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## Clinical Research

# A Very Long-term Longitudinal Study on the Evolution and Clinical Outcomes of Persistent Iatrogenic Atrial Septal Defect After Cryoballoon Ablation

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***See editorial by Hong and Glover, pages 368–369 of this issue.***

**ABSTRACT**

**Background:** Persistent iatrogenic atrial septal defect (iASD) is a common but poorly characterized complication after cryoballoon (CB) pulmonary vein isolation (PVI) procedures. We therefore investigate its prevalence, evolution, risk factors, and clinical outcomes in a prospective longitudinal study.

**Methods:** A total of 108 patients (41 women, mean age 57 ± 11.3) underwent CB PVI for AF. Serial transesophageal echocardiography (TEE) was performed 9 months and then annually until 6 years after the procedure to study the characteristics of persistent iASD.

**Results:** Persistent iASD occurred in 33 (30.6%) patients 9 months after CB PVI. Spontaneous closure of iASD was found in 6 (22.2%) and 3 (15.8%) patients 2 and 3 years after the procedures, respectively. No spontaneous closure was observed on 4, 5, and 6-year TEE follow-up. The projected long-term persistence rate of iASD after CB PVI was therefore 20% (30.6% × 0.778 × 0.842). Using multivariate logistic regression, a higher number of cryoapplications (≥ 2 minutes) was the only independent predictor of persistent iASD 9 months after CB PVI (odds ratio [OR] 1.207; 95% confidence interval [CI], 1.033-1.411, $P = 0.018$). Two (1.9%) patients with significantly larger iASD size than the others (long diameter 12.6 ± 0.8 vs 3.7 ± 1.5 mm, $P < 0.001$; short diameter 10.9 ± 0.2 vs 3 ± 1.1 mm, $P < 0.001$) required

**RÉSUMÉ**

**Contexte :** La persistance d'une communication interauriculaire iatrogène est une complication répandue, quoique mal caractérisée, des interventions visant à isoler les veines pulmonaires à l'aide d'un cryocathéter à ballonnet. Nous nous sommes donc penchés sur sa prévalence, son évolution, ses facteurs de risque et son issue clinique dans le cadre d'une étude longitudinale prospective.

**Méthodologie :** Au total, 108 patients (dont 41 femmes; âge moyen : 57 ± 11,3 ans) ont subi une intervention visant à isoler les veines pulmonaires à l'aide d'un cryocathéter à ballonnet pour traiter une fibrillation auriculaire. Des échocardiographies transœsophagiennes (ETO) réalisées 9 mois plus tard, puis chaque année pendant les 6 années qui ont suivi l'intervention ont servi à étudier les caractéristiques de la communication interauriculaire iatrogène persistante.

**Résultats :** Neuf (9) mois après l'intervention visant à isoler les veines pulmonaires à l'aide d'un cryocathéter à ballonnet, une communication interauriculaire iatrogène persistante a été observée chez 33 (30,6 %) patients. Elle s'était refermée spontanément chez 6 (22,2 %) et 3 (15,8 %) de ces patients 2 et 3 ans après l'intervention, respectivement. Aucun autre cas de fermeture spontanée n'a été détecté lors des examens par ETO réalisés lors des visites de contrôle qui ont eu lieu au bout de 4, 5 et 6 ans. Le taux prévu de persistance d'une

Cryoballoon (CB) pulmonary vein isolation (PVI) has been shown to be noninferior to radiofrequency catheter ablation in the treatment of symptomatic drug-refractory paroxysmal atrial fibrillation (AF) in terms of both efficacy and safety.[1] On the other hand, CB PVI has been increasingly adopted worldwide.[2] This procedure requires transseptal access with a 15 French steerable sheath, and persistent iatrogenic atrial septal defect (iASD) has been recognized as a common complication.[3] The reported prevalence varied from 8.4% detected at 16 months after CB PVI by transthoracic echocardiography to 37% detected 2.9 years after the procedure by transesophageal echocardiography.[4-9] Despite its common occurrence, data on its prevalence, risk factors, and clinical sequelae have been scarce and based on cross-sectional studies with a small number of patients, selection bias, relatively short-term follow-up, and heterogeneous methodology.[3-9] Therefore, we sought to investigate the prevalence, evolution, risk factors, and clinical outcomes of persistent iASD

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**percutaneous closure because of exertional dyspnea and right ventricular enlargement. Over 129.7 patient-years follow-up, during which iASD persisted, there was no occurrence of neurologic events.**

**Conclusions: Approximately one fifth of patients undergoing CB PVI will have permanently persistent iASD. Patients with defect sizes of greater than 10 mm may need percutaneous closure due to significant left-to-right shunting.**

**communication interauriculaire iatrogène consécutivement à une intervention visant à isoler les veines pulmonaires à l'aide d'un cryocathéter à ballonnet se chiffrait donc à 20 % (30,6 % × 0,778 × 0,842). Une analyse par régression logistique multivariée a permis de constater qu'un nombre particulièrement élevé de cryoapplications (≥ 2 minutes) était le seul facteur prévisionnel indépendant d'une communication interauriculaire iatrogène persistante 9 mois après une intervention visant à isoler les veines pulmonaires à l'aide d'un cryocathéter à ballonnet (risque relatif approché [RRA] : 1,207; intervalle de confiance [IC] à 95 % : de 1,033 à 1,411; $p = 0{,}018$). Deux (1,9 %) patients porteurs d'une communication interauriculaire iatrogène persistante significativement plus grande que celle des autres patients (diamètre long : 12,6 ± 0,8 vs 3,7 ± 15 mm; $p < 0{,}001$; diamètre court : 10,9 ± 0,2 vs 3 ± 1,1 mm; $p < 0{,}001$) s'étant soldée par une dyspnée à l'effort et par une hypertrophie ventriculaire droite ont dû subir une intervention percutanée afin de la refermer. Pendant les 129,7 années-patients de suivi, au cours desquelles la communication interauriculaire iatrogène a persisté, aucune manifestation neurologique n'a été recensée.**

