CONTEMPORARY REVIEW

Efficacy and safety of cryoballoon ablation for atrial fibrillation: A systematic review of published studies

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Introduction

Catheter ablation for atrial fibrillation (AF) is centered on electrical isolation of pulmonary veins (PVs) through circumferential lesions around PV ostia. Focal point-by-point radiofrequency (RF) ablation has shown considerable success in treating paroxysmal AF.[1,2] However, major complications include cardiac perforation with pericardial tamponade, injury to adjacent structures (esophagus, phrenic nerve, and aorta), and pulmonary vein stenosis (PVS).[1–5] Furthermore, the procedure is complex, time consuming, and highly dependent on operator competency given the difficulties associated with creating contiguous curvilinear lesions with focal ablation. As such, considerable effort has been directed toward deriving more effective and safer approaches.

Balloon-based ablation systems potentially offer a simpler and faster means of achieving pulmonary vein isolation (PVI) that, theoretically, is less reliant on operator dexterity. Concurrently, cryothermal energy offers advantages over RF energy, including increased catheter stability, less endothelial disruption with lower thromboembolic risk, and minimal tissue contraction with healing, an observation thought to result in less esophageal damage and PVS.[6–11] The objective of this study was to systematically review the available literature to more precisely define the efficacy and safety of cryoballoon ablation for paroxysmal and persistent AF.

Methods

This systematic review was performed using a predetermined protocol and in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.[12]

Search strategy

To identify and retrieve all potentially relevant literature describing the outcomes of cryoballoon ablation for AF, we conducted a literature search with the assistance of reference librarians and investigators trained in systematic review procedures in MEDLINE, Embase, and BIOSIS. Search terms included "atrial fibrillation" [MeSH and All Fields], "Cryosurgery" [MeSH], and "(cryo: or cryosurg" or cryoballoon).mp". The search was limited to Humans, Adults (19+ years), and publication date between January 2000 and January 2011. The language was not restricted to English.

In addition, secondary source documents were identified by manual review of reference lists, review articles, editorials, and guidelines, and by contacting experts in the field. A manual review of the Science Citation Index was undertaken for articles selected for inclusion.

Study selection

Identified abstracts were retained if they made specific reference to cryoballoon for AF ablation. Articles identified from abstract screening underwent full-text review to determine eligibility for data extraction based on the following criteria: (1) original data in humans reported (animal and *in vitro* studies were excluded); (2) study design consisting of a case series, case-control study, cohort study, or controlled trial (abstracts, case reports, letters, comments, reviews, and meta-analyses were excluded); and (3) absolute numbers for study endpoints were reported or could be derived from available data.

KEYWORDS Atrial fibrillation; Catheter ablation; Cryoablation
ABBREVIATIONS **AAD** = antiarrhythmic drug; **AF** = atrial fibrillation; **CI** = confidence interval; **PNP** = phrenic nerve palsy; **PRISMA** = Preferred Reporting Items for Systematic Reviews and Meta-Analyses; **PV** = pulmonary vein; **PVI** = pulmonary vein isolation; **PVS** = pulmonary vein stenosis; **RF** = radiofrequency; **RIPV** = right inferior pulmonary vein; **RSPV** = right superior pulmonary vein (Heart Rhythm 2011;8:1444–1451)

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Data collection and analysis

The following information was obtained using a standardized data extraction form: study population; number of patients; cohort demographics; echocardiographic parameters (left ventricular ejection fraction, left atrial dimension and/or volume); presence and composition of a comparator group (persistent AF, antiarrhythmic drug [AAD] therapy only, RF ablation); procedural data (duration, fluoroscopy time, number of balloon applications per vein, ablation time, need for RF or cryoenergy "touch-up"); procedural and delayed complications (phrenic nerve injury, PVS, esophageal complications, thromboembolic complications [stroke, transient ischemic attack, myocardial infarction], pericardial effusion/tamponade, groin complications); and outcome data (duration of follow-up, freedom from recurrent AF, repeat ablation procedures).

Efficacy outcomes were (1) acute procedural success (by patient and by vein, each subdivided into cryoballoon only success and success with combined cryoballoon and focal ablation) and (2) freedom from recurrent AF. *Acute procedural success* was defined as complete isolation of all targeted PVs. *Acute success by vein* was defined as successful electrical disconnection of a targeted PV in which PV potentials were previously demonstrated.

