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The CRYO Versus RF Trial. Introduction: Catheter ablation of paroxysmal AF using the Cryoballoon (CRYO) has yielded similar success rates to conventional wide encirclement using radiofrequency catheter ablation (RFCA), but randomized data are lacking. Pilot data suggested a high success rate with a combined approach (COMBINED) using wide encirclement with RFCA followed by 2 CRYO applications to each vein. We compared these 3 strategies in a randomized controlled trial.

Methods and Results: Patients undergoing first time paroxysmal AF ablation were randomized to RFCA, CRYO, or COMBINED. Patients were followed up at 3, 6, and 12 months with 7 days of ambulatory ECG monitoring. Success was defined as freedom from arrhythmia without antiarrhythmic drugs after a single procedure. A total of 237 patients were randomized. Success at 1 year was achieved in 47% in the RFCA group, 67% in the CRYO group, and 76% in the COMBINED group ($P < 0.001$ for RFCA vs. CRYO, $P < 0.001$ for RFCA vs. COMBINED, and $P = 0.220$ for CRYO vs. COMBINED). Procedure time was 211 (IQR 174–256) minutes for RFCA compared to 167 (136–202) minutes for CRYO and 278 (243–327) minutes for COMBINED ($P < 0.001$ for RFCA vs. COMBINED, RFCA vs. CRYO, and CRYO vs. COMBINED groups).

Conclusions: Pulmonary vein isolation for paroxysmal AF is faster with CRYO and results in a higher single procedure success rate than conventional point by point RFCA. The COMBINED approach was not superior to CRYO alone. (J Cardiovasc Electrophysiol, Vol. 26, pp. 1307-1314, December 2015)

atrial fibrillation, catheter ablation, cryoballoon, pulmonary vein isolation

Introduction

Conventional radiofrequency catheter ablation (RFCA) aims to achieve pulmonary vein (PV) isolation by creating contiguous, transmural point by point lesions at a distance from the PV ostia to isolate them as ipsilateral pairs. This is time consuming and technically challenging. Furthermore, the endpoint of acute PV isolation is achieved partly due to tissue edema and AF recurrence associated with PV reconnection remains a problem.

Alternative technologies have been developed to facilitate lasting PV isolation, one of which is the Arctic Front Cryoballoon Catheter (Medtronic Inc, Minneapolis, MN, USA). Although the Cryoballoon (CRYO) might be simple to use, the first-generation cryoballoon in particular often requires additional focal ablation to achieve PV isolation. Several studies have suggested an efficacy with CRYO similar to RFCA ablation, although there remains a shortage of randomized data comparing the two. A recent pilot study at our center utilized a novel combined approach to PV isolation. The PVs were isolated at a distance from their ostia by RFCA followed by ostial applications of the cryoballoon, aiming to reduce PV reconnection. Pilot data suggested the combined technique was feasible, safe, and efficacious.
It was hypothesized that (1) CRYO is as effective and safe as RFCA in the treatment of paroxysmal AF and is associated with a better long-term outcome, and (2) that the combination of RFCA followed by CRYO is as effective and safe as using either treatment alone and is associated with a better long-term outcome. We sought to prove this through a randomized controlled trial.

**Methods**

**Study Design**

This was a single center prospective randomized controlled trial. The study was approved by the local research ethics committee and was prospectively registered on NIH clinicaltrials.gov (NCT01038115). All patients were recruited at a single-center (St. Bartholomew’s Hospital). All patients gave written informed consent. Randomization involved a random number generator, with sealed envelopes opened on the day of the procedure.

Patients were not blinded to their treatment allocation since procedures were performed under conscious sedation. The nature of the study did not allow blinding of physicians performing procedures or those performing follow-up, as procedures were performed under conscious sedation.

The study design did not allow randomization of physicians performing procedures or those performing follow-up, as procedures were performed under conscious sedation.

