ORIGINAL ARTICLE

Initial experience of cryoballoon catheter ablation for atrial fibrillation in Hong Kong

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Objective To report the initial experience in using cryoballoon catheter ablation in the treatment of atrial fibrillation in Hong Kong.

Design Single-centre, prospective case series.

Setting Regional hospital, Hong Kong.

Patients Sixteen patients (mean age, 55 years; standard deviation, 14 years; 11 males) with paroxysmal (n=12) or persistent (n=4) atrial fibrillation.

Interventions Pulmonary vein isolation by ablation with a 28-mm cryoballoon catheter.

Main outcome measures Safety, effectiveness, and learning curve of this procedure.

Results Of 67 pulmonary veins, 61 (91%) could be successfully isolated with the cryoballoon alone. The remaining pulmonary veins were isolated with additional ablation using an 8-mm tip cryocatheter. One phrenic nerve palsy developed during right middle pulmonary vein ablation, which resolved. Another patient endured a minor guidewire dissection of the right inferior pulmonary vein. The mean (standard deviation) procedural and fluoroscopic times were 231 (32) and 62 (18) minutes, respectively. On comparing the first nine and last seven procedures, there was a significant improvement in procedural time (mean [standard deviation], 244 [32] vs 213 [24] minutes; P=0.04) and in the fluoroscopic time (70 [21] vs 51 [7] minutes; P=0.038). With a median follow-up of 21 months, nine (75%) of the 12 patients with paroxysmal atrial fibrillation and one (25%) of those four with persistent atrial fibrillation had no recurrence, without the use of anti-arrhythmic drugs.

Conclusions Pulmonary vein isolation by cryoballoon catheter ablation is safe and effective in treating patients with paroxysmal, but not for patients with persistent atrial fibrillation. A relatively short learning curve of around 10 cases was deemed appropriate.

A video of cryoballoon catheter ablation for atrial fibrillation is available at <www.hkmj.org>.

New knowledge added by this study

- Pulmonary vein isolation by cryoballoon catheter is a new treatment for atrial fibrillation.
- The procedure is safe and effective for patients with paroxysmal atrial fibrillation.
- The recurrence rate after the procedure remains high in patients with persistent atrial fibrillation.

Implications for clinical practice or policy

- Pulmonary vein isolation by cryoballoon catheter is a treatment option for patients with symptomatic paroxysmal atrial fibrillation refractory to at least one anti-arrhythmic drug.

Key words
Angioplasty, balloon; Atrial fibrillation; Catheter ablation; Cryosurgery; Pulmonary veins

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Introduction

Catheter ablation for paroxysmal or persistent atrial fibrillation (AF) is now a treatment option for symptomatic patients, especially when they are refractory to anti-arrhythmic medications.[1] According to a worldwide survey,[2] the long-term success rate of the procedure in patients not taking anti-arrhythmic medications was 75% in paroxysmal AF, 65% in those with persistent AF, and 63% in those with long-lasting AF. According to that survey, radiofrequency remained the dominant form of energy used but there was significant non-uniformity in ablation strategies; at least eight different kinds have been reported worldwide. However, the major complication rate was 4.5%, and 0.04%

developed atrio-esophageal fistulae, 0.94% endured a stroke or transient ischaemic attack, and 0.29% sustained severe pulmonary vein (PV) stenosis. The learning curve of radiofrequency ablation for AF is also long. In a study on segmental ostial pulmonary vein isolation (PVI), the mean procedural time was 232 ± 70 minutes and was regarded as dependent on operator experience.[3] A case volume above 75 (period not stated) was considered necessary to achieve a procedural time below 3 hours.[3]

A novel cryoballoon catheter was recently available for PVI, and shown to be safe and effective in early European and American experience.[4] The purpose of this study was to report on its safety, effectiveness, and necessary learning curve for undertaking this form of ablation therapy for AF in Hong Kong patients.