Data analysis

For each study, outcomes of interest were extracted as proportions, and exact binomial confidence intervals (CIs) were calculated. For studies with sufficient methodologic similarity, pooled estimates of recurrent AF and corresponding binomial CIs were calculated using a fixed-effects model with weighting by sample size. To our knowledge, no random effects meta-analysis models have been developed for binary data, and the assumption of effect size normality is clearly inappropriate for binary data. Heterogeneity was assessed for all analyses using the Q statistic and quantified with the I^2 statistic. Where significant heterogeneity was found, additional stratified analyses were performed to explore potential causes. All statistical analyses were performed using Stata (version 10.1, StataCorp, College Station, TX, USA). The authors had full access to and take full responsibility for the integrity of the data. All authors gave their approval for submission of the final manuscript.

Results

Literature search and study characteristics

Figure 1 shows a flowchart of the systematic review. Of the 539 articles screened, 23 were retained for the final analysis: 20 reporting cryoballoon ablation for paroxysmal AF, 1 reporting cryoballoon ablation for persistent AF, and 2 reporting cryoballoon ablation for both paroxysmal and persistent AF. Study characteristics are listed in Online Supplement Table 1.[13–35] Overall, 1,221 patients had cryoballoon ablation for paroxysmal AF and 87 for persistent AF. Average patient age was 57.5 ± 1.9 years, and 73.6% of patients were male. Average duration of AF was 4.7 ± 1.2 years. Average left ventricular ejection fraction was 60.9% ± 3.3%, and left atrial dimension was 44.4 ± 4.8 mm. The predominant comorbidity was hypertension (37.8%), with 10.8% of the study population having underlying structural heart disease.

Average procedural time was 206.3 ± 72.2 minutes (range 108–371 minutes), with fluoroscopy time of 46.0 ± 13.3 minutes (range 20.1–84.5 minutes). A 28-mm cryoballoon was used in 80.1% (681/842) of patients, a 23-mm cryoballoon in 13.9% (117/842), and both in 5.2% (44/842).

In 9 of 23 studies, the ablation procedure was performed exclusively with the cryoballoon (376 patients). In the re-

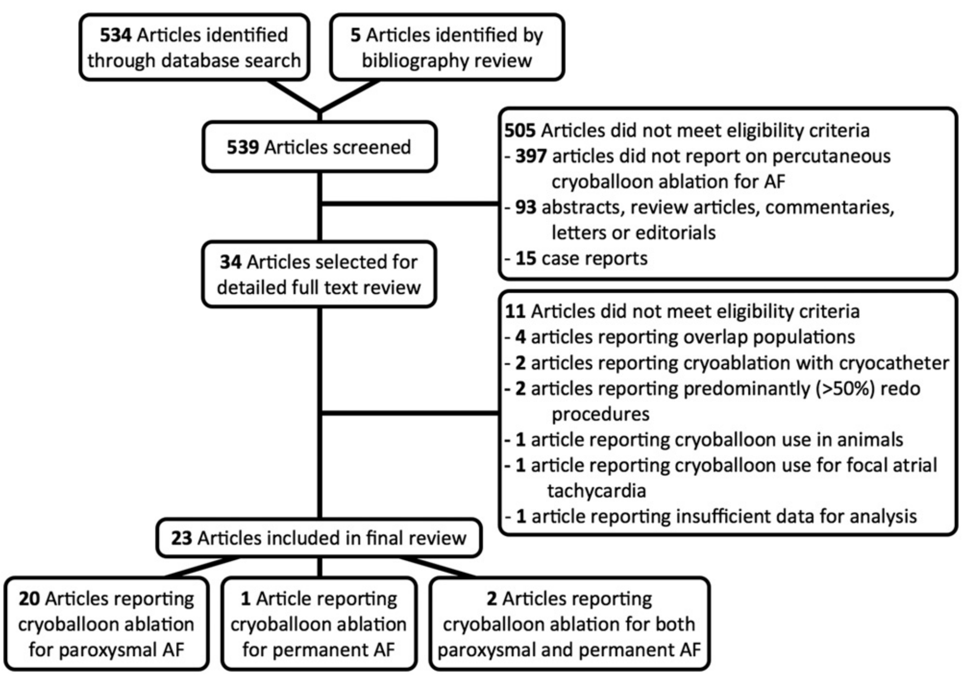

Figure 1 Flowchart showing results of the search strategy and reasons for exclusion. AF = atrial fibrillation.

