Comparison of ablation efficacy with cryoballoon or radiofrequency for the treatment of atrial fibrillation: a meta-analysis of randomized controlled trials

Yong Zheng, Hong-Wu Chen, Dong-Yu Jia, Qiang Gu, Huai-Ming Peng

1Department of Cardiology, Affiliated Hospital of Hangzhou Normal University, Hangzhou, Zhejiang, China; 2Cardiology Division, First Affiliated Hospital of Nanjing Medical University, Nanjing, China; 3Samuel Oschin Comprehensive Cancer Institute, Cedars-Sinai Medical Center, Los Angeles, CA, USA; 4Department of Anesthesiology, The First Affiliated Hospital, Zhejiang University School of Medicine, Hangzhou, Zhejiang, China; 5Department of Respiratory, Tinhu People’s Hospital, Yancheng, China

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Abstract: Radiofrequency catheter ablation (RFCA) of pulmonary vein isolation (PVI) has been the standard strategy for treatment of atrial fibrillation (AF). Cryoballoon ablation (CBA) is also frequently adopted. Here, we conducted a meta-analysis of randomized controlled trials (RCTs) to compare the efficacy of CBA and RFCA in the treatment of AF. PubMed, EMBASE and Cochrane Library were searched up to May 2016, using Boolean operators as follows: (atrial fibrillation OR pulmonary vein isolation) AND (cryoballoon OR radiofrequency ablation). All RCTs directly comparing the efficacy between CBA and RFCA were retrieved. Eight out of 367 studies, involving 1849 patients, were included in this study. The fluoroscopic time was significantly lower in the RFCA group compared with the CBA group (mean difference 2.94; 95% confidence interval [95% CI]: 0.34 to 5.54, P=0.03). However, no significant difference in total procedure time between these two groups by mean difference -11.2 (95% CI: -34.53 to 12.13, P=0.35); Total complications were not significantly different between the two groups (relative risk [RR]: 1.21; 95% CI: 0.71 to 2.04, P=0.49); however, almost all phrenic nerve palsies (PNP) occurred in the CBA group. The CBA group had similar proportion of patients free from AF as the RFCA group at the 12-month follow-up (RR: 1.02; 95% CI: 0.90 to 1.16, P=0.74). Our analysis indicates that, compared with RFCA, CBA is not inferior in total procedure time and complications except for the longer fluoroscopic time. There were also similar proportions of patients free from AF in both groups at the one-year follow-up.

Keywords: Atrial fibrillation, cryoballoon, radiofrequency ablation, pulmonary vein isolation

Introduction

Patients with atrial fibrillation (AF) are common in the clinical electrophysiology department. Pulmonary vein isolation (PVI) remains the cornerstone in the treatment of patients with drug-resistant AF [1, 2]. PVI by radiofrequency catheter ablation (RFCA) has been established as an effective treatment of AF, but still has some problems, such as a long learning curve to master the technique, point by point ablation and complications like pericardial tamponade [3, 4].

Recently, cryoballoon ablation (CBA) has become an alternative option in PVI [5-7]. Accompanied with the prevalent applications of CBA, a controversy between the use of CBA or RFCA has arisen. Some recent studies argued that CBA is more stable, and has lower risk of pain [7-10] with similar rates of acute PVI and freedom from AF [11, 12]. On the other hand, some recent randomized controlled trials (RCTs) demonstrated that RFCA had advantages in fluoroscopic time compared with CBA [13-15]. A meta-analysis performed by Xu et al. [16] showed that, compared with RFCA, CBA had a shorter total procedure time and fluoroscopic time. However, only two of the 14 studies included in their meta-analysis were RCTs. Recently, some newly reported RCTs compared the efficacy of CBA with RFCA [15, 17], and the
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### Table 1. Methodological quality of the included studies based on the 12-items scoring system

