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CLINICAL RESEARCH
Ablation for Atrial Fibrillation

Efficacy and safety of pulmonary veins isolation by cryoablation for the treatment of paroxysmal and persistent atrial fibrillation

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Aims We examined the efficacy and safety of pulmonary vein (PV) isolation, using a cryoballoon catheter.

Methods and results We studied 117 consecutive patients presenting with paroxysmal ($n = 92$) or persistent ($n = 25$) atrial fibrillation (AF), who underwent attempts at isolation of 442 PV with a cryoballoon catheter. They were followed in our ambulatory department for every 3 months, or earlier if they reported symptoms. A 48 h ambulatory electrocardiogram was recorded at the 3-month visit. We analysed the immediate and long-term procedural and clinical outcomes. We isolated 385 of 442 PV (87%) with a single cryoballoon application. In 19 patients (16%), an irrigated-tip radiofrequency (RF) catheter was used to create a supplemental focal lesion. A median of nine applications per procedure (range 6–12) was delivered. The mean, overall procedural duration was 155 ± 43 min (range 75–275), and mean duration of fluoroscopic exposure was 35 ± 15 min (range 12–73). At the end of the procedure, 103 patients (88%) were in sinus rhythm. Over a median period of 9.6 months (range 3–12), 11 patients were lost to follow-up. At 3, 6, 9, and 12 months of follow-up, respectively, 79, 79, 79, and 69% of patients presenting with paroxysmal AF had remained recurrence free, vs. 83, 73, 59, and 45% of patients, respectively, with persistent AF. Phrenic nerve palsy was the most frequent, although reversible complication.

Conclusions Pulmonary vein isolation, using a cryoballoon catheter, was completed with a high rate of procedural and long-term success and low rate of minor complications. Supplemented, when needed, by focal RF, cryoballoon ablation was a safe and an effective alternative to a circumferential RF procedure.

Keywords Paroxysmal atrial fibrillation • Pulmonary vein isolation • Catheter ablation • Cryoablation • Cryoballoon catheter

Introduction

The clinical success rate of segmental or circumferential pulmonary vein (PV) isolation, an important treatment of paroxysmal atrial fibrillation (AF), ranges between 66 and 87% among various published studies.[1–4] These results have prompted changes in professional practice guidelines, which recommend PV isolation as a second-line treatment of paroxysmal AF refractory to drug therapy, in absence of structural heart disease. Moreover, in view of the relative safety of the procedure when performed by experienced operators, the most recent European guidelines have suggested that ablation might be offered as first-line therapy in selected patients.[5]

However, standard radiofrequency (RF) ablation procedures remain technically challenging and associated with high rates of complications, including thrombo-embolisms, PV stenosis, atrio-oesophageal fistula, left atrial (LA) flutter, and pericardial effusion.[6,7]

The development of balloon catheters has enabled several new PV isolation strategies, using high-frequency focused ultrasound, endoscopic laser, or cryotherapy. The low thrombogenicity and very low risk of PV stenosis associated with the latter is particularly promising.[8] Furthermore, cryoballoons enable expeditious, complete, and safe circumferential isolations of single PV.[9–11] We report our results, using this technique,in 117 consecutive patients

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presenting with highly symptomatic, paroxysmal, or persistent AF, at a single medical centre.

Patient population and methods

Consecutive patients with histories of ≥2 episodes of paroxysmal or persistent AF, refractory to, or intolerant of ≥1 antiarrhythmic drug(s), were admitted to the hospital 1 day before undergoing the ablation procedure. The episodes of persistent AF were ≤3 months; no patient included in this study presented with long-persistent AF. They were orally anticoagulated for ≥1 month, to reach an international normalized ratio between 2.0 and 3.0. Oral anticoagulation was replaced by intravenous unfractionated heparin for 2 days, until 2 h before the ablation procedure. The detailed anatomy and diameters of the PV were ascertained by computed tomography (CT) imaging with three-dimensional reconstruction (*Figure 1A*). The ostial diameters of the four veins were measured by the same operators (*Figure 1B*) and reviewed by the electrophysiologist who performed the procedure. The measurements were made at the narrowest segment of the vein at its junction with the atrium.