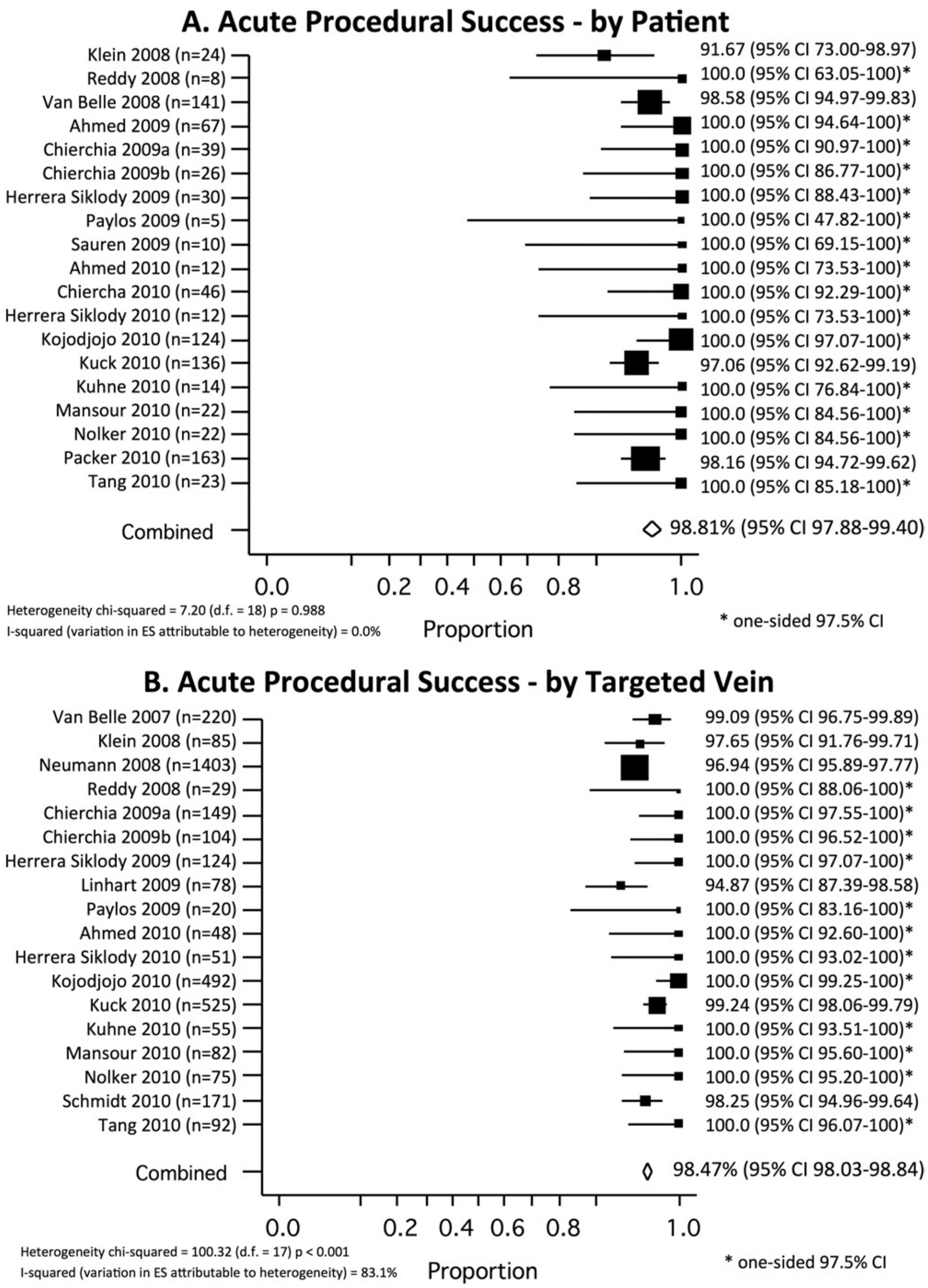

Figure 2 Acute procedural success as defined by complete isolation of all targeted pulmonary veins. **A:** Per patient analysis. **B:** Per vein analysis. CI = confidence interval.

maining 14 studies, the cryoballoon was combined with focal ablation in up to 17.1% of patients (cryocatheter in 13/14 studies, N = 910; irrigated RF catheter in 1/14 studies, N = 22). The addition of focal ablation was associated with longer procedural and fluoroscopy times (Online Supplement Table 2).