<table>
<thead>
<tr>
<th>Study</th>
<th>Randomized adequately</th>
<th>Allocation concealed</th>
<th>Patient blinded</th>
<th>Care provider blinded</th>
<th>Outcome assessor blinded</th>
<th>Acceptable drop-out rate</th>
<th>ITT analysis</th>
<th>Avoided selective reporting</th>
<th>Similar baseline</th>
<th>Similar or avoided cofactor</th>
<th>Patient compliance</th>
<th>Similar timing</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Herrera et al. 2012 [24]</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Unsure</td>
<td>Unsure</td>
<td>Yes</td>
<td>No</td>
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<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Moderate</td>
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<tr>
<td>Pokushalov et al. 2013 [13]</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
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<td>Unsure</td>
<td>Yes</td>
<td>No</td>
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<td>Yes</td>
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<td>Schimidt et al. 2013 [25]</td>
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<td>No</td>
<td>No</td>
<td>Unsure</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Moderate</td>
</tr>
<tr>
<td>Perez et al. 2014 [23]</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Unsure</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>High</td>
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<tr>
<td>Hunter et al. 2015 [14]</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>Unsure</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Moderate</td>
</tr>
<tr>
<td>Luik et al. 2015 [16]</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Unsure</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>High</td>
</tr>
<tr>
<td>Kuck et al. 2016 [15]</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Unsure</td>
<td>Unsure</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>High</td>
</tr>
<tr>
<td>Straube et al. 2016 [26]</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>Unsure</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Moderate</td>
</tr>
</tbody>
</table>

*a Only if the method of sequence made was explicitly introduced could get a “Yes”; sequence generated by “Dates of Admission” or “Patients Number” receive a “No”. b Drop-out rate < 20% could get a “Yes”, otherwise “No”. c ITT = intention-to-treat, only if all randomised participants were analysed in the group they were allocated to could receive a “Yes”. d “Yes” items more than 7 means “High”; more than 4 but no more than 7 means “Moderate”; no more than 4 means “Low”.  

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main results were totally different from previous studies [18-20].

According to new evidence, we conducted a meta-analysis with all the RCTs available to directly compare the efficacy and safety between these two strategies.

Materials and methods

Literature search

Electronic databases (PubMed, EMBASE, Cochrane Central Register of Controlled Trials) were searched without limit by two independent investigators (YZ, HC). Results were last updated on May 31, 2016. Boolean operators were used as follows: (atrial fibrillation OR pulmonary vein isolation) AND (cryoballoon ablation OR radiofrequency ablation) restricting the publication language to English. The reference lists of the manuscripts were also hand-searched to detect other reports not identified by our original search. This study strictly followed the following recommendations of the PRISMA 2009 checklist [21] and the Cochrane Handbook for Systematic Reviews of Interventions 5.0.2. Two investigators (YZ, HC) independently reviewed the titles and abstracts and strictly followed the inclusion criteria: [1] The study must be a direct comparison of efficacy and safety between the CBA and RFCA for PV isolation; [2] The study must compare either total procedure time, fluoroscopic time, the percentage of patients free from AF without anti-arrhythmia drugs (AAD) or major complications between CBA and RFCA; [3] The study must be a prospective randomized controlled trial. Exclusion criteria included studies where: [1] Case reports, reviews, observational studies, or retrospective studies were reported; [2] The outcome data were not available; [3] The sample size was less than 20. The primary clinical outcome was the proportion of patients free from AF. Freedom from AF was defined as no symptoms of AF and no atrial arrhythmias lasting > 30 s on electrocardiogram or Holter monitoring after a single procedure, without antiarrhythmic drugs, and after a 3-month blanking period. The secondary clinical outcomes were procedure time, fluoroscopy time and complications [22].

