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Evaluation of a Novel Cryoablation System: In-vitro Testing of Heat Capacity and Freezing Temperatures

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Summary

Objective—Cryoablation has been used to ablate cardiac tissue for decades and has been shown to be able to replace incisions in the surgical treatment of atrial fibrillation. This in-vitro study evaluates the performance of a novel cryoprobe, and compares it to existing commercially available devices.

Methods—A new malleable 10cm aluminum cryoprobe was compared to a rigid 3.5cm copper linear-probe using in-vitro testing to evaluate performances under different thermal loads and with different tissue thicknesses. Radial dimensions of ice formation were measured in each waterbath by a high-precision laser 2 minutes following the onset of cooling. Probe-surface temperatures were recorded by thermocouples. Tissue temperature was measured at depths of 4mm and 5mm from the probe-tissue interface. Time to reach tissue temperatures of -20°C was recorded.

Results—Ice formation increased significantly with lower waterbath temperatures ($p<0.001$). Width and depth of ice formation was significantly less for the rigid linear probe ($p<0.012$ and $p<0.001$, respectively). There was no difference between the probes in the maximal negative temperature reached under different thermal loads or at different tissue depths. The malleable probe achieved significantly lower temperatures at the proximal compared to the distal end (-61.7°C vs. -55.0°C , respectively; $p<0.001$). A tissue temperature of -20°C was reached earlier at 4mm than at 5mm ($p<0.001$) and was achieved significantly faster with the 3011-Maze-Linear probe ($p<0.021$).

Conclusions—The new malleable probe achieved rapid freezing to clinically relevant levels in up to 5mm thick tissue. Both probes maintained their performance under a wide range of thermal loads.

Keywords

Ablative therapy; arrhythmia therapy; atrial fibrillation

Introduction

The mechanisms of cardiac tissue injury caused by cryotherapy have been examined for more than half a century. In 1951, Taylor et al. reported the creation of transmural lesions in

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a canine model using expanding carbon dioxide to cool cardiac tissue to -60°C .¹ While the mode of cellular and tissue injury leading to necrotic and apoptotic cell death cascades caused by low temperature exposure was initially used exclusively in the therapy of malignancy and palliative management of pain², it became obvious that cardiac cells were as or more sensitive to cryo-injury than cancerous cells³. Cardiac tissue is destroyed by the formation of intra- and extracellular ice crystals, which disrupt cell membranes and organelles. This had made this energy source potentially useful for the interventional treatment of cardiac arrhythmias.⁴⁻⁸

As opposed to other alternative energy sources such as radiofrequency, focused ultrasound, microwave or laser, cryoablation creates direct physical injury, cumulative sub-lethal cellular stress response, and molecular-based cell death by freezing.⁹⁻¹¹ Cryodestruction occurs through immediate and delayed mechanisms of cell injury. As cardiac tissue temperature approaches -32°C , cell membranes become less fluid and transport capacity of ion pumps change, which increases action potential duration. Cardiac cellular dysfunction has been demonstrated by decreased Ca^{2+} -sensitivity related to protein kinase A and C phosphorylation of cardiac troponin I in hypothermic cooling and rewarming experiments mimicking ischemia and reperfusion.^{12, 13} As temperature continues to drop, intracellular pH decreases, ionic imbalance occurs and energy levels (ATP) drop, leading to further membrane injury and an accumulation of free radicals. The reversibility of these cell alterations is inversely related to the degree of tissue cooling and the duration of application. Recent cryogenic techniques claim to rapidly freeze tissue down to -160°C . Ice formation is the cornerstone of tissue injury and the mode of ablation in modern devices. The onset of ice formation at the cryoprobe provides cryo-adhesion to maintain and ensure tissue contact and creates an area at which heat is extracted from the tissue. As heat is removed by various cryogens such as nitrous oxide, argon or liquid oxygen, extracellular fluid freezes at -20°C , creating a hyperosmotic environment that causes cell shrinkage and ultimately cell death.¹⁴ Rapid freezing to -40°C induces expansion of intracellular ice formation that disrupts organelles and cell membranes even before osmotic imbalance occurs.¹⁰ A fast rate of cooling will increase cell death, while slowly thawing the tissue is also effective in prolonging the mechanisms of cell destruction.¹⁴

