Experiences of Cryoballoon Ablation of AF: Post-approval Study in Japan

Akihiko Nogami, MD, PhD
University of Tsukuba
CONFLICT OF INTEREST
Akihiko Nogami

Research Grant: Medtronic
Johnson and Johnson

Honoraria: Daiichi Sankyo
St. Jude Medical
Japan Lifeline
CRYO-Japan PMS Study Design

- Prospective, multi-center, non-randomized, single arm, unblinded condition of approval study
- Designed to assess the safety and effectiveness of the Arctic Front Advance™ Cardiac Cryoablation System
- Patients with drug-refractory, recurrent symptomatic paroxysmal atrial fibrillation
- 33 Sites in Japan planned to enroll 630 patients
  - Patients treated using cryoablation from July 2014 – January 2015
  - Study enrollment was completed

**CRYO-Japan PMS Monitoring / Study Follow-up**

<table>
<thead>
<tr>
<th>Enrollments</th>
<th>Registration</th>
<th>First Ablation to Discharge</th>
<th>6 Month FU</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with 6 Month FU (Patient: 1~330)</td>
<td>●</td>
<td>●</td>
<td>●</td>
</tr>
<tr>
<td>Patients with Acute Stage Assessment (Patient: 331~630)</td>
<td>●</td>
<td>●</td>
<td></td>
</tr>
</tbody>
</table>
616 Enrolled

607 Paroxysmal AF Patients with Procedural Data

9 Patients Excluded for Persistent AF (6) or Missing Data (3)

607 Patients in Acute Efficacy Evaluation

328 Patients with 6 Months Follow-up
The usage ratio of 28 mm balloon is 96.2%.

- 96.2% (N=584)
- 3.8% (N=23)
Cryoablation was performed with a 180–240 s application as the standard application. Pulmonary vein isolation was achieved in 606/607 patients (99.8%).

<table>
<thead>
<tr>
<th>Pulmonary Vein</th>
<th>Application</th>
<th>Lowest Temperature (°C)</th>
<th>PVI using Balloon Only</th>
</tr>
</thead>
<tbody>
<tr>
<td>RSPV (n=606)</td>
<td>2.0 (2.0; 2.0)</td>
<td>-52.0 (-56.5; -46.0)</td>
<td>97.0 %</td>
</tr>
<tr>
<td>RIPV (n=602)</td>
<td>2.0 (2.0; 2.0)</td>
<td>-45.0 (-51.0; -40.5)</td>
<td>90.0 %</td>
</tr>
<tr>
<td>LSPV (n=604)</td>
<td>2.0 (2.0; 2.0)</td>
<td>-49.0 (-53.0; -44.5)</td>
<td>98.0 %</td>
</tr>
<tr>
<td>LIPV (n=597)</td>
<td>2.0 (2.0; 2.0)</td>
<td>-43.5 (-47.0; -40.5)</td>
<td>96.1 %</td>
</tr>
</tbody>
</table>

*n= number of each vein, Median (Q1;Q3) or the proportion*
6 month Efficacy

Kaplan Meier Freedom from AF (N=328 patients at 6 month FU; 189±23 days)
- Treatment failures / recurrence (outside blanking): AF recurrence, Repeat AF ablation procedure

- 1/328 (0.3%) repeat AF ablations in blanking
Two-year outcome after pulmonary vein isolation using the second-generation 28-mm cryoballoon: lessons from the bonus freeze protocol

Andreas Metzner¹ · Christian-Hendrik Heeger¹ · Peter Wohlmuth¹ · Bruno Reißmann¹ · Andreas Rillig¹ · Roland Richard Tilz¹ · Shibu Mathew¹ · Christine Lemes¹ · Sebastian Deiß¹ · Tilman Maurer¹ · Ardan Saguner¹ · Feifan Ouyang¹ · Karl-Heinz Kuck¹ · Erik Wißner¹

Clin Res Cardiol
DOI 10.1007/s00392-015-0890-8

84% @ 6M

Survival Probability

Time to recurrence [months] from first procedure

At Risk

<table>
<thead>
<tr>
<th></th>
<th>58</th>
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<th>52</th>
<th>49</th>
<th>48</th>
<th>46</th>
<th>43</th>
<th>43</th>
<th>38</th>
<th>25</th>
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6 month Efficacy

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Learning curve

- The procedure related time decreases by increasing experience.
- Learning curve in Cryo might be shorter than RF.