**Study Patients**

The study population consisted of patients with symptomatic paroxysmal AF refractory to $\geq 1$ antiarrhythmic drug. Exclusion criteria were as follows: persistent AF, a potentially reversible cause of AF, any contra-indication to ablation, severe valvular heart disease, or prior left atrial ablation. Preprocedure imaging of the left atrium and PVs was not performed routinely.

Patients were randomized to undergo PV isolation using 1 of 3 strategies:

(i) Conventional point by point RFCA.

(ii) Cryoablation (CRYO), aiming for PV isolation with the cryoballoon alone, but accepting the use of focal ablation where needed to achieve PV isolation.

(iii) RFCA followed by CRYO as a novel combined technique (COMBINED).

Where focal ablation was needed to achieve PV isolation in the CRYO group focal cryoablation was used in the first instance, with focal radiofrequency ablation used only where PV isolation could not be achieved with cryoablation alone. This was, first, to investigate the proportion of PVs that could be isolated with cryo energy alone, and, second, to keep the CRYO group as much as possible to cryoablation alone for the purposes of comparison with the other 2 groups.

**Catheter Ablation**

All patients underwent transesophageal echocardiography immediately preprocedure. Procedures were performed on oral anticoagulation under moderate sedation. Catheters were introduced through the right femoral vein. A quadripolar catheter was positioned in the coronary sinus. Activated clotting time was maintained 300–350 seconds with boluses of heparin.

After transseptal puncture 2 Mullin’s sheaths (Cook Medical, Bloomington, IN, USA) were positioned in the left atrium. A steerable multipolar PV mapping catheter was introduced. During the course of the trial, the Achieve mapping catheter (Medtronic Inc.) was launched, which is essentially a small caliber nondeflectable PV mapping catheter that passes through the cryoballoon catheter in place of the guide wire. This resulted in only a single transseptal puncture being required in the CRYO only group.

In patients randomized to RFCA, ablation was delivered using an irrigated 3.5 mm ablation catheter (Navistar Thermocool, Biosense Webster, Diamond Bar, CA, USA) guided by CARTO 3 (Biosense Webster), with lesions placed 1–2 cm outside the PV ostia to isolate them in ipsilateral pairs. The procedural endpoint in all 3 groups was PV electrical isolation. Entrance block was considered when PV potentials were no longer recorded by the circular mapping catheter. Evidence of exit block was also sought by looking for dissociated PV potentials and by pacing around the poles of the PV mapping catheter to look for PV capture dissociated from the LA (although it is accepted that PV capture was not achieved in all patients). Power was limited to 30 W and flow was 2–30 mL/min.

In patients randomized to CRYO, after transseptal puncture the Mullin’s sheath was exchanged for a 12 F FlexCath sheath (CryoCath, Medtronic Inc.). Cryoablation of all PVs was then performed using the first-generation cryoballoon (Arctic Front, Medtronic Inc.). The choice of cryoballoon size (23 or 28 mm) was at the discretion of the operator. After applying the cryoballoon to the PV ostium, contrast was injected and delayed emptying was taken to mean an adequate “seal” and an occluded PV ostium.

At least two 5-minute freezes were performed at each PV ostium. Temperatures of $\leq -40 ^\circ C$ were considered adequate. During ablation of the right PVs, the coronary sinus catheter was moved to the SVC and used to pace the phrenic nerve, so that cryoablation could be halted early in the event of phrenic nerve injury. Electrical isolation was determined by the PV mapping catheter.

Where PV isolation was not achieved after 2 applications of the cryoballoon, further freezes were delivered with the same balloon. If this was not successful the operator had the option to try a second size of balloon. If PV isolation with the cryoballoon failed then focal ablation was applied with an 8 mm cryoablation catheter (Freezor Max, Medtronic, Inc.) in the first instance. If this failed a 3.5 mm RF ablation catheter (Thermocool Celsius, Biosense Webster) was used without a 3D mapping system. As in all groups, the procedural endpoint was PV electrical isolation.

