include oxidative stress, atrial dilatation, calcium overload, inflammation, and microRNAs. However, it is not clear yet how, when, or how much these alterations affect the remodeling process for AF sustentation.[16] On the other hand, osteopontin level in patients undergoing AF ablation and its impact on AF recurrence had not previously been studied.

Defining predictors for recurrence following catheter AF ablation may help guide appropriate selection of patients and may increase procedural success rate by preventing unnecessary procedures. Relationship between LA fibrosis and recurrence was demonstrated in previous studies by using inflammatory markers and imaging techniques, such as MRI.[17,18] Oakes et al. evaluated patients scheduled for AF ablation before the procedure with cardiac MRI and revealed that fibrosis rate was positively correlated with postprocedural recurrence rate.[17] Some other studies using cardiac MRI of patients scheduled for AF ablation also reported association between atrial fibrosis and procedural success rate.[18,19] Fibrosis rate was higher in patients with permanent AF in the mentioned studies.[18,19] Wu et al. demonstrated that transforming growth factor beta 1(TGF-β1) level was independent predictor for recurrence in patients with non-paroxysmal AF.[20] Canpolat et al. reported that high level of TGF-β1 was associated with significant fibrosis in patients scheduled for AF ablation and that high TGF-β1 level predicted AF recurrence.[21] In our study, persistent AF was a predictor for AF recurrence, which is consistent with current literature. Positive correlation between AF recurrence and elevated osteopontin level supported role of fibrosis in AF etiology.

We also think that increased postprocedure osteopontin level may be used as a surrogate marker for increased fibrosis caused by PVI, but this hypothesis remains to be proven with further investigation. In our study, lack of association between postoperative increase and recurrence may be due to small sample size and measuring osteopontin level earlier (6-month follow-up visit) than relevant studies. Kawamura et al. measured level of type 3 procollagen n-peptide (P3NP), which participates in fibrosis and scar formation, like osteopontin, and reported that decrease of P3NP level in patients undergoing cardioversion was not observed until 24 months.[22]

Study limitations

Small sample size and short duration of follow-up may have decreased the power of statistical tests. Utilizing a biochemical marker to assess underlying fibrosis provides an easy-to-use tool; however, its value may be diminished without information about location and distribution of fibrosis. Combined use of imaging techniques to assess fibrosis status could provide more powerful and precise results. Even though presence of chronic inflammation and diseases related to fibrosis were exclusion criteria for this study, informative value of osteopontin level is limited by the fact that osteopontin is a systemic inflammatory marker, rather than a cardiac-specific one.

Conclusion

Persistence of AF and elevated preprocedural level of osteopontin are predictors for AF recurrence in patients undergoing cryoballoon AF ablation. Association of a biochemical marker with recurrence following ablation may be beneficial for selection of appropriate patients for cryoballoon procedure and assessment of long-term procedural success.

Acknowledgements

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