Procedure related time based on experience (n=607)

- #1-16 case in each center (n=373)
- #17-32 case in each center (n=174)
- #33-50 case in each center (n=60)
Complications
<table>
<thead>
<tr>
<th></th>
<th>STOP AF¹</th>
<th>STOP AF PAS</th>
<th>Europe Study²</th>
<th>CRYO-JAPAN</th>
</tr>
</thead>
<tbody>
<tr>
<td>(n)</td>
<td>259</td>
<td>351</td>
<td>500</td>
<td>616</td>
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<tr>
<td>Freedom from AF</td>
<td>69.9% @ 12M</td>
<td>86.4% @ 12M</td>
<td>81.2% @ 7.5M</td>
<td>89.0% @ 6M</td>
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<td>Recurrence</td>
<td></td>
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</table>
| Definition         | • Episode of AF lasting longer than 30 sec after blanking  
|                    | • Use of a non-study, antiarrhythmic drug after blanking  
|                    | • Non-protocol intervention for AF (i.e., RF ablation) after blanking | • Episode of AF lasting longer than 30 sec after blanking  
|                    |          |             |               |            |
| Phrenic Nerve      | 11.2 %   | 3.1 %       | 7.2 %         | 1.46 %     |
| Injury             |          |             |               |            |
| PV Stenosis        | 3.1 %    | 0.6 %       | 0.0 %         | 0.2 %      |
| PV Stenosis        | Reduction of >75% in cross-sectional area (approximately a 50% reduction in diameter) | Reduction of >75% in cross-sectional area (approximately a 50% reduction in diameter) | 70% diameter reduction |          |


Safety: PNP resolution timing

- # of PNP persisted at discharge is 9 patients.
- All patients are asymptomatic.
- 7 out of 9 resolved at 6 months after the procedure.
The PNP incidence ratio in CRYO-Japan PMS is less than other studies. The reason why the ratio decreases gradually is due to PN monitoring and other preventive methods.

<table>
<thead>
<tr>
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<th># of patients (Type of balloon)</th>
<th>PNP incidence ratio</th>
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<tr>
<td>CRYO-Japan PMS</td>
<td>N=616 (CB2)</td>
<td>Persistent at discharge: 1.5%</td>
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<td>Persistent at 6months after procedure: 0.2%</td>
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<tr>
<td>FIRE AND ICE</td>
<td>N=374 (CB1, CB2)</td>
<td>Persistent at discharge: 2.7%</td>
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<td>Persistent at 12months after procedure: 0.3%</td>
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<tr>
<td>STOP AF PAS</td>
<td>N=341 (CB2)</td>
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<td>Persistent at 12months after procedure: 0.6%</td>
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CB1 = Arctic Front, CB2 = Arctic Front Advance
CMAP
(compound motor action potential)
Phrenic nerve monitoring with diaphragmatic electromyography during cryoballoon ablation for atrial fibrillation: The first human application

(Heart Rhythm 2011; 8:1068–1071)

Frédéric Franceschi, MD, Marc Dubuc, MD, FHRS, Peter G. Guerra, MD, Paul Khairy, MD, PhD

From the Electrophysiology Service, Montreal Heart Institute, Université de Montréal, Montreal, Canada.

One electrode 5 cm above the xiphoid process and the second along the right costal margin, spaced 16 cm apart.
Recordings of diaphragmatic electromyograms during cryoballoon ablation for atrial fibrillation accurately predict phrenic nerve injury  
(Heart Rhythm 2014;11:369–374)

Mayur Lakhani, MD, Faisal Saiful, MD, Valay Parikh, MD, Nikhil Goyal, MD, Soad Bekheit, MD, PhD, Marcin Kowalski, MD, FHRS

From the Electrophysiology Department, Staten Island University Hospital, Staten Island, New York.
PN Injury by RSPV Cryoballoon Ablation
Before Cryo-ablation
10 sec after Cryo-ablation
15 sec after Cryo-Ablation