Ablation procedure

The patients were lightly sedated before undergoing catheterization of both femoral veins. We used the right femoral vein for standard transseptal catheterization with a BRK™ needle (St Jude Medical, St Paul, MN, USA) guided by fluoroscopy alone or associated with transoesophageal echocardiography as needed. Immediately after the transseptal puncture, the sheath was flushed with 5000 units/ml of concentrated heparin solution. A bolus of 80 IU/kg of body weight of heparin was administered, followed by an infusion, to maintain an activated clotting time between 300 and 350 s, measured at 30 min intervals throughout the procedure.

We introduced an 8F Fast-Cath™ SL1 sheath (St Jude) into the left atrium, then advanced a model 2515 10-pole Lasso® catheter (Biosense-Webster Inc., a Johnson & Johnson Company, Diamond Bar, CA, USA) to perform angiography of the PV and detect the presence of electrical activity in each vein. A Bard™ woven multipolar catheter (Bard electrophysiology Inc., Lowell, MA, USA) was placed in the coronary sinus from the left femoral vein. We paced the distal coronary sinus to confirm the presence of left PV

Figure 1 Computed tomography scan. (*A*) Details of the left atrial and pulmonary veins anatomy. (*B*) Measurement of the pulmonary vein diameters. (*C*) Intracardiac electrograms after pulmonary vein isolation showing complete dissociation between the pulmonary vein (asterisk) and the atrial potentials (arrows).

potentials. Following this confirmation, we proceeded with the ablation procedure without continuous Lasso monitoring. We removed the SL1 sheath and replaced it by a 12F FlexCath® steerable sheath (Medtronic Inc., Minneapolis, MN, USA), over a 0.032 in., 180 cm Super Stiff® guidewire (St Jude). An Arctic Front®, double-lumen cryoballoon catheter (Medtronic), 23 or 28 mm in size, as appropriate for the diameter of the PV, was introduced inside the 12F sheath, and positioned over a 0.032 in. Amplatz Extra-Stiff® guidewire (Cook Medical Inc., Bloomington, IN, USA). The cryoballoon catheter was optimally positioned in the PV antrum, with the aim of occluding the ostium of the PV when inflated, which we confirmed by angiography. In the presence of common ostia, we usually used a 28 mm balloon which we advanced first across the superior and then across the inferior veins. A common ostium is usually too wide to be completely occluded directly.

Cryoablation was applied for 4 min at least twice in each vein, directed towards the major side branches, using the guidewire. We attempted $\geq$1 cryoapplication in each vein during complete occlusion. If the occlusion was incomplete, we changed the position of the balloon or curve of the sheath. The procedure systematically began with the left superior (LS), then the left inferior (LI), followed by the right inferior (RI), and ended with the right superior (RS) PV. When we targeted a right PV, we positioned the Lasso catheter in the superior vena cava to continuously stimulate the phrenic nerve during the cryoapplication.

Since the proximity of the phrenic nerve to the right-sided veins cannot be ascertained, continuous monitoring of phrenic nerve capture is essential to prevent its palsy. When phrenic nerve capture ceased, we immediately discontinued the cryoapplication and confirmed with the Lasso catheter that the vein was completely isolated. We have observed that the development of PNP is an indication of transmural lesion and coincides with an effective isolation of the vein, in which case no further cryoapplication is needed. Since we have never observed the development of PNP from cryoapplications in the RIPV, we systematically begin the procedure in this vein, and have always been able to end it in the RSPV.

After treatment of all the PV, we reintroduced the Lasso catheter into each vein to verify their complete electrical disconnection during sinus rhythm and during pacing. If PV potentials remained present, we reintroduced the cryoballoon, guided by the circular catheter and fluoroscopy, to maximize the wall contact at the location of the persisting potentials. If that was unsuccessful, we used a conventional 4 mm irrigated RF catheter (Biosense-Webster) to perform further segmental isolation through the same transseptal puncture. The procedural endpoint was complete electrical isolation of the PV (*Figure 1C*) based on the elimination of all ostial PV potentials, or complete entrance conduction block into the PV. We used balloons of different diameters in the same patient, as needed, if the endpoint was not reached with the first balloon used. In the presence of four PV $<$16 mm in diameter, particularly in women presenting with low body weights, we use a 23 mm balloon. For patients presenting with PV of variable dimensions, we systematically begin with a 28 mm and continue with a 23 mm balloon, if the isolation is not completed in the small veins. We attempt to isolate all PV with a single cryoballoon and use several sizes only in cases of unsuccessful ablation with the 28 balloon.

