One-Year Clinical Outcome of Pulmonary Vein Isolation Using the Second-Generation Cryoballoon: A Meta-Analysis

XIN HE, M.D.,* YILI CHEN, Ph.D.,* YUE ZHOU, M.S.,* YIYI HUANG, M.S.,† and JIANGUI HE, Ph.D.*

From the *Department of Cardiology, The First Affiliated Hospital of Sun Yat-sen University, Yuexiu District, Guangzhou, Guangdong, China; and †Emergency Department, The First Affiliated Hospital of Sun Yat-sen University, Yuexiu District, Guangzhou, Guangdong, China

Background: The second-generation cryoballoon (CB-2G) is a promising technique to treat atrial fibrillation (AF). It is necessary to summarize and analyze the available data on 1-year clinical outcome of pulmonary vein isolation (PVI) with CB-2G.

Methods: PubMed and the Web of Science were searched in May 2015. Studies that reported the 1-year clinical success rates after PVI using CB-2G were included. The 1-year clinical success rates were pooled using the random-effect model. Complication rates and acute success rates were also analyzed. Subgroup analyses were conducted based on AF type and ablation strategy.

Results: Fifteen studies involving 2,363 AF patients met the inclusion criteria. The overall clinical success rate of PVI using CB-2G was 81%. A total of 82% of paroxysmal AF patients and 70% of persistent AF patients were in stable sinus rhythm 1 year after the procedure. The clinical success rates of the “no-bonus” strategy were 81% in all patients, 82% in paroxysmal AF patients, and 73% in persistent AF patients. The corresponding success rates of the “bonus” strategy were 81%, 83%, and 63%. Acute success rate was high. The overall rates of phrenic nerve palsy (PNP) and other procedure-related complications were 5.8% and 1.5%, respectively. Compared with “bonus” strategy, there was a trend of fewer PNPs in “no-bonus” strategy (4.6% vs 6.5%).

Conclusions: CB-2G is highly effective in the treatment of both paroxysmal AF and persistent AF. The “no-bonus” strategy is as effective as the “bonus” strategy in terms of 1-year clinical outcome. (PACE 2016; 39:182–189)

second-generation cryoballoon, pulmonary vein isolation, atrial fibrillation, meta-analysis

Introduction

Atrial fibrillation (AF) is one of the most common cardiac arrhythmias and an independent risk factor for stroke and death.1,2 Cryoballoon has been increasingly adopted to achieve pulmonary vein isolation (PVI), which is the cornerstone of AF ablation.3 The initial first-generation cryoballoon is an effective method to achieve acute PVI, but the incidence of pulmonary vein reconnection is high. This may be attributed to the inhomogeneous surface cooling of the balloon.4 The recently released second-generation cryoballoon (CB-2G) has been redesigned with technical modifications. The number of injection ports has been increased from four to eight, which are also positioned more distally. The broader, more uniform freezing zone of CB-2G has been tested by in vitro study.5 The 1-year clinical outcomes of several studies have been published recently, but the numbers of patients are limited.6,7 Therefore, it is necessary to summarize and analyze the available data.

Method

A predefined protocol was developed before conduct of this study. This study was carried out according to PRISMA guideline.8

Search Strategy

We performed a literature search of PubMed and the Web of Science in May 2015, using the terms “second-generation cryoballoon,” “second generation cryoballoon,” and “Arctic Front Advance.” No restrictions to regions or languages were applied. We also manually searched the reference lists of all publication and review articles. When several studies involved the same
population, the most recent or complete one was selected.

**Inclusion Criteria**

To be included, studies had to fulfill the following criteria: (1) the study involved patients with AF, (2) patients were treated with PVI using CB-2G, (3) 1-year clinical success rates were reported, (4) follow-up periods were longer than 12 months, and (5) studies were published as full-text articles. Studies were excluded if: (1) they were case reports or published as conference abstracts, (2) they involved fewer than 20 patients, (3) they did not report clinical success rates, and (4) the maximum follow-up period was shorter than 12 months.

**Data Extraction and Outcomes**

Three reviewers (Xin He, Yili Chen, and Yue Zhou) independently extracted data from included studies and a fourth reviewer (Jiangui He) was responsible for confirmation and adjudication of disagreement. The primary outcome was 1-year clinical success rate. A clinical success was defined as maintenance of stable sinus rhythm during the 1-year follow-up.