RSPV Isolated

70%

20%
25 sec after Cryo-ablation

Loss of Capture

80% 90%
Persisted PNP

Before PVI  1D  2M  9M  17M

04/20/2015  04/22/2015  07/01/2015  01/06/2016  09/14/2016
Zone A: Low risk

Zone B1: Highest risk

Zone B2: Low risk
Automatic Measurement of CMAP
PV Stenosis
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|                   | • Non-protocol intervention for AF (i.e., RF ablation) after blanking  
|                   |          |             |               |            |
|                   | • Episode of AF lasting longer than 30 sec after blanking  
|                   | • Repeat AF ablation procedure after blanking  
|                   | • Symptomatic atrial flutter /tachycardia after blanking  
|                   |          |             |               |            |
|                   | • All documented episodes of atrial tachyarrhythmias lasting  
|                   | • ≥ 30 seconds  
|                   | • Episode of AF after blanking  
|                   | • Episode of AF within blanking and unsolved through 6 month FU  
|                   | • Repeat AF ablation procedure after blanking  
| Phrenic Nerve Injury | 11.2 %   | 3.1 %       | 7.2 %        | 1.46 %     |
| PV Stenosis       | 3.1 %    | 0.6 %       | 0.0 %         | 0.2 %       |
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|                   | Reduction of >75% in cross-sectional area (approximately a 50% reduction in diameter)  
|                   | Reduction of >75% in cross-sectional area (approximately a 50% reduction in diameter)  
|                   | 70% diameter reduction  

Pulmonary Vein Stenosis After Second-Generation Cryoballoon Ablation

JUNJI MATSUDA, M.D.,* SHINSUKE MIYAZAKI, M.D.,* HIROAKI NAKAMURA, M.D.,* HIROSHI TANIGUCHI, M.D.,* TAKATSUGU KAJIYAMA, M.D.,* HITOSHI HACHIYA, M.D.,* TAKAMITSU TAKAGI, M.D.,* YOSHITO IESAKA, M.D.,* KENZO HIRAO, M.D.,† and MITSUAKI ISOBÉ, M.D.‡

From the *Cardiovascular Center, Tsuchiura Kyodo Hospital, Tsuchiura, Ibaraki, Japan; †Heart Rhythm Center; and ‡Department of Cardiovascular Medicine, Tokyo Medical and Dental University, Tokyo, Japan


In 406 PVs (103 pts):
• Minimal (10-25%) stenosis in 6 PVs (1.5%)
• Mild (25-50%) stenosis in 4 PVs (1.0%)
• Moderate (50-70%) stenosis in none
• Severe (>70%) stenosis in none
Pulmonary vein stenosis after second-generation cryoballoon ablation for atrial fibrillation

Kenichi Tokutake, MD, Michifumi Tokuda, MD, PhD, Takayuki Ogawa, MD, PhD, Seiichiro Matsuo, MD, PhD, Michihiro Yoshimura, MD, PhD, Teiichi Yamane, MD, PhD, FHRS

From the Division of Cardiology, Department of Internal Medicine, The Jikei University School of Medicine, Tokyo, Japan.

Heart Rhythm Case Reports 2017; 3: 36-39

MDCT at 3 months

Tc-99m perfusion images

78% stenosis

LSPV

PLSVC
Balloon Dilation in the Left Superior Pulmonary Vein
(78% stenosis to 40%)

Silent Cerebral Infarctions
Incidence of silent cerebral infarctions after catheter ablation of atrial fibrillation utilizing the second-generation cryoballoon

Tomofumi Nakamura\textsuperscript{1*}, Kaoru Okishige\textsuperscript{1}, Toshiro Kanazawa\textsuperscript{2}, Mitsumi Yamashita\textsuperscript{1}, Naohiko Kawaguchi\textsuperscript{1}, Nobutaka Kato\textsuperscript{1}, Hideshi Aoyagi\textsuperscript{1}, Yasuteru Yamauchi\textsuperscript{1}, Tetsuo Sasano\textsuperscript{3}, and Kenzo Hirao\textsuperscript{3}