**Radiofrequency Ablation Followed by Cryoablation (COMBINED)**

PVs were isolated as in the RFCA group. This step was performed first since an intact PV isolation line could not be created if PVs had been isolated by CRYO. Two successful 5-minute freezes were then applied (as judged by an occlusive venogram and temperatures of $\leq -40 ^\circ C$) to each PV ostium. As PVs were already isolated, there were no electrical endpoints for cryoablation in this group.

No waiting periods were observed following PV isolation in any of the 3 groups and adenosine was not given to look for dormant PV conduction. In all 3 groups the PVs were...
The CRYO Versus RF Trial

Follow-Up

Antiarrhythmic drugs were stopped postprocedure and patients were discharged the next day. Patients were followed up at 3, 6, and 12 months with 7 days of ambulatory monitoring and freedom from arrhythmia was adjudicated at these time points. There was open access for review between appointments in the event of recurrent symptoms, with additional monitoring in the form of continuous monitoring for up to 7 days or an event recorder for less frequent symptoms. Any recurrent arrhythmia was adjudicated at the next study time point (3, 6, or 12 months).

Study Endpoints

Success was defined as freedom from documented AF/AT lasting ≥ 30 seconds (whether symptomatic or not) following a 3-month blanking period, as per current guidelines. The use of antiarrhythmic drugs after the 3-month blanking period was also counted as failure. The primary endpoint of the study was the success rate at 1 year following a single procedure without antiarrhythmic drugs. Secondary endpoints were complication rates, procedure times, and fluoroscopy times.

Statistical Analysis

The study was powered based on pilot data from our center suggesting that 80% of patients in the COMBINED group and 60% of patients in groups with either treatment alone remain free from AF at 1 year. Assuming this, 79 patients in each group would give an 80% power to detect a 20% difference between groups with an alpha of 0.05.

All data were analyzed according to intention to treat. Continuous data were presented as mean ± standard deviation if normally distributed or median (range, or inter quartile range where stated) if not. Categorical data were described as count (percentage).

The primary endpoint of freedom from AF at 1 year was compared using a chi-square test. A Bonferroni adjustment was applied for the prespecified pair-wise comparisons of this primary endpoint, giving an alpha of 0.017. For all other pair-wise comparisons of the secondary end-points a Tukey HSD correction was used.

Continuous data were compared using ANOVA for normally distributed data or Kruskal–Wallis where data were not normally distributed. Categorical data were compared using a chi-square test and further pair-wise comparisons used Fisher’s exact test.

To ensure that the primary endpoint analysis was not affected by uneven matching of groups a binary logistic regression analysis was conducted including the demographic variables presented in Table 1. Variables were then removed stepwise from the model when the P-value exceeded 0.10, and variables with P < 0.05 in the final model were considered to be significant predictors of failure.

Analysis was performed using SPSS 16 (SPSS, Inc., Chicago, IL, USA).

Results

Patients

Figure 1 shows a summary of the patients screened, randomized, and followed up. A total of 237 patients were randomized between July 2009 and December 2012. After randomization, 3 patients did not undergo ablation and were withdrawn from the study. In the CRYO group 1 patient was rendered asymptomatic after a change to medication; in the RF group 1 patient had a persistent left atrial appendage thrombus despite increasing the target INR and 1 had a malignancy diagnosed and declined the procedure. The demographics for the remaining 234 patients are shown in Table 1. The groups were well matched and there were no significant differences between groups. All 234 patients were followed up for 1-year postablation, with none lost to follow-up. Although freedom from arrhythmia was adjudicated at the 3-, 6-, and 12-month time points, 48/234 patients (20.5%) were also evaluated in between appointments and subjected to additional monitoring.