Data extraction

The relevance and accuracy of the data were checked by two authors independently. The primary outcome was the proportion of patients free from AF without AAD after 12-month follow-up; secondary outcome consists of total procedure time, fluoroscopic time and the overall complications including groin hematoma, femoral pseudoaneurysm, phrenic nerve palsy, pericardial effusion, PV stenosis and TIA/stroke. We used intention-to-treat (ITT) data whenever possible. If the data we wanted could not be found in the article, we tried to email the authors to get the additional useful information.

Study quality assessment

Two investigators (YZ, HC) independently evaluated the methodological quality of all included studies depending on the 12-item scale from the Cochrane Back Review Group [23]. When there was disagreement, a third investigator (HP) adjudicated the differences. According to
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### Table 2. Baseline characteristics of all included studies

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Location</th>
<th>Ethnicity</th>
<th>AF-d (year)</th>
<th>LAD (mm)</th>
<th>PAF</th>
<th>Manufacturer</th>
<th>CB type</th>
<th>CAD</th>
<th>Hypertension</th>
<th>Gender (males)</th>
<th>Follow-up (months)</th>
<th>Age (year)</th>
<th>Complications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Herrera et al. 2012</td>
<td>Germany</td>
<td>Caucasian</td>
<td>4.2/5.6</td>
<td>41.4/40</td>
<td>21/17</td>
<td>Arctic Front</td>
<td>23 or 28 mm</td>
<td>3/4</td>
<td>13/14</td>
<td>25/23</td>
<td>12</td>
<td>57/56</td>
<td>4/0</td>
</tr>
<tr>
<td>Pokushalov et al. 2013</td>
<td>Russia</td>
<td>Caucasian</td>
<td>3.1/3.7</td>
<td>46/48</td>
<td>40/40</td>
<td>Arctic Front</td>
<td>28 mm</td>
<td>NA/NA</td>
<td>6/7</td>
<td>31/33</td>
<td>812</td>
<td>56/56</td>
<td>0/0</td>
</tr>
<tr>
<td>Schimidt et al. 2013</td>
<td>Germany</td>
<td>Caucasian</td>
<td>NA/NA</td>
<td>40/41</td>
<td>33/33</td>
<td>NA</td>
<td>28 mm</td>
<td>7/6</td>
<td>25/23</td>
<td>NA/NA</td>
<td>NA</td>
<td>66/63</td>
<td>1/1</td>
</tr>
<tr>
<td>Perez et al. 2014</td>
<td>Spain</td>
<td>Caucasian</td>
<td>NA/NA</td>
<td>42/42</td>
<td>25/25</td>
<td>Arctic Front</td>
<td>23 or 28 mm</td>
<td>NA/NA</td>
<td>6/8</td>
<td>17/22</td>
<td>12</td>
<td>58/56</td>
<td>1/1</td>
</tr>
<tr>
<td>Hunter et al. 2015</td>
<td>United Kingdom</td>
<td>Caucasian</td>
<td>4.7/5</td>
<td>42/43</td>
<td>79/79</td>
<td>Arctic Front</td>
<td>23 or 28 mm</td>
<td>NA/NA</td>
<td>27/23</td>
<td>56/47</td>
<td>12</td>
<td>56/61</td>
<td>4/4</td>
</tr>
<tr>
<td>Luik et al. 2015</td>
<td>Germany</td>
<td>Caucasian</td>
<td>NA/NA</td>
<td>156/159</td>
<td>NA/NA</td>
<td>Arctic Front</td>
<td>23 or 28 mm</td>
<td>19/20</td>
<td>96/103</td>
<td>100/91</td>
<td>12</td>
<td>61/60</td>
<td>19/8</td>
</tr>
<tr>
<td>Kuck et al. 2016</td>
<td>Germany, Netherlands, United Kingdom, France, Italy</td>
<td>Caucasian</td>
<td>4.6/4.7</td>
<td>41/41</td>
<td>374/376</td>
<td>Arctic Front</td>
<td>23 or 28 mm</td>
<td>31/32</td>
<td>215/221</td>
<td>221/236</td>
<td>18</td>
<td>60/60</td>
<td>36/49</td>
</tr>
<tr>
<td>Straube et al. 2016</td>
<td>Germany</td>
<td>Caucasian</td>
<td>NA/NA</td>
<td>41/41</td>
<td>193/180</td>
<td>NA</td>
<td>23 or 28 mm</td>
<td>19/29</td>
<td>113/133</td>
<td>113/106</td>
<td>12</td>
<td>61/65</td>
<td>20/19</td>
</tr>
</tbody>
</table>