**Conclusions : Environ un patient sur cinq subissant une intervention visant à isoler les veines pulmonaires à l'aide d'un cryocathéter à ballonnet sera atteint d'une communication interauriculaire iatrogène permanente. Ceux porteurs d'une communication de plus de 10 mm pourraient avoir besoin d'une intervention percutanée pour la refermer en raison d'un shunt artérioveineux important.**

after CB PVI with a very long-term longitudinal follow-up study using transesophageal echocardiography (TEE).

## Materials and Methods

### Study design and patient population

This was a single-centre prospective study on consecutive patients undergoing CB PVI procedures for AF in the period between May 2008 and April 2017, in Princess Margaret Hospital in Hong Kong. Exclusion criteria included previous history of left atrial (LA) catheter ablation or other transseptal procedures, pre-existing ASD and other congenital heart disease, LA thrombus, and pregnancy. The study complies with the Declaration of Helsinki, and the study protocol was approved by the Ethics Committee of the investigation centre. All patients gave written informed consent before recruitment into the study.

### Preablation management

Cardiac computed tomography was performed to reveal the LA and PV anatomy before ablation. All patients were put on either warfarin with international normalized ratio maintained between 2.0 and 3.0 or fixed doses of non-vitamin K antagonist oral anticoagulants (NOAC) for at least 4 weeks before the procedure. Ablation was performed with uninterrupted warfarin, whereas NOAC was stopped 2 to 5 days, according to renal function, before the procedure.[10] TEE was performed the day before the ablation procedure to rule out pre-existing ASD and LA thrombus. All antiarrhythmic drugs, including amiodarone, were discontinued at least 5 days before the procedure.

### Cryoballoon PV isolation procedure

The CB PVI procedure has been described previously.[1] In brief, the ablation procedure was performed under local anesthesia and conscious sedation with midazolam and fentanyl. Intravenous heparin was given to maintain an activated clotting time of > 300s throughout the procedure. A decapolar electrode diagnostic catheter was placed in the coronary sinus. A steerable quadripolar electrode diagnostic catheter was placed in the right ventricle for pacing support when vasovagal reaction occurred after CB ablation of the left-sided PVs. This catheter was moved to the right subclavian vein or superior vena cava for phrenic nerve (PN) stimulation during CB ablation of the right-sided PVs. A single transseptal puncture was performed under fluoroscopic guidance with the Brockenbrough needle and an 8 French sheath (SL1 guiding catheter [St Jude Medical, St Paul, MN] or Mullin transseptal guiding introducer [Medtronic, Minneapolis, MN]), which was then exchanged for a 15 French steerable transseptal sheath (FlexCath or FlexCath Advance; Medtronic Cryocath, Minneapolis, MN). The 10.5 French 28 or 23mm cryoballoon catheter (Arctic Front or Arctic Front Advance; Medtronic Cryocath) was then introduced via the steerable transseptal sheath to the left atrium for PVI. Mapping of PV potentials was achieved with the use of a stand-alone circular catheter (Optima Plus; St Jude Medical) or an inner lumen catheter (Achieve; Medtronic Cryocath) placed inside the cryoballoon catheter since its availability in May 2011. In general, 2 consecutive cryoapplications of 4 minutes each were delivered to each PV ostium or antrum with the use of first-generation CB (Arctic Front) and for second-generation CB (Arctic Front Advance), 2 consecutive cryoapplications of 3 minutes each were used for each PV. Additional cryoapplications were delivered to achieve PVI, if necessary. The

procedural endpoint was electrical isolation of all pulmonary veins with entry +/− exit block. Touch-up with an 8-mm−tip cryoablation catheter (Freezor Max, Medtronic) was performed if procedural endpoint could not be achieved with CB alone. Compound motor action potential (CMAP)[11] of the right hemidiaphragm was monitored while pacing the PN in the right subclavian vein or superior vena cava during CB ablation of right-sided PVs since September 2013. Before that, palpation of diaphragmatic contraction was used for prevention of PN injury.

### Transesophageal echocardiography

All patients underwent TEE 1 day before, 9 months after, and then from the second year onward, annually until 6 years after the procedure if there were persistent iASD. Commercially available equipments (Vivid 7 [GE Medical Systems, Milwaukee, WI] or IE33 [Philips Medical, Andover, MA]) with a multiplane 7MHz transducer were used. Atrial anatomy was examined with TEE from the mid- to upper esophagus at angles ranging between 0 and 120°. Both 2D images and color Doppler flow mapping of the interatrial septum were obtained from multiple views. ASD was defined as interatrial shunt confirmed by Doppler flow mapping beside the fossa ovalis but not fulfilling the echocardiographic criteria for patent foramen ovale.[12] In case of confirmed iASD during TEE, the size of the defect was measured and the direction of shunt was determined. Agitated saline contrast echocardiography was performed at rest and after Valsalva manoeuvre within 3 cardiac cycles from right atrial opacification.