Although there are many encouraging reports of cryoablation in the surgical treatment of AF¹⁵⁻¹⁷, investigations evaluating the heat capacity and the actual temperature achieved in the targeted tissue have been limited. In this study, the novel malleable nitrous oxide cryoablation system was compared to one that has been widely used for surgical cryoablation for decades. The new aluminum probe Cryo1 (AtriCure Inc, West Chester, OH USA) as well as the gold plated copper 3011 Maze Linear probe (AtriCure Inc, West Chester, OH USA), formally called the Frigitonics 3011 probe, were evaluated to document their capacity to reach clinically relevant freezing temperatures over a wide range of physiological thermal loads. Neither probe has been previously examined *in vitro* or *in vivo* despite widespread clinical use.

Methods

Two cryoablation devices, the Cryo1 and the 3011 Maze Linear probe, were used in this study (Figure 1). The Cryo1 probe is a malleable, smooth, disposable, 10cm long aluminum cylindrical probe with an outer diameter of 4.24mm, an inner diameter of 2.97mm and a thermal conductivity coefficient of $222 \text{ W}\cdot\text{K}^{-1} \text{ m}^{-1}$. The 3011 Maze Linear probe is a reusable device that has a rigid 3.5cm gold plated copper cylindrical probe with an outer diameter of 5.18mm, an inner diameter of 3.66mm and a thermal conductivity coefficient of $400 \text{ W}\cdot\text{K}^{-1} \text{ m}^{-1}$. Both probes are cooled by nitrous oxide and have an active defrost feature

to free the probe from frozen tissue. Cooling and gas flow were controlled using the Cardiovascular Cryosurgical System CCS200 (AtriCure, Inc., West Chester, OH USA).

Ice Formation

The width and depth of ice formation on the cryoprobes in a water bath set to temperatures of 32, 25 and 10°C were measured. Each device was placed in the water bath with the probe half-submerged along its longitudinal axis, imitating the probe-tissue interface during ablation (Figure 2). The temperatures were chosen to meet the clinical scenarios of both normothermic beating heart ablation and arrested heart ablation. The width and depth of the ice formation along the probes following two minutes after the onset of cooling were measured for both devices using a non-contact high precision laser measurement system (Keyence Optical Micrometers, Keyence Corporation, Osaka, Japan). Ice formation measurements were taken at 4 positions along the 10cm Cryo1 probe and at 3 positions along the 3.5cm 3011 Maze Linear probe. The measurements were repeated six times for each cryoprobe.

Probe Surface Temperature

The probe surface temperatures were measured at 4 positions along the 10cm Cryo1 probe and at 3 positions along the 3.5cm 3011 Maze Linear probe by wire thermocouples (Type T, Omega Thermocouples, Stamford, CT USA) across the length of the probes as shown in Figure 3. Temperatures were continuously recorded and plotted as a function of time during a two-minute cooling period while the cryoprobe was placed half-submerged in 32, 25 and 10°C water baths. The measurements were repeated three times for each cryoprobe.

Tissue Temperature

Tissue temperatures during cryoablation were measured for both devices using fresh bovine myocardium cut in 5 and 6mm thickness. A 4mm spacer was used to hold the myocardial tissue off a platform. Four hypodermic thermocouples measuring 5mm in length (Model HYP-1; Omega Thermocouples, Stamford, CT) extended from the platform's base and penetrated 1mm into the myocardial tissue. These thermocouples were positioned to lie evenly distributed and centered below the overlying cryoprobe (Figure 4). Tissue temperatures were measured at 4 and 5mm from the tissue-cryoprobe interface for the 5 and 6mm thick bovine myocardial samples, respectively. To ensure constant probe-tissue contact, a weight of 200g was applied to the cryoprobes from above until cryoadhesion occurred. This was done to simulate the clinical use of the ablation devices. The bovine myocardial tissue samples were initially at room temperature. The spacer was removed 10 seconds after starting cryoablation when cryoadhesion was sufficient to maintain tissue-probe contact. The spacer was used to minimize thermal losses caused by tissue contact to the platform. Cryoablation was continued for two minutes followed by active defrost to free the probes from the tissue. Tissue temperatures measured by each thermocouple were plotted as a function of time. For both cryoprobes these measurements were repeated six times for each tissue thickness. Based on previous studies, which revealed that a temperature of -20°C was needed to cause cardiac cell death^{14, 18}, the time needed to reach this goal temperature was identified for each ablation.

