Biophysics of the Second-Generation Cryoballoon
Cryobiology of the Big Freeze

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Current guidelines recommend antral isolation of the pulmonary veins (PV) as the cornerstone of atrial fibrillation ablation. Although conventional radiofrequency energy has traditionally been used with a point-by-point approach, cryoablation has emerged as a viable alternative to radiofrequency energy. The clinical success of cryoablation has been driven by the introduction of the cryoballoon.

Cryoenergy has been studied as early as the 1940s using CO₂ gas injected in a probe to produce controlled myocardial tissue damage and studied in a variety of experimental animal models. In these early experiments, cryoinjury was demonstrated to cause sharply demarcated myocardial lesions. In marked contrast to radiofrequency ablation (RFA) lesions, cryolesions result in preservation of tissue architecture, including fibrocytes and collagen, and there is significantly less damage to large vascular structures or to the endocardium. These characteristics contribute to an increased safety profile compared with RFA, including less thrombogenicity (preserved endocardium) and less risk of perforation (preserved tissue structure). Another advantage is that cryomapping may be used by temporarily cooling the tissue to sublethal temperatures to predict possible consequences (ie, AV block) of a prolonged ablation. Although safety of point-by-point cryoablation has been demonstrated in clinical studies, long-term efficacy in treating various supraventricular arrhythmias is thought to be reduced when compared with RFA. Moreover, feasibility of creating extensive longitudinal lesions is hampered by slow conductive cooling of the tissue and heat-sink effect from surrounding high-flow vascular areas. Development of cryoballoon technology (with recently introduced more efficient second-generation balloons) has been a game-changer for atrial fibrillation ablation because it allows for rapid cooling of large areas in the left atrium (LA) and has proved to be an effective modality to create permanent lesions in a time-efficient manner. The first randomized, multicenter trial (Cryoballoon ablation of pulmonary veins for paroxysmal atrial fibrillation: first results of the North American Arctic Front [STOP AF pivotal trial) confirmed the superior efficacy of cryoballoon ablation compared with antiarrhythmic drug treatment. During the past decade, the worldwide experience with cryoballoon ablation has grown to >50000 cases and multiple clinical studies reported an overall comparable efficacy to point-by-point RFA. Procedural time and complication rates with the cryoballoon seem to be similar to RFA and a final determination of comparative efficacy and safety will await the results of a large European trial (FIRE AND ICE: Comparative Study of Two Ablation Procedures in Patients With Atrial Fibrillation, ClinicalTrials.gov Identifier: NCT01490814).

There remain several outstanding and important clinical questions on cryoballoon ablation. There seems to be a clinically higher rate of phrenic nerve injury using older methods of phrenic nerve (PN) monitoring (temporary, 12%; permanent, 2%;) and there are concerns on (rare) injuries to other nearby structures (bronchus, esophagus, and left phrenic nerve). Unlike point-by-point RFA, cryoenergy cannot be modified selectively in different regions around the veins. The best titration of cryoballoon energy while maintaining maximal efficacy to avoid collateral damage remains unknown for the second-generation cryoballoon. It is unclear how long each lesion should be applied and if and when a lesion should be repeated especially if acute PV isolation is already achieved (ie, do we need any bonus lesions?).

In contrast to the large amount of biophysical data, we have about radiofrequency energy, we have relatively little data on cryoballoon ablation. Packer et al from the Mayo Clinic performed a careful analysis of their cryoballoon experiments to provide us with some of this data. In the present study by Takami et al using a canine model, cryoablation was performed in each PV with intracardiac ultrasound guidance. Tissue temperature was monitored by thermocouples, placed at the PV/LA junction (3 per vein), the esophagus (4, close to the right inferior pulmonary vein), and next to the right phrenic nerve (1–2, next to right superior pulmonary vein). The distance from the thermocouple to the balloon was measured from fluoroscopic images (left and right anterior oblique projections). Additional temperature measurements were made from the inside and the surface of the cryoballoon. Ablation was performed in 20 canines, using the second-generation 28 mm Arctic Front Advance catheter (Medtronic, Minneapolis, MN) after trans-septal access to the LA. Results were reported from ablation of 40 veins. Cryoablation lesions were limited to maximum of 2 applications per vein, each ablation lasted for 3 to 4 minutes. Ablation was stopped if PN injury developed. Long-term outcome and histology were assessed 4 to 8 weeks after recovery from the ablation. The ablation protocol...
resulted in successful acute and chronic PV isolation in 90% and 68% of the veins, respectively, and without any temporary or permanent PN injury. Changes in the esophageal mucosa was noted in only 1 animal without any sequelae. There was 1 instance of moderate PV stenosis (60%). The main findings of the study are that complete transmural lesions were required for chronic PV isolation, failed ablation was related to gap(s) around the veins, and these locations were correlated with incomplete balloon occlusion and leak from the PV during ablation. The conductive cooling spread radially from the balloon and tissue temperature change was related to distance from the balloon with a cooling rate of 0.68°C/s at 1 mm and 0.15°C to 0.19°C/s at 5 mm. The average temperature at the PV/LA junction was higher than expected (15.0±14.6°C).