After the procedure, the patients remained treated with heparin until they were fully anticoagulated orally to a target international normalized ratio $>$2.0.

Patients follow-up

The patients remained under continuous monitoring of the electrocardiogram (ECG) for 48 h. On the day following the procedure, transthoracic echocardiography was performed to ascertain the absence of pericardial effusion. For the next 3 months, the patients remained on the antiarrhythmic drug regimen they were prescribed before the ablation procedure, except for amiodarone, and were orally anticoagulated to a target international normalized ratio of 2.5. Since cryoablation is rarely associated with PV stenosis,[12] transoesophageal echocardiography and CT scan were only performed for suspected stenosis, in the presence of dyspnoea, cough, haemoptysis, or fever.

The patients returned to our ambulatory department at 1 month and for every 3 months thereafter, or earlier if they developed symptoms consistent with recurrent AF. A 48 h ambulatory ECG was recorded 3 months after the procedure, usually during antiarrhythmic therapy other than amiodarone. In the absence of arrhythmia, all antiarrhythmic drugs were discontinued and another ambulatory ECG was recorded 3 months later. The need for oral anticoagulation was also evaluated after 3 months, based on the $CHA_2DS_2VAS_c$ score.[5] If the score was $>$1, oral anticoagulation was continued. Furthermore, the patients received an ECG event monitor if they reported symptoms suggestive of AF. Procedural success was defined as the absence of symptoms of AF and documentation of stable sinus rhythm during the 48 h ambulatory ECG.

Antiarrhythmic medications and oral anticoagulation were discontinued after 3 months in the absence of symptomatic or recorded episodes of AF.

Statistical analysis

The results are expressed as means $\pm$ standard deviations. Comparisons of continuous data between paroxysmal and persistent AF were made by unpaired *t*-test, whereas categorical data were compared in both groups using the χ^2 test. Cumulative survivals free from AF were estimated using to the Kaplan–Meier method and survival curves were compared, using the log-rank test. A *P* value $<$0.05 was considered statistically significant. All analyses were performed, using the SPSS software, version 10.0 (SPSS Inc., Chicago, IL, USA).

Results

Baseline patient characteristics

The mean age of the 117 consecutive patients (89 men) who underwent PV isolation with a cryoballoon was 55 $\pm$ 11 years (range 27–76), 92 of whom (79%) presented with histories of symptomatic, paroxysmal AF, and 25 (21%) with persistent AF. A single patient had a depressed (30%) left ventricular ejection fraction. Radiofrequency ablation of atrial flutter had been successfully performed previously in six patients, and previous unsuccessful attempts at AF RF ablation were made in two patients.

The mean LA diameter was 55 ± 6 mm (range 30–55) and mean PV diameter, measured with CT scan, was 17.7 ± 0.5 mm. The mean diameter of the superior PV was 18.0 mm, and that of the inferior PV was 15.0 mm. A left common PV was found in eight patients, a right common PV in one, and a common RI and LIPV ostium in one patient (*Figure 2B* and *C*).

Ablation procedures

In 117 procedures, potentials were recorded in 442 of 468 PV (94%), including 117 LS, 110 LI, 109 RS, and 106 RIPV. Ablation was attempted in the 442 PV-containing potentials. The remaining 26 PV (6%) were too small. We used a 28 mm cryoballoon in 79 patients, a 23 mm balloon in 33, and both cryoballoons in five patients.