The Primary Endpoint: Freedom from AF at 1 Year

The single procedure success rate without antiarrhythmic drugs at 1 year was 36/77 (47%) in the RFCA group, 52/78 (67%) in the CRYO group, and 60/79 (76%) in the COMBINED group (difference between groups P < 0.001; RFCA vs. COMBINED P < 0.001; RFCA vs. CRYO P < 0.001; CRYO vs. COMBINED P = 0.220). A Kaplan–Meier analysis of AF/AT free survival is shown in Figure 2 and curves are compared using the log-rank test.

Multivariate Analysis

Of the factors listed in Table 1, the only factors that emerged as significant predictors of failure were study group (difference between groups P = 0.001; RFCA vs. COMBINED P < 0.001; RFCA vs. CRYO P = 0.024; CRYO vs. COMBINED P = 0.132), female gender (P = 0.009), and the number of antiarrhythmic drugs failed (P = 0.035). The full results of the multivariate analysis are shown in Table 2.

Procedures

All 4 PVs were isolated in all procedures. Procedure and fluoroscopy times are shown in Figure 3 and summarized in Table 3. Procedure times were significantly shorter in the CRYO group compared to the other 2 groups, and procedures in the COMBINED group were significantly longer than the RFCA group. Fluoroscopy times were significantly shorter in the RFCA group compared to the other 2 groups, and the fluoroscopy time in the COMBINED group was significantly longer than the CRYO group.

In the CRYO group, procedures requiring additional focal ablation to achieve PV isolation were longer than those where PVs were isolated with the balloon alone (210 minutes [IQR 181–238 minutes] vs. 150 minutes [IQR 130–184 minutes]; P < 0.001) and had a longer fluoroscopy time (48 minutes [37–56 minutes] vs. 30 minutes [IQR 24–41 minutes]; P < 0.001). For CRYO patients requiring additional focal ablation, procedure time was no different to that in the RFCA group (P = 0.772).

In the RFCA group, the median radiofrequency ablation time was 39.1 minutes (IQR 28.7–51.8 minutes). The
TABLE 1

<table>
<thead>
<tr>
<th>Patient Demographics</th>
<th>RF</th>
<th>Cryo</th>
<th>Combined</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>77</td>
<td>78</td>
<td>79</td>
<td>–</td>
</tr>
<tr>
<td>Male</td>
<td>47 (61%)</td>
<td>56 (72%)</td>
<td>49 (63%)</td>
<td>0.331</td>
</tr>
<tr>
<td>Age</td>
<td>61 ± 12</td>
<td>56 ± 11</td>
<td>58 ± 12</td>
<td>0.066</td>
</tr>
<tr>
<td>Hypertension</td>
<td>23 (30%)</td>
<td>27 (35%)</td>
<td>30 (38%)</td>
<td>0.563</td>
</tr>
<tr>
<td>Diabetes</td>
<td>5 (6%)</td>
<td>4 (5%)</td>
<td>6 (8%)</td>
<td>0.819</td>
</tr>
<tr>
<td>Ischemic heart disease</td>
<td>6 (8%)</td>
<td>6 (8%)</td>
<td>5 (6%)</td>
<td>0.811</td>
</tr>
<tr>
<td>Prior stroke or TIA</td>
<td>6 (8%)</td>
<td>7 (9%)</td>
<td>9 (12%)</td>
<td>0.734</td>
</tr>
<tr>
<td>AF duration (years)</td>
<td>5.0 (2.0–7.5)</td>
<td>4.7 (2.0–10)</td>
<td>5.0 (2.0–10.0)</td>
<td>0.522</td>
</tr>
<tr>
<td>Left atrial diameter (cm)</td>
<td>4.3 ± 0.5</td>
<td>4.2 ± 0.4</td>
<td>4.3 ± 0.4</td>
<td>0.832</td>
</tr>
<tr>
<td>Cardiac failure</td>
<td>4 (5%)</td>
<td>7 (9%)</td>
<td>9 (12%)</td>
<td>0.378</td>
</tr>
<tr>
<td>Antiarrhythmics failed</td>
<td>2.3 ± 1.1</td>
<td>2.4 ± 1.0</td>
<td>2.4 ± 1.2</td>
<td>0.780</td>
</tr>
<tr>
<td>Failed amiodarone</td>
<td>10 (13%)</td>
<td>7 (9%)</td>
<td>17 (22%)</td>
<td>0.075</td>
</tr>
</tbody>
</table>

Data shown as mean ± SD, median (IQR), or proportion (%) as appropriate.

