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Persistent iatrogenic atrial septal defect after cryoballoon ablation for atrial fibrillation

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ABSTRACT

Aims: Pulmonary vein isolation (PVI) by cryoballoon ablation (CB) technology is effective and safe treatment option for atrial fibrillation (AF). CB is performed by large diameter, 15Fr (4.95mm) transseptal sheath that may lead to creation of iatrogenic atrial septal defect (iASD). The objective of this study was to assess the incidence of iASD in patients who had undergone CB.

Methods: Patients with AF having undergone Arctic Front® CB ablation and a subsequent transesophageal echocardiography (TEE) examination during post-ablation follow up period were consecutively enrolled. During all CB procedures, 15Fr transseptal sheath (Flex Cath, Medtronic, Minneapolis, MN) was utilized via single transseptal puncture (TsP).

Results: Twenty-eight patients (15 females, mean age 55.8+15.5) with paroxysmal (n=24) or persistent (n=4) AF formed study group. iASD was present 11 (39.3%) of them after mean follow-up time of 17.3+6.2 months. The procedural time is significantly longer in patient with iASD (119.0+8.8 minutes, p=0.01). No patients died or suffered from any clinically significant cerebral ischemic event. There was no sign of increase in systolic pulmonary arterial pressure (sPAP).

Conclusion: iASD after CB was found to be present in 39.3% of patient during a mean follow-up time of 17.3+6.2 months. The prolonged CB procedural time was the only factor that predicted iASD in our study. No adverse clinic events that might be related to iASD was observed during follow-up period.

Keywords: Iatrogenic atrial septal defect, cryoballoon ablation, pulmonary vein isolation, atrial fibrillation

INTRODUCTION

Pulmonary vein isolation (PVI) is an effective and safe treatment option in symptomatic paroxysmal atrial fibrillation.[1] In all catheter ablation procedures for atrial fibrillation (AF), transseptal puncture (TsP) is needed to gain access to left atrium (LA). One of the complications of TsP is residual iatrogenic atrial septal defect (iASD) which was first recognized after percutaneous mitral balloon valvuloplasty (PMBV) procedures.[2] Residual iASD is also observed after AF ablation procedures, but the literature is sparse on this topic.

Cryoballoon ablation (CBA) system is newly developed technology to make PVI more effective and feasible. The CBA procedure was found to be effective and safe method of pulmonary vein isolation for AF in the first clinical researches.[3,4] Because transseptal sheath with large outer diameter, 15 Fr (4.95mm), is used for delivery and manipulation of the cryoballoon catheter in the LA, risk of residual iASD is thought to increase. The objective of this study was to assess the prevalence of iASD in patients who had undergone CB.

METHODS

Ethics

This study protocol has been approved by Ankara University Faculty of Medicine Clinical Researches Ethics Committee (Date: 13.01.2014, Decision No: 01-06-14). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Study Population

Between December 2011 and November 2013, pulmonary vein isolation using Arctic Front cryoballoon was performed on 84 patients with persistent atrial fibrillation at our clinic. Among these patients, 28 individuals who underwent transesophageal echocardiography for any reason following the ablation procedure were included in the study. .patients with AF who were treated by Arctic Front® Cryoballoon between December 2011 and November 2013 and undergoing subsequent transesophageal echocardiography (TEE) examination for any reason after CBA were

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consecutively enrolled in our retrospective analysis. The indications of reperforming TEE, obtained from medical records were unexplained chest pain and dyspnea, further examination of mitral valve regurgitation and anatomy, suspicion of interatrial shunt and poor transthoracic ultrasound wave transmission. Exclusion criteria include previous LA ablation for AF or other transseptal puncture, second TsP during or after the index CB procedure for any reasons, and ASD, patent foramen ovale or other congenital heart disease prior to ablation.

Echocardiographic Examination

The preprocedural transthoracic/transesophageal echocardiography was performed in all patients. Pre-and post- procedural TTEs enabled assessment of diameter, diastolic and systolic function of left ventricle, right ventricle functions, left atrial diameter, anatomy and function of valves, atrial and ventricular septum. Ventricular systolic pressure was estimated from tricuspid valve regurgitation jet velocity by the modified Bernoulli equation and was considered equal to the systolic pulmonary artery pressure (sPAP). TEE was performed using pre and post commercial equipment (Vivid S5, GE Medical System, Milwaukee, MI, USA) and LA thrombus and anatomy, valves anatomy and function, interatrial septum with 2D and color doppler flow were examined from multiple views (Figure). iASD was defined as interatrial shunt confirmed by doppler flow beside the fossa ovalis but not fulfilling the criteria of patent foramen ovale (PFO).[5] In a case of confirmed iASD, the characteristic of transseptal flow was also examined thereafter injection of agitated saline before and after Valsalva maneuver.