Centers with extensive experience reported a progressive decrease in procedural time, fluoroscopy time, number of cryoballoon applications, and need for additional focal ablation with increasing operator familiarity (Online Supplement Table 3). Likewise, single procedural success rates increased progressively with increasing familiarity with the procedure (77.5% for the latest quartile of patients treated vs 39.5% for the earliest quartile of patients treated).[32]

Acute procedural outcomes

Twenty-three studies reported the procedural success of cryoballoon ablation for AF. Acute procedural success was achieved in 91.67% to 100% of patients (19 studies, N = 924 patients) and 94.87% to 100% of targeted veins (18 studies, N = 3,803 veins). Overall, 98.81% of patients achieved complete PVI (95% CI 97.88%–99.40%), and 98.47% of targeted veins were successfully isolated (95% CI 98.03%–98.84%; Figure 2). Ablation with the cryoballoon catheter alone (i.e., excluding concomitant focal abla-

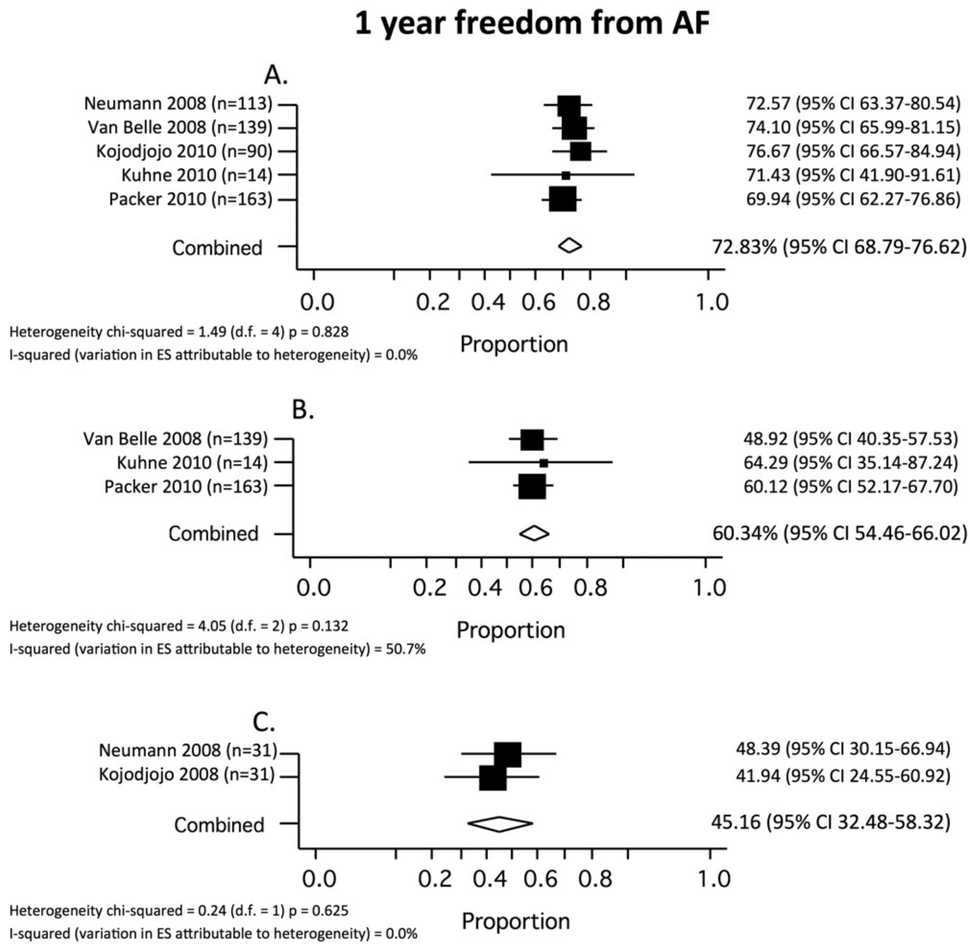

Figure 3 One-year freedom from recurrent atrial fibrillation (AF). **A:** Patients with paroxysmal AF after a 3-month blanking period. **B:** Patients with paroxysmal AF without a 3-month blanking period. **C:** Patients with persistent AF after a 3-month blanking period. CI = confidence interval; ES = effect size.

tion) resulted in PVI in 92.64% of targeted veins (95% CI 91.76%–93.45%) and complete PVI in 77.81% of patients (95% CI 74.99%–80.45%).

Studies using a prespecified exclusive cryoballoon ablation strategy achieved complete PVI in 98.74% of patients (8 studies, 317 patients; 95% CI 96.80%–99.66%) and 99.23% of targeted veins (6 studies, 912 targeted veins; 95% CI 98.42%–99.69%). Studies reporting a hybrid approach of cryoballoon ablation combined with concomitant focal cryoablation achieved complete PVI in 98.85% of patients (11 studies, 607 patients; 95% CI 97.69%–99.54%) and 98.24% of targeted veins (12 studies, 2,891 targeted veins; 95% CI 97.69%–98.68%). Rates of PVI with cryoballoon alone were lower in studies that combined cryoballoon ablation with focal ablation (66.89% of patients achieved complete PVI [95% CI 62.98–70.62] and 90.56% of targeted veins isolated with the cryoballoon only [95% CI 89.43%–91.60%]).