Figure 1. Flow diagram of study patients. The patients included at each stage of the study are shown.

The median cryoablation time was 50.1 minutes (IQR 41.4–61.5 minutes). Where additional focal ablation was needed in the Cryo group, the ablation time was 5.1 minutes (IQR 1.7–6.0 minutes). In the COMBINED group, the median radiofrequency ablation time was 38.7 minutes (IQR 29.2–49.7 minutes) with additional cryoablation time of 40.2 minutes (IQR 35–42.2 minutes). The median temperature reached with cryo applications was –45 °C (IQR –39–50 °C), with 75% of all applications reaching the target of –40 °C.

Ablation with the Cryoballoon

The 28 mm cryoballoon alone was used in 57/78 (73%) of patients in the CRYO group, the 23 mm cryoballoon alone in 13/78 (17%) and both were used in 8/78 (10%). Only 30/78 (38%) patients had all 4 PVs isolated with just 2 applications of the cryoballoon, which increased to 54/78 (69%) with further applications. A total of 24/78 (31%) required focal ablation with the Freezeor Max that achieved isolation in 13/78 (17%). The remaining 11/78 (14%) required RF ablation to achieve PV isolation. The 1-year success rate in those achieving PV isolation with the cryoballoon alone was no different from those requiring additional focal ablation: 36/54 (67%) versus 16/24 (67%), respectively (P = 1.000).

Learning Curve with the Cryoballoon

The proportion of patients in whom all 4 PVs were isolated with the cryoballoon alone increased over the course of the study: 16/26 (62%) in the first third of study patients, 18/26
Figure 2. Freedom from arrhythmia. Kaplan–Meier analysis of the survival free from AF or other atrial tachyarrhythmias. Survival curves were compared using the log-rank test. For a high quality, full color version of this figure, please see Journal of Cardiovascular Electrophysiology's website: www.wileyonlinelibrary.com/journal/jce

TABLE 2
Multivariate Analysis of Factors Predicting Recurrent Atrial Arrhythmias

<table>
<thead>
<tr>
<th>Factor</th>
<th>Hazard Ratio</th>
<th>95% C.I.</th>
<th>P-Value</th>
<th>Hazard Ratio</th>
<th>95% C.I.</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female gender</td>
<td>2.38</td>
<td>1.25–4.55</td>
<td>0.008</td>
<td>2.22</td>
<td>1.22–4.01</td>
<td>0.009</td>
</tr>
<tr>
<td>Age</td>
<td>1.00</td>
<td>0.97–1.03</td>
<td>0.906</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1.46</td>
<td>0.76–2.81</td>
<td>0.261</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Diabetes</td>
<td>0.94</td>
<td>0.27–3.24</td>
<td>0.918</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>IHD</td>
<td>0.76</td>
<td>0.24–2.42</td>
<td>0.646</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Prior stroke or TIA</td>
<td>0.82</td>
<td>0.29–2.30</td>
<td>0.707</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>AF duration</td>
<td>1.19</td>
<td>0.58–2.44</td>
<td>0.632</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Left atrial diameter</td>
<td>1.76</td>
<td>0.59–5.24</td>
<td>0.309</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Cardiac failure</td>
<td>1.35</td>
<td>1.01–1.80</td>
<td>0.041</td>
<td>1.33</td>
<td>1.02–1.72</td>
<td>0.035</td>
</tr>
<tr>
<td>Number of antiarrhythmic drugs failed</td>
<td>0.482</td>
<td>0.20–1.19</td>
<td>0.113</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Failed amiodarone</td>
<td>0.42</td>
<td>0.205–0.84</td>
<td>0.015</td>
<td>0.46</td>
<td>0.23–0.90</td>
<td>0.024</td>
</tr>
<tr>
<td>Cryo vs RFCA</td>
<td>0.40</td>
<td>1.91–8.59</td>
<td>&lt; 0.001</td>
<td>3.81</td>
<td>1.86–7.78</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>RFCA vs Combined</td>
<td>1.68</td>
<td>0.80–3.54</td>
<td>0.171</td>
<td>1.75</td>
<td>0.845–3.61</td>
<td>0.132</td>
</tr>
</tbody>
</table>