香港以冷凍球囊導管消融術治療房顫的初步經驗

目的 報告香港以冷凍球囊導管消融術治療房顫的初步經驗。

設計 單中心前瞻性病例研究。

安排 香港一所分區醫院。

患者 共16名房顫患者，平均年齡55歲，標準差14歲。其中11名為男性；陣發性房顫12例，持續性房顫4例。

干預 以28毫米冷凍球囊導管消融術進行肺靜脈電隔離。

主要結果測量 手術的安全性、效度和學習曲線。

結果 67條肺靜脈中，61（91%）條成功以冷凍球囊隔離；餘下的肺靜脈須再以8毫米冷凍導管消融術隔離。當中，1名患者在進行右中肺靜脈消融期間出現隔神經痲痺，及後回復正常；另1名患者的右下肺靜脈則曾出現輕微導線剝離。平均手術時間為231分鐘（標準差32分鐘），透視時間為62分鐘（標準差18分鐘）。將前9名和後7名患者的手術結果比較，不論手術時間（平均〔標準差〕244〔32〕比213〔24〕分鐘，P=0.04）和透視時間（平均〔標準差〕70〔21〕比51〔7〕分鐘，P=0.038）皆顯著改善。在沒有服用抗心律失常藥物情況下，9名（75%；n=12）陣發性房顫患者和1名（25%；n=4）持續性房顫患者於中位數為21個月的隨訪期內沒有復發。

結論 以冷凍球囊導管消融術進行肺靜脈隔離，是治療陣發性房顫安全和有效的方法，唯對持續性房顫的效用不大。以相對較短的10例手術作為學習曲線被認為是合適的。

Methods

Study population and pre-ablation management

The study protocol was approved by the Ethics Committee of the Investigation Centre. Patients fulfilling the entry criteria were interviewed and invited to join the study and recruited so long as they signed the consent forms. Over the period between May 2008 and July 2010, 16 patients with symptomatic paroxysmal or persistent AF refractory to treatment with at least one anti-arrhythmic drug were recruited from either the out-patient Specialist Cardiology Clinic or hospital in-patients. For patients with paroxysmal AF, they had had at least one electrocardiogram (ECG)–documented episode within the last 3 months. Exclusion criteria were: severe valvular stenosis or regurgitation, congenital heart disease, contra-indication to warfarin or heparin, previous left atrial (LA) ablation for AF, LA thrombus, pregnancy, or severe co-morbidity. Patients received therapeutic anticoagulation with warfarin, with the international normalised ratio (INR) maintained between 2.0 and 3.0. Warfarin was withdrawn 3 days before the ablation procedure and transoesophageal echocardiography was performed to rule out LA thrombus. All anti-arrhythmic drugs including amiodarone were discontinued at least 5 days before the procedure. Before ablation, all the patients underwent computed tomography (CT) to delineate the LA-PV anatomy.

Cryoballoon catheter ablation

The ablation procedures were performed under local anaesthesia; whenever deemed necessary conscious sedation with midazolam and fentanyl could be used. Infusion of heparin was given to maintain an activated clotting time (ACT) of more than 300 seconds; measurement of the ACT was performed every 30 minutes.

Diagnostic 6F catheters were positioned in the coronary sinus (decapolar), the His bundle region (quadripolar) and the right atrium (quadripolar). The diagnostic catheters served as landmarks for transseptal puncture and allowed pacing during mapping of PV ostia. A single transseptal puncture was performed by means of a Brockenbrough needle and an 8F sheath (Mullin transseptal guiding introducer, St Jude Medical, Minnetonka, US) was introduced into the LA. The sheath was then exchanged for the 12F steerable transseptal sheath (FlexCath, Medtronic CryoCath, Minneapolis [MN], US) with the Amplatz extra-stiff guidewire (Cook Incorporated, Bloomington, US). All the PVs were catheterized by the steerable transseptal sheath and PV angiography was performed. Baseline mapping of each PV ostium was performed using a multipolar circular catheter (Inquiry Optima, St Jude Medical, Irvine [CA], US).

In all patients, the 28-mm cryoballoon catheter (Arctic Front, Medtronic CryoCath, Minneapolis [MN], US) was used for PVI. With the deflated cryoballoon catheter inside the steerable transseptal sheath, the Amplatz extra-stiff guidewire was positioned in a branch of a left-sided PV. The cryoballoon catheter

was then advanced towards the LA and inflated. The cryoballoon catheter was pushed against the PV ostium to ensure excellent occlusion, as shown by full retention of contrast medium distal to the catheter tip during injection of 50% diluted contrast medium through the central lumen (Fig 1). A good occlusion was defined as a small contrast leak of less than a quadrant.