### Postablation management and follow-up

All patients underwent continuous electrocardiographic (ECG) monitoring in the coronary care unit for 24 hours after the procedure. For patients on NOAC, the first dose was resumed 24 to 48 hours after the procedure. Oral anticoagulation was continued for 3 months after the procedure. Subsequent need for oral anticoagulation depended on the **C**ongestive Heart Failure, **H**ypertension, **A**ge ≥ 75 Years, **D**iabetes Mellitus, **S**troke, **V**ascular Disease, **A**ge 65 to 74 Years, **S**ex **C**ategory ($CHA_2DS_2$-VASc) score of the patients. Previously used antiarrhythmic drugs were given for 3 months after the procedure. Patients were scheduled for clinical follow-up 1 month and then quarterly after the procedure. Clinical examination including full neurologic assessment was performed during each follow-up. History on symptom recurrence of palpitations was specifically taken and a 12-lead ECG was performed during each follow-up. A 24-hour Holter monitoring was performed during each follow-up for the first 12 months after the procedure. A 3-month blanking period was adopted for recurrence of AF. Recurrence was defined as documented occurrence of AF, atrial flutter, or atrial tachycardia lasting more than 30 seconds.

### Statistical analysis

Descriptive statistics are presented for all data. For normally distributed data, they are expressed as mean and standard deviation and comparison was performed by Students' *t*-test. For non-normally distributed data, they are expressed as median with maximum and minimum values stated, and the Mann−Whitney U test was used to assess statistical significance. For categorical data, absolute and relative frequencies were determined, and the 95% confidence intervals were calculated. Fishers exact test or $\chi^2$ test was performed to assess statistical significance. Independent predictors of persistent iASD at 9 months were modelled by multivariate logistic regression. Kaplan−Meier survival analysis was used to study long-term spontaneous closure of iASD. For regression analysis, a univariate analysis was performed first and variables with a $P$ value of $< 0.1$ were included for multivariate analysis. Statistics were performed with the Statistical Package for Social Science (SPSS version 19; IBM, Chicago, IL). A $P$ value of $< 0.05$ was considered to be statistically significant.

## Results

### Patient and procedural characteristics

A total of 119 patients underwent CB PVI for AF in the period between May 2008 and April 2017 in Princess Margaret Hospital in Hong Kong. Eleven of them (6 refused TEE follow-up, 2 had congenital ASD, and 3 died before 9-month TEE follow-up) were excluded, and the remaining 108 patients (41 women, mean age 57 ± 11.3) formed the study population. No interatrial septal aneurysm was present on TEE examination performed 1 day before the procedure. The prevalence of persistent iASD revealed by 9-month TEE was 30.6% (95% CI, 26.2%-35% [33/108]). No dissection of the interatrial septum was observed. Baseline characteristics of the patients are summarized in Table 1. The prevalence of chronic renal impairment (creatinine > 200 μmol/L) was significantly higher in patients with persistent iASD shown by 9-month TEE (iASD+ group) compared with those without (iASD− group) (9.1% vs 0, $P = 0.027$). The procedural characteristics are summarized in Table 2. The number of cryoapplications (≥ 2 minutes in duration) was significantly higher in the iASD+ group compared with the iASD− group (10.6 ± 3.8 vs 8.9 ± 2.6, $P = 0.032$). Use of pull-down technique during ablation of the right inferior PV was similarly observed in iASD+ and iASD− groups (45.5 vs 44%, $P = 0.834$). Using CB alone, acute procedural success was achieved in 101 (93.5%; 95% CI, 91.1%-95.8%) patients, and the remaining 7 patients were treated successfully with touch-up using 8-mm−tip cryoablation catheters. Arrhythmic recurrence on 1-year follow-up occurred in 30 (27.8%; 95% CI, 23.5%-32.1%) patients.

### Very long-term evolution and predictors of persistent iASD

Among 33 patients with persistent iASD shown by 9-month TEE, 27 of them underwent 2-year TEE and 6 (22.2%; 95% CI, 14.2%-30.2%) had spontaneous closure of iASD (Fig. 1). Nineteen patients underwent 3-year TEE, and 3 (15.8%; 95% CI: 7.4%-24.2%) had spontaneous closure of iASD. No more spontaneous closure was observed on 4-, 5-, and 6-year TEE follow-up (Fig. 2). Therefore, the projected long-term persistence rate of iASD after CB PVI was 20% (30.6% × 0.778 × 0.842; 95% CI, 16.2%-24.3%). Using multivariate logistic regression, the number of cryoapplications (≥ 2 minutes in duration) was the only