Data Analyses

All continuous data were expressed as mean $\pm$ standard deviation and were compared using ANOVA testing (Systat Statistical Software, Version 13, Chicago, IL USA). Multiple comparisons were made using Fisher's LSD-Test. A $p < 0.05$ was considered significant.

Results

Ice Formation

The radial dimensions of ice formation on both cryoprobes increased significantly with lower water bath temperatures ($p < 0.001$). The average depth of ice formed for the Cryo1 probe was 5.41 ± 0.38 mm, 7.13 ± 0.48 mm and 11.16 ± 0.70 mm at water bath temperatures of 32°C , 25°C and 10°C , respectively. There was significantly less depth of ice formed along the 3011 Maze Linear probe at water bath temperatures of 25°C and 10°C , respectively, when compared to the Cryo1 device ($p < 0.001$). The average width of ice formed along the surface of the water on either side of the Cryo1 probe was 3.03 ± 0.18 mm, 4.40 ± 0.34 mm and 6.21 ± 0.33 mm at water bath temperatures of 32, 25 and 10°C , respectively. The width of ice formed along the 3011 Maze Linear probe was significantly more with 3.80 ± 0.56 mm at 32°C , but was significantly less with 4.07 ± 0.65 mm and 6.93 ± 0.37 mm at water bath temperatures of, 25 and 10°C , respectively, when compared to the Cryo1 device ($p < 0.012$). Overall, ice formation was homogeneously distributed along the probe on both devices with no significant differences between the proximal and distal ends (Figure 2, Table 1).

Probe Surface Temperature

There was no significant difference in the maximum negative temperature reached by the Cryo1 probe ($-58.9 \pm 3.2^\circ\text{C}$) or the Maze-Linear-3011 probe ($-61.2 \pm 2.9^\circ\text{C}$, $p = 0.101$). The temperature of the waterbath did not affect the maximum negative temperature reached by either cryoprobe ($p = 0.114$, Figure 5). The maximum negative temperature measured at the Cryo1 probe surface was significantly lower at the proximal end (-61.7°C) than at the distal end (-55.0°C , $p < 0.001$). The same trend could be found for the 3011 Maze Linear probe, but the difference in the maximum negative temperature achieved along the probe did not reach significance for this device (proximal: -63.3°C , distal: -58.3°C ; $p = 0.058$).

Tissue Temperature

The average tissue temperature measured from the thermocouples along each probe's length after 2 minutes of ablation at a distance of 4mm from the probe-tissue interface were $-34.3 \pm 6.3^\circ\text{C}$ for the Cryo1 probe and $-36.6 \pm 6.6^\circ\text{C}$ for the 3011 Maze Linear probe (Figure 6). There was a trend for a lower temperature measured at a distance of 5mm from the probe-tissue interface with an average of $-28.9 \pm 3.7^\circ\text{C}$ for the Cryo1 probe and $-31.0 \pm 8.6^\circ\text{C}$ for the Maze-Linear-3011 device ($p = 0.071$). The maximum negative tissue temperature achieved was not significantly affected by the device used ($p = 0.439$) or the position of measurement ($p = 0.750$). The measured tissue temperatures beneath the distal and proximal end of the devices did not show significant differences for either device ($p = 0.205$). For the Cryo1 probe, the time of cryoablation necessary to attain a tissue temperature of -20°C was 60.5 ± 25.8 seconds at 4mm distance and 86.0 ± 9.3 seconds at 5mm distance from the tissue-probe interface. For the Maze-Linear- 3011 device 39.4 ± 15.9 seconds at 4mm distance and 73.5 ± 21.8 seconds at 5mm distance were needed to achieve a temperature of -20°C . Overall, the goal temperature of -20°C was reached by both devices significantly faster at 4mm than at 5mm distance ($p < 0.001$) but was achieved significantly faster by the 3011 Maze Linear probe than by the Cryo1 probe ($p < 0.021$).