Studies reporting intraprocedural use of intracardiac or transesophageal echocardiography achieved complete PVI in 99.36% of patients (8 studies, 314 patients; 95% CI 97.72%–99.92%) and 99.59% of targeted veins (8 studies, 716 targeted veins; 95% CI 98.78%–99.91%). Studies not using intraprocedural imaging reported complete PVI in 98.63% of patients (9 studies, 437 patients; 95% CI 97.04%–99.49%) and 98.22% of targeted veins (11 studies, 3,087 targeted veins; 95% CI 97.69%–98.66%). One study reported a randomized comparison between intracardiac echocardiography added to fluoroscopy versus fluoroscopy alone in patients with paroxysmal AF undergoing cryoballoon PVI.[33] Although acute procedural success and AF recurrence rate at 6 months were similar in the two groups, patients without intracardiac echocardiographic guidance had significantly longer procedural and fluoroscopy times.

Chierchia et al[20] observed acute procedural reconnection in 2.8% (3/104) of veins within a 60-minute postablation observation period. In all cases, reconnection occurred in the right inferior pulmonary vein (RIPV), in the inferior portion in two and in the posterior portion in one. Another study did not report any acute reconnection after a postablation observation period of up to 30 minutes.[36]

Longer-term outcomes

Eligible data regarding 1-year freedom from recurrent paroxysmal AF were available in five studies (Figure 3). All included a structured means to detect both symptomatic and asymptomatic recurrence (i.e., combination Holter monitoring and event recording or transtelephonic monitoring). In studies reporting a 3-month blanking period (time frame during which transient episodes of arrhythmia were not considered recurrences), the 1-year freedom from recurrent AF was 72.83% (519 participants; 95% CI 68.79%–

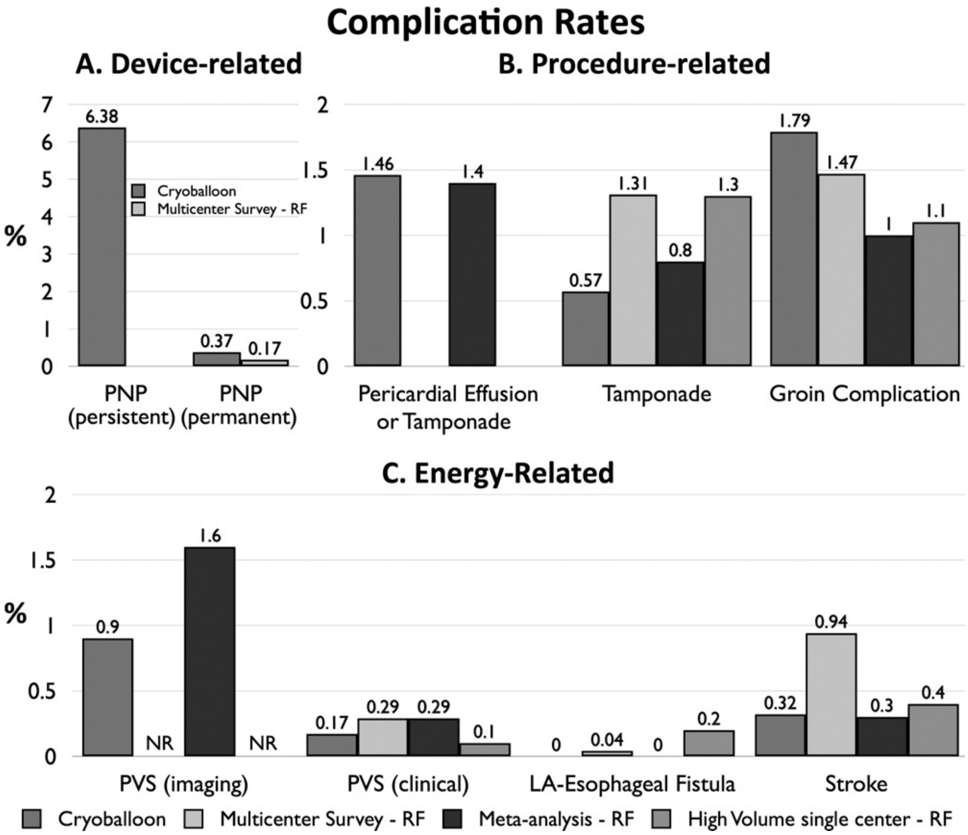

Figure 4 Complication rates for cryoballoon atrial fibrillation ablation. **A:** Device-related complications. **B:** Procedure-related complications. **C:** Energy-related complications. For comparison, three studies reporting complications with radiofrequency (RF) ablation are depicted: a multicenter survey,[4] a meta-analysis,[2] and a high-volume single center.[3] LA = left atrium; NR = not reported; PNP = phrenic nerve palsy; PVS = pulmonary vein stenosis.