Hazard ratios are presented for recurrence of atrial arrhythmia by 12 months. The hazard ratio for age is for each additional year of age beyond the mean, the hazard ratio for AF duration is for each additional year of paroxysmal AF beyond the mean, the hazard ratio for left atrial diameter is for each additional cm beyond the mean.

(69%) in the middle third, and 20/26 (77%) in the latter third (P = 0.001). However, there was no change in the 1-year success rate: 17/26 (65%) in the first third of study patients, 19/26 (73%) for the middle third and 16/26 (62%) in the latter third (P = 1).

Complications

Major complications were seen in 11 patients overall (4.7%) with no significant difference between the 3 groups. The 4 complications in the RF group (5.2%) were 1 tamponade that was drained percutaneously, 1 hematoma, 1 asymptomatic PV stenosis (found on PV angiography at the end of the procedure and confirmed subsequently on CT imaging), and 1 case of Dressler’s syndrome presenting 5 weeks post-procedure with symptomatic pleural and pericardial effusions requiring drainage. The 4 complications in the CRYO group (5.1%) were all phrenic nerve palsies, all of which resolved during follow-up. The 3 complications in the COMBINED group (3.8%) were a femoral pseudoaneurysm treated with thrombin injection, and 2 phrenic nerve palsies that resolved during follow-up.

Including the CRYO and COMBINED groups there were 6 phrenic nerve palsies in 157 patients (3.8%). All occurred despite phrenic nerve pacing as described in the Methods section. Monthly fluoroscopic screening showed that all recovered after a median of 8.5 months (range 3–17 months). Only 1 patient was symptomatic, also having asthma and ankylosing spondylitis.
Figure 3. Procedural data. Procedure times (A) and fluoroscopy times (B) for the 3 study groups. The box plots show median (center line), interquartile range (box), and 95% confidence intervals (whiskers). For a high quality, full color version of this figure, please see Journal of Cardiovascular Electrophysiology’s website: www.wileyonlinelibrary.com/journal/jce

### TABLE 3
Procedural Data

<table>
<thead>
<tr>
<th>Procedure time (minutes)</th>
<th>RF</th>
<th>Cryo</th>
<th>Combined</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>RF</td>
<td>211 (174–256)</td>
<td>167 (136–202)</td>
<td>278 (243–327)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Fluoroscopy time (minutes)</td>
<td>28.7 (20.1–41.6)</td>
<td>35.7 (26.5–48.2)</td>
<td>48.9 (38.8–64.2)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Figures show median with IQR in brackets. Pair-wise comparisons are shown in Figure 3.

### Repeat Procedures and Pulmonary Vein Reconnection
The success rates reported are following a single procedure. Nevertheless, data were recorded at repeat procedures (i.e., in patients counted as failures). During the 1-year study period 16 patients (20.8%) in the RFCA group underwent a repeat procedure, 15 patients (19.2%) in the CRYO group, and 7 patients (8.9%) in the COMBINED group (comparison between groups $P = 0.089$; RFCA vs. combined $P = 0.043$; CRYO vs. COMBINED $P = 0.069$; CRYO vs. RFCA $P = 0.843$). At the repeat procedures there were 2.7 ± 1.1 PVs reconnected in the RF group, 2.2 ± 1.1 in the CRYO group, and 1.0 ± 0.8 PVs in the COMBINED group (comparison between groups $P = 0.007$; RFCA vs. combined $P = 0.002$; CRYO vs. COMBINED $P = 0.022$; CRYO vs. RFCA $P = 0.223$).