The duration of each freezing cycle was 300 seconds. A minimum of two consecutive freezing cycles for each targeted PV were delivered with excellent or good occlusion. Left-sided PVs were always targeted first. During cryoablation of the right-sided PVs, phrenic nerve function was monitored by frequent intermittent fluoroscopy of diaphragmatic movement. If phrenic nerve palsy (PNP) was observed, ablation of the right-sided PVs was aborted. As a result, the right inferior PV rather than the right superior PV was preferred for ablation. For patients who remained in AF after ablation of all PVs, external biphasic electrical cardioversion was performed for conversion to sinus rhythm. Mapping with the multipolar circular catheter (Inquiry Optima) after ablation of all the PVs was performed. Successful PVI was defined as loss of all PV potentials at the level of PV ostia. An 8-mm tip cryoablation catheter (Freezor Max, Medtronic CryoCath, Minneapolis [MN], US) was used to achieve PVI, if repeated cryoballoon ablation failed to do so.

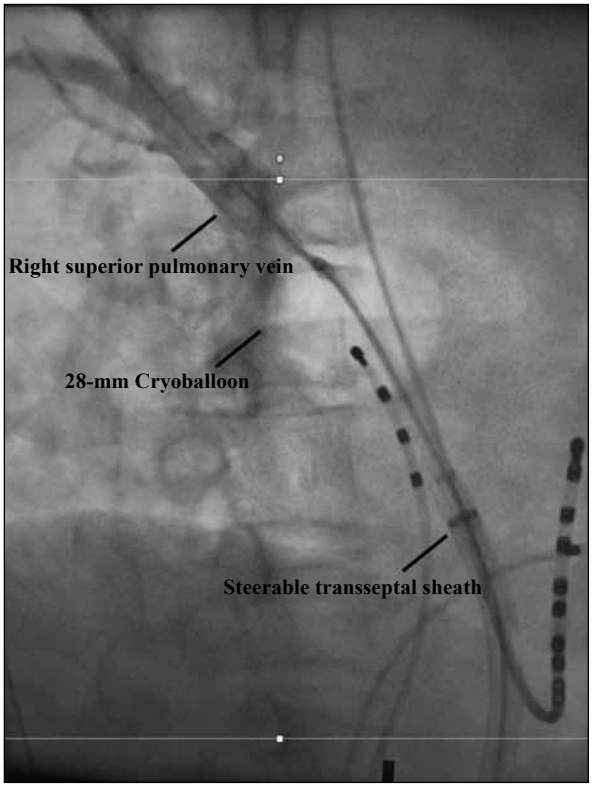

FIG 1. Excellent occlusion of right superior pulmonary vein with 28-mm cryoballoon with full retention of contrast medium distally, taken with a right anterior oblique 40° projection

Post-ablation management and follow-up

After the procedure, the patients underwent continuous ECG monitoring in the coronary care unit for 24 hours. After uncomplicated procedures, they were discharged the next day. Oral anticoagulation with warfarin was started 1 day after PVI, targeting an INR of 2.0 to 3.0 and continued for 3 months. Subsequent need for anticoagulation depended on the patients' $CHADS_2$ score.[5] Previously used anti-arrhythmic drugs were given for 3 months after the procedure, which served as a blanking period for recurrence of AF. Patients were scheduled for follow-up (including ECG) after 1 month and then every 3 months after the procedure. Holter-type 24-hour monitoring was performed at 3, 6, and 12 months and as required when patients reported sustained palpitations. A reassessment CT of the LA-PV anatomy was performed between the 3- and 12-month follow-up to assess possible PV stenosis.

Study end-points

The study end-points consisted of acute success rates in PVI and preventing AF recurrence, times for the procedure (from right femoral venous puncture to withdrawal of cryoballoon catheter) and fluoroscopy (recorded by the fluoroscopic system counter), and complications (including PV stenosis and PNP).