The 442 treated PV were completely isolated, 385 (87%) with the cryoballoon alone. The procedural success rate in the RIPV was 94% (100/106), significantly higher than 81% (95/117) in the LSPV ($P = 0.005$), and 85% (93/109) in the RSPV ($P = 0.05$), although similar to the 88% (97/110) rate in the LIPV ($P = 0.17$). In 19 patients (16%), an irrigated-tip RF catheter was used to create a supplemental focal lesion. At the end of the procedure, all PV were isolated, with the supplemental application of focal irrigated RF in 19 patients. The mean duration of cryoablation was 585 ± 22 s per vein. A median of nine applications per procedure (range 6–12) was delivered. The mean temperatures reached during cryoablation was −56 ± 10°C in the LS, −55 ± 13°C in the LI, −51 ± 14°C in the RS, and −52 ± 10°C in the RIPV. The mean temperature reached with the 23 mm balloon was −63 vs. −48°C with the 28 mm balloon. The mean, overall procedural duration was 155 ± 43 min (range 75–275), and the mean duration of fluoroscopic exposure was 35 ± 15 min (range 12–73). The mean procedural duration decreased progressively when comparing consecutive groups of 10 patients, reflecting a procedural learning curve (*Figure 2A*). The procedure was discontinued early in a single patient, who developed phrenic nerve