### Discussion

#### Main Findings
CRYO and the combined approach were both superior to conventional RFCA. Although the combined approach was not significantly better than CRYO, there was a 9% difference in success rates favoring the COMBINED group with lower rates of PV reconnection in this group at repeat procedures, which may be a signal of a small effect that this trial was not powered to detect. Procedure times were significantly shorter with CRYO than RFCA and were markedly longer with the combined approach. Additional focal ablation was needed for 31% of CRYO patients in order to achieve PV isolation.

#### Success Rates with CRYO
The single procedure success rate off antiarrhythmic drugs at 1 year was 67% with cryoablation compared to 47% with RFCA. This is the first study to demonstrate superiority of the cryoballoon over conventional RFCA, which is currently the standard of care for paroxysmal AF. PV isolation with the cryoballoon was also quicker than RFCA, with no difference in complication rate.

The only other large randomized study to evaluate the cryoballoon was STOP AF (which compared ablation to antiarrhythmic drugs); the cryoballoon achieved a 1-year success rate of 70%. A meta-analysis of mostly nonrandomized data estimated the success rate to be 73%. These data suggest a consistent experience with the cryoballoon.

Only 1 other randomized study has compared the cryoballoon to RFCA. The COR Trial randomized 50 patients with paroxysmal AF to RFCA or cryoablation. They delivered 2 applications of the cryoballoon to each PV, documented isolation of all PVs in 48% of patients, but did not use additional focal ablation to isolate PVs. Freedom from AF was 68% with RFCA and 48% with CRYO ($P = 0.05$). However, of the CRYO patients who achieved PV isolation, 67% were successes. Therefore, a cryoballoon strategy without the
endoine of PV isolation is inferior to RFCA. Three registries comparing the cryoballoon to conventional RF ablation reported approximately equal success rates.\textsuperscript{3, 5}

**Ablation with the Cryoballoon**

Isolation of all 4 PVs was achieved in a minority of patients (38%) with 2 applications of the cryoballoon to each PV. This increased to 69% of patients with repeated cryoballoon applications. \textsuperscript{1} With further experience this increased to 77% in the latter third of the study. \textsuperscript{1, 2} A significant proportion required the use of both balloon sizes (10%) and ultimately 31% required focal ablation to achieve isolation of all PVs. \textsuperscript{1} This could be considered procedural failure of the cryoballoon, although a strategy involving additional focal ablation where necessary to achieve PV isolation is common and matches real world practice.\textsuperscript{1, 2} Although the high proportion of patients needing focal ablation detracts from the advantages of this technology, it should be noted that PV isolation was achieved with focal cryoablation in most of these patients and only 14% received focal radiofrequency ablation. \textsuperscript{1} The comparison between CRYO and RFCA groups is therefore a genuine test of cryoablation versus radiofrequency ablation as much as is possible within a study design aiming for PV isolation at the index procedure. Notably, outcomes in patients receiving additional focal ablation were identical to patients receiving ablation with the cryoballoon alone.\textsuperscript{3, 10}

In STOP AF 17% of patients received additional focal radiofrequency ablation to achieve PV isolation.\textsuperscript{2} A meta-analysis suggested that focal radiofrequency ablation is needed to achieve PV isolation in 33% of patients using the first-generation cryoballoon alone.\textsuperscript{1} However, recent data suggest that PV isolation can be achieved with the cryoballoon alone in nearly all patients using the second-generation cryoballoon.\textsuperscript{8-10}

As there was no preprocedure imaging this was an anatomically unselected population. Although these data will be reassuring to physicians considering this simple and economic approach, a more selective approach might have improved procedural parameters and/or outcomes.