Statistical analysis

Means and standard deviations (SDs) were calculated for parametric data. Student's *t* test was used for analysis of continuous variables. The threshold of significance was set at 0.05.

Results

Patients

In all, 16 patients (mean age, 55 years; SD, 14 years; 11 males) with paroxysmal (n=12) or persistent (n=4) AF underwent PVI by means of cryoballoon catheter ablation, with clinical characteristics as shown in the Table.

Procedural characteristics

All patients received local anaesthetics for the procedures; none received additional drugs for conscious sedation. Of 67 PVs targeted, 61 (91%) were successfully isolated with a single 28-mm cryoballoon catheter. The remaining six PVs (2 left superior PVs, 2 left inferior PVs and 2 right inferior PVs) were successfully isolated with additional ablation using an 8-mm tip cryoablation catheter. The average number of freezing cycles per PV was 2.6. One patient developed a right PNP during ablation of the right middle PV but diaphragmatic function had normalised after 1 week (as judged

TABLE. Baseline characteristics (n=16)

Characteristics*	Data†
Men/women	11 / 5
Age (years)	55 ± 14
Paroxysmal/persistent AF	12 / 4
Time interval between first documentation of AF and procedure (months)	
All patients	40 ± 33
No. with paroxysmal AF	37 ± 31
No. with persistent AF	47 ± 45
No. with failed anti-arrhythmic drug treatment before the procedure	1 ± 1
LVEF (%)	67 ± 12
LA size (cm)	4 ± 1
Lone AF	9
Co-morbidities	
Hypertension	6 (38%)
Hyperlipidaemia	2 (13%)
Ischaemic heart disease	1 (6%)
Sick sinus syndrome	1 (6%)

* AF denotes atrial fibrillation, LVEF left ventricular ejection fraction, and LA left atrium

† Data are shown in No., No. (%), or mean ± standard deviation

by fluoroscopic screening). There was one minor guidewire dissection of the right inferior PV; the patient remained asymptomatic. The mean ± SD procedural and fluoroscopic times were 231 ± 32 and 62 ± 18 minutes, respectively. On comparing the respective mean ± SD procedural and fluoroscopic times of the first nine and last seven procedures (Fig 2), there were significant improvements (244 ± 32 vs 213 ± 24 minutes, P=0.04; 70 ± 21 vs 51 ± 7 minutes, P=0.038).

Follow-up

With a median follow-up of 21 months and a mean follow-up of 17 (SD, 9) months, there was no recurrence of AF in 10 (63%) of the patients despite no anti-arrhythmic drug treatment. In patients with paroxysmal AF, nine (75%) of the 12 patients had no recurrence of AF whilst taking no anti-arrhythmic drugs. In the four patients with persistent AF, only one remained in sinus rhythm throughout the follow-up period. The six patients with recurrences had ECG-documented AF at the 1-month follow-up. At the 12-month follow-up, 10 patients had experienced no recurrence. No PV stenosis of more than 30% diameter narrowing was observed based on CT reassessment of LA-PV anatomy.

