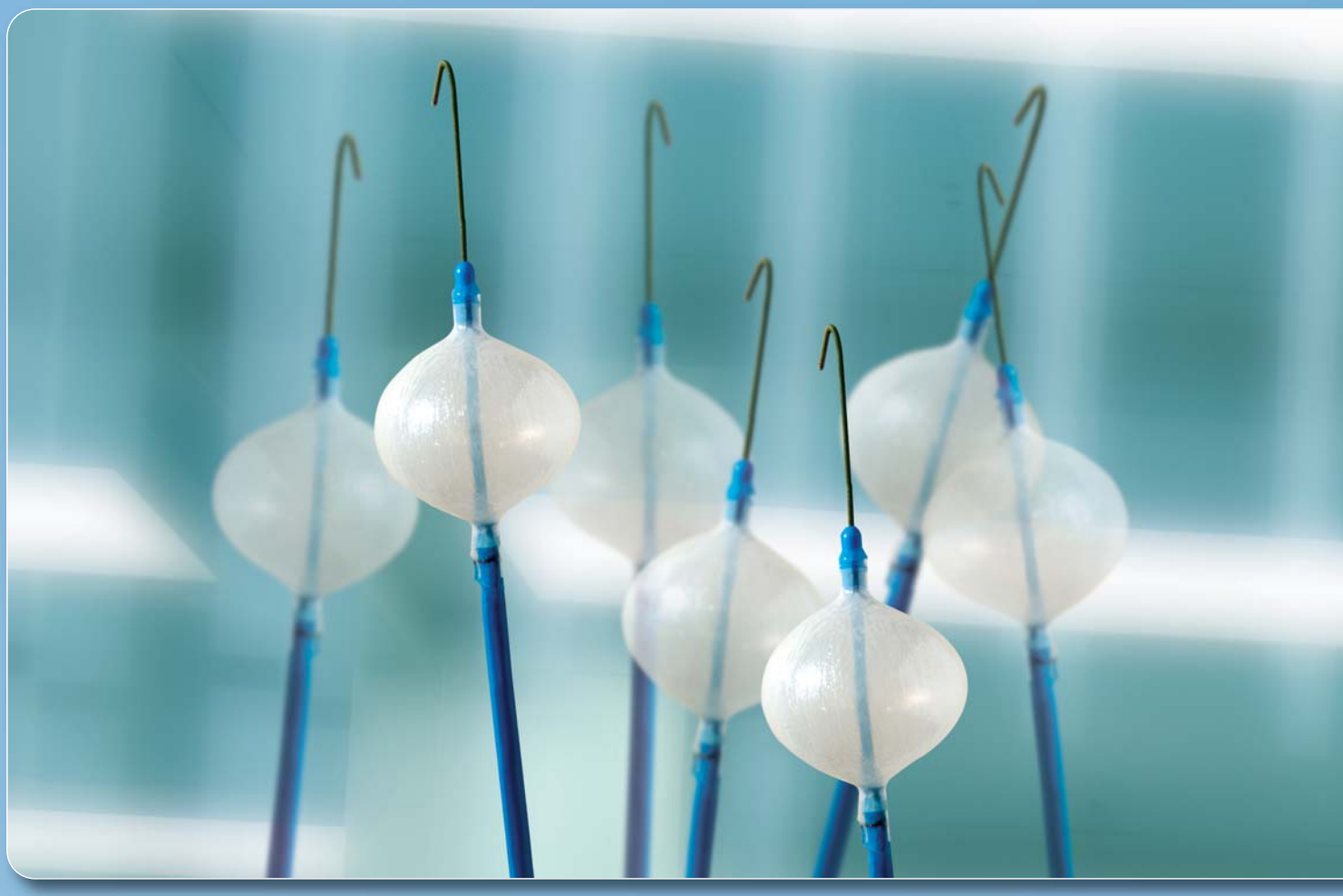
Summary Notes from

The Arctic Front® Advisory Board Meeting

Berlin, Germany – Tuesday August 12, 2008



Chair

M. Antz | Oldenburg, DE

In attendance

F. Anselme | Rouen, FR
G.B. Chierchia | Brussel, BE
C. De Chillou | Nancy, FR
J.C. Deharo | Marseille, FR
J.S. Hermida | Amiens, FR
M. Koller | Bad Neustadt, DE
K.H. Kuck | Hamburg, DE
M. Kuniss | Bad Nauheim, DE
A. Schirdewan | Berlin, DE
C. Tondo | Rome, IT
J. Vogt | Bad Oeynhausen, DE
F. Voss | Heidelberg, DE

Objectives of the Advisory Board Meeting

The most recent Advisory Board meeting was the third of its kind, following previous assemblies in 2006 and 2007. The advisors discussed potential enhancements to the devices that CryoCath designs and manufactures. They reviewed the existing professional education programs and suggested additional program enhancements and future training tools. Above all, participants shared current results, summarized key procedural best practices, and discussed the design of future studies to continue to build additional evidence for Arctic Front.

