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CONTEMPORARY REVIEW

Cryotherapy of cardiac arrhythmia: From basic science to the bedside

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This review focuses on the basic science of cellular destruction by tissue freezing and application to treat cardiac arrhythmia with the use of transvenous cryocatheter technology. Ideally, foci for arrhythmias are selectively ablated, arrhythmogenic tissues are destroyed, and reentry circuits are bisected in order to silence adverse electrical activity, with the goal of restoring normal sinus rhythm. The mechanism of ablation using cryotherapy results in distinct lesion qualities advantageous to radiofrequency (Khairy P, Chauvet M, Lehman J, et al. Lower incidence of thrombus formation with cryoenergy versus radiofrequency catheter ablation. Circulation 2003;107:2045–2050). This review is devoted to the mechanism of cryoablation, postablation histopathological changes, and how this information should be used by the clinicians to improve safety and maximize ablation success.

KEYWORDS Cryoablation; Pulmonary vein isolation; Arrhythmia; Cryoballoon

ABBREVIATIONS AVNRT = atrioventricular nodal reentry tachycardia; **J-T effect** = Joule-Thomson effect; **PV** = pulmonary vein; **RF** = radiofrequency

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Introduction

The mechanism of cryoablation differs considerably from that of radiofrequency (RF) ablation.[1] Tissue heating with RF energy is a result of resistive heating at the interface between the catheter and the tissue. This heating is a direct function of the current density at the catheter ablation electrode onto the myocardial interface extending a few millimeters into the tissue.[2,3] Resistive heating increases the tissue's kinetic energy by virtue of increasing molecular movement. In contrast, cryotechnologies remove heat from tissues, lowering molecular movement and stored kinetic energy, which results in tissue cooling and ice formation.[4] Blood flow and surrounding body tissues return heat to the deficit area, a potential obstacle during ablation of a highly perfused organ such as the heart.

Cryocatheters come in 2 distinct types: traditional tip ablation catheters used for focal ablation and balloon used for PV isolation. Focal cryocatheters can have 4-, 6-, and 8-mm tips and have 3 additional proximal ring electrodes allowing for electrophysiological recordings. Medtronic has 3 focal cryocatheters: Freezor (7 F, 4 mm), Freezor Xtra (7 F, 6 mm), and Freezor MAX (9 F, 8 mm). The catheter ablation tip contains an expansion chamber to produce the Joule-Thomson effect (J-T effect). In the adult patient, focal cryoablation is often used for the treatment of right-sided anterior septal accessory pathways in close proximity to the His bundle and the 4-mm tip is currently Food and Drug Administration approved for the treatment of atrioventricular nodal reentry tachycardia (AVNRT). The 6-mm tip is currently being evaluated for AVNRT treatment.

The cryoballoon catheter features an inflatable balloon that acts as the expansion chamber as the liquid nitrous oxide converts to gas. Rapid and intense cooling leads to ice formation of the tissues in contact with the balloon. It has internal thermocouples to monitor temperature within the balloon. There are 2 sizes—23- and 28-mm balloon diameters—and 2 generations—first and second. Compared to the first generation, the second generation has twice the number of refrigerant spray ports, which were moved distally to produce a more homogeneous cooling effect on the distal hemisphere of the balloon. Because of improved clinical outcomes in acute and long-term clinical studies,[5,6] an exclusive use of the second-generation balloons is recommended.

J-T effect

The mechanism responsible for inducing freezing in transvenous catheter ablation capitalizes on the phenomenon known as the J-T effect. At the most basic level, the J-T effect is the change in temperature of an expanding gas. In order for the J-T effect to occur, a specific set of parameters must be maintained. A liquefied gas is kept under constant pressure and insulated to prevent heat and energy exchange with the surrounding environment. This gas is passed under

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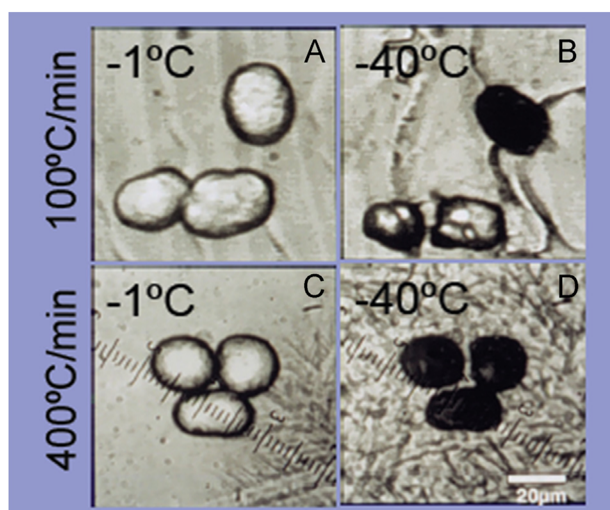

Figure 1 Variance in freezing rate affects intracellular ice formation. At temperatures of −1°C, little to no intracellular ice forms (**A and C**). Rapid freezing to −40°C will result in more intracellular ice (**D**). Slow freezing to −40°C yields less intracellular ice. If temperatures drop low enough, intracellular ice will form (**B**). Also note from panel A to B that cells shrink because of intracellular dehydration.[19]

constant pressure from a small vessel (such as tubing or catheter stem) into an expansion chamber.[7] In the expansion chamber the liquefied gas converts to gas, resulting in absorption of heat to produce tissue cooling and freezing.