**Table 1.** Baseline characteristics

| | All (n = 108) | iASD+ group (n = 33) | iASD− group (n = 75) | *P* value |
|---|---|---|---|---|
| Mean age | 57 ± 11.3 | 55.6 ± 12.1 | 57.6 ± 11 | 0.414 |
| Sex (F), n (%) | 41 (38) | 14 (42.4) | 27 (36) | 0.528 |
| Types of AF | | | | |
| Paroxysmal AF | 73 (67.6) | 24 (72.7) | 47 (62.7) | 0.520 |
| Persistent AF | 11 (10.2) | 2 (6.1) | 9 (12) | |
| Long-standing persistent AF | 26 (24.1) | 7 (21.2) | 19 (25.3) | |
| Medical conditions | | | | |
| Hypertension, n (%) | 45 (41.7) | 15 (45.5) | 30 (40) | 0.596 |
| Diabetes, n (%) | 10 (9.3) | 6 (18.2) | 4 (5.3) | 0.065 |
| Hyperlipidaemia, n (%) | 25 (23.1) | 6 (18.2) | 9 (12) | 0.469 |
| Coronary artery disease, n (%) | 18 (16.7) | 4 (12.1) | 14 (18.7) | 0.576 |
| Heart failure, n (%) | 6 (5.6) | 3 (9.1) | 3 (4) | 0.367 |
| Valvular heart disease, n (%) | 1 (0.9) | 1 (3) | 0 | 0.306 |
| Stroke/TIA, n (%) | 9 (8.3) | 1 (3) | 8 (10.7) | 0.274 |
| CRI (creatinine > 200 μmol/L) | 3 (2.8) | 3 (9.1) | 0 | 0.027 |
| Dilated cardiomyopathy, n (%) | 8 (7.4) | 2 (6.1) | 6 (8) | 1.0 |
| Obstructive sleep apnoea, n (%) | 4 (3.7) | 0 | 4 (5.3) | 0.311 |
| Sinus node dysfunction, n (%) | 8 (7.4) | 2 (6.1) | 6 (8) | 1.0 |
| Mean $CHA_2DS_2$-VASc score | 1.6 ± 1.4 | 1.7 ± 1.5 | 1.6 ± 1.4 | 0.827 |
| LA size (cm) | 3.7 ± 0.8 | 3.7 ± 0.9 | 3.7 ± 0.8 | 0.702 |
| LVEF (%) | 61 ± 13.9 | 61.3 ± 14.3 | 60.1 ± 13.8 | 0.902 |

AF, atrial fibrillation; $CHA_2DS_2$-VASc, **C**ongestive Heart Failure, **H**ypertension, **A**ge ≥ 75 Years, **D**iabetes Mellitus, **S**troke, **V**ascular Disease, **A**ge 65 to 74 Years, **S**ex **C**ategory; CRI, chronic renal impairment; iASD+, persistent iatrogenic atrial septal defect on 9-month TEE; iASD−, no persistent iatrogenic atrial septal defect on 9-month TEE; LA, left atrium; LVEF, left ventricular ejection fraction; TEE, transesophageal echocardiography; TIA, transient ischemic attack.

independent predictor of persistent iASD 9 months after CB PVI (OR 1.207; 95% CI, 1.033-1.411, $P = 0.018$) (Table 3).

### Clinical outcomes of persistent iASD

For persistent iASD detected on 9-month TEE, the mean short diameter was 3.6 ± 2.4 mm, and mean long diameter was 4.4 ± 2.8 mm. Left-to-right interatrial shunting was observed in all iASD, and in 13 (39.4%; 95% CI, 30.9%-48.3%) patients, small right-to-left interatrial shunting was observed during Valsalva manoeuvre. Two (1.9%; 95% CI, 0.6%-3.2%) patients underwent percutaneous closure of iASD 9 and 22 months after CB PVI because of large size of defects (13.1 × 10.7 mm and 12 × 11 mm), symptom of exertional dyspnea, and right ventricular enlargement. The interatrial shunt ratio was 1.5 and 2.4, respectively. The symptoms in both patients remarkably improved after iASD closure. The mean short diameter (10.9 ± 0.2 vs 3.0 ± 1.1 mm, $P < 0.001$) and long diameter (12.6 ± 0.8 vs 3.7 ± 1.5 mm, $P = 0.01$) of these 2 patients were significantly larger than those without the need for iASD closure. A 10-mm long-diameter line plus a 10-mm short-diameter line separates these 2 patients from the other patients in the scatter diagram (Fig. 3). Among 33 patients with persistent iASD 9 months after CB PVI, 16 (48.1%; 95% CI, 39.4%-56.8%) were not on long-term oral anticoagulation because of low $CHA_2DS_2$-VASc score. Over 129.7 patient-years follow-up, during which iASD persisted, there were no neurologic events. There was also no significant difference between patients with and without persistent iASD 9 months after CB PVI in very long-term AF recurrence (log-rank test $P = 0.682$, Fig. 4).

## Discussion

### Prevalence, evolution and predictors of persistent iASD after CB PVI

Since the first report of a high prevalence of persistent iASD after CB PVI on short-term follow-up by TEE,[3] there

**Table 2.** Procedural characteristics

| | All (n = 108) | iASD+ group (n = 33) | iASD− group (n = 75) | *P* value |
|---|---|---|---|---|
| Types of cryoballoon, n (%) | | | | |
| 1st-generation cryoballoon | 52 (48.1) | 14 (42.4) | 38 (50.7) | 0.531 |
| 2nd-generation cryoballoon | 56 (51.9) | 19 (57.6) | 37 (49.3) | |
| Size of cryoballoon | | | | |
| 28 mm, n (%) | 101 (93.5) | 30 (90.9) | 71 (94.7) | 0.312 |
| 23 mm, n (%) | 6 (6.5) | 2 (9.1) | 4 (5.3) | |
| 23 and 28 mm, n (%) | 1 (0.9) | 1 (3) | 0 | |
| Procedural duration (min) | 174.5 ± 42 | 175.2 ± 44.7 | 174.2 ± 41 | 0.912 |
| Fluoroscopic duration (min) | 46.6 ± 15 | 47.7 ± 14.6 | 46.2 ± 15.2 | 0.630 |
| No. of cryoapplications (≥ 2 min), mean | 9.4 ± 3.1 | 10.6 ± 3.8 | 8.9 ± 2.6 | 0.032 |
| Use of pull-down technique, n (%) | 48 (44.4) | 15 (45.5) | 33 (44) | 0.834 |
| APS with cryoballoon alone, n (%) | 101 (93.5) | 31 (93.9) | 70 (93.3) | 1.0 |
| Recurrence on 1-year follow-up, n (%) | 30 (27.8) | 9 (27.3) | 21 (28) | 0.902 |