Discussions

The mechanisms of cell injury during cryoablation are complex. Intra- and extracellular ice formation causes either a hyperosmotic environment eventually leading to cell death or disruption of organelles and cell membranes. Earlier studies have suggested a tissue temperature of -20°C to be sufficient to induce necrosis^{10, 18}. To accomplish low

temperatures, modern systems allow compressed gas to expand into a lower pressure environment within the probe, called the Joule-Thomson effect. Newton's law of cooling can evaluate the rate at which heat is removed ($\dot{Q}$) from a system by the working fluid as a function of change in enthalpy (Δh) and the mass flow rate (m): $\dot{Q} = \dot{m} \cdot C_p \cdot \Delta T = \dot{m} \cdot \Delta h$. The chosen coolant can impact the level of heat removal in the analysis of enthalpy, which is a function of the specific heat (C_p) and change in temperature (ΔT). Two widely used refrigerants in cardiac procedures are monatomic argon (Ar) and polyatomic nitrous oxide (N₂O). A measure of the heat that is required to raise the substance's temperature of a unit quantity by a unit degree is the specific heat. N₂O as a polyatomic gas has multiple free vibrational modes resulting in a high specific heat of 0.890 KJ/(kg·C) and is therefore capable of absorbing more heat with a smaller rise in temperature than other refrigerants. Thus, the amount of heat energy that is removed from a system is contingent on the specific heat of the cooling fluid, the final temperature of the cooling fluid after the throttling process, and the mass flow rate of the fluid through the system. The optimal freeze-thaw cycle of an ablation device should consist of a fast cooling rate and a slow thawing rate to maximize tissue injury.^{14, 19} In this study, our results revealed the capability of the nitrous oxide system to rapidly cool down both probes tested to a goal temperature of -20°C that is felt to ensure induction of cell necrosis.

In addition to the cooling capability, probe material and surface contact with the targeted tissue impact heat conduction. The probe design strongly influences the thermal resistance

(R_{th}) of a system when t considering the equation $R_{th} = \frac{t}{A \cdot k}$, where t is the probe wall thickness, A is the contact surface area and k represents the thermal conductivity of the probe material. The thermal conduction coefficient (k) is the prediction of the rate of heat transfer or heat loss, respectively, through a unit thickness of material. Copper, which is used as probe material in the 3011 Maze Linear probe device has a thermal conduction coefficient of 400 W·K⁻¹·m⁻¹ and was expected to extract heat faster from the targeted tissue than the aluminum probe of the Cryo1 device with a thermal conduction coefficient of only 222 W·K⁻¹·m⁻¹.

In our study, the maximal negative temperature achieved in the tissue was similar for both devices, but the 3011 Maze Linear probe reached a goal temperature of -20°C temperature significantly faster than the Cryo1 probe according to its 2 times higher thermal conduction coefficient. However, our results did not show a significant difference in negative tissue temperature reached at a depth of 4 or 5mm over the examined length of about 3.5cm for this device and maximal negative tissue temperatures reached within 2 minutes of ablation were well below the critical -20°C mark. This indicates a similar freezing performance with an increase in probe malleability and lesion length of the new 10cm long probe. Importantly, the ice formation measured in the water bath testing was homogenous along the entire Cryo1 probe. This indicated homogeneous cooling which can be an issue for long, flexible probes. There were no significant differences in probe surface temperatures between the two probes.

The wall thickness of the human cardiac atria differs depending on region, coexisting cardiac disease or age²⁰⁻²², but is an important predictor for failure in creating transmural lesions.²³ In this study, temperature was measured at a tissue depth of 4 and 5mm, chosen because it approximated average wall thickness most human atria.²² The maximum negative temperature after 2 minutes of ablation was significantly lower at 4mm than at 5mm distance from the probe-tissue-contact interface for both devices. As the rate of cooling and the maximum negative temperature decreases with increasing distance from the probe-tissue interface, extracellular ice formation results in a zone of incomplete and reversible tissue damage.²⁴ This confirms findings of earlier animal studies revealing differences in the performance of cryoablation depending on the targeted atrial wall structures and

thicknesses.^{15, 23, 25} Our findings also suggest that in thick atrial tissue >5mm, ablation times of over 2 minutes are warranted. There are limitations to this study. It utilized an in-vitro model, which allowed for accurate measurement of probe temperature, ice ball formation but did not fully simulate living tissue. However, the study was designed to assess the relative performance of the two probes in a well-controlled environment. Another limitation is that the laboratory setup may not fully replicate clinical use.

