Shortening of freezing cycles provides equal outcome to standard ablation procedure using second-generation 28 mm cryoballoon after 15-month follow-up

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Aims
Complications such as thermal oesophageal lesions, phrenic nerve injury, and pulmonary haemorrhage were found in cryoballoon (CB) ablation. Whether shortening of freezing times translates into equal efficacy rate and outcome is unknown. The aim of this study was to test the hypothesis that a single freeze cycle per pulmonary vein (PV) without dormant conduction during adenosine infusion is equally effective to standard CB procedure with a bonus freeze after documented PV isolation (PVI).

Methods and results
In 53 patients with drug-refractory atrial fibrillation (AF) demonstrating PVI after a single 240 s freeze cycle without PV activity during adenosine no additional bonus freeze was applied (study group). In 139 patients, PVI was performed using a bonus freeze (240 s) after documented PVI (control group). Primary endpoint was recurrence of AF. Secondary endpoint was the assessment of quality of life (QoL-score from 1 to 6, being 1 the best and 6 the worst). Follow-up (FU) was performed at 3, 6, and 12 months. Freedom from symptomatic AF during a mean FU of 458 ± 107 days was achieved in 43 (81%) patients in the study group and in 110 (79%) control patients (P = ns). The QoL-score improved equally in both groups (4.8 ± 0.9 to 2.1 ± 0.7, P < 0.05 and 4.7 ± 0.6 to 2.2 ± 0.6, P < 0.05). Procedure duration (79 ± 16 min, P < 0.01) was shorter in the study group. Complication rate was similar in both groups.

Conclusion
Shortening of freezing times to 4 min per PV without residual dormant PV conduction after adenosine provocation is equally effective to the standard CB ablation protocol using a bonus freeze.

Keywords
Catheter ablation • Cryoballoon ablation • Atrial fibrillation • Phrenic nerve palsy • Adenosine

Introduction
Second generation cryoballoon (CB) catheter ablation for pulmonary vein isolation (PVI) shows freedom from atrial fibrillation (AF) in 80% of patients after 1-year follow-up1 2 and is more efficient, with a 90% isolation rate after a single 240 s freeze and shorter procedure duration compared with the first generation CB.4 5 However, a higher incidence of transient phrenic nerve palsy (PNP), up to 24%, and persistent PNP (2–4%) have been reported.1 – 8 Thermal oesophageal lesions have been described in up to 12–19% of patients.9 10 In addition, three cases of lethal atrio-oesophageal fistula,11 12 as well as pulmonary haemorrhage,13 have been reported. Since the purpose of CB ablation is to create transmural lesions, subsequent collateral damage of tissues adjacent to the left atrium must be taken into consideration. Nadir CB return gas temperatures and duration of freezing cycles were considered to be related to thermal injury of the oesophagus and the phrenic nerve. Also, a modified protocol was proposed to avoid damage, including stopping the freezing cycle if nadir temperature exceeded −60°C and shortening of the freezing time to 180 s if real-time PVI is achieved in <80 s. However, there is no study to show that an additional bonus freezing cycle after confirmed PVI is required.
What’s new?

- Cryoballoon ablation with a single 4 min freeze is highly effective with 80% in sinus rhythm after 15 months.
- A single freeze provides a low prevalence of adenosine-induced dormant conduction.
- The procedure duration in a single freeze group is significantly shorter compared with the bonus freeze group.

Therefore, we compared two CB ablation strategies of a prospective registry with and without an additional bonus freeze after a short duration of a third degree AV block to unmask dormant PV conduction. A freezing cycle of 240 s was applied. After successful PVI was achieved, a through the central lumen. Once the best occlusion was obtained, a PV close to the LA were acquired during baseline and coronary sinus recordings of the left superior pulmonary vein (LSPV). The 28 mm CB was introduced into the LA via the sheath and PV recordings of the left superior pulmonary vein (RIPV). Before ablation of the RIPV, the decapolar catheter in the CS was placed into the superior vena cava to continuously pace the right phrenic nerve at 2000 ms cycle length with high output and pulse width. Freezing was immediately discontinued in case of loss of diaphragmatic contraction. A maximum of two freezing cycles were applied to each PV. Following CB ablation, both sheaths were removed and transthoracic echocardiography was undertaken to rule out pericardial effusion.

Oral anticoagulation was started the day after the procedure for at least 2 months according to the CHA2DS2-VASc score.

Follow-up

After discharge from the hospital, all patients were scheduled for outpatient clinic visits at 3, 6, 12, and 18 months, including 24-h Holter monitoring and external event recording for 4 weeks in case of suspicious symptoms. After a blanking period of 3 months, all documented episodes of AF > 30 s were considered as a recurrence. Quality of life (QoL) was assessed using a simplified score with a range from ‘1’ (best) to ‘6’ (worst). It measures patient-perceived symptom severity and impairment comparable to the CCS-SAF scale.14

Endpoints

The primary endpoint of this consecutive study was first electrocardiogram-documented recurrence of AF after a blanking period of 3 months. Secondary endpoint was the assessment of QoL.