Publications

As of August 12, 2008, the following articles have been published in peer-reviewed journals:

Klein G, et al:
Efficacy of pulmonary vein isolation by cryoballoon ablation in patients with paroxysmal atrial fibrillation.
Heart Rhythm, June 2008

Neumann T, et al:
Circumferential Pulmonary Vein Isolation with the Cryoballoon Technique: Results from a Prospective 3-Center Study.
JACC, July 2008

Reddy V, et al:
Balloon catheter ablation to treat paroxysmal atrial fibrillation: What is the level of pulmonary venous isolation?
Heart Rhythm, March 2008

Van Belle Y, et al:
Pulmonary vein isolation using an occluding cryoballoon for circumferential ablation: feasibility, complications, and short-term outcome.
Eur Heart J, June 2007

Dr. Malte Kuniss of Bad Nauheim, Germany, who represents one of the three participating centers, gave an overview of the results recently published in JACC (see reference above). These very favorable results from large cohorts of patients at three centers were viewed as a positive development by the advisors. The multi-center prospective study reported that, at 12 months follow-up, 74% of paroxysmal patients were free from atrial fibrillation and off anti-arrhythmic therapy after just one procedure.

Number of Completed Cases and Results

CryoCath announced that over 3,100 procedures have been completed using Arctic Front and FlexCath in over 50 centers in Europe and in clinics as far away as Australia and Hong Kong. The advisors acknowledged that the new FlexCath, available since January 2008, is a significant improvement over the original version. The group was very encouraged by the consistently favorable nature of all of the results that have been published and presented. Results confirm that Arctic Front produces consistent outcomes across multiple physicians and centers.

Avoiding Complications: RSPV Ablation and Monitoring the Phrenic Nerve

The group reviewed the incidence of phrenic nerve palsy from peer-reviewed articles, available data, and reports made directly to CryoCath. In the peer-reviewed articles, the incidence of phrenic nerve palsy was approximately 7 to 8%. In the more recent presentations from HRS and Cardiostim, the incidence is lower at approximately 4%.

CryoCath continues to track the reported incidence of phrenic nerve palsy without recovery by the end of the procedure or prior to discharge. In over 3,100 cases completed, only 41 cases of phrenic nerve palsy without recovery by the end of the procedure or prior to discharge have been reported – for a global incidence under 2%.

The group agreed on the importance of reporting all incidences of persistent phrenic nerve palsy and subsequent recovery to enable CryoCath to maintain an accurate record. The group reported that all of the patients they have followed recovered within a year post procedure.

The group also discussed how to minimize the risk of this specific complication when using Arctic Front. There was general agreement that the balloon size/vein size ratio and placement of the balloon are important considerations in prevention efforts. It makes more sense to use the larger 28mm balloon when ablating in the vicinity of the phrenic nerve; however, such use is no substitute for observing a vigilant monitoring protocol (in the light of the fact that members reported incidence of palsy with both the 23mm and 28mm Arctic Front catheters).

Participants at this year's Advisory Board continue to use both methods of monitoring (pacing the phrenic nerve from the superior caval vein and breathing maneuvers). The members reiterated the importance of pacing the phrenic nerve from a location above the ablation site. Phrenic nerve monitoring should not be limited to the RSPV as there have been reports of phrenic nerve palsy during ablation of the RIPV. In conclusion, the group emphasized the need to proceed with caution and adopt as antral a position as possible in all ablation attempts on the right side. Ablation should be stopped immediately in case of phrenic nerve impairment and/or reduced diaphragm movement.