APS, acute procedural success; iASD+, persistent iatrogenic atrial septal defect on 9-month TEE; iASD−, no persistent iatrogenic atrial septal defect on 9-month TEE; TEE, transesophageal echocardiography.

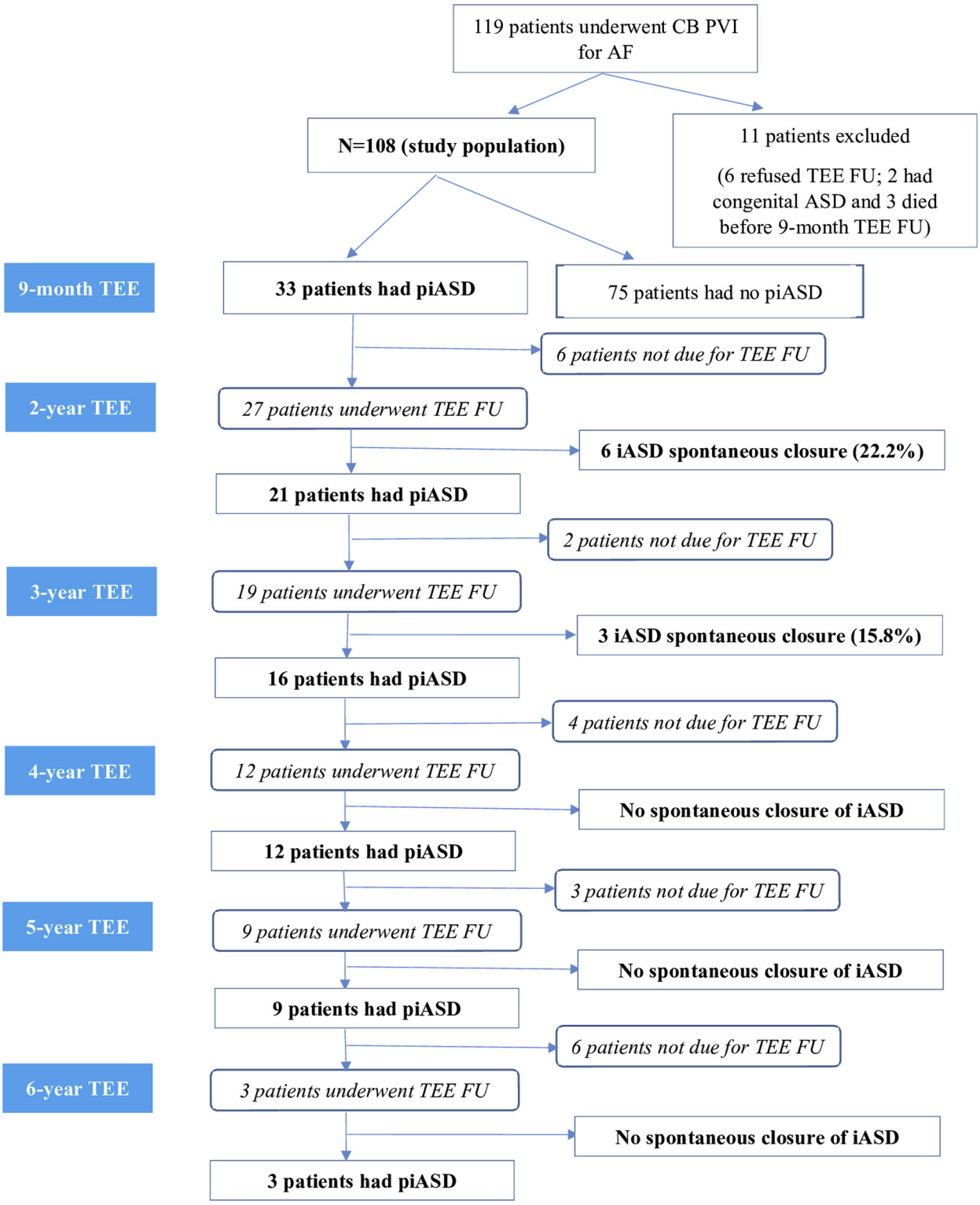


**Figure 1.** Detection of persistent iatrogenic atrial septal defect with serial transesophageal echocardiography. AF, atrial fibrillation; ASD, atrial septal defect; CB, cryoballoon; FU, follow-up; piASD, persistent iatrogenic ASD; PVI, pulmonary vein isolation; TEE, transesophageal echocardiography.

have been growing data in this important area. However, all existing studies are limited by small number of patients, selection bias, relatively short-term follow-up, and heterogeneous methodology. Importantly, apart from the first study reported by Chan et al., all other studies were cross-sectional in design.[3-9] It is thus expected that the reported prevalence varies widely from 8.4% to 38%. With a prospective longitudinal study design, and using serial TEE over a very