The secondary outcomes were phrenic nerve palsy (PNP) rate, other complication rate, and acute success rate. An acute success was defined
Table I.
Characteristics of Included Studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Location</th>
<th>Number of Patients</th>
<th>Follow-Up, Months</th>
<th>AF Type</th>
<th>Ablation Strategy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aytemir et al.</td>
<td>2015</td>
<td>Turkey</td>
<td>109</td>
<td>10 (8–13)†</td>
<td>Mixed</td>
<td>“Bonus”</td>
</tr>
<tr>
<td>Kumar et al.</td>
<td>2015</td>
<td>Netherlands</td>
<td>90</td>
<td>12.4†</td>
<td>Mixed</td>
<td>“Bonus”</td>
</tr>
<tr>
<td>Metzner et al.</td>
<td>2014</td>
<td>Germany</td>
<td>49</td>
<td>14.7 ± 1.3†</td>
<td>Mixed</td>
<td>“Bonus”</td>
</tr>
<tr>
<td>Cicone et al.</td>
<td>2015</td>
<td>Belgium</td>
<td>143</td>
<td>12.1 ± 4.4†</td>
<td>Mixed</td>
<td>“No-bonus”</td>
</tr>
<tr>
<td>Wissner et al.</td>
<td>2015</td>
<td>Germany</td>
<td>44</td>
<td>13.1 ± 1.9†</td>
<td>Mixed</td>
<td>“No-bonus”</td>
</tr>
<tr>
<td>Aryana et al.</td>
<td>2015</td>
<td>United States</td>
<td>773</td>
<td>12‡</td>
<td>Mixed</td>
<td>Unknown</td>
</tr>
<tr>
<td>Liu et al.</td>
<td>2015</td>
<td>Germany</td>
<td>68</td>
<td>12 ± 4†</td>
<td>Mixed</td>
<td>Unknown</td>
</tr>
<tr>
<td>Tebbenjohanns et al.</td>
<td>2015</td>
<td>Germany</td>
<td>192</td>
<td>15.3 ± 3.6†</td>
<td>Mixed</td>
<td>Mixed</td>
</tr>
<tr>
<td>Furnkranz et al.</td>
<td>2014</td>
<td>Germany</td>
<td>55</td>
<td>13.9 ± 2.5†</td>
<td>Paroxysmal</td>
<td>“Bonus”</td>
</tr>
<tr>
<td>Greiss et al.</td>
<td>2015</td>
<td>Germany</td>
<td>188</td>
<td>15†</td>
<td>Paroxysmal</td>
<td>“Bonus”</td>
</tr>
<tr>
<td>Jourda et al.</td>
<td>2015</td>
<td>France</td>
<td>75</td>
<td>12†</td>
<td>Paroxysmal</td>
<td>“Bonus”</td>
</tr>
<tr>
<td>Squara et al.</td>
<td>2015</td>
<td>France</td>
<td>178</td>
<td>12 (10–18)†</td>
<td>Paroxysmal</td>
<td>“Bonus”</td>
</tr>
<tr>
<td>Chierchia et al.</td>
<td>2015</td>
<td>Belgium</td>
<td>287</td>
<td>11.5 ± 3.9†</td>
<td>Paroxysmal</td>
<td>Mixed</td>
</tr>
<tr>
<td>Cicone et al.</td>
<td>2015</td>
<td>Belgium</td>
<td>63</td>
<td>12‡</td>
<td>Persistent</td>
<td>“Bonus”</td>
</tr>
<tr>
<td>Lemes et al.</td>
<td>2015</td>
<td>Germany</td>
<td>49</td>
<td>13.9 ± 5.9†</td>
<td>Persistent</td>
<td>Mixed</td>
</tr>
</tbody>
</table>

†Mean or median.
‡Maximum; Mixed, both paroxysmal and persistent AF were included or both the “no-bonus” strategy and the “bonus” strategy were adopted; Unknown, ablation strategies were not reported.

AF = atrial fibrillation.

as achievement of PVI with only CB-2G. Any additional radiofrequency or freezing-tip ablation was regarded as a failure.