**Success with Conventional Point-by-Point RF Ablation**

A recent meta-analysis showed a wide range of single procedure success rates at 1 year, with a mean of 57%.\textsuperscript{11} Recent multicenter trials and a large prospective registry have reported single-procedure success rates without antiarrhythmic drugs of 43–50%.\textsuperscript{12-14} The modest 47% success rate with conventional RFCA in the present study is therefore consistent with “real world” practice.

**Success Rates with the Combined Strategy**

No data were acquired on the anatomical site of the lesions with CRYO and RFCA in this study. Others have used voltage mapping after ablation with the cryo balloon to show that scarring occurs mostly within the tubular portion of the PV and at the ostia;\textsuperscript{15} nevertheless, it remains uncertain to what extent the lesion sets overlapped in the COMBINED group. The success rate with the combined approach was higher than that achieved with conventional RFCA but was not significantly better than cryoablation alone. However, although the success rate was 9% higher in the COMBINED group than the CRYO group, this trial was not powered to detect a difference between groups of this magnitude. It is noteworthy that there were fewer repeat procedures in the COMBINED group than the RFCA group, and a trend toward fewer repeat procedures compared to the CRYO group. Furthermore, there were fewer PVs reconnected in the COMBINED group than the other 2 groups at repeat procedures. Nevertheless, with the markedly longer procedure times, longer fluoroscopy times, and greater expense, the COMBINED approach is unlikely to be seen as an attractive option compared to CRYO without a clear difference in success rates.

**Complications and Procedural Safety**

The major complication rates were the same in the 3 groups and are within expected ranges. The complications with CRYO comprised entirely phrenic nerve palsies, all of which resolved subsequently. Phrenic nerve palsy has been reported in up to 11% of patients, although recent reports have been as low as 0%.\textsuperscript{2, 16} A meta-analysis suggested an average of 4.7%, with 90% resolving within a year.\textsuperscript{1} Efforts to minimize this risk will clearly be key to the safety of cryoablation. Other serious complications such as stroke, tamponade, and PV stenosis can all still occur with cryoablation.\textsuperscript{16} Nevertheless, these results are compatible with those of a large registry suggesting that serious complications other than phrenic nerve palsy may occur less frequently with cryoablation than conventional RFCA.\textsuperscript{17}

**Limitations**

Catheter contact force sensing technology is now available, as is the second-generation cryoballoon. It remains to be seen whether these advances or others will substantially impact success rates, as this will inevitably influence any comparison between these treatment modalities. Following RFCA it is now also commonplace to observe a waiting period and/or give adenosine to look for PV reconnection, which may improve and standardize outcomes.

Furthermore, 31% of patients in the CRYO group required additional focal ablation to achieve PV isolation, which is more than some studies using the first-generation cryoballoon (17% in STOP AF),\textsuperscript{2} but is lower than the average of 33% reported in a meta-analysis.\textsuperscript{1} The use focal cryoablation as first line meant that focal radiofrequency ablation was used in only 14% of patients in the CRYO group meaning that this group was restricted as much as possible to cryoenergy. Notably focal ablation is rarely necessary with the second-generation cryoballoon.\textsuperscript{8-10}

Larger multicenter studies are needed to confirm whether these findings are applicable to the wider community and to repeat this comparison with subsequent generations of technology and refinements in practice. “FIRE and ICE” (NCT01490814) is a larger multicenter trial aiming to clarify this.

**Conclusions**

PV isolation for paroxysmal AF was faster with the cryoballoon and resulted in a higher single procedure success rate than conventional RFCA. Further multicenter trials are needed to confirm whether these findings are applicable with subsequent generations of Cryo and RF technologies. The combined approach was superior to RFCA but was not shown to be superior to cryoablation alone (although the latter finding may have been a type II error). Nevertheless, with
the longer procedure times and fluoroscopy times in the COMBINED group without clear evidence of benefit, this approach is unlikely to be seen as attractive.

References