The group noted that there has been no incidence of atrial esophageal fistula reported with Arctic Front, providing further evidence that the risk of this complication is very low. The discussion highlighted data that was presented at the 2008

Scientific Sessions by Dr. Hiroshi Nakawaga of Oklahoma City, OK. While Dr. Nakagawa's study suggests that cryo is able to cause esophageal ulceration, no atrio-esophageal fistula was noted with cryoablation in a model in which heat-based ulceration progressed to fistula formation.

One of the hypotheses for the low risk of fistula formation with cryoablation is associated with the preservation of structural tissue integrity and a healing process that differentiates cryo from heat-based energy sources.

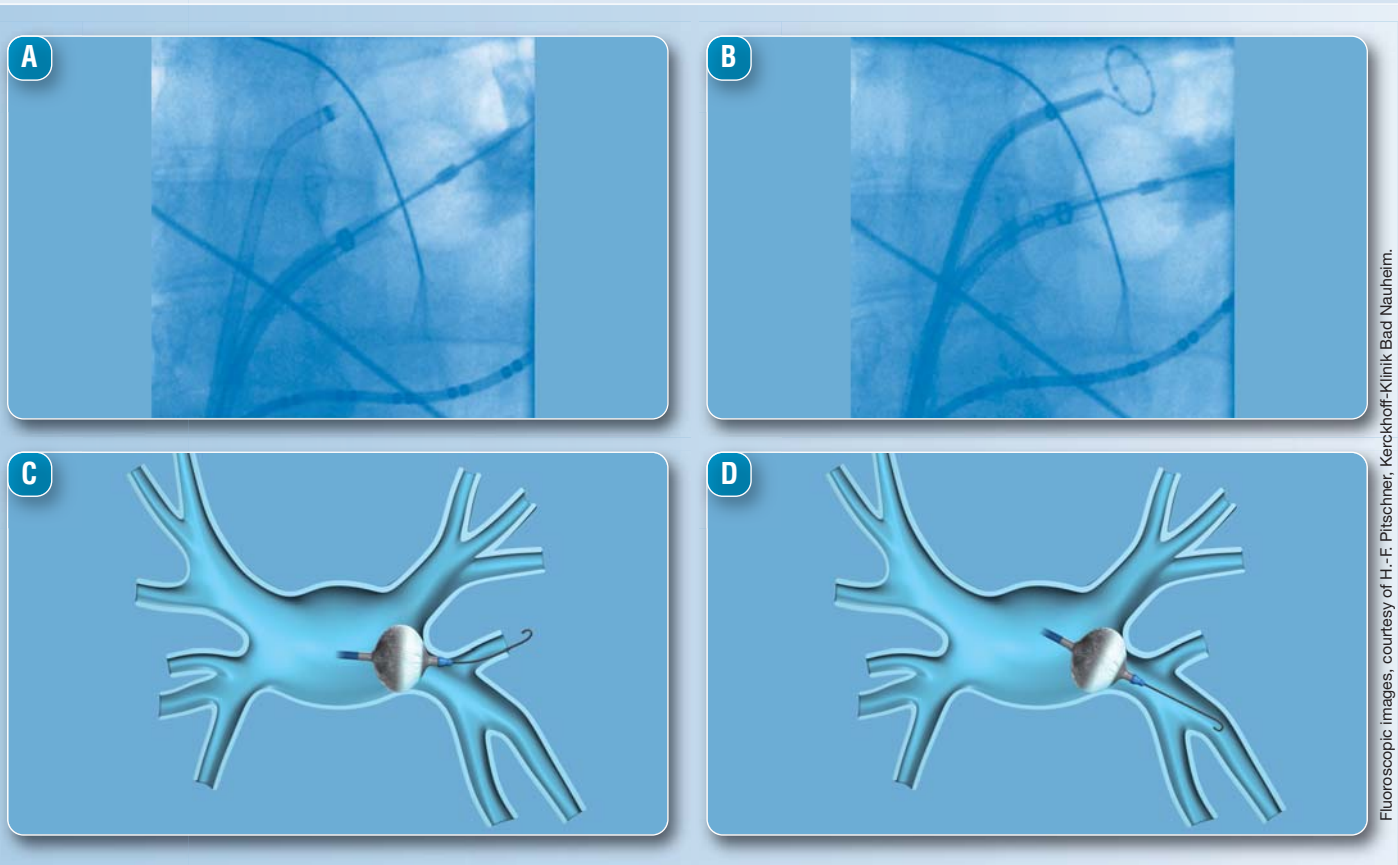
Professional Education & Training

This year's group included a mix of physicians who have been either faculty members or attendees at Arctic Front training programs. The physicians who attended the courses emphasized the usefulness of the programs in accelerating their early learning experience with the device. Comments included: "The program satisfied my curiosity about this new approach, making me comfortable enough to propose it to my patients and incorporate it into my practice"; "We learned helpful tips and techniques that made it possible to start using the device right away"; and "It was great having your clinical staff on hand during our first cases." Everyone was convinced of the usefulness and value of these training programs and agreed that CryoCath should continue to offer them and encourage all new customers to attend. CryoCath is already planning Arctic Front training programs in the United Kingdom and other countries.