Statistical Analysis

All data analyses were performed using STATA 12 (StataCorp LP, College Station, TX, USA). The included studies were synthesized using random-effect model. Subgroup analyses were carried out based on AF type and ablation strategy. Clinical success rates of paroxysmal AF and persistent AF were analyzed separately. Studies were considered using a “no-bonus” strategy if no additional bonus freeze was applied following successful PVI. If a study applied one additional bonus freeze after successful PVI, it was considered using a “bonus” strategy. Studies systematically applied two applications to each pulmonary vein were also considered using a “bonus” strategy, because PVI is actually achieved during the first application in most patients.

Statistical heterogeneity among studies was explored by I² test. An I² value > 50% was defined as significant heterogeneity. Potential publication bias was tested using funnel plot.

Results

Study Characteristics

Fifteen studies were identified (Fig. 1). The characteristics of the included studies were summarized in Table I. All the involving patients completed a 1-year follow-up. There were five studies involving only paroxysmal AF patients, two studies involving only persistent AF patients, and eight studies involving both types of AF. As for ablation strategy, eight studies adopted the “bonus” strategy, two studies adopted the “no-bonus” strategy, three studies adopted both strategies, and the remaining two studies did not provide sufficient information on their ablation strategies. Although several studies were carried out by the same authors’ groups, we ruled out the possibility of patient groups duplication based on study methods and patient characteristics.

Primary Outcome

Original Analysis

Pooling data from 15 studies involving 2,413 patients demonstrated that the 1-year clinical success rate of PVI using CB-2G was 81% (95% confidence interval [CI]: 78–84%). Heterogeneity among studies was significant (I² = 74.2%; Fig. 2).

Subgroup Analysis

Nine studies reported the clinical success rates of patients with paroxysmal AF. PVI with CB-2G resulted in a 1-year clinical success rate of 82% (95% CI: 79–86%) in paroxysmal AF. There was significant heterogeneity...
among studies ($I^2 = 64.8\%$; Fig. 3). Pooling data from five studies\textsuperscript{7,14–16,22} that reported outcomes of persistent AF demonstrated a 1-year clinical success rate of 70\% (95\% CI: 66–75\%). No significant heterogeneity was noted ($I^2 = 0$; Fig. 4).

Five studies\textsuperscript{10,15,18,21,22} reported the 1-year clinical success rates of the “no-bonus” strategy. The pooled estimates showed that “no-bonus” strategy achieved clinical success in 81\% (95\% CI: 78–84\%) of all patients, 82\% (95\% CI: 79–86\%) of paroxysmal AF patients, and 73\% (63–83\%) of persistent AF patients. There were no significant heterogeneities noted in these analyses ($I^2 = 0$). Eleven studies\textsuperscript{6,7,10–13,15,17–19,21} reported the 1-year outcome of the “bonus” strategy. Pooling data from these studies showed that during the 1-year follow-up, the “bonus” strategy achieved clinical success rates of 81\% (95\% CI: 75–86\%) in all patients, 83\% (95\% CI: 77–89\%) in paroxysmal AF patients, and 63\% (95\% CI: 53–73\%) in persistent AF patients. Significant heterogeneity was noted in analyses of all patients and paroxysmal AF patients, but not in analysis of persistent AF patients ($I^2 = 78.2\%, 72.9\%, \text{and} 0\%$, respectively; Figs. 2–4).

**Secondary Outcomes**

**Original Analysis**

All the included studies reported rates of procedure-related complication. Pooled rates of PNP and other complication were 5.8\% (95\% CI: 4.1–7.5\%) and 1.5\% (95\% CI: 0.8–2.1\%), respectively (Supporting Information Figs. S1 and S2). Meta-analysis of acute success rates was not performed because acute success rates were 100\% in most of the included studies. Four studies\textsuperscript{16,17,19,20} reported acute success in 98\%, 99.5\%, 98.3\%, and 96.6\% of pulmonary veins, respectively.
Subgroup Analysis

Five studies\textsuperscript{10,15,18,21,22} reported the procedure-related complications of “no-bonus” strategy and 11 studies\textsuperscript{6,7,10–15,17,19,21} reported the complications of “bonus” strategy. PNP rates were 4.6% (95% CI: 1.2–8.0%) in “no-bonus” strategy and 6.5% (95% CI: 4.1–8.9%) in “bonus” strategy. Rates of other complications were 1.6% and 1.7% in “no-bonus” strategy and “bonus” strategy, respectively (Supporting Information Figs. S1 and S2).