76.62%). In the three studies reporting no blanking period, 1-year freedom from recurrent AF after a single cryoballoon procedure off AADs was 60.34% (316 participants; 95% CI 54.46–66.02).

Two studies reported a comparison of cryoballoon ablation with conventional RF for paroxysmal AF. Linhart et al[22] compared 20 patients with paroxysmal AF who underwent their first PV ablation with the cryoballoon and matched them to 20 patients undergoing RF ablation. Six-month freedom from documented AF did not differ between groups (55% with cryoballoon vs 45% with RF), although there was a nonsignificant trend toward decreased AF burden in those with a recurrence after cryoballoon ablation. Similarly, Kojodjojo et al[29] reported no difference in 12-month freedom from recurrent AF between those who underwent cryoballoon ablation for paroxysmal AF (90 patients) and those who underwent RF ablation (53 patients) (77% and 72%, respectively).

One randomized study, the STOP-AF trial, reported a comparison of cryoballoon ablation with AADs for patients with paroxysmal AF who had previously failed at least one AAD.[32] After a 3-month blanking period, 69.9% (114/163) of the cryoballoon group was free of recurrent AF at 1 year versus 7.3% (6/82) of the AAD group. At 12 months, there was a statistically significant improvement in symptoms and every aspect of quality of life as measured by the SF-36 questionnaire in the cryoablation group. For all metrics, symptomatic improvement was greater in the cryoablation group compared with the AAD group.

Reconnection

Four studies reported the results of a repeat ablation procedure at variable time intervals (Online Supplement Table 4).[17,25,31,37] During the second procedure, a total of 270 previously isolated veins were examined in 71 patients. On average, 2.7 ± 0.4 veins had electrically reconnected per patient. Left-sided veins demonstrated electrical reconnection more frequently than did right-sided veins (7 left common, 55 left inferior, 51 left superior, 44 right inferior, 35 right superior).

Safety outcomes

Twenty-two studies reported rates of adverse events among 1,308 patients undergoing cryoballoon ablation of paroxysmal AF (Figure 4 and Online Supplement Table 5). A single study comprising 67 participants reported only esophageal complications, and another study comprising 10 patients reported only neurologic complications.[18,24] Another study reported rates of phrenic nerve palsy (PNP) among 259 participants, but rates of other complications could be verified for only 163 participants.[32] As a result, rates for PNP were reported for 1,349 participants, esophageal complications for 1,298 participants, and all other acute complications for 1,231 participants.

The most common complication was PNP, with an overall incidence of 6.38% (86/1,349 procedures). The incidence of PNP persisting after the ablation procedure was 4.73% (67/1,349). Delayed recovery was the predominant outcome, with only 0.37% (5/1,349) experiencing PNP that persisted beyond 1 year. Interestingly, 64.71% of cases of PNP occurred with a 23-mm balloon and 35.29% with a 28-mm balloon. PNP occurred in a much higher proportion of procedures that used the 23-mm cryoballoon compared to the 28-mm cryoballoon (12.37% vs 3.53%, P = .0001). PNP most often complicated ablation of the right superior pulmonary vein (RSPV), although it also rarely occurred with ablation of the RIPV.

In studies reporting systematic screening for PVS with noninvasive imaging performed between 1 and 12 months after the index ablation procedure, the incidence of radiographic PVS was 0.90% (7/773 procedures).[15,17,21,23,27,28,32–34] All cases were observed in a single study and may reflect differing diagnostic definitions. Using a definition of a >75% reduction in cross-sectional area from baseline, Packer et al[32] observed 10 stenotic PVs (of 927 treated veins) in 7 (3.07%) of 228 patients. In studies that used the standard definition based on reduction in PV diameter, the incidence of PVS was 0% (0/545).[15,17,21,23,27,28,33,34] Overall, the incidence of significant PVS resulting in symptoms or requiring intervention was 0.17% (2/1,163).