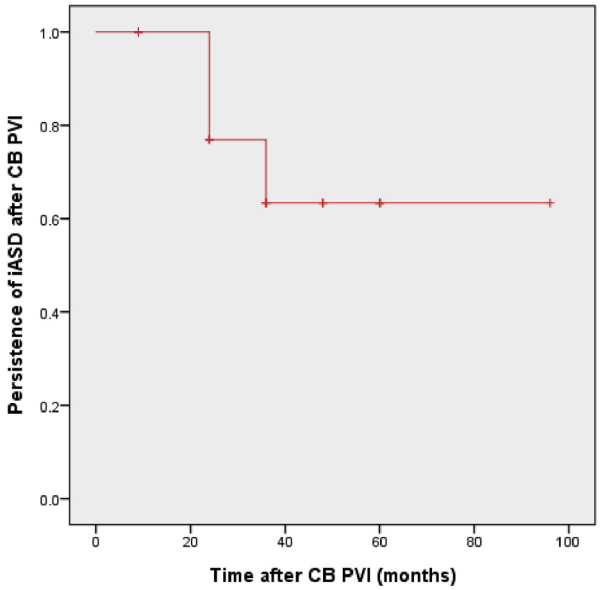


**Figure 2.** Kaplan–Meier curve for persistence of iatrogenic atrial septal defect (iASD) after cryoballoon (CB) pulmonary vein isolation (PVI).

long-term follow-up period, the true prevalence and evolution of iASD after CB PVI can be studied more clearly. In addition, a high recruitment rate (108/119 = 90.8%) was achieved, and a relatively large number of patients were included in our study. We observed a prevalence rate of 30.6% for persistent iASD 9 months after CB PVI. This is in close consistency with the data reported by Chan et al.[3] Spontaneous closure of iASD was no longer observed over 3 years

**Table 3.** Univariate and multivariate logistic regression model to predict persistent iASD on 9-month follow-up TEE

| | Univariate | | Multivariate | |
|---|---|---|---|---|
| | *P* value | OR | 95% CI | *P* value |
| Patient characteristics | | | | |
| Sex | 0.527 | | | |
| Age | 0.392 | | | |
| Types of AF | 0.312 | | | |
| Hypertension | 0.597 | | | |
| Diabetes | 0.045 | 2.126 | 0.475-9.51 | 0.324 |
| Coronary artery disease | 0.404 | | | |
| Heart failure | 0.3 | | | |
| CRI (creatinine > 200 umol/L) | 0.999 | | | |
| Stroke/TIA | 0.228 | | | |
| Procedural characteristics | | | | |
| Procedural duration | 0.908 | | | |
| Fluoroscopic duration | 0.632 | | | |
| Number of cryoapplications | 0.018 | 1.207 | 1.033-1.411 | 0.018 |
| Types of cryoballoon | 0.430 | | | |
| Size of cryoballoon | 0.290 | | | |
| Use of pull-down technique | 0.784 | | | |
| Echocardiographic parameters | | | | |
| LA size | 0.678 | | | |
| LVEF | 0.899 | | | |

AF, atrial fibrillation; CI, confidence interval; CRI, chronic renal impairment; LA, left atrium; LVEF, left ventricular ejection fraction; OR, odds ratio; TEE, transesophageal echocardiography; TIA, transient ischemic attack.

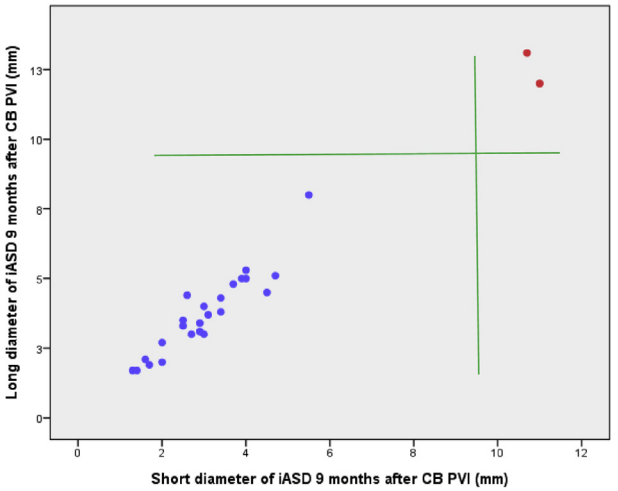


**Figure 3.** Scatter diagram showing the long and short diameters of persistent iatrogenic atrial septal defects (iASDs) 9 months after cryoballoon (CB) pulmonary vein isolation (PVI) procedures. **Red dots** represent iASDs requiring percutaneous closure.

after the CB procedure. From the spontaneous closure rates of 22.2% and 15.8% at 2 and 3 years, respectively, it can be estimated that 20% of all patients undergoing CB PVI will suffer from a permanently persistent iASD. With the rapidly increasing number of CB procedures worldwide, these new data are important and somewhat concerning. In previous studies, female sex,[4] lower left atrial appendage flow velocity on echocardiography,[8] and smaller atrial septal angle (defined as the angle between atrial septum and the sagittal line on the horizontal section at the level of fossa ovalis) on computed tomography were shown to be predictors for persistent iASD