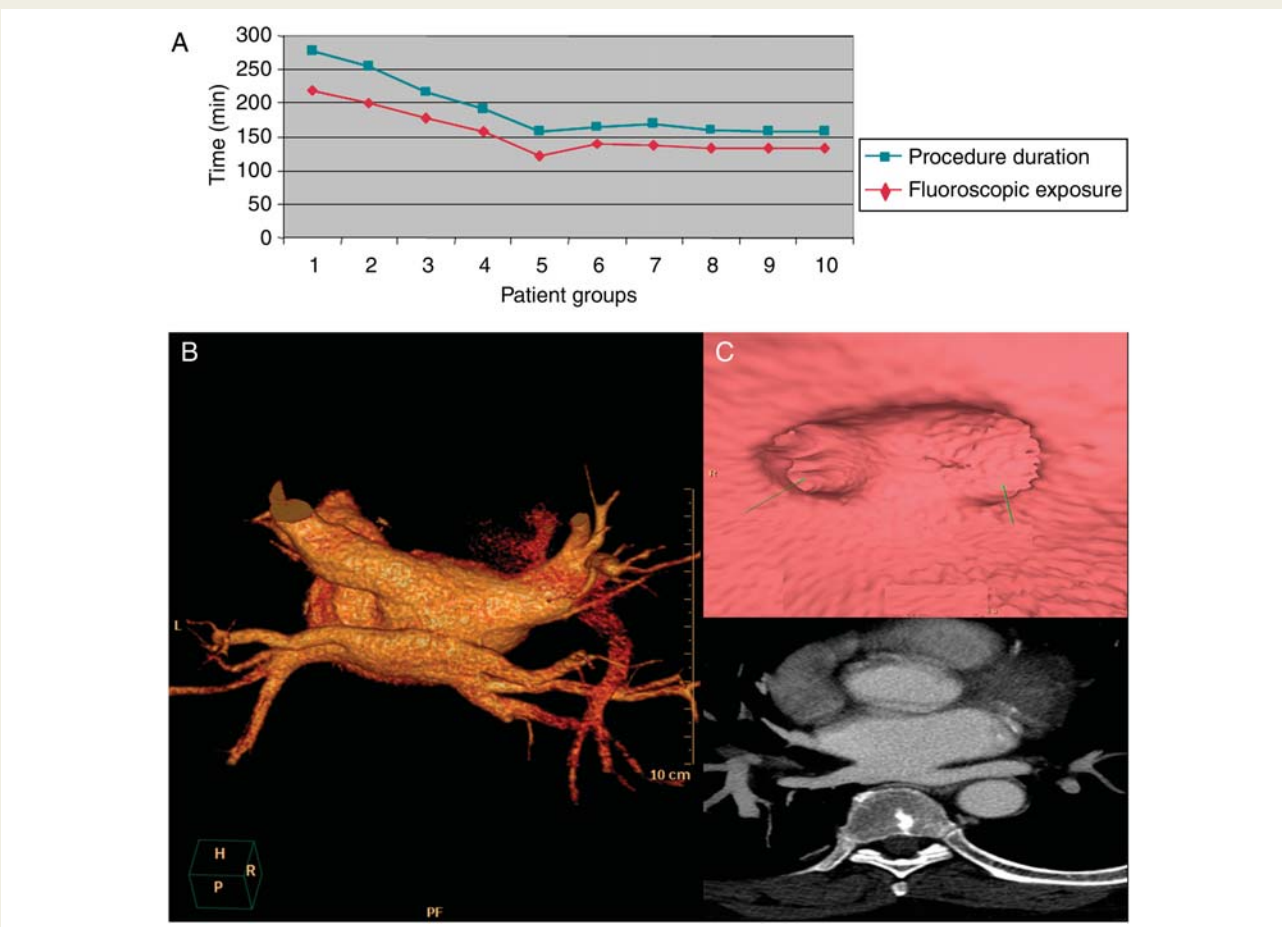


Figure 2 (*A*) Decreases in the duration of procedures and fluoroscopic exposures between the first and last groups of 10 procedures. This decrease illustrates the ease of use of the cryoballoon and of the rapid learning of the technique by the operators. (*B*) Volume-rendered three-dimensional computed tomography illustration of the common ostium of the left inferior and right superior pulmonary vein. (*C*) Intraatrial view of the common ostium connecting both inferior pulmonary vein to the left atrium and both inferior pulmonary vein entering the left atrium via a common ostium. LSPV, left superior pulmonary vein; RSPV, right superior pulmonary vein; LIPV, left inferior pulmonary vein; RIPV, right inferior pulmonary vein; CO, common ostium.

palsy (PNP) after isolation of both LPV. In another patient, the procedure was complicated by a coronary air embolism, although it was completed after resolution of the complication.

At the end of the procedure, 103 patients (88%) were in sinus rhythm, while 14 patients underwent transthoracic cardioversion of AF to sinus rhythm under deep sedation.

Use of radiofrequency ablation

Radiofrequency was used to complete the isolation of the PV in 12 patients (13%) presenting with paroxysmal AF vs. seven patients (28%) suffering from persistent AF ($P = 0.07$).

Long-term outcomes

The patients were followed for a median of 9.6 months (range 3–12), At 3 months, 11 patients had been lost to follow-up, and the antiarrhythmic drug regimens were discontinued in 80 of the 106 remaining patients (75%). At 3, 6, 9, and 12 months of follow-up, respectively, 79, 79, 79, and 68% of patients presenting with paroxysmal AF had remained free from symptomatic or documented AF vs. 83, 73, 59, and 45% of patients, respectively, with persistent AF (*Figure 3*).

Procedural complications

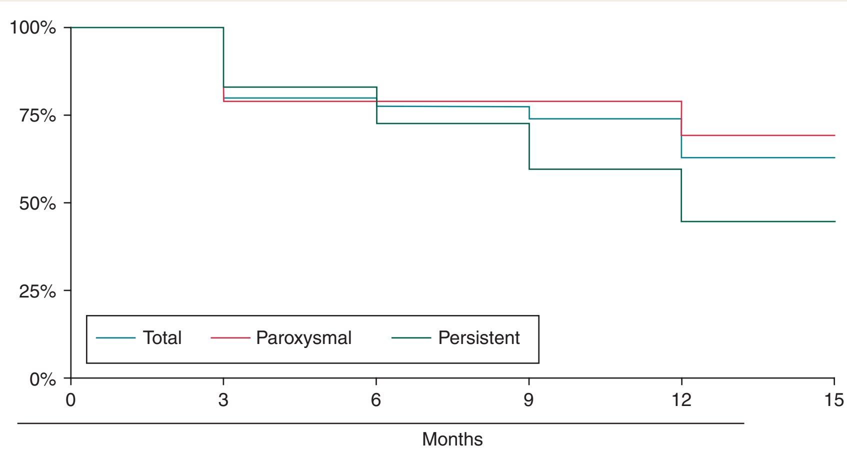
Transient PNP lasting only a few minutes was observed in four patients, of whom three had been treated with a 28 mm balloon. Chest pain and haemoptysis developed 2 days after the procedure in one patient. A CT scan showed a haematoma near the ostium of the RIPV and a mediastinal effusion, both of which resolved spontaneously. Pericardial effusions developed during the procedure in three patients, complicated by tamponade treated by open pericardiocentesis in one patient. One patient complained of light headedness during the procedure, associated with sinus bradycardia and prominent ST segment elevation in the inferior leads of the surface ECG, managed with atropine, fluid challenge, and sublingual nitroglycerin, before resumption and successful completion of the procedure. Finally, two patients who developed right atrial flutter at the end of the procedure underwent cavo-tricuspid ablation, and one patient developed sustained right atrial flutter at 2 months of follow-up, treated with amiodarone.