**Abbreviations:** AF-d, atrial fibrillation duration; LAD, left atrium diameter; PAF, paroxysmal atrial fibrillation; CAD, coronary artery disease; NA, not available. Digital data were expressed as counting or percentages between cryoballoon/radiofrequency techniques unless otherwise indicated.
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Figure 2. Forest plots of proportion free from AF for (A) cryoballoon ablation versus radiofrequency ablation, (B) cryoballoon ablation versus radiofrequency ablation after excluded the trials with either persistent AF or re-isolation.

the item standard (Table 1), a total of four high-quality studies [13, 15, 17, 24] explicitly introduced the randomization and the allocation concealment; the other four studies [14, 25-27] were evaluated as moderate quality.

Statistical analysis

All data analysis were conducted using the Revman software package (Review manager, Version 5.3, The Cochrane Collaboration, Oxford, UK) and the STATA software 12.0 (StataCorp, College Station, texas, USA). Continuous data are described as weight mean differences (WMD), whereas dichotomous variables are shown by relative risk (RR) with 95% confidence interval (CI). The $X^2$ and $P$ test were used to measure the heterogeneity. $P$ values of 25%, 50% and 75% were graded as low, medium and high statistical heterogeneity, respectively. The random-effect models were used for pooled analysis. Risk of bias graph was applied to assess the bias of all included studies and the evidence quality was evaluated by the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach [28].

Results

Literature review

Based on our literature search strategy, 367 relevant citations were initially identified, among which 70 were excluded by title and 231 were ruled out based on the review of the abstract. Among the remaining 66 studies, 58 were excluded after full-text evaluation. Ultimately, only 8 prospective RCTs [13-15, 17, 24-27] were included in this study (Figure 1).

Baseline characteristics of included study

The included publications range from 2012 to 2016. There were a total of 1849 patients in this study, 929 were allocated to the CBA
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Figure 3. Forest plots of changes of total procedure time for (A) cryoballoon ablation versus radiofrequency ablation, (B) cryoballoon ablation versus radiofrequency ablation after excluded the trials with either persistent AF or re-isolation.

Seven of the eight trials in this study made a 12-month follow-up except the one study [26] which the follow-up time was less than one year. The total proportion of patients in 7 trials free from AF was 65.1% (810 patients) and 62.7% (806 patients) in the CBA group and RFCA group, respectively. There was no significant difference in the proportion free from AF between two groups (RR: 1.02; 95% CI: 0.90 to 1.16, P=0.74; Figure 2A) and moderate heterogeneity was observed in these studies (I²=56%, P=0.03). A total of 140 patients with either persistent AF [25] or re-isolation [13] in the two trials were excluded, and the remaining were pooled for subgroup analysis. No significant difference was detected between two groups (66.4% vs. 62.2%; RR: 1.08; 95% CI: 0.95 to 1.23, P=0.22; Figure 2B) and the heterogeneity was still moderate (I²=52%, P=0.08).

Primary clinical outcome

Seven of the eight trials in this study made a 12-month follow-up except the one study [26] which the follow-up time was less than one year. The total proportion of patients in 7 trials free from AF was 65.1% (810 patients) and 62.7% (806 patients) in the CBA group and RFCA group, respectively. There was no significant difference in the proportion free from AF between two groups (RR: 1.02; 95% CI: 0.90 to 1.16, P=0.74; Figure 2A) and moderate heterogeneity was observed in these studies (I²=56%, P=0.03). A total of 140 patients with either persistent AF [25] or re-isolation [13] in the two trials were excluded, and the remaining were pooled for subgroup analysis. No significant difference was detected between two groups (66.4% vs. 62.2%; RR: 1.08; 95% CI: 0.95 to 1.23, P=0.22; Figure 2B) and the heterogeneity was still moderate (I²=52%, P=0.08).