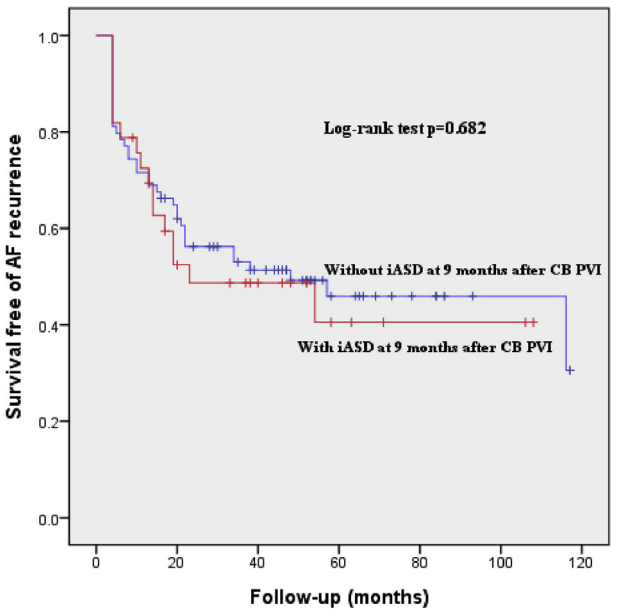


**Figure 4.** Kaplan–Meier curves of atrial fibrillation (AF) recurrence. Comparing patients with and without persistent iatrogenic atrial septal defects (iASDs) 9 months after cryoballoon (CB) pulmonary vein isolation (PVI).

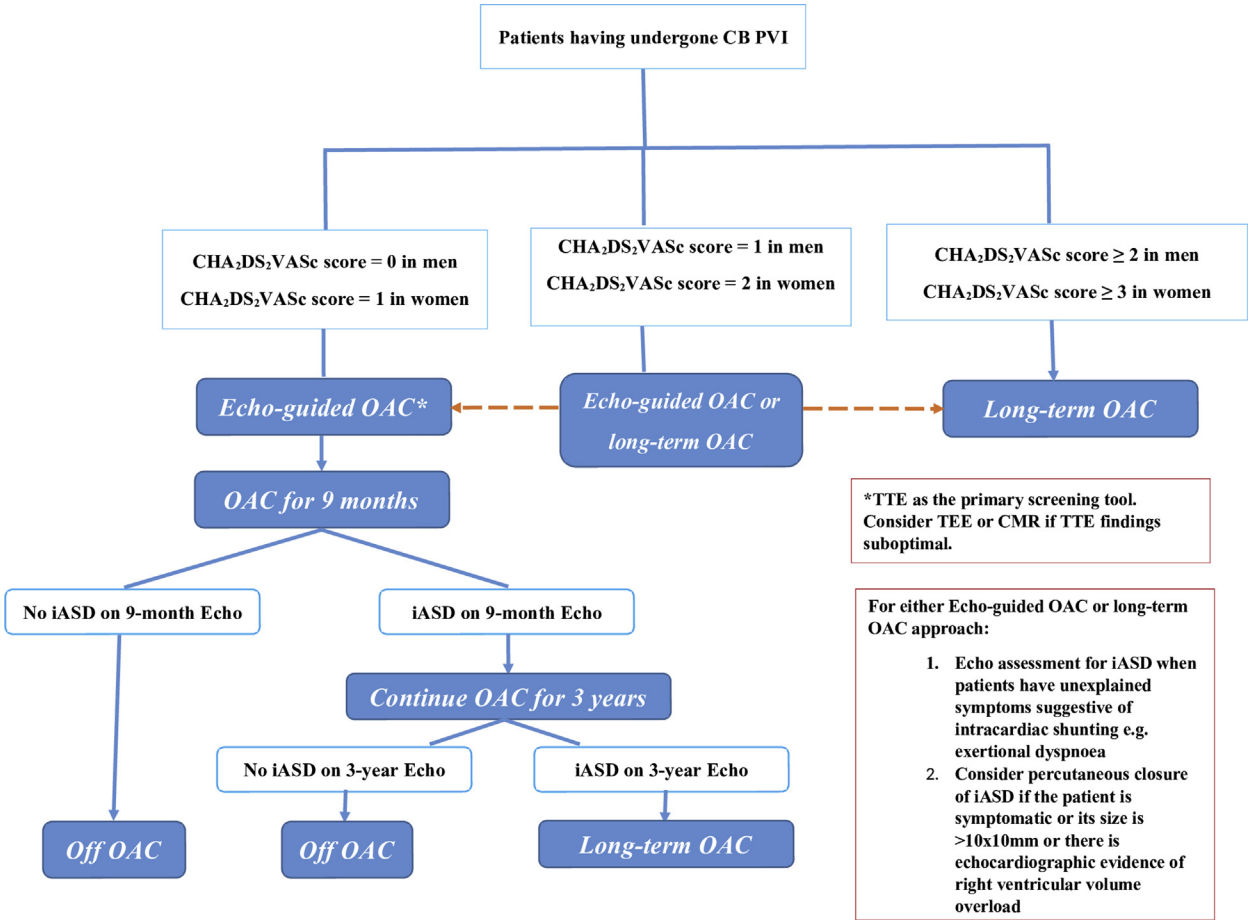


**Figure 5.** A proposed management algorithm for persistent iatrogenic atrial septal defect (iASD) complicating cryoballoon (CB) pulmonary vein isolation (PVI). $CHA_2DS_2$-VASc, **C**ongestive Heart Failure, **H**ypertension, **A**ge ≥ 75 Years, **D**iabetes Mellitus, **S**troke, **V**ascular Disease, **A**ge 65 to 74 Years, **S**ex **C**ategory; CMR, cardiac magnetic resonance imaging; Echo, echocardiography; OAC, oral anticoagulation; TEE, transesophageal echocardiography; TTE, transthoracic echocardiography.