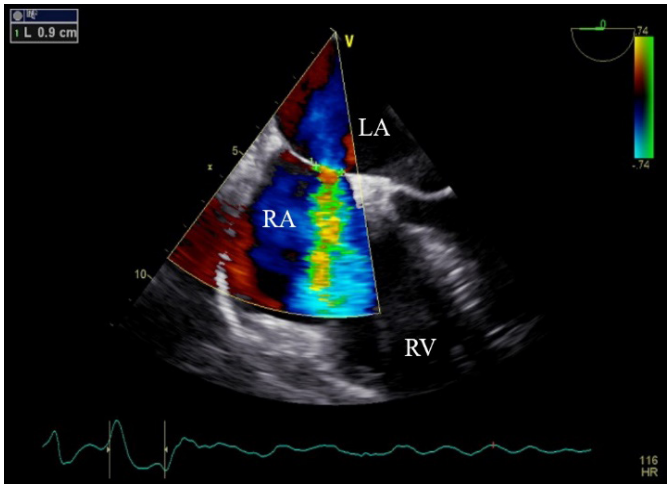

Figure. Mid esophageal view of interatrial septum with color flow doppler demonstrating left-to-right shunt across 0.9cm persistent iatrogenic septal defect. LA: left atrium, RA: Right atrium, RV: right ventricle

Transseptal Puncture and Cryoballoon Ablation Procedure

In our study all pulmonary vein ablation procedures were performed with Arctic Front® Cryoballoon Ablation System (Medtronic, Inc.). In all patients single TsP was performed by Brockenborough needle and 8F sheath (Mullins transseptal guiding introducer, St Jude Medical, Minnetonka, MN, USA). TsP was performed with guide of TEE and fluoroscopy. The 8F sheath was exchanged for 300cm 0.035inch J guidewire and then was utilized to left superior pulmonary vein. Then the outer diameter 15Fr, inner diameter 12Fr Ts catheter (Flex Cath, Medtronic, Minneapolis, MN) was introduced to LA along the guidewire. Inside the sheath the arctic front balloon was introduced to LA and the balloon was inflated. Once inflated and pushed against the pulmonary vein (PV) ostium, PV occlusion was evaluated by dye injection. After flushing the line with saline, N2O was pumping into balloon for freezing. After that, thawing, deflation of balloon and pulling back the system were performed in an order. Because in all patient single TsP was performed, the mapping catheter for evaluating the isolation PV could be introduced to LA only after arctic front system was pulled back. During the whole procedure activated clotting time was maintained above 300 seconds with supplement of heparin infusion as required. After CBA procedure all patients were in sinus rhythm. There was no acute complication during hospital stay.

Post Ablation Treatment And Follow-Up

After the day of CBA procedure all patient underwent TTE to evaluate the pericardial effusion. Oral anti-coagulant (OAC) and low molecular weight heparin (LMWH) therapy was started at the same day with CB. When the INR level reached the target[2,6], LMWH was stopped. OAC therapy was continued at least 3 months, and then anti-thrombotic therapy was decided according CHA2DS2 VASc risk assessment of individual patient. Anti-arrhythmic therapy was introduced at least 3 months following the procedure to all patients and discontinued thereafter if the patient was free of AF relapse.

During follow-up period, the information about whether the patient suffered or died from ischemic cerebrovascular event/transient ischemic attack was obtained from medical records and patients were examined for signs and symptoms of ischemic cerebral emboli.

Statistical Analysis

Continuous data are expressed as mean+standard deviation, categorical data as number and percentages. Comparisons of continuous variables were done with Student's t tests or Mann-Whitney as appropriate and binominal variables with chi-square or Fischer test. Two-tailed p values <0.05 were considered significant. Statistical analyses were conducted using SPSS software (SPSS v11.5 IBM Inc., Chicago, IL, USA).

RESULTS

Patients and Baseline Echocardiographic Characteristics

Twenty-eight patients (15 females, mean age 55.8+15.5) with paroxysmal (n=24) or persistent (n=4) AF formed study group. There were no left or right ventricle dilatation/dysfunction or severe heart valve dysfunction in pre-ablation echocardiography. The mean E/E′ ratio was 7.6+2.2 and there was no patient with E/E′ ratio more than 15 in our study population. The other clinical and baseline TTE characteristics are given in Table 1.