Statistical analysis

Normally distributed variables were expressed as mean ± SD and compared by using the Student’s t-test. A P-value of <0.05 was considered statistically significant.

Results

Patient characteristics

We enrolled 192 patients, 53 (28%) in the study group and 139 (72%) in the control group. Patients in the study group were older (66 ± 10 vs. 61 ± 11 years, P < 0.05) and had a slightly longer history of AF (6 ± 4 vs. 5 ± 3 years, P < 0.05). No differences were found in gender distribution, CHA2DS2-VASc score, LA diameter, type of AF, and number of prior external cardioversions (Table 1).

Ablation procedure

Mean procedure duration was shorter in the study group (78 ± 12 vs. 93 ± 12 min, P < 0.01). Also, the freezing cycle times were significantly shorter in the study group (1059 ± 174 vs. 1725 ± 334 s,

<table>
<thead>
<tr>
<th>Variable</th>
<th>Study group (n = 53)</th>
<th>Control group (n = 139)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>66 ± 10</td>
<td>61 ± 11</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Female, n (%)</td>
<td>26 (49)</td>
<td>64 (46)</td>
<td>ns</td>
</tr>
<tr>
<td>Years with AF</td>
<td>6 ± 4</td>
<td>5 ± 3</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>CHA2DS2-VASc score</td>
<td>1.8 ± 1.2</td>
<td>1.9 ± 1.3</td>
<td>ns</td>
</tr>
<tr>
<td>LA diameter (mm)</td>
<td>40 ± 6</td>
<td>41 ± 7</td>
<td>ns</td>
</tr>
<tr>
<td>Paroxysmal AF, n (%)</td>
<td>38 (72%)</td>
<td>87 (63%)</td>
<td>ns</td>
</tr>
<tr>
<td>Persistent AF, n (%)</td>
<td>15 (28%)</td>
<td>51 (37%)</td>
<td>ns</td>
</tr>
<tr>
<td>Prior external cardioversion, n</td>
<td>2 ± 4</td>
<td>2 ± 8</td>
<td>ns</td>
</tr>
</tbody>
</table>
No difference was found in mean fluoroscopy time (14 ± 3 vs. 14 ± 4 min, P = ns) and the use of external cardioversion during the procedure (25 vs. 36%, P = ns) (Table 2).

In the study group, a total of 211 PV were identified, including one left common PV (1.9%). During the first CB application, electrical PVI was achieved in 188/211 (89%) PVs, in 47/52 (90%) LSPVs, in 49/52 (94%) LIPVs, in 46/53 (87%) RSPVs, in 46/53 (87%) RIPVs, and in 0/1 left common pulmonary vein. Adenosine was used in 188 PVs and unmasked dormant PV activity in 4/188 (2%) in 4/53 (8%) patients (Figure 1). A bonus freeze CB application was applied to these four PVs.

### Complications

TIA/stroke occurred in 1/53 (1.9%) patient in the study group and in 2/139 (1.4%) patients in the control group. The patient in the study group was an 80-year-old male with persistent AF and a high CHA₂DS₂VASc score of 7 who developed a stroke with subsequent hemiplegia after removal of the sheaths. After exclusion of intracranial hemorrhage, intravenous thrombolysis was applied and full recovery occurred within 12 h. The two patients in the control group had TIA with some minor transient disorders and no persistent deficit.

Pericardial effusion was noted in one patient at the end of the ablation procedure.

### Follow-up

During a mean follow-up of 458 ± 107 days including a 3-month blanking period, 43/53 (81%) patients of the study group and 110/139 (79%) patients of the control group were in stable sinus rhythm without symptomatic and/or observed episode of AF (Figure 2. The QoL-score improved equally and significantly in both groups. Best result = ‘1’; worst result = ‘6’; study group in white bars; control group in black bar.