Secondary clinical outcome

After analysis of the pooled data of the studies, we found the procedure time was simi-
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### Figure 4

Forest plots of changes of fluoroscopy time for (A) cryoballoon ablation versus radiofrequency ablation, (B) cryoballoon ablation versus radiofrequency ablation after excluded the trials with either persistent AF or re-isolation.

The fluoroscopic time was significantly shorter in the RFCA group (WMD: 2.94; 95% CI: 0.34 to 5.54, P=0.03, Figure 4A). When 140 patients with either persistent AF or re-isolation in two trials were excluded [13, 25], and the other studies were pooled together, the fluoroscopic time became similar in both groups (WMD: 0.00; 95% CI: -2.12 to 2.12).

### GRADE analysis

GRADE analysis was applied to evaluate the evidence quality in our study. The evidence quality for the procedure time was low due to the controversial and skillful applications of

[Text continues with Table and Figure information]
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the two technical procedures. Furthermore, the high heterogeneity also reduced the quality levels. The low levels for the proportion freedom from AF and complications were due to the inconsistent results of the included studies and the search of English publications only. The fluoroscopic time had moderate level of quality.

Discussion

The main findings of this study were that no significant difference was observed in procedure time between the two strategies; however, there was a longer fluoroscopic time in the CBA procedure. If trials with persistent and paroxysmal AF and trials with re-isolation ablation were excluded, the fluoroscopic time would be similar. In addition, the proportion of patients free from AF at the 12-month follow-up showed no difference between the two groups; almost all the PNP occurred in the CBA group recovered during the follow-up.

PVI via RFCA for the treatment of AF has been successfully applied for more than two decades [1, 29], while CBA as an alternative strategy has been popular during recent years [5, 7, 30-32]. Some previous studies emphasized that CBA had a shorter procedure time compared with RFCA [33-35], however, other trials reached different conclusions [13, 24, 26]. In our study, after pooling all relevant RCTs, no difference of procedure time was found between the two groups, even after excluding the re-isolation and the trials, which included paroxysmal and persistent AF together, the results were still similar. This result is consistent with a recent meta-analysis conducted by Cheng et al. [22], who pooled 3 RCTs and 8 observational stu-
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The present meta-analysis which included all available RCTs still has some limitations: first, the grades of our evidence were either low or moderate, and the conclusions may be overturned by future studies; second, the heterogeneity in the procedure time is considerable despite the fact that it is acceptable in terms of fluoroscopic time, total complications and the proportion of patients free from AF during the follow-up; third, due to the restriction of RCTs, the total sample size of 1849 patients may not be large enough to reach a firm conclusion. Furthermore, publication bias may exist, as we only search and retrieved articles in the English language.

In conclusion, current evidence from all RCTs suggests that there is no difference in efficacy between CBA and RFCA for the treatment of AF, as similar outcome and total number of complications were observed between the two techniques. The fluoroscopic time is shorter in RFCA, and the PNP should be noted in CBA.

In cases when an electrophysiological doctor is hesitant about selecting a technique for a better treatment of AF, our suggestion is that no bias exists between the 2 techniques. However, it is reasonable to choose the technique, in which the specific doctor has more experience performing it.

Disclosure of conflict of interest

None.

Address correspondence to: Yong Zheng, Department of Cardiology, Affiliated Hospital of Hangzhou Normal University, 126 Wenzhou Rd., Hangzhou 310015, Zhejiang, China. Tel: +86 571-88668917; E-mail: xh.8917@163.com

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