As often is the case when an established technology is applied in a new clinical situation, investigation to understand some of the basic mechanisms and principles of that technology may lag behind advances in clinical application. This has certainly been the case for cryoablation of atrial fibrillation. The current study is indeed a welcome addition to our understanding of the thermodynamics of the second-generation cryoballoon. First, as with any animal model, the limitations should be acknowledged. Although the anatomy and properties of the LA and PVs are similar in humans and canines, important structures, such as phrenic nerve and esophagus, have slightly different topographical locations. As demonstrated in the current study, the smallest distance between the PN and the right PVs was 8.5 mm, likely beyond the therapeutic temperature reach of the balloon. Furthermore, as the authors elaborate, the size of the PVs are smaller than in humans (average diameter, 1.2 versus 1.7±0.4 cm), making proper seating and occlusion with 28-mm balloon challenging. This has likely contributed to a lower acute and chronic success rates in the current study.

It is suggested by this and previous studies that balloon distance from the PN determines the chance of nerve damage. The new, larger balloon does promote a more antral ablation and potential increased distance to the PN as long as the catheter is not aggressively maneuvered to the inside of the vein. In the current study, the balloon position was kept at the antral region thereby maximizing the distance to the PN. Additional options to limit PN injury include visualization of right phrenic artery (which runs along the PN) in the preprocedure CT or MRI study for procedural planning. Loss of PN capture during ablation or measurement of changes in diaphragmatic compound motor action potential may signal early changes to nerve function and allow timely cessation of ablation. A single-center study indicates that additional early balloon deflation may halt the development of permanent nerve damage.

Another intriguing finding is a relatively high tissue temperature at the PV/LA junction, a finding that is unexpected based on our understanding of cryoinjury. The mechanism of tissue injury during cryoablation is complex and has been extensively studied. Injury to the cells during the freezing process is related to extracellular (interstitial) and intracellular ice formation and development of osmotic gradient between the cells and the interstitium. As the extracellular space gradually freezes, osmolality increases in the remnant unfrozen fluid and the cells shrink as water moves out. If the freezing rate is rapid, the osmotic changes are minimal before freezing and water content of the cell remains the same. In this case, intracellular ice formation will occur at a higher temperature when compared with cells with increased solute concentration because of increased water loss. Thus, intracellular ice formation is determined not only by the final tissue temperature but also by the rate of cellular water loss and the rate of rise of the temperature. At cooling rate of 100°C/min (approximate cooling rate in the proximity of the cryoballoon), the intracellular ice formation would occur at around −10°C. If lower temperatures are reached (−20°C to −40°C), paradoxically recrystallization may take place during thawing with further structural destruction. These temperatures are estimates, as much of our understanding is derived from in vitro studies and acquired by studying nonmyocardial cells. Thermodynamic properties of various tissues differ significantly and different temperatures/cooling protocols may provide contradictory results. Thus, applicability of in vitro testing or extrapolation of data from other tissue examinations may have significant limitations. The velocity of the thawing process has significant effect on further osmotic insult. A slow thawing in general is more likely to cause fluid shifts and worse osmotic trauma to the cells. After thawing, there are 3 distinct phases of histological changes. Initially, there is a swelling of myocytes and mitochondria and subsequently disruption of cellular transport mechanisms, membrane function, and membrane integrity (minutes to hours; freeze/thaw phase), followed by hemorrhage, edema, and inflammation—coagulation necrosis (day to weeks, hemorrhagic phase) and subsequently fibrosis (2–4 weeks, fibrosis phase). Acute cell death is related to intracellular ice formation or osmotic injury during the freeze and thaw cycle. Thus, ice crystal formation at least in the extracellular compartment is required to produce acute injury and even in the most ideal circumstances, a tissue temperature has to reach below −1°C. In the current study, either the fidelity of thermocouple locations may be suboptimal in relation with the ablation lesion (ie, placed too far away) or an alternative mechanism was responsible for tissue injury. Mild hypothermia may induce temporary biochemical changes related to thermal inhibition and uncoupling of cellular functions or cause microvascular damage and apoptosis. These secondary changes may take place subacutely. Significant late changes were not suggested in the current study because none of the acutely failed veins developed conduction block by the end of the study. Thus, the mode of tissue injury cannot be reliably determined from this study. Additional studies will need to focus on more precise tissue temperature assessments to establish the temperature limits for irreversible injury.

In summary, the current study confirmed the importance of complete PV occlusion to optimize outcomes during cryoballoon ablation. As long as occlusion is achieved, PV isolation may be expected with few (1–2) ablation lesions and development of transmural lesions. Although conductive cooling rate should be confirmed by further studies, the current data suggest that temperature-sensitive noncardiac structures at a distance of ≥5 mm from the balloon are unlikely to be permanently affected until 3 minutes into ablation. The authors are to be congratulated for this elegant study, which begins to provide clinicians with the scientific framework to better understand the best use of the cryoballoon.
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References


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