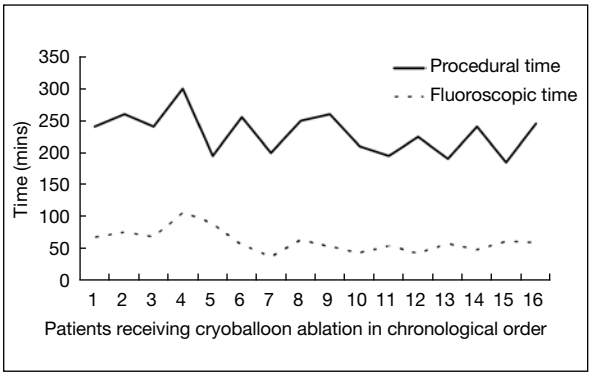

FIG 2. Learning curve of cryoballoon ablation procedures for atrial fibrillation

Discussion

Resorting to PVI has been shown to be an integral part of catheter ablation for AF.[6] The cryoballoon catheter is a recently available device for this purpose. Preliminary experience in European and American patients has been encouraging.[4,7] It was recently reported that such ablation is significantly more effective than anti-arrhythmic drugs in maintaining sinus rhythm in patients with drug-refractory paroxysmal AF.[7] The current study is the first report on using the cryoballoon catheter to treat patients with AF in Asia. Comparable to both European and American data, our 91% PVI success rate was high. In our study and others, the larger 28-mm cryoballoon was used, so as to avoid cryoablation deep inside the PVs.[8] The success rate of PVI achieved with a single 28-mm cryoballoon can be improved by employing special techniques.[8] As for the results of the aforementioned studies, our long-term clinical success rate with cryoballoon ablation was significantly better in paroxysmal than persistent AF. After a median follow-up of 21 months without the use of anti-arrhythmic drugs, 75% of our patients with paroxysmal AF had no documented recurrence. In contrast, only 25% of those with persistent AF remained in sinus rhythm throughout the follow-up period.

One major reason for using alternative energy sources in AF ablation was to reduce complications caused by radiofrequency. Notably, focal cryoablation for PVI seemed to avoid producing PV stenosis,[9] which advantage was also reported by other users of the cryoballoon catheter.[4] However, in a recently reported study,[7] seven (3%) of 228 patients developed PV stenosis (>75% reduction from baseline cross-sectional area after cryoballoon ablation). Among these patients, five were asymptomatic, one who was symptomatic underwent angioplasty and stenting, and another symptomatic patient refused intervention. The latter's symptoms resolved within 12 months. The exact reason for the discrepancy between studies is still unknown, but may be related to the level of PVI procured by cryoballoon ablation. It has been shown that the isolation can be either ostial or antral, depending on the relative size of the cryoballoon and the PVs,[10,11] and that there may be a risk of PV stenosis if the ablation is ostial rather than

antral. In our study, the large 28-mm cryoballoon was used in all patients and no PV stenosis was observed.

According to Neumann et al,[4] the most common complication from cryoballoon ablation was PNP. In 26 (7.5%) of 346 of the patients, right-sided PNP developed during cryoablation of the right superior PV after 24 (92%) of them were ablated using the small 23-mm cryoballoon. Importantly, we observed a case of right PNP during cryoablation of the right middle PV. This underscores the need for surveillance of phrenic nerve function during cryoballoon ablation for right-sided PVs. Our strategy of ablating the right inferior PV followed by the right superior PV maximises the numbers ablated, in case the procedure has to be aborted due to development of PNP during right superior PVI.

Another potential advantage of using a balloon catheter for such energy delivery was to reduce procedural complexity and duration. Neumann et al[4] reported a three-centre study involving 346 patients. With procedural experience on more than 100 patients per centre, a median procedural time of 170 minutes and fluoroscopic time of 46 minutes were achieved. In contrast, Packer et al[7] reported another multicentre study involving 163 patients undergoing cryoballoon ablation in 26 centres. With significantly less procedural experience (fewer than 10 patients per centre), the mean procedural and fluoroscopic times were 371 and 63 minutes, respectively. In our study, the mean procedural and fluoroscopic times were 231 (SD, 32) and 62 (18) minutes, respectively, from which we inferred a learning curve of around 10 cases.

Study limitations

The number of patients in this study was small and those recruited were heterogeneous, having paroxysmal or persistent AF. There was no observation period after acute PVI, so that early electrical re-connection of PVs might not have been detected. Surveillance of AF recurrence depended on self-reporting of symptoms and 24-hour Holter-type monitoring performed at 3, 6, and 12 months. Thus, recurrences might have been underestimated. The numbers of patients invited to join the study, and the numbers who subsequently refused to join or did not satisfy the inclusion/exclusion criteria, were not recorded. Lastly, because of the relatively small number of patients, factors other than accumulation of experience were not analysed in the comparison of procedural times for early and late cases.

Conclusions

Pulmonary vein isolation by cryoballoon ablation is a safe and effective treatment for patients with paroxysmal AF. However, the recurrence rate in patients with persistent AF is high. The complication of PV stenosis was not observed in our series, while PNP is a known complication following cryoballoon ablation of right-sided PVs. With accumulation of experience, both the procedural and fluoroscopic times can be reduced. The learning curve is relatively short, and inferred to be around 10 cases in the current study.

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