No cases of left atrial–esophageal fistula were reported (0/1,298 procedures). Three studies comprising 116 participants reported the results of systematic upper endoscopy after cryoballoon ablation.[18,33,38] Ahmed et al[18] found a 17% incidence of esophageal ulceration after cryoballoon ablation (6/35 participants) compared to a 0% incidence after focal cryoablation (0/7 participants). Conversely, similar studies demonstrated no thermal esophageal lesions in 38 and 43 patients who underwent systematic esophageal endoscopy.[33,38]

The incidence of thromboembolic complications including periprocedural stroke, transient ischemic attack, or myocardial infarction was 0.57%. Two of the three periprocedural myocardial infarctions were due to air embolism and resolved during the procedure without long-term sequelae. Three of the four cerebrovascular events were observed in the same study and resolved completely within 24 hours.[32] Given the association between the number of cerebral microembolic signals and neurologic impairment and stroke, Sauren et al[24] compared the incidence of cerebral microembolic signals in 30 patients during three percutaneous endocardial ablation strategies: segmental PVI using a 4-mm conventional (nonirrigated) RF ablation catheter, segmental PVI using a 4-mm irrigated-tip RF catheter, and circumferential PVI with a cryoballoon. Compared to conventional RF catheters, the observed microembolic signals in middle cerebral arteries were significant lower with cryoballoon and irrigated RF catheters (3,908 ± 2816 vs 935 ± 463 and 1,404 ± 981 total microembolic signals, respectively).

Pericardial effusion or cardiac tamponade occurred in 1.46% of cases (0.57% rate of tamponade alone) and was most commonly diagnosed within 24 hours of the procedure. In a small prospective comparison of systematic echocardiography within 24 hours of the index ablation procedure, Chierchia et al[26] found no significant difference in the incidence of pericardial effusion between cryoballoon and RF ablation. Independent predictors of pericardial effusion included longer procedural time, concomitant coronary artery disease, and hypertension. The ablation technique was not associated with subsequent pericardial effusion.

The incidence of vascular access complications was 1.79%, with 5 (0.41%) arteriovenous fistulae, 4 (0.32%) femoral artery pseudoaneurysms, and 5 (0.41%) cases of bleeding requiring transfusion. One subclavian vein rupture and one pulmonary artery rupture were observed.

Persistent AF

Eligible data regarding 1-year freedom from recurrent AF in patients undergoing PV ablation for persistent AF were available in three studies including 84 patients.[15,29,35] Two studies reported a strategy of PVI with combination cryoballoon and spot cryocatheter without additional left atrial ablation (Figure 3). Using this approach, the pooled 1-year freedom from recurrent AF off AAD after a 3-month blanking period was 45.16% (95% CI 32.48%–58.32%).[15,29] Mansour et al[35] reported a strategy of combined cryoballoon PVI with additional electrogram-guided RF ablation (19/22 participants) and linear lines (roof, mitral isthmus, septum [10/22 participants]). At 6 months, the freedom from AF without AAD was 86.4%.

Heterogeneity

Tests of heterogeneity were performed for each summary estimate. Despite differences in design and execution, no significant heterogeneity was observed for acute (per patient) procedural outcomes (Figure 2A) and for 1-year efficacy outcomes (freedom from paroxysmal or persistent AF; Figure 3). Significant heterogeneity was observed only when acute procedural efficacy was analyzed on a per vein basis. The heterogeneity was not accounted for by study size, date of publication, or whether patients with persistent AF were included. Heterogeneity was largely attributable to whether or not focal ablation was allowed in addition to cryoballoon application, likely relating to markedly different thresholds for the use of cryofocal ablation.

Discussion

Electrical isolation of PVs is the cornerstone of catheter ablation for AF. Success rates and limitations of RF ablation have been well characterized.[39] The combination of a theoretically safer cryothermal energy source with the ease of use associated with balloon-based catheter ablation systems have positioned the expandable cryoablation balloon catheter technique at the forefront of promising new technologies.

Clinical implications

Efficacy

Balloon-based technologies offer the advantage of "single-shot" isolation of the PV, thus decreasing dependence on operator dexterity. Compared to other balloon-based ablation technologies (high-intensity focused ultrasound and endoscopic laser), the cryoballoon is less direction dependent, as the refrigerant jet inside the balloon is directed to produce the lowest ablation temperatures in a large circular zone on the anterior third of the balloon. As such, cryoballoon ablation may be expected to isolate the muscular PV sleeves as well as the PV antrum.[40,41] In this systematic review, we observed an acute procedural success rate greater than 98%. Not unexpectedly, the most challenging PV to isolate was the RIPV, although special techniques ("hockey-stick", "pull-down," or "large loop") and focal cryoablation were helpful in achieving PVI in the majority of cases.[28]