Discussion

Since the description, by Haissaguerre *et al.*,[13,14] of the role played by PV arrhythmogenicfoci in the initiation of paroxysmal AF, isolation of the PV has become a highly successful treatment of this common arrhythmia. The latest professional practice guidelines recommend ablation of PV potentials as a treatment of paroxysmal AF.[15,16] New techniques have emerged, including circumferential cryoablation with a balloon catheter, as alternatives to RF ablation to increase the effectiveness and safety of the procedure.[17]

Optimal placement and contact of the cryoballoon inside a targeted vein cools the tissue to create a well-defined cryothermal zone and homogeneous lesion.[18] Using this technique, we isolated 87% of the PV we had targeted, a result consistent with previously published studies.[19] Because of atypical anatomy, including unusual shapes and angles, we were unable to isolate 27 (6%) and access 10 (2%) veins with cryoablation. Since the slope of the procedural learning curve is steep, we believe that the procedural results will continue to improve as the manufacturing of new cryoballoons of various sizes will tighten their fit with the veins and, perhaps, facilitate their manoeuvring.[20]

Complete occlusion of the vein by the inflated balloon and low temperatures during the cryoapplication are predictors of successful PV isolation.[21] In our study, the veins were often completely



	3	6	9	12
Numbers at risk				
All patients	104	62	45	20
Paroxysmal AF	81	46	34	16
Persistent AF	23	16	11	4

Figure 3 Cumulative atrial fibrillation-free survivals of patients who underwent cryoablation for paroxysmal vs. persistent atrial fibrillation. $P = 0.167$.

occluded. Of the two variables, temperature is a less dependable predictor, as the temperature sensor, located proximally inside the balloon, is outside the vein and underestimates the tissue temperature attained during the application. The sensor is warmed by blood flow in nearby veins, which may explain the higher rate of successful isolation in the RIPV despite the moderate temperatures measured in that vein.Our results confirm the importance of choosing a proper balloon size and of obtaining a tight occlusion.[21]

Compared with RF procedures, we found the isolation of the RIPV with the cryoballoon relatively easy, owing probably to the performance of the Flexcath steerable sheet, which can be perfectly oriented through the RIPV. This might also be attributable to the 'pull-down' technique described by Chun *et al.*,[20] and to the 23 mm balloon, which was used in rare cases after unsuccessful cryoisolation with the 28 mm balloon. Using multislice cardiac CT, Sorgente *et al.*[22] found an inverse correlation between (i) the ovality index of the left (although not the right) PV and (ii) the degree of occlusion.[22] The occlusion of the right veins does not seem dependent on their shape. A high rate of isolation was also found for the LIPV, which can be explained by a 'cross-talk' effect during isolation of the LSPV. Indeed, isolation of the LSPV with a large-sized balloon can also contribute to the isolation of sleeves common with the LIPV.[22]

It is noteworthy that cryoablation seemed better tolerated than RF ablation, particularly on the left side, where general anaesthesia is sometimes necessary. All procedures were carried out under local anaesthesia and light sedation. The only complaints offered by the patients were occasional headaches due to the cold reflex. Few analgesics were administered during the cryoapplications. The avoidance of general anaesthesia is a major advantage. The anaesthetized state may conceal marked changes in vital signs and delay the management of adverse events, including tamponade and neurological complications. The major advantage of sedation compared with general anesthesia is to allow the performance of shorter procedures. The patients were continuously monitored and an echocardiogram could be instantly obtained in case of development of chest pain or hypotension.