Table 1. Baseline characteristics

Number of patients	28
Women, n (%)	15 (53.6)
Age, year	55.8+15.5
BMI, kg/m^2	29.9+4.6
Creatinine clearance*, mL/min	106.5+40.4
HT, n (%)	13 (46.4)
DM, n (%)	5 (17.9)
CHA2DS2 VASc score	1.0 (0–5)
Paroxysmal AF, n (%)	24 (85.7)
OAC treatment during TEE, n (%)	10 (35.7)
LA diameter/BSA, cm/m^2	2.22+0.24
sPAP, mmHg	30 (20–55)
E/E′ ratio	7.6+2.2

BMI, body mass index; HT, hypertension; DM, diabetes mellitus; HL, hyperlipidemia; AF, atrial fibrillation; TEE, transesophageal echocardiography; OAC, oral anticoagulant; LA, left atrium; BSA, body surface area; sPAP, systolic pulmonary artery pressure
*estimated creatinine clearance that is calculated by Cockcroft-Gault formula [[(140-age) x weight/73 x serum creatinine] x if woman 0.85]

Post-Ablation Follow-Up

Mean follow-up was 17.3+6.2 months. In the post-procedural TEE, iASD was detected in 11 (39.3%) patients. In all patients with iASD, there were left to right shunt in color doppler examination. Clinic and echocardiographic characteristics of patients are given in Table 2. No significant difference in clinic and echocardiographic characteristics was identified between the patient with or without residual iASD. In study group, post-ablation change in sPAP was not significantly different between two groups (p=0.805).

In our study, the mean duration of CBA procedure was 106.9+20.1 minutes and the mean duration of fluoroscopy was 106.9+20.1 minutes. The comparison of duration of CBA, fluoroscopy and follow up period between the patients with and without iASD are given in Table 3. Procedural duration in patients with and without iASD was 119.0+8.8 and 92.9+21.0 minutes, in order. The mean procedural time was significantly longer in patients with iASD than the patients without iASD (p=0.010).

We divided the study population into two subgroups according date of procedure to evaluate the learning curve. No significant difference in procedural time or iASD prevalence was observed between the patients that CBA performed in the first 3 month (n=14) and after the first 3 months (n=14) (p=0.699 and p=0.220).

In our study, nobody suffered or died from cerebrovascular event or transient ischemic attack during follow up period.

Table 2. Comparison of clinical and echocardiographic parameters between patient with or without iASD

	with iASD	without iASD	p
Sex, women, n (%)	5 (45.5)	10 (58.9	0.488
Age, year	50.4+15.8	59.3+14.7	0.138
BMI, kg/m^2	29.4+4.2	30.2+4.9	0.647
Creatinine clearance*, mL/min	92.6 (54–216)	93 (71–194)	0.746
HT, n (%)	5 (45.5)	8 (47.1)	0.934
DM, n (%)	1 (9.1)	4 (23.5)	0.619
HL, n (%)	1 (9.1)	4 (23.5)	0.619
CHA_2DS_2 VASc score	1.0 (0–2)	1.0 (0–5)	0.285
Paroxysmal AF, n (%)	10 (90.9)	14(82.4)	1.00
OAC treatment during TEE, n (%)	3 (27.3)	7(41.2)	0.689
Baseline TTE characteristics			
LA diameter/BSA, cm/m^2	2.24 (1.65–2.32)	2.21 (1.81–2.88)	0.639
sPAP, mmHg	27.5 (20–35)	30 (25–55)	0.077
E/E′ ratio	6.96+1.75	8.19+2.57	0.304
Postprocedural TTE characteristic			
sPAP, mmHg	30 (25–50)	30 (25–35)	0.383

iASD, iatrogenic atrial septal defect; BMI, body mass index; HT, hypertension; DM, diabetes mellitus; HL, hyperlipidemia; AF, atrial fibrillation; TEE, transesophageal echocardiography; OAC, oral anticoagulant; LA, left atrium; BSA, body surface area; sPAP, systolic pulmonary artery pressure
*estimated creatinine clearance that is calculated by Cockcroft-Gault formula [[(140-age) x weight/73 x serum creatinine] x if woman 0.85]

Table 3. The comparison of procedural characteristics and follow up time

	Duration of CBA (min)	p	Fluoroscopy duration (min)	p	Time between CBA and TEE (months)	p
with iASD	119.0+8.8	0.010	46.6+ 14.1	0.804	15 (6.0–24.5)	0.134
Without iASD	92.9+21.0		44.8+21.9		21 (6.0–26.0)	

iASD, iatrogenic atrial septal defect; CBA, Cryoballoon ablation; TEE, transesophageal echocardiography; min, minute

DISCUSSION

In experienced hand, transseptal puncture can be performed with minimal complication; but acute procedure related ASDs are inevitable. This study assessed the prevalence of iASD in patients undergoing transseptal catheterization with 15F sheath during cryoballoon ablation. The main findings of this study are (1) iASD was found to be present in 39.3% of patients by TEE during a mean follow-up time of 17.3+6.2 months[2]; no significant relationship between baseline characteristics of patient and development of iASD[6]; Procedural time was found to be only predictor of iASD in our population (119+8.8 minutes, p=0.010).