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Table 2 Ablation procedure

<table>
<thead>
<tr>
<th>Variable</th>
<th>Study group (n = 53)</th>
<th>Control group (n = 139)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Procedure duration (min)</td>
<td>78 ± 12</td>
<td>93 ± 12</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Fluoroscopy (min)</td>
<td>14 ± 3</td>
<td>14 ± 4</td>
<td>ns</td>
</tr>
<tr>
<td>Freeze duration (s)</td>
<td>1059 ± 174</td>
<td>1725 ± 334</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Phrenic nerve palsy, n (%)</td>
<td>3 (6)</td>
<td>7 (5)</td>
<td>ns</td>
</tr>
<tr>
<td>Pericardial effusion</td>
<td>0 (0)</td>
<td>1 (0.7)</td>
<td>ns</td>
</tr>
<tr>
<td>TIA/Stroke</td>
<td>1 (1.9%)</td>
<td>2 (1.4%)</td>
<td>ns</td>
</tr>
<tr>
<td>External cardioversion, n</td>
<td>13 (25)</td>
<td>49 (36)</td>
<td>ns</td>
</tr>
</tbody>
</table>
Discussion

Clinical outcome
The most important finding of this study is that a single 240 s freeze per PV was as equally effective as conventional second generation CB ablation using a bonus freeze after proven PVI. Freedom from symptomatic AF and improvement of QoL were similar in both groups with 80% of the patients in sinus rhythm after a mean follow-up period of 15 months.

Duration of freezing cycles
Our results with a recent study that showed similar efficacy of a single freeze cycle of 3 min with an isolation rate of 91% after the first CB application and an arrhythmia-free survival of 80% after 12 months. Our data support the hypothesis that, with the technical improvements of the second generation CB, the need for a standard bonus CB application after observed PVI is questionable. A bonus freeze failed to demonstrate further benefit and was associated with a higher complication rate, at least using the first generation CB. The second generation CB has been redesigned. The number of injection ports was doubled from four to eight and were positioned more distally, with a consequent more uniform zone of freezing on the balloon surface. The second generation CB provides lower temperature of the refrigerant and faster isolation time in comparison with the first generation CB. Animal studies have shown durable PV isolation even with shorter freeze cycle duration. In this canine model, no difference was found histologically in lesion depth and in circumferential transmural lesions between 2 and 4 min application duration. In fact, stricture of the PV due to neointimal proliferation was observed after 4 min freezes but not with 2 min freeze duration. In addition, at least focal cryolesions have shown a constant lesion size with a 3 min freeze cycle. These observations from animal studies raise the question of optimal freezing cycles in second generation CB ablation. The proposed 4 min freeze time was from animal studies raise the question of optimal freezing cycles in second generation CB ablation. The proposed 4 min freeze time was determined many years ago using the focal cryo technique with a different refrigerant. The data from Ciconte et al. using a single 3 min CB freeze are very promising and show comparable outcome results to our findings with 80% in sinus rhythm after 1-year follow-up. Whilst the optimal ablation duration has to be defined it becomes more and more evident that a bonus freeze after proven isolation of the PV is not necessary with the second generation CB. Since complications, such as thermal oesophageal lesions, with atrio-oesophageal fistula, phrenic nerve injury, PV stenosis, and pulmonary haemorrhage, were found in CB ablation, a reduction of the freeze cycles times with additional shortening of the procedure duration should contribute to a safe procedure in terms of reduction or even avoidance of serious adverse events.

Adenosine effect
Our study showed reconnection after proven PVI with adenosine in only 2% of the PVs and 8% of the patients. Ciconte et al. showed similar results with a trend to higher rates of PV activity after adenosine (4% of the PVs and 12% of the patients tested). In another study with the second generation CB adenosine showed dormant reconnection in four patients (10%), in four PVs (5%). The difference might be explained by a longer waiting period after initial PVI and isoproterenol administration before adenosine testing. These results and ours are in contrast to an earlier study that demonstrated PV activity in 9/132 (8%) PVs in 7/38 (21%) patients. Patients with dormant PV conduction underwent further CB application and showed significantly fewer AF recurrences during long-term follow-up (34 vs. 54% in the control group). However, in that study the first generation CB was used and one can consider that in our study with the second generation CB, the amount of tissue with only mild and reversible damage was smaller. This finding may also contribute to the well accepted observation that the second generation CB is more efficient and provides a better outcome. Reversible injury of the surrounding tissue is a common effect in radiofrequency ablation of the PVs and explains the even higher rates of dormant PV activity up to 35% of the PVs.

Limitations
The present study was not randomized and the single freeze group (study cohort) was compared with a retrospective analysed bonus freeze group (control group). There is, thus, a difference between the baseline characteristics of the two groups (study group patients were older and had a longer history of AF). Also, we did not specifically addressed the potential complication of thermal injury of the oesophagus by routine gastroscopy. However, collateral damage such as oesophageal thermal injury is related to minimal balloon temperature, minimal oesophageal temperature, and duration of freeze cycles. Finally, the QoL-score is not yet validated but, likewise, showed an expected result that correlated to procedure success.

Conclusions
Shortening of freezing times to 240 s without a bonus freeze with adenosine provocation is equally as effective as the standard CB ablation protocol using a bonus freeze in 15-month follow-up. This shortened CB ablation protocol significantly cuts down procedure duration.

Conflict of interest: Tebbenjohanns has received honoraria from Medtronic for lectures.

References

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