For patients with paroxysmal AF, the 1-year freedom from recurrent AF off AAD (73% with a 3-month blacking period and 60% with no blanking period) compares favorably with results reported in the global RF literature. In the systematic review and meta-analysis by Calkins et al,[2] the single procedural success rate of RF catheter ablation off AAD therapy after mean follow-up of 14 months was 57% (50%–64%) when a 2- to 14-week blanking period was included in a sizeable proportion of patients. In a prospective long-term cohort study of RF ablation, the actuarial arrhythmia-free survival rate after a single procedure was 39.8% ± 5.1% with no blanking period.[2,39]

Cryoballoon-based PVI alone for persistent AF resulted in a 1-year freedom from AF of 45%. Unlike cases of paroxysmal AF, there is evidence that catheter ablation of persistent and permanent AF may require more extensive ablation beyond PVI. Staged ablation strategies involving additional linear ablation as well as complex fractionated electrogram–based ablation have yielded superior results.[42] Indeed, one study examining a more extensive cryoballoon-based approach with electrogram-guided PVI and linear RF ablation reported 83% freedom from recurrent AF at 6 months.[35]

Safety

Major complications were reported in 5% to 6% of patients undergoing RF ablation for AF.[1–5] This includes an approximate 0.3% incidence of stroke or transient ischemic attack, 0.8% to 1.3% incidence of cardiac tamponade, 0.29% incidence of PVS requiring intervention (1.6% by systematic screening), and 1.2% to 1.5% incidence of groin complications (Figure 4).[3–5] In this systematic review, complication rates with cryoballoon were globally similar despite the inclusion of patients early in the operators' learning curves. As a result, there is the potential for complications to decrease with increased operator experience.

Importantly, the most frequent complication was transient PNP, observed in 6.38% of cases despite preventive measures consisting of abdominal palpation during continuous high-output diaphragmatic pacing in the superior vena cava during ablation of right-sided PVs. Because the phrenic nerve courses closely to the RSPV orifice, a more distal ablation site within the RSPV antrum would be expected to minimize the distance between the balloon and the phrenic nerve.[11] Concordantly, cryoablation deep within the PV creates a local environment conducive to enhanced "cold" transfer to deeper tissue due to less convective heating of the balloon by atrial blood flow.[11] As such, the deployment of undersized balloons well inside the PVs appears to result in increased risk of PNP. Unfortunately, the use of larger balloons has not entirely eliminated this complication because the physical effect of oversizing the balloon within the RSPV still may cause impingement of the phrenic nerve with resultant palsy.[11] Novel techniques for preventing PNP are being explored.[43]

The incidence of PVS with cryoballoon ablation is somewhat controversial. Prior to the STOP-AF trial, PVS was thought to be nonexistent.[7] Multiple studies with systematic screening reported no PVS.[15,17,21,23,27,28,33,34] In contrast, the rate of PVS in STOP-AF was 3.07%.[32] This most likely reflects differing outcome definitions. In the AF literature, PVS is most commonly defined on the basis of diameter measurements (typically as a reduction in PV diameter >70%). STOP-AF defined PVS as a >75% reduction in cross-sectional area from baseline, which corresponds to a 50% reduction in PV diameter. As such, this more "cautious" definition may represent an overestimate of the rate of PVS and limits direct comparison to other studies. Reassuringly, the rate of symptomatic PVS or PVS requiring intervention was low (0.17%).

Study limitations

The present analysis shares the same limitations inherent to all systematic reviews and meta-analyses. Variations in study methodologies, patient characteristics, procedural characteristics, follow-up duration, and the presence and composition of comparator groups limit direct comparisons of the various trials. Nevertheless, we sought to identify potential sources of bias and confounding within and between studies and limited our summary analysis to studies that were homogeneous in design (both from a clinical and a statistical standpoint). Likewise, risk estimates from observational studies have inherent biases and are subject to known and unknown confounders. Because most of the studies were single-center case series, it is possible that efficacy outcomes and adverse events were reported with less consistency than in typical randomized controlled trials. Moreover, the majority of patients were young, male, and had relatively normal left ventricular function and left atrial size. In addition, although no quality-of-life analysis was undertaken, it should be recognized that "success" does not necessarily equate with clinical improvement. Although the absence of recurrent AF is an objective and meaningful definition of procedural success, a diminution in episode frequency and severity may be considered a clinical success in some cases.

Conclusion

This systematic review reveals that a single cryoballoon ablation procedure for paroxysmal AF results in high acute and medium-term efficacy rates, with lower success rates when used as stand-alone therapy for persistent AF. The rate of complications is relatively low and includes a 6.38% incidence of PNP, most of which is transient. Further studies, including direct comparison to conventional RF ablation, are ongoing and will provide important insight into long-term efficacy and safety.

Appendix

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.hrthm.2011.03.050.

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