A relatively recent trail on patients undergoing PVI with second generation CB reported that iASD prevalence was 8.4% after 15.5 months median follow-up[7] and Cronin et al.[8] detected iASD in the 17.6 % and 2.4% of patients respectively CBA group and RFA group at 118.2+40.7 days follow-up. TTE was performed to detect iASD in both aforementioned studies. There are many invasive and non-invasive methods that are used to detect ASD. These are oximetry method, indicator-dilution method, two-dimensional (2-D) TTE and TEE. TTE has high sensitivity and specificity in detection ASD.[9] Moreover, addition of harmonic imaging, color doppler and provocative maneuver to TTE examination increases its sensitivity.[10] But in the presence of small defect (<5mm) and/or poor ultrasound wave transmission, TEE is superior to TTE.[11] In our study, dimension of iASD is 2mm in two patients, 4.5mm in three, 5mm in one patient and 5-6mm in five patients. Consequently, using of more sensitive diagnostic tool is thought to be the reason of higher rate of iASD in our study.

In our knowledge first report on iASD in the electrophysiology era was published by Fitchet et al.[11] In this research there was no iASD at 3 months after ablation procedure with 8Fr catheter. Afterwards Hammerstingl et al.[12] investigated iASD among the 42 patients that were divided into two groups, one that two 8Fr transseptal catheter utilized through two separate TsP and in the other two 8Fr catheter through the same, single TsP into LA. Although iASD incidence was as high as 29.6% in single TsP, no iASD was detected in two TsP group.[11] Furthermore, Rillig et al.[13] observed low incidence of iASD (3.7%, n=1) after PVI procedures through double TsP. Moreover, the incidence of iASD following PVI was founded to be significantly higher in the CBA group, which larger Ts (15F) catheter was used, compared to RF ablation group.[8,14,15] In MitraClip system the 22Fr transseptal catheter is used to reach mitral valve and iASD was found up to 50% of sixty-six patients at 6 months by TEE.[16] As a result of above-mentioned articles, smaller Ts punctures although multiple have higher tendency to close. Large sheath through interatrial septum might cause more damage to septum than small outer diameter.

As mentioned before the outer diameter, 15Fr Ts sheath was used in CBA in our study. Similar outer diameter, 14Fr Ts sheath is used to left atrial appendix (LAA) closure procedures. The incidence iASD was found to be 7% by transesophageal echocardiography at 12 months after LAA closure procedure.[17] The other procedure that larger, 8.5+14 Fr sheaths are used with remote robotic navigation system (RNS) in PVI procedure. iASD was detected by TEE in 21.1% of patients undergoing PVI with RNS.[18] In these procedures the iASD incidence was lower than our study beside same or larger outer diameter Ts catheter using. An explanation for that finding might be that more extensive sheath manipulation needed in PVI than LAA closure procedure and the position of the outer artisan sheath (in Robotic Navigation System) remains rather stable throughout the procedure as mainly the inner sheath is used for catheter navigation. Torquing and bending the sheath in many directions to reach PV antra, especially right lower PV, might cause higher level of shear stress and damage to septum. The intense of maneuvering might be more important factor of septum damage rather than overall diameter of sheath.

The first article directly reports the iASD after CB procedure in literature was published by Chan et al.[19] In that report the prevalence of iASD in the 9th month TEE after CB was 30%. Thereafter Sieira et al.[20] detected iASD by TEE in 20.5% of 39 patients at 11.7+8.2 months after CB procedures. Spontaneous closure of iASD with time was observed in previous researches.[13,17] No longer closure of iASD was observed after 3 years in patients with iASD undergoing CB ablation.[21] Davies et al.[22] observed presence of iASD in 7 out of 27 patients (26%) after median follow-up time of 553 days. Mugnai et al.[14] reported iASD prevalence was 22.5% of 127 patients at median 11.6 months. Yang et al.[15] detected iASD in 15.6 % of 141 patients at 1 year after CB operation. Linhart et al.[23] detected 37 iASD in 101 patients (37%) after median 2.9 years follow- up. Linhart et al.[23] reported nearest findings to our results. Different from all other study, patients who had PFO before intervention were included in Linhart's cohort. In our investigation the prevalence of iASD was at least 10% higher than in aforementioned articles except Linhart et al.'s[23] research. This inconsistency cannot be explained by methodology of echocardiography, difference in size or extent of manipulation of Ts sheath. The higher percentage of iASD in our study population might result from different patient characteristics or a statistical effect of small patient number in our trial.