after CB PVI. However, these factors are not modifiable. Of note, the prevalence of iASD after some procedures is remarkably lower. Hammerstingl et al. reported no iASD 9 months after double transseptal punctures with 8 French sheaths used for radiofrequency PVI,[13] and, similarly, Rillig et al. found a 3.2% prevalence of iASD 3 months after the same procedure.[14] On the other hand, using a transseptal sheath of slightly smaller size (14 French), the prevalence of iASD was reported to be 7% only 1 year after left atrial appendage occlusion with WATCHMAN device (Boston Scientific, Natick, MA).[15] These observations suggest that the prevalence of iASD increases with both the size of transseptal sheath and the extent of catheter manipulation during the procedure. In our study, consistent with the above, the number of cryoapplications was the only independent predictor of persistent iASD 9 months after CB PVI. Notably, procedural duration, fluoroscopic duration, and the use of pull-down technique were not predictors of persistent iASD. The number of cryoapplications may thus be more indicative of a complex procedure requiring more manipulation of the transseptal sheath. There are emerging data showing similar efficacy for PVI when a single instead of double cryoapplication for each pulmonary vein is delivered with the second-generation CB.[16] It is hoped that this may significantly reduce the prevalence of permanently persistent iASD after CB PVI. Needless to say, downsizing of the CB transseptal sheath is another modifiable factor to reduce this complication.

## Clinical outcomes of persistent iASD after CB PVI

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.[17] In our study population, 2 (1.9%) patients required percutaneous closure of persistent iASD because of hemodynamically significant interatrial shunting, and we observed a defect size of above 10 x10 mm, indicative of a need for closure. Consistent with this observation, Cronin et al. reported 2 (4.8%) patients, among 42 treated with CB PVI, required iASD closure. One of them had a defect size of 10.4 mm and developed reduced exercise capacity, which resolved after closure. The other had history of heart failure and developed an episode of decompensation. A 5-mm iASD was surgically repaired during implantation of a ventricular-assist device. The hemodynamic significance of the latter

was doubtful.[5] It has to be borne in mind that the severity of left-to-right shunt may worsen with an increase in the compliance of left ventricle due to hypertension, coronary artery disease, and valvular heart disease. Therefore, monitoring of symptoms and echocardiographic reassessment, as recommended in the management guidelines for congenital ASD, should be followed in patients with permanently persistent iASD.[17]

Congenital ASD with right-to-left shunt may lead to different complications. Paradoxical embolism may occur from peripheral venous or pelvic vein thromboses, atrial arrhythmias, unfiltered intravenous infusions, or indwelling venous catheters in patients.[18] Long-term oral anticoagulation is recommended for patients with congenital ASD and AF.[17] In our study, 39.4% of patients with persistent iASD 9 months after CB PVI had small right-to-left interatrial shunting during Valsalva manoeuvre. As all these patients had histories of AF, they should receive oral anticoagulation to prevent paradoxical embolism arising from persistent iASD. In our study population, 48.1% of patients with persistent iASD 9 months after CB PVI were not on long-term oral anticoagulation because of low $CHA_2DS_2$-VASc score. Although there were no neurologic events over 129.7 patient-years follow-up, during which iASD remained persistent, the number of patients may be too small—and follow-up too short—to detect cerebral embolic complications. Furthermore, subclinical cerebral embolism may go undetected in our study. Paradoxical arterial gas embolism may occur during scuba diving in patients with interatrial shunting, mostly described in patent foramen ovale.[19] However, paradoxical arterial gas embolism has also been reported in a scuba diver with congenital ASD.[20] It is thus advisable for patients with iASD to refrain from scuba diving until spontaneous closure has been documented.

Atrial arrhythmia may complicate congenital ASD due to long-standing right heart volume overload. Persistence of iASD in patients undergoing CB PVI for treating AF poses a potential risk of arrhythmic recurrence, especially in the long run. From our study, there is no significant difference in recurrence of atrial arrhythmias both at 1-year and on very long-term follow-up (Fig. 4).

### A proposed management algorithm for persistent iASD after CB PVI

Based on the data from our study, a management algorithm for persistent iASD after CB PVI is proposed (Fig. 5). TTE is proposed to be the primary screening tool for iASD. TEE or cardiac magnetic resonance imaging can be used if TTE is suboptimal. Screening is performed 9 months and 3 years after CB PVI, as persistent iASD present at 3 years will become permanent.

### Limitations

The number of patients in our study population is relatively small. Not all patients with persistent iASD 9 months after CB PVI underwent serial annual TEE examinations until 6 years. Only clinical neurologic events were assessed in this study. Silent cerebral embolism was not evaluated.

## Conclusions

Persistent iASD occurred commonly after CB PVI. A higher number of cryoapplications was found to be an independent predictor of iASD. Spontaneous closure was observed up to 3 years after the procedure. The defect would then become permanent in around one fifth of patients undergoing CB PVI. Uncommonly, patients with a defect size larger than 10 mm may need percutaneous closure owing to significant left-to-right shunting. Over very long-term follow-up, no neurologic events were observed.

## Disclosures

The authors have no conflicts of interest to disclose.

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