Nitrogen, argon, and nitrous oxide cool upon expansion. Liquid nitrogen and argon respectively have boiling temperatures of −196°C and −185.9°C at standard atmospheric pressure. These gases expand rapidly at room temperature, resulting in high pressure in the expansion chamber. Specialized vacuum containers are necessary for their storage and prevention of rupture. The size requirements of these instruments make them too large to be used transvenously, but surgical open-chest ablation procedures have been conducted using liquid nitrogen and argon probes.[8,9]

Nitrous oxide can be contained in a liquid state, but upon leaving its pressurized container it exists in a mixed liquefied gas state that can be used in percutaneous tools. Nitrous oxide has a boiling temperature of −88.47°C, providing adequate cooling power and safety margins to be used in transvascular cardiac tissue ablation.

Mechanism of damage due to freezing

Different cell types exhibit unique resistivity to freezing. The majority of cells appear to tolerate freezing temperatures between 0°C and −15°C for short periods.[10,11] Because of the solute concentration levels present in cells, freezing does not typically occur until cells reach temperatures ≤ -5°C.[12] When temperatures reach −20°C, the majority of cells die.[11] The duration of freeze time necessary for cellular death is proportional to freezing temperature, with lower temperatures requiring shorter duration of freezing. Temperatures reaching ≤ -50°C are always lethal, regardless of duration.[11] The cause of variance in freezing rate between different cells is unclear, but research by Mazur[13] suggests that water permeability of cellular membranes controls freezing rate.

Regardless of cell type, cells react similarly to variable rates of freezing. At slow and fast rates, cell survivability is low, but at intermediate rates, survivability increases.[11] This indicates that clinically the process of freezing should be either rapid or slow (freezing rate <1.67 or >6.67°C/min) for the best outcomes.

The process of freezing has been studied extensively since its discovery as a therapeutic medium in 1850 by Arnott,[12] who used cryotherapy in the form of chilled saline to treat tumors. The use of cryoablation for treating arrhythmias was first tested in the 1970s.[13] The freezing of cells and tissues is a complex process in which damage occurs both during the freezing process and afterward. There are 3 primary factors that contribute to damage from freezing done in vivo: direct cellular damage, vascular failure, and immunological effect.

Direct cellular damage

The initial state of cooling—ice crystal formation intra- and extracellularly—is accelerated by nucleation. Nucleation is a physical process in which a change of state, for example, liquid to solid, occurs in a substance around certain focal points, known as nuclei. A common example is the condensation of water vapor to droplets in the atmosphere. Spontaneous nucleation occurs in cells from −5°C to −15°C.[12] Nucleation begins in the extracellular space from the onset of cooling.[16]

Extracellular and intracellular ice formation results in dehydration as water crystallizes. Slow ice formation (≤ 1.67°C/min) results in extracellular ice crystals that expel salt, thereby increasing ion concentration in the extracellular space. This osmotic gradient shifts intracellular fluid to the extracellular space, dehydrating the cell and increasing the intracellular concentration of solutes to lethal levels.[13] During slow freezes, the prolonged duration of osmotic dumping into extracellular space increases the duration of exposure to high concentrations of solutes[17] (Figures 1A and B). Solute effects cause destruction by chemically denaturing or deactivating enzymes, proteins, and intracellular organelles.[10,17] It has been shown that the exposure to the same concentration of electrolytes seen during freeze cycles is lethal to unfrozen red blood cells.[16]

Slow freezing depends on prolonged duration of exposure to high solute concentrations, but the lethality of fast freezing (≥ 6.67°C/min) results from a shorter period of mechanical disruption caused by ice crystals. Analysis of cells after short periods of freezing (≤ 60 seconds) reveals little mechanical damage to the ultrastructure of cells during initial ice formation.[18] When freezing at very low temperatures is prolonged, ice crystals fracture and re-form into larger crystals. This process results in shearing forces and the formation of larger ice crystals that distend and disrupt cellular organelle, membranes, and small blood vessels.[10,17] The formation of intracellular ice will in most cases result in cellular death.[12]

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