Publication Bias

Figure 5 shows a funnel plot of 1-year clinical success rates of all patients. Studies were not distributed within the 95% CI area. This suggested significant publication bias.

Discussion

This meta-analysis summarized and analyzed the available data on 1-year clinical outcomes of PVI using CB-2G. The overall success rate was 81%, and success rates for paroxysmal AF and persistent AF were 82% and 70%, respectively. With similar 1-year clinical success rate to “bonus” strategy, “no-bonus” strategy might reduce PNP.

With any cardiac ablation procedure, freedom from arrhythmias is always the most important measurement of its efficacy. This study demonstrated a 1-year clinical success rate of 81% after PVI using CB-2G, which is higher than the success rates of any other ablation technique. The most widely used technique is “point-by-point” radiofrequency ablation. A meta-analysis concluded that at 1-year follow-up, the success rates of a single radiofrequency procedure are 66.6% for paroxysmal AF patients and 51.9% for nonparoxysmal AF patients.\textsuperscript{23} With the novel contact force-sensing technique, the success rate of radiofrequency ablation greatly increases, but CB-2G is safer and less time-consuming.\textsuperscript{13,24} Since the introduction of the first-generation cryoballoon, the ablation procedure has been greatly simplified. However, there has not been much improvement in terms of 1-year outcomes, both in paroxysmal...
Based on current data, CB-2G seems to be an ideal technique for treatment of AF. Given the high PVI rate during the first application with CB-2G, a bonus freeze may not be necessary for the procedure. According to our study, the “no-bonus” strategy was as effective as the “bonus” strategy in terms of 1-year outcomes. Furthermore, although a freeze cycle of 240 seconds is recommended, Ciconte et al.\textsuperscript{18} found that a single 3-minute freeze is sufficient to achieve comparable success rate. Further trial is needed to examine the efficacy of even shorter freeze duration. Interestingly, for persistent AF, the 1-year clinical success rate of the “no-bonus” strategy is higher than the success rate in persistent AF patients.\textsuperscript{25,26}
rate of the “bonus” strategy (73% vs 63%). This may represent stricter inclusion criteria in the “no-bonus” strategy studies. As the efficacy of the “no-bonus” strategy was uncertain, researchers might tend to exclude the severe persistent AF patients from the studies. In addition, there were only 54 persistent AF patients included in the analyses of each strategy. The difference between two strategies might be caused by random bias. A reduction in cryoenergy application might not only contribute to a shorter procedural time and fluoroscopy time, but also reduce risk of collateral tissue injury. In our study, PNP rate was lower in “no-bonus” strategy compared with “bonus” strategy (4.6% vs 6.5%). However, because most of the included studies did not aim to compare the two strategies, we could not test the statistical significance of the differences. Future high-volume comparative trials are needed to assess the efficacy and safety of “no-bonus” strategy compared with “bonus” strategy.

**Limitations**

This study had several limitations, which should not be ignored. First, the heterogeneity was significant. Subgroup analyses based on AF type and ablation strategy were performed, but the included studies were also characterized by different freeze durations. This might be another important source of heterogeneity, but insufficient information prevented us from conducting more detailed subgroup analysis. Differences in patients’ baseline characteristics and operators’ expertise might also contribute to the heterogeneity. Second, the funnel plot demonstrated significant publication bias. Studies reporting improved outcomes were favored in publication, which may lead to overestimate of the clinical success rate. Third, the comparison between “no-bonus” and “bonus” strategies was based on the separated pooled estimations. There could be high risk of bias, because patients involved in the two strategies were not matched. Fourth, the number of persistent AF patients was limited. This might affect the reliability of our estimated clinical success rates. Finally, this study only focused on the 1-year clinical outcome. The long-term efficacy of CB-2G remained to be tested.

**Conclusion**

PVI with CB-2G is highly effective to treat both paroxysmal and persistent AF. The “no-bonus” strategy shows comparable 1-year outcomes to the “bonus” strategy.

**References**


Supporting Information

Additional Supporting Information may be found in the online version of this article at the publisher’s website:

Figure S1. Forest plot and meta-analysis of PNP rates.
Figure S2. Forest plot and meta-analysis of other complication rates.
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