It is extremely important to have uniform probe-tissue contact. Ice formation caused by fluid or vapor trapped in the valleys of a non uniform surface is a problem as ice has a low thermal conductivity of $3 \text{ W} \cdot \text{K}^{-1} \cdot \text{m}^{-1}$ and if introduced to the system will increase thermal resistance and become an insulator. Both devices tested were loaded with a weight of 200g after establishing sufficient tissue-probe contact, which was felt to mimic realistically the pressure applied by the surgeon in the clinical application. The setting used in this study represents a nearly optimal probe surface contact that may be difficult to reproduce in surgery.

In conclusion, the nitrous oxide system with the new malleable aluminum probe of the Cryo1 device as well as the rigid copper probe of the 3011 Maze Linear probe achieved rapid freezing to clinically relevant levels in up to 5mm thick myocardial tissue in this in-vitro model. The performance of the two probes was excellent even when burdened with different thermal loads. Freezing capacity dropped, as expected, with increasing tissue thickness. However, the critical freezing temperature to induce tissue necrosis was reached within 2 minutes.

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Clinical Perspective

This is the first of two articles in this issue of *Innovations* comparing the performance of a new, flexible, disposable cryoprobe with a previously available, rigid, reusable probe. Using nitrous oxide as the refrigerant for both probes, this in vitro study demonstrates that both probes reliably achieve a cell killing temperature of minus 20 degrees Centigrade with 2 minute freezes of 5mm sections of bovine myocardium. However, the margin of efficacy is relatively narrow in that the flexible probe requires 86 seconds to reach this critical temperature. Given that human atria, particularly in the mitral isthmus/atrioventricular groove area, can be substantially thicker than 5 mm, the application time of the probe may require significantly longer times than the 2 minutes recommended by the manufacturer. In addition, this supports the fact that endocardial and epicardial applications that “mirror” each other across the mitral isthmus are required to reliably achieve a uniform, transmural lesion.

Future studies should examine the performance characteristics of the flexible nitrous oxide probe with the flexible argon probe. Another practical point in the article is the importance of avoiding “pleats” when applying the probe to the atrium. By virtue of its low thermal conductivity, the ice produced in the pleats will act as an insulator and possibly prevent formation of a uniform, transmural lesion. All in all, this paper is an important contribution to our understanding of cryothermia as a power source for the surgical treatment of cardiac arrhythmias.

Harold G. Roberts, MD, is the guest editor.

Figure 1.
Cryoablation devices. A: Cryo1 probe. B: 3011 Maze Linear probe.

Figure 2. Testing ice formation in water bath for each probe. A: Photographs of the probe in water bath during and after ice formation. B: Schematic for measuring width and depth of ice formation around the probe.

Figure 3.
Positions of wired thermocouples on the A: Cryo1, B: 3011 Maze Linear probes.

Figure 4.

Test apparatus used to measure tissue temperature at 4 and 5mm depth. A. Photograph of the apparatus where the cryoprobe is resting on the myocardium while a weight of 200g is applied. B. Cross sectional view of the apparatus where different components are identified.

Figure 5.

Average tissue surface temperature over time at different water bath temperatures using Cryo1 (left column) and 3011 Maze Linear (right column) devices. Temperature measurements by each thermocouple from the proximal to the distal end of each probe (shown in the graph legend) were performed.

Figure 6. Average tissue temperature at 4 and 5mm tissue depth using Cryo1 (left column) and 3011 Maze Linear (right column) probes. Temperature measurements by each thermocouple from the proximal to the distal end of each probe (shown in graph legend) were performed.

Table 1

Ice formation at different water bath temperatures.

	32°C			25°C			10°C			p-value (Width/Depth)		
	Width (mm)	Depth (mm)		Width (mm)	Depth (mm)		Width (mm)	Depth (mm)		32°C vs. 25°C	25°C vs. 10°C	32°C vs. 10°C
Cryo1	3.03±0.31	5.41±0.37		4.40±0.60	7.13±0.55		6.21±0.37	11.16±0.66		<0.001/<0.001	<0.001/<0.001	<0.001/<0.001
3011	3.81±0.55	5.87±0.42		4.07±0.61	6.35±0.35		6.94±0.36	8.57±0.54		0.382/0.080	<0.001/<0.001	<0.001/<0.001
p-value	0.016	0.056		0.342	0.007		0.003	<0.001				