Arctic Front Best Practices: Procedural Techniques & Ablation Strategies

The participants discussed a number of procedural best practices they have adopted to help ensure optimal Arctic Front positioning and optimal patient outcomes. Main points include:

- Always ensure the best possible contact between Arctic Front and the targeted tissue as complete occlusion is the best predictor of successful isolation
- Maximize alignment of the balloon with the vein (see fluoroscopy images and diagrams)
- Wire different branches, if indicated by anatomy, to achieve different balloon positions and broaden the isolation zone
- Employ a freeze-thaw-freeze strategy to ensure effect and potentially reduce the chance of conduction recovery – rather than prolong the freeze duration beyond the recommended dose



Fluoroscopic images, courtesy of H.-F. Pitschner, Kerckhoff-Klinik Bad Nauheim.

Figure A. Fluoroscopic view of a 28mm Arctic Front that is not optimally centered in the LIPV as demonstrated with contrast below the guidewire. **Figure B.** Arctic Front is now optimally centered in the pulmonary vein as demonstrated with the contrast evenly distributed around the guidewire. **Figure C.** Illustration of Arctic Front not optimally centered. **Figure D.** Illustration of optimally centered Arctic Front.

Product Benefit and Potential Enhancements

The majority of the members have adopted Arctic Front as their primary tool for performing pulmonary vein isolation in their paroxysmal patients. The group agreed that the anatomically based Arctic Front procedure is straightforward and does not require the use of a 3D mapping system – which contributes to keeping the procedure simple, quick, and efficient.

The group suggested that it would be important to have additional success markers during the ablation procedure to judge time-to-effect or the efficacy of the ablation in real time.

The Importance of Clarity and Accuracy

The group discussed how best to communicate key Arctic Front procedure and cryo-related messages from the podium. For example, the word leak, when used to describe a balloon-based device, may have multiple interpretations. Also all of the participants appreciated the importance of refraining from absolutes such as “zero risk” or “no risk.” The advisors discussed some possible messaging as follows:

- Due to incomplete occlusion, there was a small escape of contrast around Arctic Front.
- There is a reduced risk of damage to the AV node or esophageal fistula when compared to other energy sources.

Attendees also discussed appropriate means of describing the incidence or risk of phrenic nerve palsy associated with balloon-based ablation. It is important to recognize that when the ablation is quickly terminated, there is often diaphragmatic recovery prior to the end of the procedure: this may be a result of the nerve only being transiently affected by hypothermic temperatures. In some cases, palsy is still present at the end of the procedure; however, as recovery reports demonstrate, it is not permanent.

Supporting Evidence-Based Medicine

A number of different studies are already under way or will be starting shortly. There are three main themes to the ongoing and upcoming studies. First, CryoCath plans to continue supporting investigator lead studies that investigate the safety profile of cryoablation. One of the proposed topics for this research is the effect of cryotherapy on the phrenic nerve. Second, a number of studies will focus on continuing to build additional sound clinical evidence for the existing indication of paroxysmal atrial fibrillation and start comparing Arctic Front with heat-based devices and accepted anti-arrhythmic therapy. Finally, CryoCath plans to support studies that will continue to expand the indication for its devices.

Two study proposals comparing cryoablation with Arctic Front to anti-arrhythmic therapy (Amiodarone and Flecainide) were presented by the investigators; subsequently, the group discussed the merits of both studies.

The group also commented on the need for uniformity in the way atrial fibrillation studies are conducted and their results reported. Whenever possible, CryoCath will support studies that adhere to the HRS Expert Consensus Guidelines for standards for reporting outcomes in clinical trials. To be considered, all study proposals must be submitted in writing to CryoCath, to the attention of Chief Scientific Officer Jean-Pierre Desmarais. All submissions will be answered in writing.

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