The role of operator experience in the use of this new technique has been discussed previously.[22,23] The mean duration of the procedure decreased progressively according to a steep learning curve (*Figure 2A*) decreasing by an average of 86 min between the first 10 and the last 10 procedures. The same trend was observed with fluoroscopy, the mean duration of which decreased by 33 min. These progressions point to a rapid learning of the technique by the operators.

We observed three episodes of paroxysmal AF in three separate patients during the first 3 months of follow-up, after ablation of persistent AF,[24] when lesion maturation was incomplete.These three patients were in sinus rhythm and asymptomatic at 6 and 9 months of follow-up. Paroxysmal AF is usually successfully eliminated by balloon ablation, as it only requires isolation of the PV, and is rarely followed by early recurrences. In contrast, more persistent forms of AF may require additional ablation, as suggested by our observations.

Cryoablation tends to be associated with fewer complications than RF.[25–27] The most frequently reported complication is PNP, which may occur when the cryoablation is performed in the ostium of the RSPV, near the phrenic nerve.[26,28] This risk is greater when the balloon is positioned very distally inside the vein, and is therefore increased by the use of a 23 mm cryoballoon.[22] However, while a concern, the risk of phrenic nerve injury is also an indication that cryoballoon can cause transmural lesions. In our study, four patients developed transient PNP, whereas in other studies it has persisted for up to 12 months after cryoablation. However, no case of permanent PNP has been reported.[12,23] Phrenic nerve injury complicating RF ablation is slower to recover.[29] In our study, PNP resolved rapidly, as we continuously monitored phrenic nerve function during RSPV isolation, and immediately discontinued the cryoisolation procedure at first sign of abnormality. A close surveillance and early detection of PNP seem essential for a prompt recovery. We observed no atrio-oesophageal fistula, a rare, although potentially lethal complication of PV isolation by delivery of RF energy, or of procedures using balloons that create lesions by the delivery of heat.[30] By contrast, cryoenergy does not cause atrio-oesophageal fistulas and rarely causes PV stenosis, both of which are major complications.

While fistulas have not been reported after cryoballon ablation, Ahmed *et al.*[31] have observed asymptomatic oesophageal ulcerations after the procedure in 17% of patients. Likewise, PV stenosis, which was not observed in our study, was described in a recent presentation of the North-American STOP-AF trial.[32] In that trial, 169 patients were randomly assigned to cryoablation and 82 patients were assigned to antiarrhythmic drug therapy. In the primary effectiveness analysis, 70% of the patients assigned to cryoablation were free from AF on the long term vs. 7% of patients assigned to antiarrhythmic drug therapy ($P < 0.001$). Unexpectedly, stenoses (>75% area narrowing) developed in 10 out of 927 PV, and 2 PV had to be dilated. These stenoses were probably due to the inflation of the balloon deep inside the PV instead of at the ostium. It is noteworthy that the trial was conducted at medical centres where the top of the learning curve had not been reached with regard to cryoablation. In contrast, no stenosis has been described in the studies conducted in Europe.

Comparisons with previous studies

In a previous study of 346 patients who underwent PV isolation with a cryoballoon, the immediate success rate was ~93%, and increased when a focal cryocatheter was used in conjunction with the cryoballoon.[24] Both 23 and 28 mm balloons were used in some patients. We reached an 87% success rate with a cryoballoon alone. Additional focal RF applications allowed us to attain a 100% immediate success rate in 442 treated veins. These results are slightly better than reported by others and similar to the best results achieved with RF energy. Our cryoballoon ablation combined with focal RF applications is an approach unlike that used in other studies.

Conclusions

Our study confirmed the feasibility, safety, and efficacy of circumferential PV isolation with a cryoballoon. In comparison with most standard RF techniques, which require a double transseptal puncture, cryoballoon ablation can be performed with a single puncture, shortening the procedure, and lowering its complexity and the risks of complications. Phrenic nerve palsy is the most common complication associated with cryoballoon ablation, although it is resolved in all cases. Other complications were rare. The long-term success rate was high and compared favourably with that attained with RF ablation. Finally, cryothermy seemed better tolerated than RF ablation. Altogether, these factors contribute to our choice of cryoballoon ablation as first-line therapy for the treatment of paroxysmal AF.

Conflict of interest: none declared.

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