43 of 160 patients (27\%, 1.5 lesions per case)

\begin{tabular}{|c|c|c|c|c|}
\hline
Medication & Number & \% & \% & \% \\
\hline
Dabigatran & 11 & 30 & 30 & 20 \\
Rivaroxaban & 14 & 35 & 35 & 20 \\
Apixaban & 5 & 25 & 25 & 20 \\
Edoxaban & 12 & 30 & 30 & 20 \\
Warfarin & 1 & 5 & 5 & 5 \\
\hline
\end{tabular}
1: Inflation in heparinized warm saline

2: Massage

3: Complete removal of bubbles

4: Re-Folding
5: Re-cap in heparinized saline

6: Flush of the Sheath
The Effect of Air Removal with Extracorporeal Balloon Inflation on the Incidence of Asymptomatic Cerebral Embolism during Cryoballoon Ablation of Atrial Fibrillation.
The Effect of Air Removal with Extracorporeal Balloon Inflation on the Incidence of Asymptomatic Cerebral Embolism during Cryoballoon Ablation of Atrial Fibrillation.
AF Recurrence
• PV Reconnection
• Extra PV Foci
AF Recurrence

- PV Reconnection
- Extra PV Foci
Spatial and Time-Course Thermodynamics During Pulmonary Vein Isolation Using the Second-Generation Cryoballoon in a Canine In Vivo Model

Mitsuru Takami, MD; Juna Misiri, MD; H. Immo Lehmann, MD; Kay D. Parker, CVT; Susan B. Johnson, BS; Ray I. Sarmiento, MD; Douglas L. Packer, MD

(Circ Arrhythm Electrophysiol. 2015;8:186-192. DOI: 10.1161/CIRCEP.114.002137.)

A During Cryoablation

Follow-Up Study (After 30–60 Days)
- PVI by Only Cryoballoon
  - Long-term good outcome
- PVI by Cryoballoon + Touch up
  - Risk of PV reconnection
AF Recurrence

• PV Reconnection

• Extra PV Foci
Quantitative Analysis of the Isolation Area During the Chronic Phase After a 28-mm Second-Generation Cryoballoon Ablation Demarcated by High-Resolution Electroanatomic Mapping

Shinsuke Miyazaki, MD; Hiroshi Taniguchi, MD; Hitoshi Hachiya, MD; Hiroaki Nakamura, MD; Takamitsu Takagi, MD; Jin Iwasawa, MD; Kenzo Hirao, MD; Yoshito Isaka, MD

(Circ Arrhythm Electrophysiol. 2016;9:e003879. DOI: 10.1161/CIRCEP.115.003879.)
Cryoballoon Ablation for Common PV Tract
Left Common PV

AP

LAO
Cryoballoon at Left Common PV
Lt Common PV Cryoballoon Ablation
Cryoballoon Ablation for Big Common PV
Left Common PV

AP

LAO
Left Common PV
Touch-up (Freezer MAX) to Left Common PV
Isolation of Left Common PV

Antero-inferior touch-up by Freezer MAX
Acute efficacy, safety, and long-term clinical outcomes using the second-generation cryoballoon for pulmonary vein isolation in patients with a left common pulmonary vein: A multicenter study

Group I = standard ablation approach
Group II = sequential ablation approach
Cryoballoon Ablation without Contrast Media
Cryoballoon Ablation without Contrast Media

ICE in LA

ICE in LA
Cryoballoon Ablation with Intracardiac Echo
LSPV

Color Doppler

Saline injection

Total Occlusion
(Grade 4)
Total occlusion (Grade 4): Contrast was seen to the distal of LSPV.
LIPV Roof

Color Doppler

Saline injection

Bottom Posterior Leak (Grade 2)
The leak at LIPV bottom posterior (Grade 2).
LIPV Bottom

The leak at LIPV roof (Grade 2).

SY 53M 5252154 2015/8/31
LIPV Bottom

Color Doppler

Saline injection

Roof Leak
(Grade 2)
Summary & Conclusions

• Pulmonary vein isolation using 2nd generation of cryoballoon (CB2) is an effective treatment for patients with drug-refractory recurrent symptomatic paroxysmal AF.

• In CRYO-Japan PMS study, freedom from AF was 89.0% in patients reporting at 6 months.
Thank You

관심을 가져 주셔서 감사합니다.