Female sex, hypertension had been described as risk factors for iASD after CBA procedures[15,22]; but no demographic and baseline echocardiographic parameters was found to be predictor of iASD in our trail. Linhart et al.[23] reported that lower left atrial appendage flow velocity was associated with higher risk of persistence of iASD. In our study, left atrial appendage flow velocity was not measured before or after the procedure. In this study, CBA procedural time was found to be the only predictor of iASD. In some patients because of anatomic variation in LA the cannulation of PV antra, especially right inferior PV, is challenging. This challenge that increases in shear stress on septum is thought to be most likely one of the explanations of longer procedural time in patients with iASD. Consistent with our hypothesis, the atrial septal angle[7], left atrial operation time[15] and number of cryo-application[21] were described as iASD predictors. It might be speculated that experience of operator affects the procedural time and intense of sheath manipulation. We divided the study group into two according to date of CBA to evaluate the effect of learning curve on iASD incidence, but no significant difference in iASD rate and procedural time was detected between group. Low experience of operator (<25 procedures/year) and/or center (<50 procedures/year) were founded to increase in-hospital complications of AF ablation but chronic complication didn't search.[24] Despite we don't have acute complications in our study group, as result of prolongation of procedure duration the higher incidence of persistent iASD in our center where 28 cases were performed in 2 years might be the chronic complication of low operator experience.

The adverse clinical outcomes in patients with unrepaired congenital ASD include left-to-right shunt causing right ventricular volume overload, paradoxical embolism and atrial arrhythmias. iASD that required closure after CB PVI was reported 2 (1.9%) large size (10-10mm) by Chan et al.[21] and 2 (4.8%) Cronin et al.[8] Yang et al.[15] reported that the recurrence rate of in patients with iASD was significantly higher than patient without iASD (53.13vs.28.74%, P<0.05) and the analysis of CB and RF subgroup of the cohort was consistent with this finding. There was no significant difference in the 6-min walk test, new stroke and rehospitalization rate between iASD and non-iASD group. In our study population, no patient suffered from right ventricular failure or required closure of iASD, but recurrence AF rate was not searched. Large right to left shunt (RLS), atrial septal aneurysms, PFO size are known risk factors for paradoxical embolism and stroke[25] and long-term oral anticoagulation is recommended for patients with congenital ASD and AF[26]. In our study, RLS only in late cardiac cycle (>3 beats) was present in 4 (33.3%) patients. No patients died or suffered from any clinically significant cerebral ischemic event, during follow up period. Absence of high-risk criteria for paradoxical emboli, treatment with OAC at least 3 months, short-term follow-up period and small number of patients might be reasons that prevent clinically significant cerebral emboli in our study.

Limitations

The small number of patients and limited follow-up and retrospective design are the main limitations of our study. We did not perform immediate TEE which would have helped us to evaluate the closure rate or size of iASD in a different stage of follow-up. All patients were treated with OAC at least 3 months after CB procedure and then continued with anti-platelet or anti-coagulation therapy. This fact may affect the occurrence of systemic embolism. After AF ablation, cerebral emboli might be silent and could have been detected by specific imaging technique.[27] No specific imaging technique has been ruled out silent cerebral ischemia in our study.

CONCLUSION

In our study we investigate the residual iASD with TEE after CB procedures. iASD was detected by TEE in 11 (39.3%) patients at 17.3+6.2 months. Clinically significant cerebral ischemia or increase in sPAP that might be related to iASD was not observed during follow-up. CB procedural time was only predictor of iASD after TsP. this finding supports hypothesis that increase stress and damage might cause residual iASD. Further studies with larger population and longer follow-up might be required to confirm our findings.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was carried out with the permission of Ankara University Faculty of Medicine Clinical Researches Ethics Committee (Date: 13.01.2014, Decision No: 01-06-14).

Informed Consent

All patients signed and free and informed consent form.

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

The authors declared that this study has received no financial support.

Author Contributions

All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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